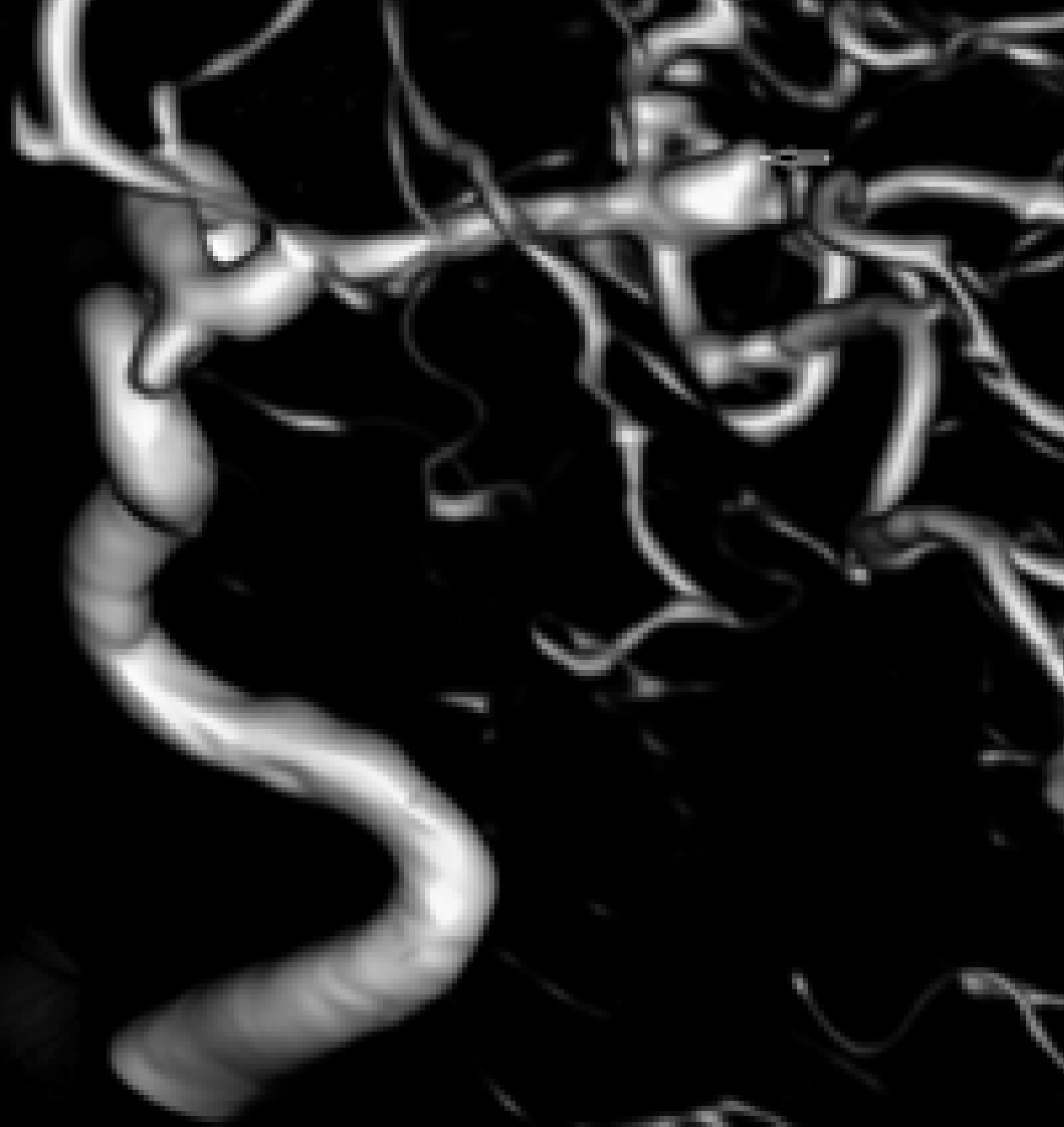

Introduction

Incidentally discovered lesions

Cormac O. Maher, M.D.,[1] Paul Klimo Jr., M.D.,[2] and Edward R. Smith, M.D.[3]

[1]Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan; [2]Semmes-Murphy Neurologic and Spine Institute, Memphis, Tennessee; and [3]Department of Neurosurgery, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts

The decision to treat a lesion of the CNS that has been discovered on imaging can have potentially serious consequences for our patients. When we are confronted with an imaging abnormality, we need to know what to do. Furthermore, it is imperative that we provide justification for these vital decisions. Ongoing advances in medical imaging, coupled with greater accessibility of these technologies, have increased the likelihood of unexpected discoveries of brain and spine lesions. Once a lesion is found, patient anxiety and a referral to a specialist for treatment often follow. This phenomenon, referred to as the cascade effect in the clinical care of patients, can be mitigated by either more selective use of diagnostic imaging or better information on the correct management of these incidental findings.[1,2] Because referral to a specialist is usually made after the lesion has been discovered, the role of the specialist in the cascade effect is usually limited to proper interpretation of the imaging findings and management recommendations. Unfortunately, we are often not prepared to make treatment decisions given the relative paucity of information that is available on these lesions. Important questions that must be answered include the prevalence, natural history, and treatment risk for each of these findings.

The purpose of this *Neurosurgical Focus* issue is to attempt to fill some of these gaps in our knowledge. The importance of this topic cuts across traditional lines of specialization. In this issue, Lanzino et al. have provided new data on the management of small intracranial aneurysms, an area of ongoing controversy. The proper management of other types of incidental lesions such as cysts, benign tumors, Tarlov cysts, os odontoideum, and syringomyelia is also examined in this issue.

As editors, we are deeply indebted to all of the outstanding groups from around the world that have shared their expertise on these lesions. We hope that these articles will stimulate further study of this important topic. *(DOI: 10.3171/2011.10.FOCUS11269)*

Disclosure

The authors report no conflict of interest.

References

1. Deyo RA: Cascade effects of medical technology. **Ann Rev Public Health 23:**23–44, 2002
2. Mold JW, Stein HF: The cascade effect in the clinical care of patients. **N Engl J Med 314:**512–514, 1986

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Management of incidentally discovered intracranial vascular abnormalities

Nohra Chalouhi, M.D., Aaron S. Dumont, M.D., Ciro Randazzo, M.D., Stavropoula Tjoumakaris, M.D., L. Fernando Gonzalez, M.D., Robert Rosenwasser, M.D., and Pascal Jabbour, M.D.

Department of Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, Pennsylvania

With the widespread use of brain imaging studies, neurosurgeons have seen a marked increase in the number of incidental intracranial lesions, including vascular abnormalities. Specifically, the detection of incidentally discovered aneurysms, arteriovenous malformations, cavernous angiomas, developmental venous anomalies, and capillary telangiectasias has increased. The best management strategy for most of these lesions is controversial. Treatment options include observation, open surgery, endovascular procedures, and radiosurgery. Multiple factors should be taken into account when discussing treatment indications, including the natural history of the disease and the risk of the treatment. In this article, the authors focus on the natural history of these lesions and the risk of the treatment, and they give recommendations regarding the most appropriate management strategy based on the current evidence in the literature and their experience with intracranial vascular abnormalities. *(DOI: 10.3171/2011.9.FOCUS11200)*

Key Words • **aneurysm** • **arteriovenous malformation** • **cavernous angioma** • **developmental venous anomaly** • **capillary telangiectasia** • **incidental finding**

Brain vascular abnormalities including aneurysms, AVMs, CAs, DVAs, and capillary telangiectasias are common incidental findings on imaging studies. With brain imaging becoming available ubiquitously, these common lesions are expected to be discovered more and more in an asymptomatic stage. The management of most of these vascular abnormalities is still controversial. As a general rule, the natural history of these lesions should be balanced against the risk of morbidity and mortality that may result from treatment. With the conflicting results of recent studies, uncertainty remains concerning the natural history and the risk of treatment, further complicating the neurosurgeon's task. This article reviews the current evidence in the literature regarding the management of incidentally discovered aneurysms, AVMs, CAs, DVAs, and capillary telangiectasias and provides neurosurgeons with a decision-making paradigm for each of these lesions.

Abbreviations used in this paper: ARUBA = A Randomized Trial of Unruptured Brain AVMs; AVM = arteriovenous malformation; CA = cavernous angioma; DVA = developmental venous anomaly; ISUIA = International Study of Unruptured Intracranial Aneurysms; SAH = subarachnoid hemorrhage.

Aneurysms

The management of unruptured intracranial aneurysms has been a very controversial topic in neurosurgery. There is no clear consensus today as to when an incidental aneurysm should be treated and when it should be observed. Moreover, the magnitude of this problem is expected to increase in the future commensurate with increased detection due to advances in imaging quality and availability. The prevalence of aneurysms in the general population is thought to be somewhere between 1% and 7%.[63,67,102,118] However, aneurysmal SAH remains a rare event with an incidence of 6–20 cases per 100,000 persons per year.[49,60,92] This underscores the importance of patient selection for treatment. Because most aneurysms remain asymptomatic throughout the patient's life, it is crucial to weigh the risks of treatment against the natural history of these lesions. Treatment should only be offered to patients whose risk of SAH exceeds the risk of surgical or endovascular intervention.

Natural History

The natural history of intracranial aneurysms continues to be a controversial topic mainly because of the con-

flicting results of the different studies. The largest study to date that evaluated the risk of rupture of intracranial aneurysms is the ISUIA (International Study of Unruptured Intracranial Aneurysms).[58,147] This prospective study involved 1692 patients and reported 5-year rupture rates for anterior circulation aneurysms with respect to their size as follows: 0% for lesions smaller than 7 mm in diameter, 2.6% for those 7–12 mm, 14.5% for those 13–24 mm, and 40% for those larger than 25 mm. The annual rate of SAH was 0.05% for aneurysms less than 10 mm in diameter and 1% for those 10 mm or greater. The 5-year rupture rates for posterior circulation aneurysms (including posterior communicating artery aneurysms) were 2.5% for those less than 7 mm, 14.5% for those 7–12 mm, 18.4% for those 13–24 mm, and 50% for those larger than 25 mm. Results also showed that the relative risk of rupture was 11.6 for aneurysms 10–24 mm in diameter and around 13 for posterior circulation aneurysms. Thus, the size and the location of the aneurysms are 2 important factors in predicting the risk of rupture of these lesions. Patients with a history of SAH from another aneurysm were found to have an annual risk of rupture of 0.5%, which is substantially higher than the risk for patients with no history of SAH (0.05%). Despite being heavily criticized by many authors for the flaws in the design, as well as a significant selection bias, the ISUIA has challenged the reports of previous studies and has had an enormous impact on the contemporary management of intracranial unruptured aneurysms. Based on the results of this study, the Stroke Council of the American Heart Association published guidelines for the management of unruptured aneurysms favoring observation over treatment for aneurysms less than 10 mm in diameter.[19] They also recommended special consideration for treatment of small aneurysms approaching the 10-mm–diameter size, those with daughter sac formation, patients with a positive family history for aneurysms or aneurysmal SAH, and if changes in aneurysmal size or configuration are observed.[19]

In contrast to the findings of the ISUIA, several studies have reported results showing that the majority of SAH resulted from aneurysms less than 10 mm in size.[21,34,70] Winn et al.[150] found that 80% of aneurysmal SAH resulted from aneurysms that were smaller than 10 mm in their greatest diameter. They also suggested that the yearly rate of rupture of intracranial aneurysms falls between 1% and 2%. Similarly, in a study from Finland that followed 142 patients with 181 unruptured inrtracranial aneurysms for a period of 19.7 years, the overall annual incidence of SAH was found to be 1.3% in patients with prior SAH and 1% in those with incidental aneurysms.[68] A recent meta-analysis that included 19 studies with 4705 patients and 6556 unruptured aneurysms showed an annual risk of rupture ranging from 0.6% to 1.3%.[146] These results were significantly higher than the annual risk of rupture reported by the ISUIA. The meta-analysis also identified higher age, female sex, smoking, location at the posterior circulation, and increasing size of the aneurysm as risk factors for SAH. In our practice, most patients present with SAH harbor aneurysms smaller than 10 mm, and a significant proportion present with ruptured aneurysms less than 5 mm in diameter.

Risk Associated With Treatment

The 30-day rate of mortality from aneurysmal SAH approaches 50%.[14,56] Preventive treatment of the aneurysm can avoid this deadly and profoundly disabling event. Treatment of unruptured aneurysms can be achieved either by surgical clipping or by endovascular means. In either case, the risk of the intervention should be weighed against the potential benefit because the rate of morbidity and mortality is substantial with these procedures.[17,54,58,114,147] The ISUIA reported a combined morbidity and mortality rate at 1 year equal to 12.2% for surgery and 9.5% for coil embolization.[58,147] Many studies have reported, however, a better benefit-risk profile for endovascular techniques than for surgery.[54,64,65] In a series of 2069 patients with unruptured aneurysms, Johnston and colleagues[65] found that adverse outcomes were more frequent in patients treated with surgery (25%) than in those treated with endovascular procedures. In a recent large study that evaluated 2535 unruptured aneurysms, endovascular treatment was associated with fewer adverse outcomes (6.6% vs 13.2%) and decreased mortality (0.9% vs 2.5%) than surgical treatment.[54] Many studies published recently have noted a very low rate of complications or death related to aneurysm treatment. Moroi et al.[97] reported a remarkable 0.3% mortality and 2.2% morbidity after treating 549 unruptured aneurysms. In a recent report Benes and colleagues[20] suggested that unruptured aneurysms can be treated with coil embolization with low rates of complication (6-month combined morbidity and mortality rate of 1.5%), justifying offering treatment to most patients with unruptured aneurysms. Along similar lines, surgical treatment has produced low rates of morbidity and mortality in patients with unruptured aneurysms in expert hands.[5,108,109,123,141] Tuffiash et al.[141] demonstrated no cognitive effects of craniotomy for unruptured aneurysms. Furthermore, the unparalleled team of Dr. Charles Drake and colleagues was able to clip unruptured basilar bifurcation aneurysms smaller than 12.5 mm in diameter with a 3.6% risk of poor outcome and no mortality.[108] Later in their monumental series, the combined risk of morbidity and mortality was reduced below 3%. Therefore, it is clear that the rate of morbidity and mortality of microsurgery or endovascular techniques is largely dependent on the experience of the neurosurgical team.

Management of Incidentally Discovered Aneurysms

Neurosurgeons should consider many factors before deciding whether to treat or watch an incidentally discovered aneurysm. If the risk of SAH is substantial, treatment should be considered. Two important factors that help predict the risk of rupture are the size and the location of the aneurysm. Aneurysms larger than 10 mm and those located in the posterior circulation are at increased risk of rupture.[58,147] Conversely small intracavernous internal carotid artery aneurysms are less prone to rupture and do not lead to SAH; observation is therefore recommended for these lesions.[19] Many studies also showed that multilobed aneurysms are at increased risk of hemorrhage compared with single-lobed lesions.[14,122] Another parameter that showed association with the risk of rupture is the aspect ratio (height/neck width).[55,99] In a study by Nader-Sepahi and

colleagues,[99] the mean aspect ratio was 2.70 for ruptured aneurysms, compared with 1.8 for unruptured aneurysms. It is currently accepted that the risk of hemorrhage is high when the aspect ratio is greater than 3.[78]

Active cigarette smoking has been shown to be an important risk factor for aneurysm growth[39,66] and therefore should be considered in the decision whether to treat or watch an aneurysm.[39] Patients should also be strongly advised to quit smoking. Although female sex has been cited in 1 article as a potential risk factor for aneurysm growth,[66] more evidence is needed before including this factor in the decision-making algorithm for these lesions. Hypertension is the most obvious risk factor for aneurysm growth and rupture in the brain and elsewhere in the body.[39,101,106] A recent article that linked arterial hypertension to cerebral aneurysm growth and rupture strongly recommended that hypertension be considered when treatment indications for small unruptured aneurysms are discussed.[39]

The ISUIA showed that patients with prior SAH have a greater risk of rupture of intracranial aneurysms. Similarly, a family history of SAH is a significant risk factor for aneurysm growth and ruprture.[27,94,126] In a study that followed 130 patients with unruptured aneurysms using serial magnetic resonance angiography, a family history of SAH was found to be an independent risk factor for aneurysm growth.[94]

According to the recommendations of the Stroke Council of the American Heart Association, any changes in aneurysm size or configuration should lead to special consideration for treatment.

A recent study showed that growth and rupture risks of aneurysms in the autosomal dominant polycystic kidney disease group are not higher than those in the general population.[59]

Finally the patient's age (and life expectancy) is a crucial factor when discussing treatment indications. A defined cutoff age, however, has not been determined. Mitchell et al.[93] concluded in their study that patients with remaining life expectancy of less than 20 years should be informed that from a statistical point of view the benefits of treatment do not outweigh the risks. Additional data are necessary to more clearly determine the impact of age and establishment of a potential age cutoff. An absolute cutoff age is unlikely to be established as many other factors play into the decision-making process.

Treatment decisions should obviously be individualized to every patient, and the choice between surgical clip placement and endovascular treatment should take into consideration the configuration and location of the aneurysm, as well as the patient's age and preferences. In patients managed conservatively, periodic follow-up (every 6–12 months) with noninvasive imaging studies (MR angiography or CT angiography) is recommended .

Based on the current evidence in the literature, the recommendations of the Stroke Council of the American Heart Association, and our institutional experience with aneurysms, we suggest the following paradigm in the decision-making process with respect to incidentally discovered intracranial aneurysms (Fig. 1).

We grouped risk factors of growth and rupture of intracranial aneurysms into 2 categories:

The Type A category represents risk factors that favor intervention over observation. These factors include active smoking, arterial hypertension, posterior circulation aneurysm, prior SAH, history of familial SAH, and an aspect ratio greater than 3.

The Type B category represents risk factors that warrant strong consideration for treatment regardless of the size of the aneurysm. These include young patient age, change in the size or configuration of the aneurysm, and the presence of multiple, multilobed, or symptomatic aneurysms.

We recommend that aneurysms larger than 7 mm in diameter be treated because of their propensity to rupture, except in older patients and those with significant medical comorbidities and short life expectancy. Aneurysms less than 5 mm in diameter should only be treated in the presence of 2 or more Type A risk factors or in the presence of any of the Type B risk factors. Finally, aneurysms that are 5–7 mm in diameter should be treated if any risk factor (Type A or Type B) is present.

Arteriovenous Malformations

Brain AVMs are the leading cause of intracerebral hemorrhage in the young population. They are responsible for 3% of strokes in young adults and 9% of SAHs.[8] The prevalence of these lesions is 1 per 1000 adults,[144] and their incidence is 1 per 100,000 per year.[7] The most common manifestation of an AVM is an intracranial hemorrhage, accounting for as many as 50% of initial presentations.[145] AVMs may also cause headaches, seizures, or focal neurological deficits. More recently, however, more AVMs are being incidentally discovered with noninvasive imaging techniques. At present there is a paucity of high-quality evidence in the literature. Consequently, the optimal management of these lesions is not clear, and neurosurgeons are left to make difficult clinical decisions with respect to the management of incidental brain AVMs.

Natural History

The most dreaded complication of an AVM is an intracerebral hemorrhage. The annual rate of hemorrhage varies widely and depends on the number of risk factors. In most series, a previous hemorrhage, a central location, a deep venous drainage, and the presence of intranidal aneurysms greatly increase the risk of future hemorrhage.[30,38,132,134] In unruptured lesions not deeply located and without deep venous drainage, the annual risk of bleeding is as low as 0.9%, according to the Columbia AVM database.[132] Conversely, in AVMs with all the previously mentioned risk factors, the annual rate of hemorrhage can reach 34.4%. The strongest risk factor for subsequent AVM bleeding is an intracranial hemorrhage at initial presentation.[132] A small AVM size was also associated with hemorrhage in 3 series,[35,46,132] but several other studies failed to demonstrate this association.[30,48] Furthermore, Stefani et al.[134] reported that large and deep-seated AVMs were more prone to hemorrhage during prospective follow-up of 390 patients with brain AVMs at the University of Toronto (Toronto Brain Vascular Malfor-

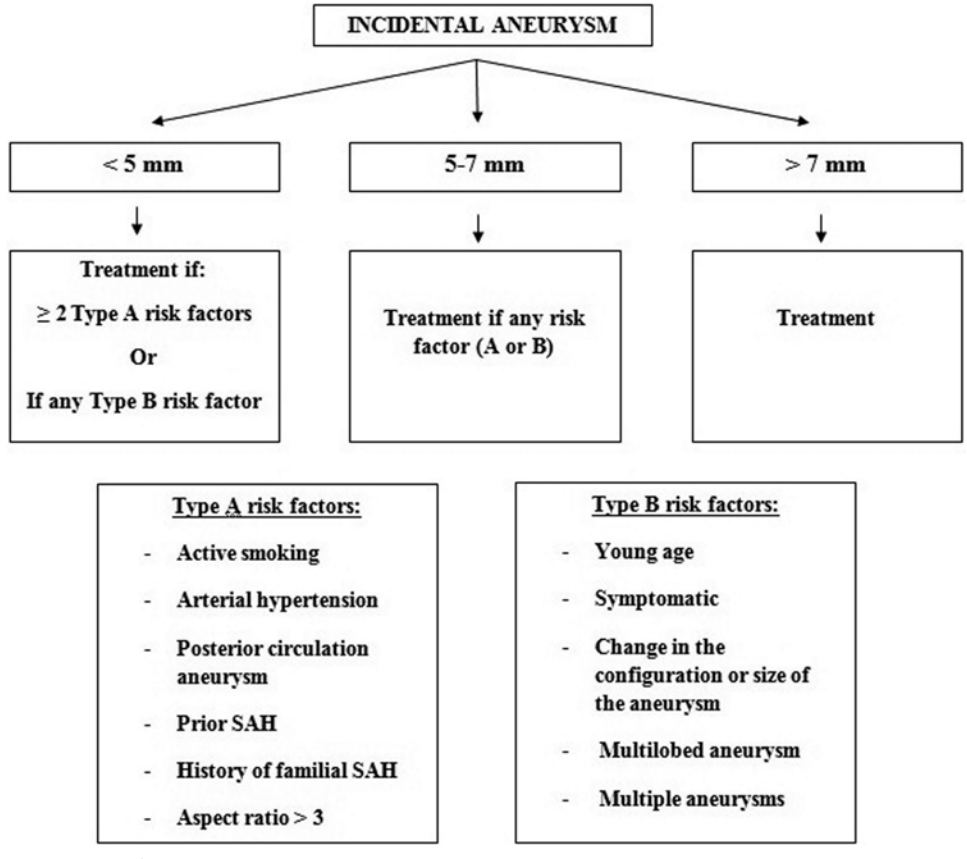

Fig. 1. Management of incidental aneurysms.

mation Study Group). Studies have also shown that the presence of venous stenosis on angiography increases the rate of intracranial hemorrhage.[85,104] It is estimated that for unruptured AVMs, regardless of the other risk factors, the average annual rate of bleeding ranges from 2% to 4%.[13,107] Kondziolka et al.[73] proposed the following formula taking into account the patient's age to estimate the lifetime risk of hemorrhage for an AVM:

$$\text{risk of hemorrhage} = 1 - (\text{risk of no hemorrhage})^{\text{expected years of remaining life.}}$$

Based on a 3% annual risk of hemorrhage, Brown[28] proposed a simple and reasonable approximation of the above formula:

$$\text{lifetime risk of hemorrhage} = 105 - \text{patient's age in years.}$$

It is also estimated that the average annual case fatality rate is around 1% for AVMs.[132] A hemorrhage from the AVM remains a deadly and extremely morbid event; the mortality rate is around 10%–15% and the morbidity rate can be as high as 53–81%.[41] Such morbidity and mortality rates could prompt neurosurgeons to offer treatment to all incidentally discovered AVMs. However, the low rate of hemorrhage of unruptured AVMs and the mild clinical syndrome from such rupture reported in the Columbia database raise doubt about the benefit of interventional therapy for AVMs that have not been associated with any hemorrhage.[133] The results of the Columbia database provided impetus for ARUBA (A Randomized Trial of Unruptured Brain AVMs).[131] This ongoing project is a prospective, multicenter, randomized, controlled trial that enrolls 800 patients with unruptured brain AVMs and aims to determine whether medical management improves long-term outcomes of patients with unruptured AVMs compared with interventional therapy.

At present, there are limited data in the literature about the natural history of AVMs. Additional information may become available from studies such as ARUBA.

Management of Incidentally Discovered AVMs

The management of incidentally discovered AVMs aims to prevent an intracranial hemorrhage. Arteriovenous malformations are classically treated by open surgery, radiosurgery, endovascular techniques, or a combination of the three. It is not clear, however, if an intervention improves the outcome of incidentally discovered AVMs. A recent study by Wedderburn et al. [145] in Scotland compared the 3-year outcome for adults who received interventional treatment for their unruptured AVMs (63 patients) with those who did not (51 patients). They found no difference in the functional outcome between the 2 groups. Moreover, interventional treatment was found to be an independent predictor of progression to poor outcome, as was AVM size. The results of this study should be interpreted with much caution for 2 main reasons. First, the 2 groups were not comparable at baseline, which means that confounding factors were not neutralized and have probably biased the study. Second, the follow-up was limited to only 3 years, which greatly underestimates any long-term benefits from interventional treatment and partly explains why the 2

groups had comparable outcomes. Another study by Lawton et al.[79] compared the benefits from resection in 224 patients with ruptured or unruptured AVMs. The condition of patients with ruptured AVMs improved after surgery, whereas patients with unruptured AVMs were susceptible to slight worsening of their neurological status. However, again the mean follow-up period was just 1.3 years, so no meaningful conclusions can be drawn from this study regarding the benefit of treatment. A recent analysis of the Columbia database showed that the initiation of any invasive treatment strategy was associated with a 3-fold increased risk of AVM hemorrhage and an increased risk of clinical impairment, raising questions about the benefit of treating unruptured AVMs.[133] Conversely, in a study involving 623 patients harboring AVMs, with a median follow-up of 11.9 years, Laakso et al.[75] found that active treatment of these lesions improved outcome and that even partial treatment enhances survival, but this benefit is not apparent until 6 years after the intervention. This may explain why the previously cited studies reported no benefit from treatment of unruptured AVMs. We hope that ARUBA, discussed above, will help solve the dilemma, although we are concerned that the planned follow-up period may be too short.

With the recent advances in endovascular techniques, embolization has become a safe and effective primary treatment modality for AVMs. In a series of 387 patients with a brain AVM, Valavanis and Yaşargil[142] achieved a 40% angiographic cure with morbidity and mortality rates as low as 1%. Endovascular embolization can completely cure an AVM, especially small lesions with limited arterial feeders, which were reported to have a cure rate close to 85% according to a recent series.[12] It can also be used before surgery to decrease the size of the nidus and occlude surgically inaccessible feeders, reducing the amount of blood loss and shortening operative time.[29,87] In addition, embolization decreases the target size of the AVM; this reduction in target size has been associated with less morbidity and higher cure rates following radiosurgery,[45] although it remains the subject of controversy. Finally, embolization can be palliative for patients with large nonresectable AVMs, intractable seizures, or progressive neurological deficits.[42,82] A variety of embolic materials are currently used for the treatment of AVMs. N-butyl cyanoacrylate (NBCA) and Onyx (ev3, Inc.) are nonabsorbable embolic agents that can achieve complete obliteration of an AVM. Due to its nonadhesive nature, Onyx allows longer, slower, and more controlled injections with subsequent embolization of a larger percentage of the AVM from a single catheter position. In a very recent article, Saatci et al.[121] reported achieving complete obliteration in more than 50% of brain AVMs using prolonged intranidal Onyx injection. The authors concluded that this technique leads to higher rates of anatomical cures than previously reported with other embolic agents. In addition, the more effective intranidal penetration of the embolic agent with this technique allows high-grade AVMs to be made radiosurgically treatable.

In radiosurgical treatment of AVMs, the goal is obliteration of the vessels in the nidus. It is known to provide high cure rates and low morbidity rates, especially in small lesions.[88,136] It is also useful in treating small deeply located AVMs that are otherwise challenging to surgical treatment or embolization.[11,89] Maruyama et al.[89] reported a 66% obliteration rate for brainstem AVMs after radiosurgery (at 3-year follow-up). However, as the size of the AVM increases, the cure rate decreases and the complication rate increases.[33,47,105] Another major disadvantage of radiosurgery is the risk of hemorrhage until the AVM is totally obliterated.[103,111] In a retrospective study of 500 patients with AVMs who were treated with Gamma Knife surgery, Maruyama et al.[88] reported that 23 patients had a hemorrhage during the first 2 years following radiosurgery, and 6 patients had a hemorrhage even after angiographic obliteration. The risk of hemorrhage declined by 54% after 2 years and by 88% after obliteration of the lesion. In a recently published article, Blamek and colleagues[26] reported that annual hemorrhage rates after radiosurgery were 3.4% and 1.1% during the 1st and 2nd year of follow-up, respectively. The authors also concluded that a 3-year follow-up period is required to accurately assess the outcome after radiosurgery for brain AVMs.

Surgical excision of AVMs has long been considered the mainstay of treatment, with the advantage of completely removing the lesions. However, potential morbidity and mortality rates associated with the procedure warrant careful patient selection especially for incidentally discovered AVMs. The Spetzler-Martin classification takes into account the AVM size, eloquence of the adjacent brain, and the pattern of venous drainage of the AVM to estimate the surgical risk.[129] The initial classification (1986) included 5 categories[129] (Table 1). In a prospective evaluation of the classification system, morbidity rates for Grades I, II, and III were 0%, increasing to 21.9% in patients with Grade IV and 16.7% in patients with Grade V AVMs.[50] Similarly, Heros and Tu[53] reported good surgical results in 100%, 94.3%, 88.6%, 61%, and 28.6% of patients with Grade I, II, III, IV, and V AVMs, respectively. It is therefore clear that Grades I and II and even Grade III lesions (low-grade AVMs) can totally be excised with a low rate of observed morbidity. Conversely, Grade IV and V AVMs (high-grade AVMs) are associated with a high rate of complications, and surgery should therefore be avoided in patients with these lesions. A few studies have assessed the risk of hemorrhage of AVMs based on the Spetzler-Martin grade with conflicting results. A high annual risk of bleeding for high-grade AVMs (10.4%) was

TABLE 1: The Spetzler-Martin classification for AVMs

Lesion Characteristics	Points
size	
small (<3 cm)	1
medium (3–6 cm)	2
large (>6 cm)	3
eloquence of the adjacent brain	
noneloquent	0
eloquent	1
pattern of venous drainage	
superficial only	0
deep	1

reported in a study by Jayaraman and coworkers.[62] Elsewhere, the risk was found to be even lower (1.5%) than that for all AVMs on average (3%).[51] In a recently published article, Spetzler and Ponce[130] proposed a new classification for AVMs (2011) that consists of 3 classes: Spetzler-Martin Grades I and II AVMs were combined into Class A and Grades IV and V lesions into Class C; Grade III AVMs became Class B (Table 2). This was justified by the finding that surgical outcomes in 1476 cases from 7 surgical series were similar for Grades I and II AVMs (Class A) and for Grades IV and V AVMs (Class C).[130] The new classification system also offers a paradigm for management of AVMs; surgical excision is recommended for Class A, multimodality therapy for Class B, and observation for Class C. Treatment of Class C AVMs is only recommended in the presence of recurrent hemorrhages, progressive neurological deficits, steal-related symptoms, and AVM-related aneurysms.[130]

In our institution, we perform endovascular embolization for some Grade IV AVMs even in the absence of the previously cited factors, especially in cases involving young patients. Embolization can safely decrease the size and the grade of the lesion, allowing for surgical excision or radiosurgery.[84,121,148,149] Blackburn et al.[25] recently evaluated endovascular therapy followed by radiosurgery in 21 patients with high-grade AVMs (12 lesions were Spetzler-Martin Grade IV or V). Interestingly, they found an obliteration rate close to 80% and a major neurological complications rate as low as 0%. In the previously discussed study by Saatci et al.,[121] which involved 350 patients with brain AVMs, including high-grade lesions, the authors reported complete obliteration by endovascular means in 50% of the population, with 38% and 6% of the patients referred to radiosurgery and surgical excision, respectively. It is also well known that the Spetzler-Martin classification is not applicable for embolization procedures because deep venous drainage is not associated with increased risk of complications for this treatment modality. Furthermore the classification system does not take into account important factors for embolization like the number of vessels feeding into the AVM and the presence of fistulous components.[40]

Based on the current evidence in the literature and our experience, we suggest the following algorithm (Table 3).

We recommend surgical excision for Spetzler-Martin Grade I and II AVMs. Grade III AVMs should be treated with a combination of surgery, endovascular techniques, and radiosurgery. Grade IV AVMs should be strongly considered for endovascular therapy followed whenever possible by surgery or radiosurgery. Observation is also an option in the latter group. Finally, we recommend observation in cases of Grade V AVMs because of the high morbidity rate associated with treatment. In some cases, especially those involving young patients, Grade V AVMs can be considered for endovascular therapy followed by radiosurgery.

TABLE 2: The 3-tier classification of cerebral AVMs

Spetzler-Martin Class	Grade	Management
A	I & II	resection
B	III	multimodality treatment
C	IV & V	no treatment*

* Exceptions for treatment of Class C AVMs include cases characterized by recurrent hemorrhages, progressive neurological deficits, and steal-related symptoms, as well as AVM-related aneurysms.

TABLE 3: Management of incidental AVMs

Spetzler-Martin Grade	Management
I & II	surgery
III	multimodality treatment
IV	endovascular treatment followed by surgery/radiosurgery, or observation
V	observation or endovascular treatment followed by radiosurgery (especially for young patients)

Cavernous Angiomas

Cavernous angiomas, more commonly known as cavernomas, are low-flow vascular abnormalities of the brain composed of clusters of dilated, thin-walled capillaries filled with thrombus.[44] These lesions account for 15% of all vascular malformations[18,86] and have an estimated prevalence approaching 0.6% in the general population.[18,37,120] Up to 50% of CAs are familial[77] and follow an autosomal dominant pattern of inheritance linked to the *CCM1*, *CCM2*, and *CCM3* genes on 7q, 7p, and 3q, respectively.[22,61,77] Patients with familial CAs typically harbor multiple lesions, unlike those with a sporadic form who usually present with a single lesion.[77,152] Cavernous angiomas are typically located supratentorially; brainstem lesions account only for 8%–22% of all cases.

Patients with CAs usually present in the 4th or 5th decade of life, although in 25% of cases, patients present in childhood.[98] Depending on their location, the lesions can manifest with seizures, headaches, progressive neurological deficits, or intracranial hemorrhage. The most common presentation in patients with supratentorial CA is a new-onset seizure (40%–70% of cases).[4,71,151] Seizures are due to recurrent microhemorrhages and hemosiderin deposition in the perilesional area.[152] Headaches are also a common presentation and occur in 30%–50% of cases.[74,151,152] Infratentorial CAs are rarely clinically silent and typically produce progressive neurological deficits.[52,143] Intracranial hemorrhages are seen in both supratentorial and infratentorial lesions and are typically mild in severity, but severe and fatal hemorrhages do occur. With the increased use of MR imaging for brain imaging, it is now estimated that almost 40% of CAs that are identified represent incidental findings.[18]

Cavernous angiomas are known as angiographically occult vascular malformations because they do not appear on angiography, which therefore has little value in the diagnosis or management of these lesions except for detecting the presence of an associated atypical venous drainage.[24] Magnetic resonance imaging is the most sensitive and specific imaging modality for the diagnosis and

follow-up of CAs.[57,116] Typically, the lesions appear as areas of mixed signal intensity on T1- and T2-weighted images and are surrounded by a peripheral area of hypointensity (representing a hemosiderin ring) on T2-weighted images.[119] According to recent reports, the highly sensitive T2-weighted gradient-echo imaging has become the gold standard MR imaging sequence for visualization of CAs.[31,81]

Natural History and Management of Incidentally Discovered CAs

The annual rate of symptomatic hemorrhage from a CA ranges from 0.7% to 6% according to multiple studies and varies with a number of factors.[76,113,120,152] The risk of significant bleeding is higher in patients with a prior history of hemorrhage.[6,72] In a study involving 122 patients with CAs, Kondziolka et al.[72] reported an annual hemorrhage rate of 0.6% in patients with no hemorrhagic presentation versus 4.5% for patients with hemorrhagic presentation. It is worth noting that the risk of rebleeding is particularly high in the 2 years following the initial hemorrhage but seems to significantly decrease thereafter. This phenomenon is known as "temporal clustering" and has been reported in several series.[16,143] Deeply located CAs, especially those in the brainstem, have been found to carry a worse prognosis than superficial lesions.[112] Porter et al.[112] reported that the risk of bleeding for infratentorial CAs is 3.8% compared with 0.4% for supratentorial CAs. Female sex also appears to negatively impact the outcome for patients with CAs.[6,113] Seizures and a familial form have been proposed as potential risk factors for hemorrhage, but there is not enough evidence in the literature to support this hypothesis.

The treatment of symptomatic CAs is image-guided resection. If a DVA is associated, it is recommended not to excise the DVA, as doing so would pose an unnecessary risk of venous infarction.[3] Surgery is classically performed in patients with repetitive episodes of hemorrhage, intractable seizures, and progressive neurological deficits, especially when the CA is located in noneloquent areas of the brain.[24,36,115] Conversely, in deep and eloquent areas, the risk of complications is substantial and the threshold for surgery is even higher.[10,23,135] There is a recent tendency in some institutions to extend surgical indications to mildly symptomatic CAs, even in the brainstem. In a recent study involving 300 patients with surgically treated brainstem cavernomas, Abla et al.[2] reported that surgery markedly improved the risk of rehemorrhage and related symptoms. They concluded that surgery should be considered in patients with accessible lesions. However, new or worsening neurological symptoms developed in 53% of patients after the procedure, 36% had permanent new deficits, and perioperative complications developed in 28%.[2] Due to the significant potential morbidity associated with resection of CAs in eloquent areas like the brainstem, we have adopted a more conservative approach. More evidence is needed to ascertain whether patients with mildly symptomatic but accessible brainstem CAs actually benefit from surgery.

Finally, the role of radiosurgery in the treatment of CAs is still controversial despite encouraging reports. In a recent study involving 68 patients with brainstem CAs treated with Gamma Knife surgery, Monaco et al.[95] found that radiosurgery decreased the annual hemorrhage rate from 32% before treatment to 1.3% after 2 years of follow-up. However 11.8% of patients experienced new neurological deficits as a result of adverse radiation effects. Lunsford et al.[83] were also able to demonstrate that radiosurgery reduced the risk of bleeding from 32% to just 1% after 2 years of follow-up. The rate of morbidity was 13.5% in this series. There are concerns about the high risk of complications associated with radiosurgery for CAs, particularly in the brainstem and deep locations.[9,69,95] It is also known, as discussed above, that the risk of bleeding of a CA significantly decreases by itself beyond 2 years after the initial hemorrhage. Consequently, the positive results associated with radiosurgery in the previously cited studies could simply reflect the natural history of these lesions. The utility of radiosurgery in the treatment of CAs remains unproven and continues to be a subject of debate.

Purely incidental CAs should be managed conservatively and followed with yearly MR imaging. We recommend treating cavernous angiomas only in the following situations: intractable seizures, progressive significant neurological deficit, after the first clinically significant hemorrhage in noneloquent areas, and after the second clinically significant hemorrhage in eloquent areas including the brainstem.

Developmental Venous Anomalies

Developmental venous anomalies, formerly known as venous angiomas, are enlarged venous vessels that drain into a large-caliber vein with a characteristic appearance of caput medusa on angiography. They are congenital malformations of the brain that are viewed as a normal variant of the cerebral venous system. Their prevalence is 2.5% according to autopsy studies.[43,125] Developmental venous anomalies are the most commonly diagnosed intracranial vascular malformation and are typically discovered incidentally on brain MR imaging studies or CT scans.[139] They are associated with a CA in 13%–18% of cases,[124,139] and it is thought that there is a causative link between these 2 lesions. It has been postulated that the recurrent microhemorrhages from a DVA induce angiogenesis in the surrounding brain, leading to CA formation.[110]

Developmental venous anomalies have a benign natural history with an extremely low morbidity rate and a mortality rate of 0%.[91,100] The annual risk of hemorrhage is negligible (0.25%–0.34%),[37,91] and it is thought that a hemorrhage in the setting of a DVA is due to an associated CA.[117] Nevertheless, DVA thrombosis can lead to a venous infarct with a secondary hemorrhagic transformation, although this remains a rare event.[90] No relationship has been established to date between DVAs and headaches or seizures.[96,137]

A DVA is primarily visualized on MR images as a signal-void linear structure especially on T2-weighted sequences.[140] Magnetic resonance imaging also offers the possibility of detecting an associated cavernoma. Contrast-enhanced MR imaging is the sequence of choice and shows the classic caput medusa appearance.[140] Similar

findings are seen on contrast-enhanced CT. Angiography is performed only in patients with an ischemic or hemorrhagic presentation and in those in whom an AVM should be ruled out.

Surgical obliteration of a DVA can lead to venous thrombosis, venous congestion, and infarct with a secondary hemorrhagic conversion.[1,128] This is due to the fact that a DVA drains normal brain tissue. Developmental venous anomalies should always be left untreated, even when associated with a CA.[1] Given their benign natural history, DVAs do not require follow-up imaging studies.

Capillary Telangiectasias

Capillary telangiectasias are dilated thin-walled capillaries surrounded by normal brain parenchyma and associated with other vascular abnormalities.[15] They are relatively common and account for 4%–12% of all vascular malformations.[127] Capillary telangiectasias are incidental findings on imaging studies and are frequently misdiagnosed as glial tumors. Patients typically remain typically asymptomatic throughout life, although the lesions may occasionally cause seizures, vertigo, cranial nerve dysfunction, visual changes, and dizziness.[80,138] In a recent study, Sayama et al.[127] reported that 28.6% of large capillary telangiectasias (> 1 cm) were symptomatic, whereas none of the small ones were.

Capillary telangiectasias are visualized as small enhancing lesions on contrast-enhanced MR imaging sequences and demonstrate a signal intensity loss on gradient-echo sequences.[32] They are angiographically occult and are not usually seen on CT scan.

Capillary telangiectasias are benign lesions that do not require any treatment or follow-up.

Conclusions

Incidentally discovered intracranial vascular abnormalities are increasingly coming to the attention of neurosurgeons with the ubiquitous availability of high-quality, noninvasive imaging studies. Lesions such as intracranial aneurysms, AVMs, CAs, DVAs, and capillary telangiectasias may be incidentally discovered on brain imaging studies. Each pathological entity is associated with its own unique natural history, and management must be tailored to the type of lesion and individual circumstances of a given patient. In the present article we have attempted to provide an evidence-based resource to guide neurosurgeons in the management of these incidentally discovered intracranial vascular abnormalities. The quality and quantity of evidence, however, remains limited, and further studies are needed to elucidate the most appropriate management strategy in many situations.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References

1. Abla AA, Lekovic GP, Turner J, de Oliveira JG, Porter R, Spetzler RF: Advances in the treatment and outcome of brain stem cavernous malformation surgery: a case series of 300 surgically treated patients. **Neurosurgery** [epub ahead of print], 2010
2. Abla AA, Lekovic GP, Turner JD, de Oliveira JG, Porter R, Spetzler RF: Advances in the treatment and outcome of brainstem cavernous malformation surgery: a single-center case series of 300 surgically treated patients. **Neurosurgery 68:** 403–415, 2011
3. Abla AA, Turner JD, Mitha AP, Lekovic G, Spetzler RF: Surgical approaches to brainstem cavernous malformations. **Neurosurg Focus 29(3):**E8, 2010
4. Acciarri N, Galassi E, Giulioni M, Pozzati E, Grasso V, Palandri G, et al: Cavernous malformations of the central nervous system in the pediatric age group. **Pediatr Neurosurg 45:**81–104, 2009
5. Aghakhani N, Vaz G, David P, Parker F, Goffette P, Ozan A, et al: Surgical management of unruptured intracranial aneurysms that are inappropriate for endovascular treatment: experience based on two academic centers. **Neurosurgery 62:** 1227–1235, 2008
6. Aiba T, Tanaka R, Koike T, Kameyama S, Takeda N, Komata T: Natural history of intracranial cavernous malformations. **J Neurosurg 83:**56–59, 1995
7. Al-Shahi R, Fang JS, Lewis SC, Warlow CP: Prevalence of adults with brain arteriovenous malformations: a community based study in Scotland using capture-recapture analysis. **J Neurol Neurosurg Psychiatry 73:**547–551, 2002
8. Al-Shahi R, Warlow C: A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. **Brain 124:**1900–1926, 2001
9. Amin-Hanjani S, Ogilvy CS, Candia GJ, Lyons S, Chapman PH: Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron. **Neurosurgery 42:**1229–1238, 1998
10. Amin-Hanjani S, Ogilvy CS, Ojemann RG, Crowell RM: Risks of surgical management for cavernous malformations of the nervous system. **Neurosurgery 42:**1220–1228, 1998
11. Andrade-Souza YM, Zadeh G, Scora D, Tsao MN, Schwartz ML: Radiosurgery for basal ganglia, internal capsule, and thalamus arteriovenous malformation: clinical outcome. **Neurosurgery 56:**56–64, 2005
12. Andreou A, Ioannidis I, Lalloo S, Nickolaos N, Byrne JV: Endovascular treatment of intracranial microarteriovenous malformations. Clinical article. **J Neurosurg 109:**1091–1097, 2008
13. ApSimon HT, Reef H, Phadke RV, Popovic EA: A population-based study of brain arteriovenous malformation: long-term treatment outcomes. **Stroke 33:**2794–2800, 2002
14. Asari S, Ohmoto T: Natural history and risk factors of unruptured cerebral aneurysms. **Clin Neurol Neurosurg 95:**205–214, 1993
15. Awad IA, Robinson JR Jr, Mohanty S, Estes ML: Mixed vascular malformations of the brain: clinical and pathogenetic considerations. **Neurosurgery 33:**179–188, 1993
16. Barker FG II, Amin-Hanjani S, Butler WE, Lyons S, Ojemann RG, Chapman PH, et al: Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. **Neurosurgery 49:**15–25, 2001
17. Barker FG II, Amin-Hanjani S, Butler WE, Ogilvy CS, Carter BS: In-hospital mortality and morbidity after surgical treatment

of unruptured intracranial aneurysms in the United States, 1996-2000: the effect of hospital and surgeon volume. **Neurosurgery 52:**995–1009, 2003
18. Batra S, Lin D, Recinos PF, Zhang J, Rigamonti D: Cavernous malformations: natural history, diagnosis and treatment. **Nat Rev Neurol 5:**659–670, 2009
19. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, et al: Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. **Circulation 102:**2300–2308, 2000
20. Benes V III, Mitchell P, Molyneux AJ, Renowden SA: Endovascular coiling in 131 patients with low complication rate justifies treating most unruptured intracranial aneurysms. **Cen Eur Neurosurg 71:**1–7, 2010
21. Berenstein A, Flamm ES, Kupersmith MJ: Unruptured intracranial aneurysms. **N Engl J Med 340:**1439–1442, 1999
22. Bergametti F, Denier C, Labauge P, Arnoult M, Boetto S, Clanet M, et al: Mutations within the programmed cell death 10 gene cause cerebral cavernous malformations. **Am J Hum Genet 76:**42–51, 2005
23. Bertalanffy H, Benes L, Miyazawa T, Alberti O, Siegel AM, Sure U: Cerebral cavernomas in the adult. Review of the literature and analysis of 72 surgically treated patients. **Neurosurg Rev 25:**1–55, 2002
24. Bertalanffy H, Kühn G, Scheremet R, Seeger W: Indications for surgery and prognosis in patients with cerebral cavernous angiomas. **Neurol Med Chir (Tokyo) 32:**659–666, 1992
25. Blackburn SL, Ashley WW Jr, Rich KM, Simpson JR, Drzymala RE, Ray WZ, et al: Combined endovascular embolization and stereotactic radiosurgery in the treatment of large arteriovenous malformations. Clinical article. **J Neurosurg 114:** 1758–1767, 2011
26. Blamek S, Tarnawski R, Miszczyk L: Linac-based Stereotactic Radiosurgery for Brain Arteriovenous Malformations. **Clin Oncol (R Coll Radiol) 23:**525–531, 2011
27. Broderick JP, Brown RD Jr, Sauerbeck L, Hornung R, Huston J III, Woo D, et al: Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. **Stroke 40:**1952–1957, 2009
28. Brown RD Jr: Simple risk predictions for arteriovenous malformation hemorrhage. **Neurosurgery 46:**1024, 2000
29. Brown RD Jr, Flemming KD, Meyer FB, Cloft HJ, Pollock BE, Link ML: Natural history, evaluation, and management of intracranial vascular malformations. **Mayo Clin Proc 80:** 269–281, 2005
30. Brown RD Jr, Wiebers DO, Forbes GS: Unruptured intracranial aneurysms and arteriovenous malformations: frequency of intracranial hemorrhage and relationship of lesions. **J Neurosurg 73:**859–863, 1990
31. Campbell PG, Jabbour P, Yadla S, Awad IA: Emerging clinical imaging techniques for cerebral cavernous malformations: a systematic review. **Neurosurg Focus 29(3):**E6, 2010
32. Castillo M, Morrison T, Shaw JA, Bouldin TW: MR imaging and histologic features of capillary telangiectasia of the basal ganglia. **AJNR Am J Neuroradiol 22:**1553–1555, 2001
33. Chang JH, Chang JW, Park YG, Chung SS: Factors related to complete occlusion of arteriovenous malformations after gamma knife radiosurgery. **J Neurosurg 93 (Suppl 3):**96–101, 2000
34. Connolly ES Jr, Mohr JP, Solomon RA: Unruptured intracranial aneurysms. **N Engl J Med 340:**1440–1442, 1999
35. Crawford PM, West CR, Chadwick DW, Shaw MD: Arteriovenous malformations of the brain: natural history in unoperated patients. **J Neurol Neurosurg Psychiatry 49:**1–10, 1986
36. D'Angelo VA, De Bonis C, Amoroso R, Cali A, D'Agruma L, Guarnieri V, et al: Supratentorial cerebral cavernous malformations: clinical, surgical, and genetic involvement. **Neurosurg Focus 21(1):**e9, 2006
37. Del Curling O Jr, Kelly DL Jr, Elster AD, Craven TE: An analysis of the natural history of cavernous angiomas. **J Neurosurg 75:**702–708, 1991
38. Duong DH, Young WL, Vang MC, Sciacca RR, Mast H, Koennecke HC, et al: Feeding artery pressure and venous drainage pattern are primary determinants of hemorrhage from cerebral arteriovenous malformations. **Stroke 29:**1167–1176, 1998
39. Etminan N, Beseoglu K, Steiger HJ, Hänggi D: The impact of hypertension and nicotine on the size of ruptured intracranial aneurysms. **J Neurol Neurosurg Psychiatry 82:**4–7, 2011
40. Feliciano CE, de León-Berra R, Hernández-Gaitán MS, Rodríguez-Mercado R: A proposal for a new arteriovenous malformation grading scale for neuroendovascular procedures and literature review. **P R Health Sci J 29:**117–120, 2010
41. Fleetwood IG, Steinberg GK: Arteriovenous malformations. **Lancet 359:**863–873, 2002
42. Fox AJ, Girvin JP, Viñuela F, Drake CG: Rolandic arteriovenous malformations: improvement in limb function by IBC embolization. **AJNR Am J Neuroradiol 6:**575–582, 1985
43. Garner TB, Del Curling O Jr, Kelly DL Jr, Laster DW: The natural history of intracranial venous angiomas. **J Neurosurg 75:**715–722, 1991
44. Gault J, Sarin H, Awadallah NA, Shenkar R, Awad IA: Pathobiology of human cerebrovascular malformations: basic mechanisms and clinical relevance. **Neurosurgery 55:**1–17, 2004
45. Gobin YP, Laurent A, Merienne L, Schlienger M, Aymard A, Houdart E, et al: Treatment of brain arteriovenous malformations by embolization and radiosurgery. **J Neurosurg 85:** 19–28, 1996
46. Graf CJ, Perret GE, Torner JC: Bleeding from cerebral arteriovenous malformations as part of their natural history. **J Neurosurg 58:**331–337, 1983
47. Hadjipanayis CG, Levy EI, Niranjan A, Firlik AD, Kondziolka D, Flickinger JC, et al: Stereotactic radiosurgery for motor cortex region arteriovenous malformations. **Neurosurgery 48:**70–77, 2001
48. Halim AX, Johnston SC, Singh V, McCulloch CE, Bennett JP, Achrol AS, et al: Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. **Stroke 35:**1697–1702, 2004
49. Hamada J, Morioka M, Yano S, Kai Y, Ushio Y: Incidence and early prognosis of aneurysmal subarachnoid hemorrhage in Kumamoto Prefecture, Japan. **Neurosurgery 54:**31–38, 2004
50. Hamilton MG, Spetzler RF: The prospective application of a grading system for arteriovenous malformations. **Neurosurgery 34:**2–7, 1994
51. Han PP, Ponce FA, Spetzler RF: Intention-to-treat analysis of Spetzler-Martin grades IV and V arteriovenous malformations: natural history and treatment paradigm. **J Neurosurg 98:**3–7, 2003
52. Hauck EF, Barnett SL, White JA, Samson D: Symptomatic brainstem cavernomas. **Neurosurgery 64:**61–71, 2009
53. Heros RC, Tu YK: Is surgical therapy needed for unruptured arteriovenous malformations? **Neurology 37:**279–286, 1987
54. Higashida RT, Lahue BJ, Torbey MT, Hopkins LN, Leip E, Hanley DF: Treatment of unruptured intracranial aneurysms: a nationwide assessment of effectiveness. **AJNR Am J Neuroradiol 28:**146–151, 2007
55. Hoh BL, Sistrom CL, Firment CS, Fautheree GL, Velat GJ, Whiting JH, et al: Bottleneck factor and height-width ratio: association with ruptured aneurysms in patients with multiple cerebral aneurysms. **Neurosurgery 61:**716–723, 2007
56. Hop JW, Rinkel GJ, Algra A, van Gijn J: Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. **Stroke 28:**660–664, 1997
57. Ide C, De Coene B, Baudrez V: MR features of cavernous angioma. **JBR-BTR 83:**320, 2000
58. International Study of Unruptured Intracranial Aneurysms Investigators: Unruptured intracranial aneurysms—risk of

rupture and risks of surgical intervention. **N Engl J Med 339:** 1725–1733, 1998
59. Irazabal MV, Huston J III, Kubly V, Rossetti S, Sundsbak JL, Hogan MC, et al: Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease. **Clin J Am Soc Nephrol 6:**1274–1285, 2011
60. Iwamoto H, Kiyohara Y, Fujishima M, Kato I, Nakayama K, Sueishi K, et al: Prevalence of intracranial saccular aneurysms in a Japanese community based on a consecutive autopsy series during a 30-year observation period. The Hisayama study. **Stroke 30:**1390–1395, 1999
61. Jabbour P, Gault J, Awad IA: What genes can teach us about human cerebrovascular malformations. **Clin Neurosurg 51:**140–152, 2004
62. Jayaraman MV, Marcellus ML, Do HM, Chang SD, Rosenberg JK, Steinberg GK, et al: Hemorrhage rate in patients with Spetzler-Martin grades IV and V arteriovenous malformations: is treatment justified? **Stroke 38:**325–329, 2007
63. Jellinger K: Pathology of intracerebral hemorrhage. **Zentralbl Neurochir 38:**29–42, 1977
64. Johnston SC, Dudley RA, Gress DR, Ono L: Surgical and endovascular treatment of unruptured cerebral aneurysms at university hospitals. **Neurology 52:**1799–1805, 1999
65. Johnston SC, Zhao S, Dudley RA, Berman MF, Gress DR: Treatment of unruptured cerebral aneurysms in California. **Stroke 32:**597–605, 2001
66. Juvela S: Natural history of unruptured intracranial aneurysms: risks for aneurysm formation, growth, and rupture. **Acta Neurochir Suppl 82:**27–30, 2002
67. Juvela S: Prevalence of and risk factors for intracranial aneurysms. **Lancet Neurol 10:**595–597, 2011
68. Juvela S, Porras M, Poussa K: Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. **J Neurosurg 93:**379–387, 2000
69. Kim DG, Choe WJ, Paek SH, Chung HT, Kim IH, Han DH: Radiosurgery of intracranial cavernous malformations. **Acta Neurochir (Wien) 144:**869–878, 2002
70. King JT Jr, Berlin JA, Flamm ES: Morbidity and mortality from elective surgery for asymptomatic, unruptured, intracranial aneurysms: a meta-analysis. **J Neurosurg 81:**837–842, 1994
71. Kivelev J, Niemelä M, Kivisaari R, Dashti R, Laakso A, Hernesniemi J: Long-term outcome of patients with multiple cerebral cavernous malformations. **Neurosurgery 65:**450–455, 2009
72. Kondziolka D, Lunsford LD, Kestle JR: The natural history of cerebral cavernous malformations. **J Neurosurg 83:**820–824, 1995
73. Kondziolka D, McLaughlin MR, Kestle JR: Simple risk predictions for arteriovenous malformation hemorrhage. **Neurosurgery 37:**851–855, 1995
74. Kupersmith MJ, Kalish H, Epstein F, Yu G, Berenstein A, Woo H, et al: Natural history of brainstem cavernous malformations. **Neurosurgery 48:**47–54, 2001
75. Laakso A, Dashti R, Seppänen J, Juvela S, Väärt K, Niemelä M, et al: Long-term excess mortality in 623 patients with brain arteriovenous malformations. **Neurosurgery 63:**244–255, 2008
76. Labauge P, Brunereau L, Lévy C, Laberge S, Houtteville JP: The natural history of familial cerebral cavernomas: a retrospective MRI study of 40 patients. **Neuroradiology 42:**327–332, 2000
77. Laberge-le Couteulx S, Jung HH, Labauge P, Houtteville JP, Lescoat C, Cecillon M, et al: Truncating mutations in CCM1, encoding KRIT1, cause hereditary cavernous angiomas. **Nat Genet 23:**189–193, 1999
78. Lall RR, Eddleman CS, Bendok BR, Batjer HH: Unruptured intracranial aneurysms and the assessment of rupture risk based on anatomical and morphological factors: sifting through the sands of data. **Neurosurg Focus 26(5):**E2, 2009
79. Lawton MT, Du R, Tran MN, Achrol AS, McCulloch CE, Johnston SC, et al: Effect of presenting hemorrhage on outcome after microsurgical resection of brain arteriovenous malformations. **Neurosurgery 56:**485–493, 2005
80. Lee RR, Becher MW, Benson ML, Rigamonti D: Brain capillary telangiectasia: MR imaging appearance and clinicohistopathologic findings. **Radiology 205:**797–805, 1997
81. Lehnhardt FG, von Smekal U, Rückriem B, Stenzel W, Neveling M, Heiss WD, et al: Value of gradient-echo magnetic resonance imaging in the diagnosis of familial cerebral cavernous malformation. **Arch Neurol 62:**653–658, 2005
82. Luessenhop AJ, Mujica PH: Embolization of segments of the circle of Willis and adjacent branches for management of certain inoperable cerebral arteriovenous malformations. **J Neurosurg 54:**573–582, 1981
83. Lunsford LD, Khan AA, Niranjan A, Kano H, Flickinger JC, Kondziolka D: Stereotactic radiosurgery for symptomatic solitary cerebral cavernous malformations considered high risk for resection. Clinical article. **J Neurosurg 113:**23–29, 2010
84. Lv X, Wu Z, Jiang C, Li Y, Yang X, Zhang Y, et al: Complication risk of endovascular embolization for cerebral arteriovenous malformation. **Eur J Radiol** [epub ahead of print], 2010
85. Mansmann U, Meisel J, Brock M, Rodesch G, Alvarez H, Lasjaunias P: Factors associated with intracranial hemorrhage in cases of cerebral arteriovenous malformation. **Neurosurgery 46:**272–281, 2000
86. Maraire JN, Awad IA: Intracranial cavernous malformations: lesion behavior and management strategies. **Neurosurgery 37:**591–605, 1995
87. Martin NA, Khanna R, Doberstein C, Bentson J: Therapeutic embolization of arteriovenous malformations: the case for and against. **Clin Neurosurg 46:**295–318, 2000
88. Maruyama K, Kawahara N, Shin M, Tago M, Kishimoto J, Kurita H, et al: The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. **N Engl J Med 352:** 146–153, 2005
89. Maruyama K, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD: Stereotactic radiosurgery for brainstem arteriovenous malformations: factors affecting outcome. **J Neurosurg 100:**407–413, 2004
90. Masson C, Godefroy O, Leclerc X, Colombani JM, Leys D: Cerebral venous infarction following thrombosis of the draining vein of a venous angioma (developmental abnormality). **Cerebrovasc Dis 10:**235–238, 2000
91. McLaughlin MR, Kondziolka D, Flickinger JC, Lunsford S, Lunsford LD: The prospective natural history of cerebral venous malformations. **Neurosurgery 43:**195–201, 1998
92. Menghini VV, Brown RD Jr, Sicks JD, O'Fallon WM, Wiebers DO: Incidence and prevalence of intracranial aneurysms and hemorrhage in Olmsted County, Minnesota, 1965 to 1995. **Neurology 51:**405–411, 1998
93. Mitchell P, Gholkar A, Vindlacheruvu RR, Mendelow AD: Unruptured intracranial aneurysms: benign curiosity or ticking bomb? **Lancet Neurol 3:**85–92, 2004
94. Miyazawa N, Akiyama I, Yamagata Z: Risk factors for growth of unruptured intracranial aneurysms: follow-up study by serial 0.5-T magnetic resonance angiography. **Neurosurgery 58:**1047–1053, 2006
95. Monaco EA, Khan AA, Niranjan A, Kano H, Grandhi R, Kondziolka D, et al: Stereotactic radiosurgery for the treatment of symptomatic brainstem cavernous malformations. **Neurosurg Focus 29(3):**E11, 2010
96. Morioka T, Hashiguchi K, Nagata S, Miyagi Y, Yoshida F, Mihara F, et al: Epileptogenicity of supratentorial medullary venous malformation. **Epilepsia 47:**365–370, 2006
97. Moroi J, Hadeishi H, Suzuki A, Yasui N: Morbidity and mortality from surgical treatment of unruptured cerebral aneurysms at Research Institute for Brain and Blood Vessels-Akita. **Neurosurgery 56:**224–231, 2005

98. Mottolese C, Hermier M, Stan H, Jouvet A, Saint-Pierre G, Froment JC, et al: Central nervous system cavernomas in the pediatric age group. **Neurosurg Rev 24:**55–73, 2001
99. Nader-Sepahi A, Casimiro M, Sen J, Kitchen ND: Is aspect ratio a reliable predictor of intracranial aneurysm rupture? **Neurosurgery 54:**1343–1348, 2004
100. Naff NJ, Wemmer J, Hoenig-Rigamonti K, Rigamonti DR: A longitudinal study of patients with venous malformations: documentation of a negligible hemorrhage risk and benign natural history. **Neurology 50:**1709–1714, 1998
101. Nahed BV, DiLuna ML, Morgan T, Ocal E, Hawkins AA, Ozduman K, et al: Hypertension, age, and location predict rupture of small intracranial aneurysms. **Neurosurgery 57:** 676–683, 2005
102. Nakagawa T, Hashi K: The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. **J Neurosurg 80:**217–223, 1994
103. Nataf F, Ghossoub M, Schlienger M, Moussa R, Meder JF, Roux FX: Bleeding after radiosurgery for cerebral arteriovenous malformations. **Neurosurgery 55:**298–306, 2004
104. Nataf F, Meder JF, Roux FX, Blustajn J, Merienne L, Merland JJ, et al: Angioarchitecture associated with haemorrhage in cerebral arteriovenous malformations: a prognostic statistical model. **Neuroradiology 39:**52–58, 1997
105. Nataf F, Merienne L, Schlienger M, Lefkopoulos D, Meder JF, Touboul E, et al: [Cerebral arteriovenous malformations treated by radiosurgery: a series of 705 cases.] **Neurochirurgie 47 (2-3 Pt 2):**268–282, 2001 (Fr)
106. Ohashi Y, Horikoshi T, Sugita M, Yagishita T, Nukui H: Size of cerebral aneurysms and related factors in patients with subarachnoid hemorrhage. **Surg Neurol 61:**239–247, 2004
107. Ondra SL, Troupp H, George ED, Schwab K: The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. **J Neurosurg 73:**387–391, 1990
108. Peerless SJ, Hernesniemi JA, Gutman FB, Drake CG: Early surgery for ruptured vertebrobasilar aneurysms. **J Neurosurg 80:**643–649, 1994
109. Pereira-Filho AA, Pereira AG, Faria MB, Lima LC, Portuguez MW, Kraemer JL: Microsurgical clipping in forty patients with unruptured anterior cerebral circulation aneurysms: an investigation into cognitive outcome. **Arq Neuropsiquiatr 68:** 770–774, 2010
110. Perrini P, Lanzino G: The association of venous developmental anomalies and cavernous malformations: pathophysiological, diagnostic, and surgical considerations. **Neurosurg Focus 21(1):**e5, 2006
111. Pollock BE, Flickinger JC, Lunsford LD, Bissonette DJ, Kondziolka D: Hemorrhage risk after stereotactic radiosurgery of cerebral arteriovenous malformations. **Neurosurgery 38:**652–661, 1996
112. Porter PJ, Willinsky RA, Harper W, Wallace MC: Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. **J Neurosurg 87:**190–197, 1997
113. Porter RW, Detwiler PW, Spetzler RF, Lawton MT, Baskin JJ, Derksen PT, et al: Cavernous malformations of the brainstem: experience with 100 patients. **J Neurosurg 90:**50–58, 1999
114. Raaymakers TW, Rinkel GJ, Limburg M, Algra A: Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. **Stroke 29:**1531–1538, 1998
115. Raychaudhuri R, Batjer HH, Awad IA: Intracranial cavernous angioma: a practical review of clinical and biological aspects. **Surg Neurol 63:**319–328, 2005
116. Rigamonti D, Johnson PC, Spetzler RF, Hadley MN, Drayer BP: Cavernous malformations and capillary telangiectasia: a spectrum within a single pathological entity. **Neurosurgery 28:**60–64, 1991
117. Rigamonti D, Spetzler RF, Medina M, Rigamonti K, Geckle DS, Pappas C: Cerebral venous malformations. **J Neurosurg 73:**560–564, 1990
118. Rinkel GJ: Natural history, epidemiology and screening of unruptured intracranial aneurysms. **J Neuroradiol 35:**99–103, 2008
119. Rivera PP, Willinsky RA, Porter PJ: Intracranial cavernous malformations. **Neuroimaging Clin N Am 13:**27–40, 2003
120. Robinson JR, Awad IA, Little JR: Natural history of the cavernous angioma. **J Neurosurg 75:**709–714, 1991
121. Saatci I, Geyik S, Yavuz K, Cekirge HS: Endovascular treatment of brain arteriovenous malformations with prolonged intranidal Onyx injection technique: long-term results in 350 consecutive patients with completed endovascular treatment course. Clinical article. **J Neurosurg 115:**78–88, 2011
122. Sampei T, Mizuno M, Nakajima S, Suzuki A, Hadeishi H, Ishikawa T, et al: [Clinical study of growing up aneurysms: report of 25 cases.] **No Shinkei Geka 19:**825–830, 1991 (Jpn)
123. Samson D, Batjer HH, Kopitnik TA Jr: Current results of the surgical management of aneurysms of the basilar apex. **Neurosurgery 44:**697–704, 1999
124. San Millán Ruíz D, Delavelle J, Yilmaz H, Gailloud P, Piovan E, Bertramello A, et al: Parenchymal abnormalities associated with developmental venous anomalies. **Neuroradiology 49:**987–995, 2007
125. Sarwar M, McCormick WF: Intracerebral venous angioma. Case report and review. **Arch Neurol 35:**323–325, 1978
126. Sato Y, Kakino S, Ogasawara K, Kubo Y, Kuroda H, Ogawa A: Rupture of a concomitant unruptured cerebral aneurysm within 2 weeks of surgical repair of a ruptured cerebral aneurysm—case report. **Neurol Med Chir (Tokyo) 48:**512–514, 2008
127. Sayama CM, Osborn AG, Chin SS, Couldwell WT: Capillary telangiectasias: clinical, radiographic, and histopathological features. Clinical article. **J Neurosurg 113:**709–714, 2010
128. Senegor M, Dohrmann GJ, Wollmann RL: Venous angiomas of the posterior fossa should be considered as anomalous venous drainage. **Surg Neurol 19:**26–32, 1983
129. Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. **J Neurosurg 65:**476–483, 1986
130. Spetzler RF, Ponce FA: A 3-tier classification of cerebral arteriovenous malformations. Clinical article. **J Neurosurg 114:** 842–849, 2011
131. Stapf C: The rationale behind "A Randomized Trial of Unruptured Brain AVMs" (ARUBA). **Acta Neurochir Suppl 107:**83–85, 2010
132. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, et al: Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. **Neurology 66:**1350–1355, 2006
133. Stapf C, Mohr JP: Unruptured brain arteriovenous malformations should be treated conservatively: yes. **Stroke 38:**3308–3309, 2007
134. Stefani MA, Porter PJ, terBrugge KG, Montanera W, Willinsky RA, Wallace MC: Large and deep brain arteriovenous malformations are associated with risk of future hemorrhage. **Stroke 33:**1220–1224, 2002
135. Steinberg GK, Chang SD, Gewirtz RJ, Lopez JR: Microsurgical resection of brainstem, thalamic, and basal ganglia angiographically occult vascular malformations. **Neurosurgery 46:**260–271, 2000
136. Steiner L, Lindquist C, Adler JR, Torner JC, Alves W, Steiner M: Clinical outcome of radiosurgery for cerebral arteriovenous malformations. **J Neurosurg 77:**1–8, 1992
137. Striano S, Nocerino C, Striano P, Boccella P, Meo R, Bilo L, et al: Venous angiomas and epilepsy. **Neurol Sci 21:**151–155, 2000
138. Tang SC, Jeng JS, Liu HM, Yip PK: Diffuse capillary telangiectasia of the brain manifested as a slowly progressive course. **Cerebrovasc Dis 15:**140–142, 2003

139. Töpper R, Jürgens E, Reul J, Thron A: Clinical significance of intracranial developmental venous anomalies. **J Neurol Neurosurg Psychiatry 67:**234–238, 1999
140. Truwit CL: Venous angioma of the brain: history, significance, and imaging findings. **AJR Am J Roentgenol 159:** 1299–1307, 1992
141. Tuffiash E, Tamargo RJ, Hillis AE: Craniotomy for treatment of unruptured aneurysms is not associated with long-term cognitive dysfunction. **Stroke 34:**2195–2199, 2003
142. Valavanis A, Yaşargil MG: The endovascular treatment of brain arteriovenous malformations. **Adv Tech Stand Neurosurg 24:**131–214, 1998
143. Wang CC, Liu A, Zhang JT, Sun B, Zhao YL: Surgical management of brain-stem cavernous malformations: report of 137 cases. **Surg Neurol 59:**444–454, 2003
144. Weber F, Knopf H: Incidental findings in magnetic resonance imaging of the brains of healthy young men. **J Neurol Sci 240:**81–84, 2006
145. Wedderburn CJ, van Beijnum J, Bhattacharya JJ, Counsell CE, Papanastassiou V, Ritchie V, et al: Outcome after interventional or conservative management of unruptured brain arteriovenous malformations: a prospective, population-based cohort study. **Lancet Neurol 7:**223–230, 2008
146. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ: Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. **Stroke 38:**1404–1410, 2007
147. Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, et al: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. **Lancet 362:**103–110, 2003
148. Wikholm G: Role of transarterial embolization in the management of cerebral arteriovenous malformations. **Acta Radiol Suppl 404:**1–25, 1996
149. Wikholm G, Lundqvist C, Svendsen P: The Göteborg cohort of embolized cerebral arteriovenous malformations: a 6-year follow-up. **Neurosurgery 49:**799–806, 2001
150. Winn HR, Jane JA Sr, Taylor J, Kaiser D, Britz GW: Prevalence of asymptomatic incidental aneurysms: review of 4568 arteriograms. **J Neurosurg 96:**43–49, 2002
151. Xia C, Zhang R, Mao Y, Zhou L: Pediatric cavernous malformation in the central nervous system: report of 66 cases. **Pediatr Neurosurg 45:**105–113, 2009
152. Zabramski JM, Wascher TM, Spetzler RF, Johnson B, Golfinos J, Drayer BP, et al: The natural history of familial cavernous malformations: results of an ongoing study. **J Neurosurg 80:**422–432, 1994

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Address correspondence to: Pascal Jabbour, M.D., 909 Walnut Street, 2nd floor, Philadelphia, Pennsylvania 19107. email: pascal.jabbour@jefferson.edu.

See the corresponding articles in this issue (E3 and E4).

Neurosurg Focus 31 (6):E2, 2011

Editorial

Small incidentally found aneurysms

Robert A. Solomon, M.D.

Department of Neurological Surgery, Columbia University, New York, New York

The management of small unruptured aneurysms continues to be one of the more controversial topics in neurological surgery. Unfortunately, selection of patients for conservative management, endovascular treatment, or microsurgical clipping relies on an inexact science, with a lack of data and continually evolving technology. These issues, along with a minimal rate of complications in all 3 treatment arms, make design of a meaningful clinical trial extremely difficult. Therefore, clinicians must be satisfied with trying to glean information from single-center consecutive series as presented in these articles by Dr. Loumiotis and colleagues.[1,2]

In their 3-year study, Loumiotis and colleagues analyzed data obtained in 212 consecutive patients with incidental aneurysms less than 1 cm in diameter. A total of 125 patients were treated with observation only. These patients tended to be older and harbor smaller aneurysms than patients who underwent invasive treatment, but exact reasons for recommending treatment over observation are not detailed in these reports. The conservatively treated patients had the highest death rate due to non-aneurysmal causes, presumably reflecting the bias to withhold treatment from patients with advanced age and medical comorbidities. Endovascularly treated patients had a 3% combined serious morbidity and mortality rate, and the small surgical group had no significant complications.

The clinical experience from this group at the Mayo Clinic is of course excellent, as might be expected from such a high-level tertiary referral site. Unfortunately, it is hard to gain any insight as to how this group of patients should be treated in other settings. The authors state that their approach "has been to favor endovascular treatment over other options when it is judged a feasible and safe choice." There is very little science behind this statement, and in fact little reason not to choose microsurgical clipping as the first-choice treatment option for small unruptured aneurysms, especially in the anterior circulation. In the Mayo Clinic experience, there were no complications in the surgical treatment arm. Even in the meta-analysis of surgical results published in 1998 by Raaymakers et al.,[4] surgical morbidity and mortality for non–giant anterior circulation aneurysms was 2.7%. In the ISUIA (International Study of Unruptured Intracranial Aneurysms), patients treated surgically initially fared worse than patients treated conservatively or endovascularly. However, the survival curves crossed at 5 years and follow-up results at 8.5 years showed that surgically treated patients did better than conservatively or endovascularly treated patients.

Loumiotis and colleagues stress that careful patient selection is key to obtaining excellent results. I have seen our surgical results improve dramatically with the introduction of endovascular approaches for complex aneurysms. The important reason is that we are not forced to undertake a surgical procedure that carries a high risk if there is a good endovascular option. Similarly, high-risk endovascular treatment should not be undertaken when there is a good surgical alternative. The exact number of stented cerebral vessels is not stated in the present report, but it is interesting that 2 of the serious complications noted occurred in patients who underwent stent-assisted coiling. In the "experienced French centers" mentioned in the authors' study, there was a 12% serious morbidity and mortality rate in patients treated with stent-assisted coiling.[3]

Although there were no cases of aneurysm rupture in this series, follow-up is limited. The anatomical obliteration rate was only 20% in the endovascular group, and in the long term these patients may still be at risk for subarachnoid hemorrhage. In my experience, the surgical risk for a small anterior circulation aneurysm is under 3%, about the same as the endovascular risk for simple coiling. In young healthy patients, microsurgical clipping may be a better option than coiling, because the risks are similar but the long-term obliteration rate is better with surgery. Patients in whom a stent is required can be offered a lower-risk procedure with surgery, and therefore stenting of incidental aneurysms should be reserved for cases in which the surgical risk is high, like large paraclinoid aneurysms and posterior circulation aneurysms.

I agree with the authors that patients with small incidental aneurysms need to be considered individually on the basis of age, aneurysm anatomy, and the individual's emotional state. Expectant observation is usually the best course of action, but treatment should be offered to younger patients with larger aneurysms for which the likelihood of excellent surgical or endovascular outcome is high.

Disclosure

The author reports no conflict of interest.

References

1. Loumiotis I, Brown RD Jr, Vine R, Cloft HJ, Kallmes DF, Lanzino G: Small (< 10-mm) incidentally found intracranial aneurysms, Part 2: treatment recommendations, natural history, complications, and short-term outcome in 212 consecutive patients. **Neurosurg Focus 31(6):**E4, 2011
2. Loumiotis I, Wagenbach A, Brown RD Jr, Lanzino G: Small (< 10-mm) incidentally found intracranial aneurysms, Part 1: reasons for detection, demographics, location, and risk factors in 212 consecutive patients. **Neurosurg Focus 31(6):**E3, 2011
3. Piotin M, Blanc R, Spelle L, Mounayer C, Piantino R, Schmidt PJ, et al: Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms. **Stroke 41:**110–115, 2010
4. Raaymakers TW, Rinkel GJ, Limburg M, Algra A: Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. **Stroke 29:**1531–1538, 1998

Response

Giuseppe Lanzino, M.D.,[1] and Robert D. Brown Jr., M.D.[2]

Departments of [1]Neurologic Surgery and [2]Neurology, Mayo Clinic, Rochester, Minnesota

We thank Dr. Solomon for his thoughtful analysis of our study. We agree that the management of small incidental aneurysms poses significant challenges, and there are many unanswered questions that remain regarding the lesion's natural history as well as the risks and efficacy of different treatment modalities. However, we feel that, despite logistic challenges, a meaningful study to answer some of these questions can and should be done so that our decisions can be based on more scientific evidence. Optimally, such a study would be in the form of a randomized trial. It is understood that the challenges and feasibility of such a trial would be significant but should not be insurmountable. As an initial step, a prospective, all-inclusive registry of small aneurysms—with both short- and long-term follow-up data, and including repeat images, neuropsychological outcomes, and objective measures of quality of life—would clarify the risks of treatment, risk of bleeding for untreated aneurysms, and the role/frequency of radiological follow-up for aneurysms treated conservatively.

In our series, recommendations for either invasive treatment or conservative management were based on multiple factors that included aneurysm-related characteristics (location, size, shape, and perceived risks of treatment) and patient-related factors (age, comorbidities/life expectancy, attitude toward knowledge of harboring an intracranial aneurysm, presence or absence of family history and/or risk factors known to be associated with aneurysm formation and growth such as smoking and hypertension, and a patient's preference for one option over the other). Once we recommend treatment, we prefer endovascular treatment when feasible and safe because patients usually better tolerate it. We agree that stent-assisted coiling carries a higher risk than simple coiling alone, and for small aneurysms we consider this technique almost exclusively for wide-necked small basilar bifurcation aneurysms.

Our reliance on endovascular treatment of unruptured aneurysms (unlike ruptured aneurysms for which there is firm scientific evidence to support the benefit of coil embolization over surgical clipping) is not based on strong scientific evidence. However, there are some practical observations that would support our position. 1) We know from ISAT (International Subarachnoid Aneurysm Trial) that the risk of rebleeding associated with a previously ruptured intracranial aneurysm 1 year after endovascular treatment is exceedingly low. Thus, it is reasonable to assume that the risk of rupture is even lower (than a ruptured aneurysm) for a previously unruptured small aneurysm treated with coil embolization. 2) Despite thousands of unruptured small aneurysms treated each year with endovascular coil embolization, the rupture of a previously unruptured small incidental aneurysm remains an extremely rare event. In ISUIA (International Study of Unruptured Intracranial Aneurysms), investigators observed 9 documented ruptures of the treated aneurysm during the follow-up period in the endovascular cohort, and all but one rupture involved large or giant aneurysms (ISUIA III, unpublished data). The only rupture of a small aneurysm occurred in a patient with an 8-mm-diameter middle cerebral artery aneurysm. We certainly agree that because of the lack of rigorous scientific evidence on the efficacy and safety of endovascular treatment for small unruptured aneurysms, it is imperative that we move forward with a well-designed multicenter prospective study. The ISUIA investigators are dedicated to conducting such a study. Unfortunately, there has been ongoing resistance to the idea of such a study, and the logistics of organizing such a trial and the feasibility of patient enrollment have been used as an excuse to perpetuate obstructionism. *(DOI: 10.3171/2011.9.FOCUS11259)*

See the corresponding editorial (E2) and article (E4) in this issue.

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Small (< 10-mm) incidentally found intracranial aneurysms, Part 1: reasons for detection, demographics, location, and risk factors in 212 consecutive patients

Ioannis Loumiotis, M.D.,[1] Anne Wagenbach, R.N., C.N.P.,[2] Robert D. Brown Jr., M.D.,[3] and Giuseppe Lanzino, M.D.[2]

[1]Department of Surgery, University of Arizona, College of Medicine, Tucson, Arizona; and Departments of [2]Neurologic Surgery and [3]Neurology, Mayo Clinic, Rochester, Minnesota

Object. The widespread use of imaging techniques for evaluating nonspecific symptoms (vertigo, dizziness, memory concerns, unsteadiness, and the like) and focal neurological symptoms related to cerebrovascular disease has led to increased identification of asymptomatic incidentally discovered unruptured intracranial aneurysms (UIAs). The management of these incidental aneurysms is controversial and many factors need to be considered. The authors describe reasons leading to diagnosis, demographics, and risk factors in a large consecutive series of patients with small incidentally found UIAs.

Methods. The authors prospectively evaluated 335 patients harboring 478 small (< 10-mm) UIAs between January 2008 and May 2011. Patients with known aneurysms, possibly symptomatic aneurysms, arteriovenous malformation–related aneurysms, patients with a history of subarachnoid hemorrhage from another aneurysm, and patients harboring extradural aneurysms were excluded from the analysis. Only truly incidental small aneurysms (272 aneurysms in 212 patients) were considered for the present analysis. Data regarding the reason for detection, demographics, location, and presence of potential risk factors for aneurysm formation were prospectively collected.

Results. There were 158 female (74.5%) and 54 male (25.5%) patients whose mean age was 60.6 years (median 62 years). The most common reason for undergoing the imaging study that led to a diagnosis of the aneurysms was evaluation for nonspecific spells and symptoms related to focal cerebrovascular ischemia (43.4%), known/possible intracranial or neck pathology (24%), and headache (16%). The most common location (27%) of the aneurysm was the middle cerebral artery; the second most common (22%) was the paraclinoid internal carotid artery (excluding cavernous sinus aneurysms). Sixty-nine percent of patients were current or prior smokers, 60% had a diagnosis of hypertension, and 23% had one or more relatives with a history of intracranial aneurysms with or without subarachnoid hemorrhage.

Conclusions. Small incidental UIAs are more commonly diagnosed in elderly individuals during imaging performed to investigate ill-defined spells or focal cerebrovascular ischemic symptoms, or during the evaluation of known or probable unrelated intracranial/neck pathology. Hypertension, smoking, and family history of aneurysms are common in this patient population, and the presence of these risk factors has important implications for treatment recommendations. Although paraclinoid aneurysms (excluding intracavernous aneurysms) are uncommon in patients with ruptured intracranial aneurysms, this location is very common in patients with small incidental UIAs.
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Key Words • **brain aneurysm** • **embolization** • **cerebral angiography** • **subarachnoid hemorrhage** • **stroke**

High-resolution modern imaging techniques, often performed for evaluation of vague and nonspecific symptoms and concerns, have increased the detection of asymptomatic small UIAs. There is a large body of literature on the natural history and treatment (surgical or endovascular) of UIAs. Most studies have combined aneurysms of various sizes and various clinical presentations (history of SAH from another aneurysm, symptomatic aneurysms, and so on). There is little information on the variables that compel a patient to undergo imaging that leads to aneurysm detection, demographics, and risk factors for aneurysm formation in patients with truly incidental small UIAs, which represent the majority of intracranial aneurysms in a modern clinical practice. In this study, we analyze the reasons leading to detection, demographic data, and risk factors in a large contemporary consecutive series of 212 patients with 272 small incidentally discovered aneurysms evaluated in a 40-month period.

Abbreviations used in this paper: ICA = internal carotid artery; SAH = subarachnoid hemorrhage; UIA = unruptured intracranial aneurysm.

Methods

Data Collection

The study was approved by the local institutional review board. We reviewed a prospectively maintained database on consecutive patients with UIAs evaluated by the senior author (G.L.) from January 2008 until May 2011. Information collected included demographic data, factors that led to the discovery of the target aneurysm, potential risk factors for intracranial aneurysm formation and rupture (smoking, hypertension, and family history of intracranial aneurysms and aneurysmal SAH), known medical disorders associated with an increased occurrence of UIAs, and aneurysm location, size, and multiplicity. Aneurysm size was measured using digital subtraction angiography when available; otherwise, measurement was obtained from the available CT/MR angiograms.

Inclusion and Exclusion Criteria

For the purpose of this study, patients were considered only if they harbored a UIA ≤ 10 mm in diameter (in patients with multiple aneurysms, the largest one could measure ≤ 10 mm in diameter) and if the aneurysm was discovered incidentally—that is, there was no correlation between symptoms/complaints leading to aneurysm detection and the aneurysm itself. We excluded patients with cranial nerve palsies related to the aneurysm, patients with localized pain that could be referable to the aneurysm (for example, ipsilateral retroorbital pain in patients with posterior communicating artery aneurysms), and patients presenting with ischemic symptoms considered to be possibly related to the aneurysm. Patients with unruptured aneurysms identified during investigation for SAH from another aneurysm were also excluded. Because of the different natural history and the notion that no treatment is indicated in such cases, patients with incidentally found extradural aneurysms located in the cavernous sinus were excluded from further analysis. Only patients with newly discovered aneurysms were considered. Patients with known small incidental aneurysms that had already been followed before by other physicians were excluded. Patients with an aneurysm and associated arteriovenous malformation were excluded. Treatment recommendations and management of this cohort are specified in the accompanying manuscript.[2]

Statistical Analysis

To determine whether a difference observed between the groups was statistically significant, we used a 2-sided t-test for continuous data and the chi-square test for categorical variables. The Fisher exact test was used when more than 20% of the tables had a value less than 5. All statistical analysis was performed using JMP software version 9.0.1 (SAS Institute Inc.). A predefined p value of 0.05 was considered the cutoff point of statistical significance.

Results

Patient Population

During the study period, the senior author (G.L.) evaluated 335 patients (254 females [75.8%] and 81 males (24.2%]) with 478 small, unruptured saccular aneurysms. Excluded from further analysis were 79 patients (23.6%) with known aneurysms already being followed, 11 patients (3.3%) with unruptured aneurysms found during investigation for SAH from a different aneurysm, 26 patients (7.8%) with small, potentially symptomatic aneurysms, and 2 patients (0.6%) with aneurysms associated with an intracranial arteriovenous malformation. Two hundred seventeen patients (64.8% of the entire cohort) were evaluated for 278 newly discovered incidental small UIAs. Five of these patients only had incidental aneurysms located in the cavernous sinus and were also excluded from further analysis. Thus, 212 patients (63.3%) with 272 small incidental aneurysms are the focus of this study. Reasons for performing the imaging study that led to the discovery of the aneurysms are summarized in Table 1.

The mean age of the patient population was 60.6 years (median 62 years, range 25–88 years). There were 158 women (74.53%) and 54 men (25.47%). Demographics and potential risk factors for aneurysm formation/growth at the time of presentation are summarized in Table 2.

Aneurysm Characteristics

The most common aneurysm location was the middle cerebral artery and the second most common location was the paraclinoid region of the ICA and the anterior communicating artery–anterior cerebral artery complex. Aneurysm characteristics are summarized in Table 3. The mean size of the aneurysms was 5.5 mm (in patients with multiple aneurysms, only the largest aneurysm was considered for this calculation).

Discussion

With the widespread use of noninvasive imaging tech-

TABLE 1: Reasons leading to the diagnosis of small incidental UIAs in 212 consecutive patients*

Reason for Imaging	No. of Patients (%)
evaluation for a known/probable head or neck pathology (tumor, carotid disease, multiple sclerosis, giant cell arteritis, refractory epistaxis, trigeminal neuralgia, thyroid disease, ENT pathology, etc.)	51 (24.06)
evaluation for headache not related to aneurysm (migraine, tension type, cluster, chronic)	34 (16.04)
evaluation for trivial head trauma/motor vehicle accident	12 (5.66)
evaluation for nonspecific spells (lightheadedness, vertigo, visual blurring, memory complaints, confusion, transient global amnesia, tinnitus, tremor, etc.) or symptoms related to focal cerebrovascular ischemia	92 (43.4)
screening in patients w/ family history	9 (4.25)
evaluation for cancer staging	4 (1.89)
others	10 (4.72)
overall	212

* ENT = ear, nose, and throat.

TABLE 2: Demographic data in patients with small incidental intracranial aneurysms

Variable	No. of Cases/ Value (%)
sex	
female	158
male	54
female/male ratio	2.92:1
age on presentation (yrs)	
mean	60.6
median	62
range	25–88
risk factors	
tobacco use	
never	67 (31.6)
past	79 (37.3)
current*	66 (31.1)
family history†	
none	158 (76.5)
1 relative	30 (14.2)
>1 relative	18 (8.5)
not applicable	6 (2.8)
hypertension	
no	84 (39.6)
yes	128 (60.4)
miscellaneous history	
fibromuscular dysplasia	3
autosomal dominant polycystic kidney disease	2

* Current tobacco use also includes those patients who reported quitting smoking within 12 months of evaluation.
† History of intracranial aneurysm or aneurysmal SAH.

TABLE 3: Characteristics of incidental small UIAs*

Variable	No. of Cases/Value (%)
no. of patients	212
overall no. of aneurysms	272
no. of patients w/ multiple aneurysms	41 (19.34)
location	
cavernous	8 (2.9)†
ICA	107 (39.3)
paraclinoid	60
ICA-PCoA	28
ICA-AChA	5
ICA-bifurcation	14
ACoA-ACA	55 (20.2)
MCA	74 (27.2)
vertebrobasilar	28 (10.3)
BA	22
BA-PICA	4
BA-SCA	2
size (mm)‡	
mean max diameter	5.5 ± 2.09§
median	5.0
range	2–10

* ACA = anterior cerebral artery; AChA = anterior choroidal artery; ACoA = anterior communicating artery; BA = basilar artery; MCA = middle cerebral artery; PCoA = posterior communicating artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebral artery.
† In patients with coexisting small incidental aneurysms in other locations.
‡ Calculation is based on the maximum diameter of the largest aneurysm in patients who harbored multiple aneurysms.
§ Mean value presented ± SD.

niques, small incidentally found UIAs are detected with increasing frequency. More commonly these aneurysms are detected in patients undergoing imaging evaluation for ill-defined spells and symptoms related to focal cerebrovascular ischemia (43%). Other common reasons for performing an imaging study, which in turn leads to the discovery of a small aneurysm, include evaluation for a known or probable intracranial and neck lesion (24%), as well as headache/migraine not related to the aneurysm (16%). When a small intracranial aneurysm is detected, the treating physician is often left with a significant management dilemma. The majority of small aneurysms probably endure without rupture. However, the risk of rupture is not nil, and more importantly, when aneurysms do rupture, the prognosis is poor.[8]

Ill-defined spells, symptoms of focal cerebrovascular ischemia, and known or probable intracranial or neck pathology are more common with advanced age, and a large number of intracranial aneurysms are diagnosed in elderly individuals. This is reflected in the age (mean 60.6 years, median 62 years) of patients with small incidental intracranial aneurysms in our series. Advanced age is a factor associated with a higher risk of complications from treatment.[8] Elderly patients are also less likely to benefit from treatment because of their shorter life expectancy and the lesion's low annual risk of rupture. Diagnosis of a small incidental UIA in patients of advanced age is not uncommon. Invasive treatment, however, should be considered only in selected cases. Many patients with UIAs are already receiving or may need anticoagulation or antiplatelet therapy, given the high incidence of cardiovascular disorders. In such cases, we recommend proceeding with anticoagulation or antiplatelet therapy if clinically indicated irrespective of the status (treated or untreated) of the aneurysm. This recommendation is based on the very benign natural history of small unruptured incidental aneurysms and on the fact that anticoagulation or antiplatelet therapy per se does not increase the risk of aneurysm rupture. In no case did the need of starting antiplatelet or anticoagulation therapy influence our recommendation for management of the aneurysm. Smoking and hypertension are known risk factors for aneurysm formation and rupture.[4,6,7] In our series, 68% of patients were either current or past smokers and 60% had known hypertension. In patients who are cigarette smokers, appropriate counseling and medical managements strategies should be implemented to increase the likelihood of

smoking cessation. Elevation in blood pressure consistent with hypertension should be treated to attain normal blood pressure levels and should be monitored closely over time. It is noteworthy that in part because of the association of smoking and hypertension with intracranial aneurysms, the overall long-term health of these patients is mostly influenced by the development of cardiovascular disease and cancer rather than rupture of the aneurysm. Therefore, smoking cessation and control of hypertension and other atherosclerosis risk factors may be as effective as successful treatment of the aneurysm. In our series, only 4% of aneurysms were discovered during screening based on a familial history of aneurysms. However, 23% of patients had a history of intracranial aneurysms with or without SAH in at least one relative. Patients with a family history of aneurysmal SAH are often quite distressed by the knowledge of having an intracranial aneurysm because they have witnessed the sequelae of aneurysmal rupture. In these patients, invasive treatment of the aneurysm is often considered because of the stress and the effects on the patient's quality of life. Moreover, preliminary data from the Familial Intracranial Aneurysm study[1] may suggest a more aggressive natural history for small intracranial aneurysms in first-degree relatives of patients with aneurysmal SAH.

The location distribution of small incidental UIAs is slightly different than the distribution of small ruptured aneurysms. In particular, there is a preponderance of paraclinoid aneurysms (approximately 22% of the total, after excluding extradural intracavernous aneurysms) while these aneurysms, especially when small, are uncommon in patients with aneurysmal SAH.[3,5] This observation may suggest that the natural history of small paraclinoid aneurysms may be more benign than small aneurysms in other locations, and aneurysm location should be considered when making treatment recommendations. Such difference in rupture rate by UIA location has been noted in large natural history studies, when considering aneurysms of all locations and sizes.[8]

Conclusions

In our study, small incidental UIAs were more commonly diagnosed in elderly individuals during imaging studies obtained for investigation of ill-defined spells and symptoms related to focal cerebrovascular ischemia, or for the evaluation of known or probable other intracranial/neck pathological entities. Hypertension, smoking, and family history of intracranial aneurysm or SAH are quite common in this patient population, and the presence of these risk factors has important implications for treatment recommendations. Although paraclinoid aneurysms (excluding intracavernous aneurysms) are quite uncommon among patients with ruptured intracranial aneurysms, this location is the most common in patients with small incidental UIAs.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Lanzino. Acquisition of data: Lanzino, Loumiotis. Analysis and interpretation of data: Lanzino, Loumiotis. Drafting the article: Lanzino. Critically revising the article: Lanzino, Brown. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lanzino. Statistical analysis: Lanzino, Loumiotis. Administrative/technical/material support: Lanzino. Study supervision: Lanzino.

References

1. Broderick JP, Brown RD Jr, Sauerbeck L, Hornung R, Huston J III, Woo D, et al: Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. **Stroke 40:**1952–1957, 2009
2. Loumiotis I, Brown RD Jr, Vine R, Cloft HJ, Kallmes DF, Lanzino G: Small (< 10-mm) incidentally found intracranial aneurysms, Part 2: treatment recommendations, natural history, complications, and short-term outcome in 212 consecutive patients. **Neurosurg Focus 31(6):**E4, 2011
3. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al: International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. **Lancet 366:** 809–817, 2005
4. Nahed BV, DiLuna ML, Morgan T, Ocal E, Hawkins AA, Ozduman K, et al: Hypertension, age, and location predict rupture of small intracranial aneurysms. **Neurosurgery 57:**676–683, 2005
5. Nguyen TN, Raymond J, Guilbert F, Roy D, Bérubé MD, Mahmoud M, et al: Association of endovascular therapy of very small ruptured aneurysms with higher rates of procedure-related rupture. **J Neurosurg 108:**1088–1092, 2008
6. Sandvei MS, Romundstad PR, Müller TB, Vatten L, Vik A: Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. **Stroke 40:**1958–1962, 2009
7. Weir BK, Kongable GL, Kassell NF, Schultz JR, Truskowski LL, Sigrest A: Cigarette smoking as a cause of aneurysmal subarachnoid hemorrhage and risk for vasospasm: a report of the Cooperative Aneurysm Study. **J Neurosurg 89:**405–411, 1998
8. Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, et al: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. **Lancet 362:**103–110, 2003

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Address correspondence to: Giuseppe Lanzino, M.D., Department of Neurologic Surgery, 200 First Street SW, Rochester, Minnesota 55905. email: Lanzino.Giuseppe@mayo.edu.

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Small (< 10-mm) incidentally found intracranial aneurysms, Part 2: treatment recommendations, natural history, complications, and short-term outcome in 212 consecutive patients

Ioannis Loumiotis, M.D.,[1] Robert D. Brown Jr., M.D.,[3] Roanna Vine, R.N.,[4] Harry J. Cloft, M.D., Ph.D.,[4] David F. Kallmes, M.D.,[4] and Giuseppe Lanzino, M.D.[2,4]

[1]Department of Surgery, University of Arizona, College of Medicine, Tucson, Arizona; and Departments of [2]Neurologic Surgery, [3]Neurology, and [4]Radiology, Mayo Clinic, Rochester, Minnesota

Object. The management of incidental small unruptured intracranial aneurysms (UIAs) is controversial and many factors need to be considered in the decision-making process. The authors describe a large consecutive series of patients harboring small incidental intracranial aneurysms. Treatment strategy, natural history, complications, and short-term outcomes are presented.

Methods. Between January 2008 and May 2011, the authors prospectively evaluated 212 patients with 272 small (< 10-mm) incidental aneurysms. Treatment recommendations (observation, endovascular treatment, or surgery), complications of treatment, and short-term outcomes were assessed.

Results. Recommended treatment consisted of observation in 125 patients, endovascular embolization in 64, and surgery in 18. Six patients were excluded from further analysis because they underwent treatment elsewhere. In the observation group, at a mean follow-up of 16.7 months, only 1 patient was moved to the embolization group. Seven (6%) of the 125 patients in the observation group died of causes unrelated to aneurysm. Sixty-five patients underwent 69 embolization procedures. The periprocedural permanent morbidity and mortality rates in patients undergoing endovascular treatment were 1.5% and 1.5%, respectively (overall morbidity and mortality rate 3.0%). In the surgery group no periprocedural complications were observed, although 1 patient did not return to her previous occupation. No aneurysmal rupture was documented in any of the 3 treatment groups during the follow-up period.

Conclusions. A cautious and individualized approach to incidental UIAs is of utmost importance for formulation of a safe and effective treatment algorithm. Invasive treatment (either endovascular or surgery) can be considered in selected younger patients, certain "higher-risk" locations, expanding aneurysms, patients with a family history of aneurysmal hemorrhage, and in those who cannot live their lives knowing that they harbor the UIA. Although the complication rate of invasive treatment is very low, it is not negligible. The study confirms that small incidental UIAs deemed to be not in need of treatment have a very benign short-term natural history, which makes observation a reasonable approach in selected patients. *(DOI: 10.3171/2011.9.FOCUS11237)*

Key Words • **brain aneurysm** • **embolization** • **cerebral angiography** • **subarachnoid hemorrhage** • **stroke**

Management of small incidentally discovered UIAs is controversial. The prospective yearly risk of rupture is very low, particularly in selected locations, but outcome once rupture occurs is dismal.[3–5] Despite advancements in neuroendovascular and microsurgical techniques, however, there is still some risk of invasive treatment.[10,13] Several studies have focused on the results of specific treatments (for instance, medical, endovascular, or surgical treatment) in patients with unruptured aneurysms. The ISUIA[13] was a large multicenter study with retrospective and prospective cohorts of patients with unruptured aneurysms undergoing observation, surgery, or endovascular treatment. However, patients enrolled in the ISUIA were treated in the 1990s, and therefore treatment outcomes do not necessarily reflect current practice, particularly for those patients who underwent endovascular treatment. Therefore, the optimal management of these small incidental UIAs remains uncertain. In the present study, we analyze treatment recommendations, natural history, and short-term outcomes in a large consecutive contemporary series of 212 patients with 272 small incidental aneurysms.

Abbreviations used in this paper: ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; ISUIA = International Study of Unruptured Intracranial Aneurysms; MCA = middle cerebral artery; NIS = Nationwide Inpatient Sample; PCoA = posterior communicating artery; SAH = subarachnoid hemorrhage.

Methods

The study was approved by the local institutional review board. We reviewed a prospectively maintained database of consecutive patients with UIAs evaluated by the senior author (G.L.) from January 2008 until May 2011. Information collected included demographic data, factors that led to the discovery of the target aneurysm, potential risk factors for intracranial aneurysm formation and rupture (smoking, hypertension, and family history of intracranial aneurysms and aneurysmal SAH), known medical disorders associated with an increased occurrence of UIAs, and aneurysm location, size, and multiplicity. Aneurysm size was measured using digital subtraction angiography when available; otherwise, measurement was obtained from the available CT/MR angiograms. Patient inclusion and exclusion criteria, associated medical conditions, risk factors, demographics, and factors leading to diagnosis have been described in detail in the accompanying manuscript.[9]

The natural history of incidental aneurysms and the risks of treatment (observation and correction of risk factors, embolization, or surgery) were routinely discussed with the patients and their family members, and a final recommendation was made based on various factors that included aneurysm characteristics (location, size, shape, geometry, and presence of calcifications), the individual patient's characteristics (age, comorbidities, risk factors, family history, and personality), and the patient's preference. Reasons for recommending observation or invasive treatment were also prospectively annotated. In some patients the final decision before recommending treatment was based on additional high-resolution 3D angiography studies to better assess characteristics of the aneurysm as well as potential risks of treatment.

Except for extenuating circumstances (such as very advanced age or important medical comorbidities limiting life expectancy), patients with newly diagnosed aneurysms undergoing observation usually received a recommendation to have a follow-up noninvasive imaging study after 6–12 months to document stability of the aneurysm, with repeat imaging performed intermittently over time. In patients undergoing treatment, the type of treatment (surgical or endovascular) and details of treatment were collected. Any clinical complication resulting in a transient or permanent deficit was recorded. Length of hospital stay in treated patients was annotated. Follow-up information was obtained regularly through office visits where patients were asked to rate themselves on the modified Rankin Scale or they were contacted over the phone by a nurse practitioner or a nurse who was not directly involved with patients' treatment. Short-term and long-term cognitive outcomes were not available in this cohort.

Statistical Analysis

To determine whether a difference observed between the groups was statistically significant, we used a 2-sided t-test for continuous data and a chi-square test for categorical variables. The Fisher exact test was used when more than 20% of the tables had a value less than 5. All statistical analysis was performed using JMP software version 9.0.1 (SAS Institute Inc.). A predefined p value of 0.05 was considered the cutoff point of statistical significance.

Results

Patient Population

Two hundred seventeen patients (64.8% of the entire cohort of patients with unruptured aneurysms evaluated by the senior author during the study period) were assessed for 278 newly discovered incidental small aneurysms. Five of these patients had 6 small incidental aneurysms located within the cavernous sinus and were also excluded from further analysis. Thus, 212 patients (63.3%) with 272 small incidental aneurysms are the focus of this study.

Aneurysm Characteristics and Treatment Recommendations

Aneurysm location and size are summarized in Table 1. The mean size of the aneurysms was 5.5 mm (in patients with multiple aneurysms, only the largest aneurysm was considered for this calculation). The recommended treatment was observation with risk factor control in 126

TABLE 1: Characteristics of incidental small UIAs*

Characteristic	Value (%)
no. of patients	212
overall no. of aneurysms	272
no. of aneurysms treated†	89 (32.7)
no. of patients w/ multiple aneurysms	41 (19.34)
location of aneurysm	
cavernous	8 (2.9)‡
ICA	107 (39.3)
paraclinoid	60
ICA-PCoA	28
ICA-AChA	5
ICA-bifurcation	14
ACoA/ACA	55 (20.2)
MCA	74 (27.2)
vertebrobasilar	28 (10.3)
BA	22
BA-PICA	4
BA-SCA	2
maximum diameter (mm)§	
mean	5.5 ± 2.09¶
median	5.00
range	2–10

* AChA = anterior choroidal artery; ICA = internal carotid artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebral artery.
† Surgery or embolization.
‡ In patients with coexisting small incidental aneurysms in other locations.
§ Calculation is based on the maximum diameter of the largest aneurysm in patients with multiple aneurysms.
¶ Mean value presented ± SD.

cases (57.8%), endovascular in 72 cases (33%), and surgical in 20 cases (9.2%). Six patients were considered in the analysis of recommended treatment but excluded from further follow-up analysis because they elected to undergo treatment elsewhere. Recommended treatment in these 6 patients was endovascular embolization in 4, surgery in 1, and observation in 1. Table 2 summarizes demographic data and aneurysm size and location in the 3 management cohorts (in patients with multiple aneurysms, only the largest aneurysm is considered). Figure 1 illustrates management approach stratified by age.

Observation Group. Included in this group are 125 patients with 160 aneurysms representing 58.9% of the 212 patients with small incidental UIAs. The most common reasons for selecting observation were (either alone or in combination) age, presence of comorbidities, lack of risk factors, "benign" appearance of the lesion, imaging-documented location of the aneurysm, and patient preference for observation.

There were 2 complications in the observation group among patients who underwent digital subtraction angiography for aneurysm definition. One patient suffered a dissection of his femoral artery without significant clinical sequelae. The second patient, a 65-year-old woman, was evaluated for an unexplained left cranial nerve VI palsy in the setting of a complicated medical history. She was found to have an incidental left MCA aneurysm and endovascular treatment was recommended, but embolization was not carried out because 2 large vessel branches arose from the aneurysm neck, and treatment was considered to be extremely risky. One day following digital subtraction angiography, the patient was admitted with left facial weakness and left upper-extremity weakness. Magnetic resonance imaging of the brain demonstrated subacute infarcts in the right basal ganglia region. The patient was discharged 4 days later and her symptoms gradually improved.

Most of the patients in the observation group were advised to undergo follow-up imaging within 6–12 months to document the stability of the aneurysm.

Clinical follow-up was available for 122 patients (97.6%) after a mean of 16.7 months (median 15.1 months). Seven patients (5.73%) died after an average of 14.31

TABLE 2: Summary and comparison of the 3 management cohorts*

Characteristic	Management Approach			p Value†
	Observation	Endovascular	Surgery	
no. of patients (M/F)‡	126 (34:92)	68 (15:53)	19 (5:14)	
no. of patients treated (M/F)	125 (33:92)	64 (13:51)	18 (5:13)	
no. of procedures	NA	68	19	
mean age in yrs (range)¶	64.4 ± 11.8 (27–88)	55.34 ± 11.1 (30–79)	53.36 ± 8.36 (25–66)	a) <0.001; b) <0.001; c) 0.5008
no. of patients				
>65 yrs	72 (57.1%)	13 (19.1%)	1 (5.3%)	<0.001
w/ multiple aneurysms	22 (17.4%)	13 (19.1%)	7 (36.8%)	
aneurysm characteristic				
total no.	160	89	25	
size (mm)§				
mean¶	4.91 ± 2.02	6.37 ± 1.93	5.84 ± 1.98	a) <0.001; b) 0.058; c) 0.305
range	2–10	3–9.82	3–9	
median	4.5	6.76	5.8	
location of treated aneurysms				
ICA	NA	34	5	<0.001
paraclinoid	NA	21	0	
ICA-PCoA	NA	9	2	
ICA-AChA	NA	1	1	
ICA-bifurcation	NA	3	2	
ACoA/ACA	NA	15	3	
MCA	NA	5	12	
vertebrobasilar	NA	14	0	
mean length of hospital stay (days)¶	NA	1.4 ± 2.02	2.7 ± 1.15	0.0078

* NA = not applicable.

† Paired t-test between a) observation and embolization, b) observation and surgery, and c) embolization and surgery.

‡ One patient with 2 aneurysms had 2 different recommended and final treatments: 1 aneurysm was treated with surgery and the other with embolization.

§ For the endovascular and surgical groups, size refers to the treated aneurysm's dimensions.

¶ Mean values presented ± SD.

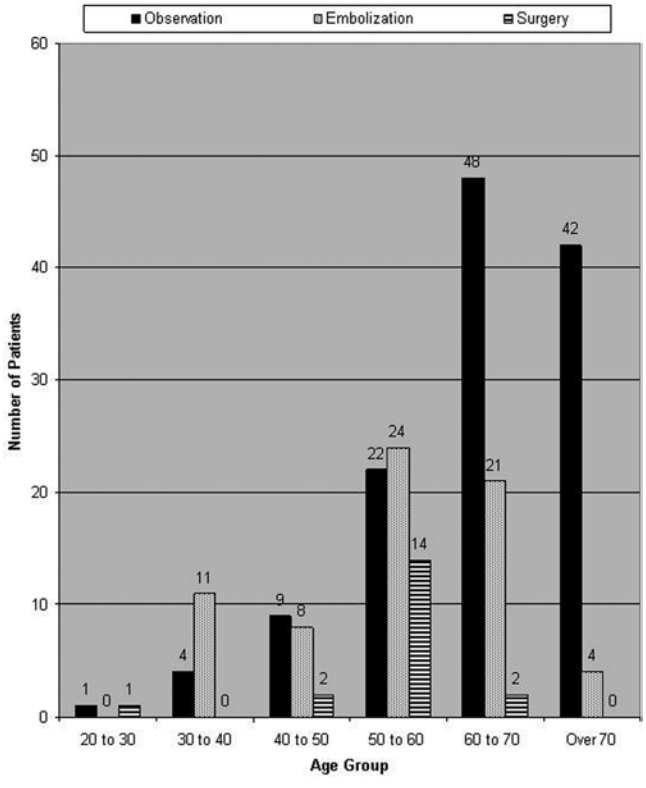

Fig. 1. Bar graph showing age group distribution by management approach.

months after initial evaluation and the causes were not related to the aneurysm (pneumonia in 1, cancer in 3, cardiac arrest in 1, respiratory failure after hypertensive intracerebral hemorrhage in 1, and unknown cause but unrelated to the intracranial aneurysm in 1). No documented SAH occurred in this cohort.

At least one type of follow-up angiographic study (digital subtraction, MR, or CT) was available for 69 (56.5%) of the available patients after a mean interval of 14.04 months (median 12.06 months). In 3 patients (4.3%), follow-up imaging studies suggested a possible increase in aneurysm size. Based on these changes, invasive treatment was recommended for 1 patient with a basilar trunk aneurysm, whereas in the remaining 2 the changes were not considered significant and further observation was recommended. The patient who underwent treatment was a 73-year-old woman who originally was evaluated for a possible ischemic stroke and was found to have an incidental basilar trunk aneurysm. Follow-up imaging 22.1 months later suggested aneurysm enlargement, and she underwent stent-assisted coil embolization (see *Endovascular Treatment*).

Endovascular Treatment. Our approach has been to favor endovascular treatment over other options when it is judged a feasible and safe choice. Because of the very benign natural history of incidental small UIAs, we have had a very low threshold for aborting treatment (this occurred in 8 cases) very early in the procedure because of perception that the procedure posed a higher risk than the benign natural history of the disease. Management of these 8 patients included observation in 5 cases, surgery in 2, and subsequent stenting in 1 patient in a separate sitting. Overall, 65 patients (30.6% of 212 patients evaluated for small incidental aneurysms) underwent 69 endovascular procedures for 69 aneurysms (including the case initially assigned to the observation group). The type of endovascular treatment is summarized in Table 3.

The mean length of hospital stay in this cohort was 1.4 days (median 1 day). Immediate digital subtraction angiography demonstrated complete obliteration in 14 cases (20.29%), near complete (≥ 90%) in 46 cases (66.67%), and incomplete (< 90%) in 9 cases (13.04%).

Complications

Periprocedural Complications (Within the First 30 Days). There were 6 (9.23%/patient, 8.69%/procedure) periprocedural (within 30 days) complications, which resulted in permanent morbidity in 1 patient (1.53%/patient, 1.45%/procedure) and death in another patient (periprocedural mortality 1.53%/patient, 1.45%/procedure). Major periprocedural complications consisted of thrombus formation in 2 patients, ischemia in 2, periprocedural rupture in 1, and death in 1. It is noteworthy that short- and long-term cognitive outcomes were not available in this cohort.

In 1 patient, treated for a basilar tip aneurysm, there was transient development of in-stent thrombosis that resolved after initiation of pharmacological therapy with no sequelae. The patient was discharged on the 1st postoperative day without any complaints. The second patient with a thrombotic complication was a 39-year-old woman who underwent treatment for a superior hypophyseal and a BA aneurysm in 2 different sittings. The second procedure (treatment of the BA aneurysm) was complicated by in-stent thrombosis, which rapidly resolved with systemic abciximab administration. The patient was discharged on the 3rd postoperative day without any complaints except minimal headache. One patient experienced transient dysarthria following uncomplicated embolization of an ACoA aneurysm. His symptoms quickly improved, and he was discharged on the 2nd postoperative day without any deficits. One additional patient underwent uneventful embolization of a left PCoA aneurysm. She was discharged the following day without any symptoms. She was readmitted 2 days later with multiple small cerebellar, thalamic, and parietal ischemic strokes that resulted in a permanent mild disability after hemorrhagic transformation of the parietal lesion. A 60-year-old woman was evaluated for episodes of transient global amnesia.

TABLE 3: Type of endovascular treatment in 65 patients with 69 aneurysms

Procedure	No. of Treated Lesions (%)
coiling	51 (73.91)
stent-assisted coiling	6 (8.70)
balloon-assisted coiling	10 (14.49)
flow diversion	1 (1.45)
stent only	1 (1.45)

During embolization of a left PCoA aneurysm, perforation of the aneurysm sac occurred, causing SAH. The patient required placement of a temporary external ventricular drain but recovered without sequelae.

The only death in this series occurred after an expanding basilar trunk aneurysm was treated by stent-assisted coiling in a 74-year-old woman. The procedure was complicated by in-stent thrombosis, and the patient suffered a thalamic and pontine infarct despite prompt pharmacologically induced recanalization of the offending thrombus. Eventually she died after hemorrhagic conversion of the thalamic infarct.

Minor early-onset complications were observed in 4 patients and consisted of systemic infection treated with antibiotic therapy (1 patient), groin infection requiring antibiotic treatment (1 patient), rectal bleeding in 1 patient receiving dual-antiplatelet therapy, and iatrogenic non–flow limiting vertebral artery dissection in 1 patient.

Late-Onset Complications. There was one significant late (> 30-day) complication occurring at approximately 7.4 months following treatment. This 50-year-old man underwent an uncomplicated stent-assisted embolization of an ACoA aneurysm. Catheter angiography performed 1.6 and 7.4 months later suggested partial aneurysm obliteration, progressive coil compaction, and significant aneurysm recurrence. The geometry of the aneurysm precluded further embolization. It was decided to proceed with surgery and the patient was taken off clopidogrel first and aspirin afterward. This resulted in thrombus formation around the stent with distal emboli and a disabling stroke in the ACA territory. The stroke caused permanent cognitive dysfunction and rendered the patient unable to return to work. No surgery was performed in this case.

Clinical and Radiological Follow-Up

Imaging follow-up was available in 41 of the patients (43 procedures); the studies were obtained at an average of 10.6 months. In the last available imaging evaluation, obliteration was complete in 21 aneurysms (48.8%), near complete (≥ 90% obliterated) in 16 (37.2%), and incomplete (< 90% obliterated) in 6 (14%). Angiographic results in patients with at least 1 follow-up imaging study are summarized in Table 4. Clinical follow-up (mean 12.6 months, range 0.5–35.6 months) was available in all 64 survivors (after 68 procedures). There was no rupture documented in this group of patients and there were no new symptoms that could be ascribed to the aneurysm. No patient underwent repeat embolization for residual/recurrent aneurysm.

Surgery. In the period between January 2008 and May 2011, 18 patients underwent craniotomy for the treatment of small incidentally discovered UIAs, representing 8.5% of the total number of patients. Surgical treatment was considered when the aneurysm was deemed not to be amenable to endovascular treatment based on aneurysm characteristics and patient-related factors. Eighteen patients underwent 19 procedures for 20 aneurysms: 16 patients with 16 aneurysms and 2 patients with 2 aneurysms each. All of the treated aneurysms were treated by clipping. Table 2 provides a summary of patient demographics as well as characteristics of the treated aneurysms. The mean length of hospital stay in patients undergoing surgery was 2.7 days (range 1–5 days, median 3 days). There were no periprocedural transient or permanent neurological deficits in this small subgroup. However, 1 patient, a 51-year-old woman with a small MCA aneurysm, did not return to her previous occupation after surgery. She was discharged on the 2nd postoperative day after uncomplicated aneurysm clipping. A month later she started complaining of fatigue, memory issues, and problems with focus and concentration. At the last follow-up, 16.3 months following surgery, she had developed obsessive-compulsive disorder and was unable to go back to work (modified Rankin Scale score of 2). A CT scan of the head obtained by her local physician was reported to show postoperative changes but no evidence of complications.

TABLE 4: Comparison of immediate and final angiographic occlusion rates in a subgroup of patients who underwent immediate and final follow-up imaging

	No. of Procedures (%)	
Extent of Occlusion	Immediate Occlusion Rate	Final Occlusion Rate
complete (100%)	11 (25.6)	21 (48.8)
near complete (≥90%)	28 (65.1)	16 (37.2)
incomplete (<90%)	4 (9.3)	6 (14)

Intraoperative indocyanine green angiography in every patient and postoperative catheter angiography in selected cases demonstrated complete aneurysm obliteration in 18 cases (90%) and near-complete obliteration (small neck remnant) in 2 cases (10%). Clinical follow-up information was available for all 18 patients after an average of 14.6 months (median 16.3 months, range 0.1–29.2 months).

Discussion

With the widespread use of noninvasive brain imaging techniques, small incidental intracranial aneurysms are commonly detected. When a small UIA is found, the treating physician is often left with a significant management dilemma. The majority of small aneurysms likely do not rupture. However, the risk of rupture of small incidental UIAs, particularly when located in certain regions, is not zero, and, more importantly, when aneurysms do rupture, the prognosis is poor.[13] Although the follow-up duration in the present study is short, only a few patients were lost to follow-up (clinical follow-up available in > 95% of patients in the observation cohort). Furthermore, findings in our observation cohort confirm that the short-term risk of rupture for those patients deemed not in need of invasive treatment is very low, as suggested by the fact that no episodes of aneurysm rupture occurred in the "observation" group. This observation is consistent with the results of ISUIA[13] and is in disagreement with some studies from Japan, although in these latter studies all patients with unruptured aneurysms, irrespective of size and symptomatic status, were considered together.[11,12] The

lack of UIA rupture in the follow-up period in our observation cohort is also in disagreement with another widely quoted study on the natural history of UIAs by Juvela and coworkers.[7,8] However, the 2 studies are not comparable to other studies, including the ISUIA (patients without a prior SAH), because careful analysis of the Juvela et al. study reveals that 102 of the 105 patients considered had an unruptured aneurysm discovered in the setting of a prior SAH from another aneurysm. It has been reported that in patients with a history of SAH the aneurysm has a worse natural history and higher risk of rupture,[13] and these patients were not included in our study because we focused exclusively on patients with truly incidental unruptured aneurysms.

Given that the natural history of very small incidental UIAs appears to be benign in Caucasian populations, any interventional treatment must be carefully considered. The availability of endovascular techniques has fostered a perception of treatment being available and safe, and there has been a significant increase in the number of patients with UIAs evaluated and treated in the past decade.[6] Analysis of data from the NIS shows that the fraction of treated UIAs managed with endovascular coiling increased from 20% in 2001 to 63% in 2008.[2] However, even though endovascular treatment is relatively well tolerated and less invasive than open surgery, complications do occur. In our study, there was 1 permanent periprocedural stroke resulting in minor disability and 1 periprocedural death, resulting in a combined short-term periprocedural morbidity and mortality rate of 3%. Given that previous data suggest that adverse cognitive outcomes are a key contributor to interventional morbidity and mortality,[13] it is important to note that such data were not available in the current cohort. These outcome data are in line with those previously reported. In a large prospective study on coiling of UIAs conducted mostly in experienced French centers,[10] the periprocedural morbidity and mortality rates were 3.1% for the standard approach with coils and 3.7% for the remodeling technique, respectively. In overall clinical practices, however, treatment complications are probably higher than noted in the literature. Following analysis of the NIS, a large administrative database containing data on a random sample of 1000 US hospitals, discharge to a site other than home (used as a surrogate for perioperative complications) was 4.1% in patients undergoing endovascular treatment and 13.8% in patients undergoing surgery.[6] Although these NIS data included unruptured aneurysms of all sizes and there was no differentiation made between truly incidental and symptomatic aneurysms, these data underscore once again that, despite recent progress in techniques, treatment of UIAs continues to be associated with serious and clinically relevant complications.

Ongoing uncertainty regarding risks and benefits of treating small incidental UIAs can only be clarified through a well-designed, randomized clinical trial. The need for such a trial is exacerbated by the large amount of health care expenditures focused on imaging follow-up of both treated and observed small aneurysms, as well as on interventional management for these cases. Although such a proposed trial will require many years of follow-up (given the low occurrence of end points in the observation group) and significant resources, it is the responsibility of the medical community to make it happen.

We believe that only a minority of patients with small incidental intracranial aneurysms should be considered for treatment, and this belief is in line with current guidelines.[1] Less than one-half of small incidental aneurysms in our cohort were recommended for treatment. Furthermore, we have maintained a low threshold to abort endovascular procedures if any difficulty is encountered. Notably, many of the patients were sent to us for a second opinion after invasive treatment had been recommended elsewhere. In our opinion, interventional treatment is likely not indicated in most older patients, for those with incidental UIAs in specific benign locations such as the paraclinoid carotid artery and selected other anterior circulation locations, and for those with significant comorbid conditions affecting their life expectancy. Factors that increase the potential recommendation for interventional treatment include a younger age patient, particularly with a family history of aneurysmal hemorrhage, a UIA in a posterior circulation or PCoA location, selected UIA morphological features, patient perspective regarding the need for treatment after hearing an unbiased presentation of the comparison of natural history and risks of intervention, and occurrence of aneurysm growth during the follow-up period. When these factors were present, especially in younger patients, invasive treatment was recommended even in those with very small aneurysms, which explains why some aneurysms as small as 3 and 4 mm were treated in this cohort.

It is notable that all deaths unrelated to the aneurysm in our cohort were in the observation group, indicating that patients with UIAs considered by us not to be in need of intervention have a substantially greater likelihood of dying from non–aneurysm related disorders compared with potential SAH as noted in other large UIA cohort studies.[13] It is also important to consider the management of risk factors for aneurysm formation and rupture in all patients, including those who undergo observation and those who undergo intervention. In patients who are cigarette smokers, appropriate counseling and medical managements strategies should be implemented to increase the likelihood of smoking cessation. Elevation in blood pressure consistent with hypertension should be treated to attain normal blood pressure levels and should be monitoring closely over time.

Our study has limitations related to being a single-institution series reflecting treatment recommendations and primarily the bias of the senior author who has dual training in surgical and endovascular procedures. In addition, cognitive outcomes were not available. Nevertheless, there are many strengths, including concentration on a very specific and homogeneous group of patients such as those with truly incidental small aneurysms, the complete follow-up, having no patient who underwent invasive treatment lost to follow-up, follow-up data available in more than 95% of the patients who underwent observation, the strict criteria adopted in reporting complications (based on patients' self-assessment of the modified Rankin Scale score), and inclusion of patients in whom complications developed in the course of evaluation or

beyond the "traditional" 30-day time window used to assess treatment-related complications. Moreover, our study population represents a contemporary series during which there have been few changes in terms of technology or patient assessment.

Conclusions

We describe our experience in the management of incidental UIAs. Cautious patient selection can yield excellent outcomes with minimal morbidity and mortality even with aggressive approaches. Coil embolization has the potential to be a cost-effective treatment approach which, unfortunately, still harbors a finite risk of serious complications. It is unlikely that this morbidity will decrease significantly, especially in view of the fact that an increasing number of elderly patients are diagnosed with intracranial aneurysms and the documentation of a high prevalence of smoking and hypertension in these patients, which increase the likelihood of atherosclerosis and increase the risk or periprocedural complications.

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Disclosure

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References

1. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, et al: Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. **Stroke 31:**2742–2750, 2000
2. Brinjikji W, Rabinstein AA, Nasr DM, Lanzino G, Kallmes DF, Cloft HJ: Better outcomes with treatment by coiling relative to clipping of unruptured intracranial aneurysms in the United States, 2001-2008. **AJNR Am J Neuroradiol 32:** 1071–1075, 2011
3. Cross DT III, Tirschwell DL, Clark MA, Tuden D, Derdeyn CP, Moran CJ, et al: Mortality rates after subarachnoid hemorrhage: variations according to hospital case volume in 18 states. **J Neurosurg 99:**810–817, 2003
4. Hackett ML, Anderson CS: Health outcomes 1 year after subarachnoid hemorrhage: an international population-based study. **Neurology 55:**658–662, 2000
5. Hop JW, Rinkel GJ, Algra A, van Gijn J: Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. **Stroke 28:**660–664, 1997
6. Huang MC, Baaj AA, Downes K, Youssef AS, Sauvageau E, van Loveren HR, et al: Paradoxical trends in the management of unruptured cerebral aneurysms in the United States: analysis of nationwide database over a 10-year period. **Stroke 42:**1730–1735, 2011
7. Juvela S: Natural history of unruptured intracranial aneurysms: risks for aneurysm formation, growth, and rupture. **Acta Neurochir Suppl (Wien) 82:**27–30, 2002
8. Juvela S, Porras M, Heiskanen O: Natural history of unruptured intracranial aneurysms: a long-term follow-up study. **J Neurosurg 79:**174–182, 1993
9. Loumiotis I, Wagenbach A, Brown RD Jr, Lanzino G: Small (< 10-mm) incidentally found intracranial aneurysms, Part 1: reasons for detection, demographics, location, and risk factors in 212 consecutive patients. **Neurosurg Focus 31(6):**E3, 2011
10. Pierot L, Spelle L, Leclerc X, Cognard C, Bonafé A, Moret J: Endovascular treatment of unruptured intracranial aneurysms: comparison of safety of remodeling technique and standard treatment with coils. **Radiology 251:**846–855, 2009
11. Tsukahara T, Murakami N, Sakurai Y, Yonekura M, Takahashi T, Inoue T: Treatment of unruptured cerebral aneurysms—a multi-center study of Japanese national hospitals. **Acta Neurochir Suppl 82:**3–10, 2002
12. Tsukahara T, Murakami N, Sakurai Y, Yonekura M, Takahashi T, Inoue T, et al: Treatment of unruptured cerebral aneurysms; a multi-center study at Japanese national hospitals. **Acta Neurochir Suppl 94:**77–85, 2005
13. Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, et al: Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. **Lancet 362:**103–110, 2003

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Address correspondence to: Giuseppe Lanzino, M.D., Department of Neurologic Surgery, 200 First Street SW, Rochester, Minnesota 55905. email: Lanzino.Giuseppe@mayo.edu.

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Management of incidental cavernous malformations: a review

Richard T. Dalyai, M.D.,[1] George Ghobrial, M.D.,[1] Issam Awad, M.D.,[2] Stavropoula Tjoumakaris, M.D.,[1] L. Fernando Gonzalez, M.D.,[1] Aaron S. Dumont, M.D.,[1] Nohra Chalouhi, M.D.,[1] Ciro Randazzo, M.D.,[1] Robert Rosenwasser, M.D.,[1] and Pascal Jabbour, M.D.[1]

[1]Department of Neurosurgery, Jefferson Hospital for Neuroscience, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; and [2]Department of Neurosurgery, University of Chicago, Illinois

Cavernous malformations (CMs) are angiographically occult vascular malformations that are frequently found incidentally on MR imaging. Despite this benign presentation, these lesions could cause symptomatic intracranial hemorrhage, seizures, and focal neurological deficits. Cavernomas can be managed conservatively with neuroimaging studies, surgically with lesion removal, or with radiosurgery. Considering recent studies examining the CM's natural history, imaging techniques, and possible therapeutic interventions, the authors provide a concise review of the literature and discuss the optimal management of incidental CMs. *(DOI: 10.3171/2011.9.FOCUS11211)*

Key Words • **cavernous malformation** • **incidental lesion** • **intracranial hemorrhage** • **vascular malformation** • **seizure**

Cerebral cavernous malformations are vascular malformations that consist of thin hyalinized vascular channels without intervening brain parenchyma.[27,34] These lesions are surrounded by hemosiderin deposits and a gliotic margin and may be thrombosed.[8] While their location is variable, 70%–80% of intracranial CMs have a supratentorial origin.[8]

With the increasing availability of MR imaging, the diagnosis of CM has risen significantly. In fact, prior to MR imaging, CMs were uncommon, and their evaluation and management were described only in case reports and small clinical series.[31] These vascular lesions are not apparent with diagnostic angiography, given their nature as low-pressure systems, and thus are known as angiographically occult vascular malformations.[27] However, improvements in radiographic imaging have led not only to the increased diagnosis of symptomatic lesions, but also to the incidental discovery of CMs, with 40% of them now being diagnosed incidentally.[6] The specific risk associated with CMs is the occurrence of hemorrhage or microhemorrhages that can lead to death, neurological deficits, epilepsy, or perhaps no clinical deficit at all. In this review, we discuss the natural history of CMs, as well as the risks and benefits of various treatment options.

Cavernous malformations are the most common, clinically significant vascular anomaly and constitute approximately 10%–15% of all vascular malformations.[6] Their incidence is roughly 0.4%–0.8% in the general population based on autopsy studies and large MR imaging series.[6,24,33] They occur throughout the age spectrum, with 25% occurring in children, although the mean patient age is in the fourth decade of life.[21]

Clinical Presentation

As previously mentioned, approximately 40% of CMs are incidental, and many patients present with only a headache (6%–65%).[6,13,20,33] Given more frequent MR imaging studies, incidental CMs are outpacing seizures as the more frequent presentation. Patients with infratentorial CMs that are initially found incidentally have an increased risk of experiencing a focal neurological deficit. The incidence of asymptomatic CMs in patients presenting with a previously unknown hemorrhage ranges between 9% and 88%, reflecting the lack of a consistent classification for hemorrhage regarding CMs.[9,14,15,20,28,33]

Abbreviation used in this paper: CM = cavernous malformation.

Genetics

In 40%–60% of cases, the lesions are multiple and a familial inheritance is suggested.[7] Three distinct gene foci on chromosomes 7q, 7p, and 3 have been linked to familial CMs.[7] Three separate genes, known as *CCM1*/*KRIT1*, *CCM2*/*MGC4607*, and *CCM3*/*PDCD10,* are implicated in familial CMs and exhibit a Mendelian autosomal dominant inheritance pattern due to a heterozygous loss-of-function mutation at 1 of the 3 distinct loci.[34] The identified proteins encoded by CM genes are expressed in neural tissue and appear to interact with the cytoskeleton and interendothelial cell junction proteins during angiogenesis.[34] More recent research suggests that there is a common pathway connecting the protein products of the CM genes, which ultimately impair endothelial cell–cell junctions and vasculogenesis.[34] The discovery and elucidation of these genes, their protein products, and a cellular pathway hold the clinical promise of a potential target for molecular and genetic therapies for CMs.[34]

Imaging Characteristics

Images of CMs are characterized by microhemorrhages surrounding the malformation.[7,27,31] Hemoglobin degradation products of methemoglobin, hemosiderin, and ferritin allow for detection on MR imaging.[22,27] Cavernous malformations are generally characterized on T2-weighted sequences as areas of mixed signal intensity in a central complicated core with decreased signal intensity along a peripheral rim. Gradient echo sequences have also been advocated as a more sensitive means of diagnosing CMs because of the more recognizable lesion hypointensities on this sequence. Gradient echo sequencing comes with the caveat that it may portray a larger apparent size of the lesion because of the hemosiderin. This illusion of a larger size may complicate surgical planning if the true lesion size does not extend to the pial surface, as it can appear. Susceptibility-weighted imaging has also been advanced as a more sensitive MR sequence for multifocal familial lesions given its sensitivity to deoxyhemoglobin and iron content.[7] Cavernous malformations are generally classified into 4 main types based on MR imaging characteristics.[27,35] Type I CMs contain subacute hemorrhage characterized by a hemosiderin core, which is hyperintense on T1 and T2 sequences. Type II CMs with loculated areas of hemorrhage are surrounded by gliotic tissue displaying a reticulated mixed signal on both T1 and T2 sequences with a classic "popcorn" appearance. Type III lesions, typically seen in familial CMs, contain chronic resolved hemorrhage, with T1, T2, and gradient echo sequences displaying an isointense lesion. Familial lesions are also thought to more frequently lack a developmental venous anomaly, which becomes apparent on contrast-enhanced MR imaging.[7,11] Type IV lesions appear similar to telangiectasias and are only seen on gradient echo MR imaging as small punctate hypointense signals.[27]

Risk of Hemorrhage

Studies vary greatly on the risk of subsequent hemorrhagic presentation for CMs, depending on the specific design of each study. Given the variability in the reported incidence of hemorrhage, recommendations on surgical management have been unclear. Earlier population studies retrospectively reviewing MR imaging documented symptomatic hemorrhage rates between 0.25% and 2.3% per patient-year and about 0.1%–1.4% per lesion-year.[9,28,33] However, many of these rates were calculated assuming that the CMs were present at birth, and the risk of hemorrhage was calculated considering a patient's entire lifespan. Prospective studies have demonstrated a rate of hemorrhage between 0.8% and 3.8% per patient-year.[14,25,28,29] This rate was increased in the patients initially presenting with hemorrhage: 7%–8.9% per patient-year.

In familial CMs, symptomatic hemorrhage rates have been reported as 6.5% per patient-year and 1.1% per lesion-year, reflecting the more common tendency for familial CMs to occur in multiples.[33] In this subpopulation asymptomatic hemorrhage rates were reported to be as high as 13% per patient-year.[35] This elevated rate increases the importance of identifying familial CMs perhaps with new MR imaging sequences such as susceptibility-weighted imaging. Identifying this subpopulation should lead to genetic screening and counseling of first-degree relatives given their potential risk for a hemorrhagic event.

Temporal Clustering

While a hemorrhagic event has been shown to put patients at an increased risk for subsequent hemorrhages, it is disputed whether this high-risk period is limited in terms of time. When looking over time periods for CMs, Barker et al.[5] reported a decline in the hemorrhage risk 2 years after the initial hemorrhagic event. They documented a decrease in bleeding rates from 2.1% per patient-month to 0.8% after 28 months. This effect, which has been termed "temporal clustering," is important when analyzing treatment options with limited efficacy until 18 months, when the risk of hemorrhage may decline based on natural history alone.

Risk Factors for Hemorrhage

Besides the already discussed risk factor of an original hemorrhagic event, several other factors can contribute to a CM's elevated risk of hemorrhage. A major study by Porter et al.[25] delineated the natural history of CMs by location. When comparing supratentorial and infratentorial CMs, the authors found infratentorial lesions to have an increased risk of hemorrhage (3.8% per patient-year) as compared with supratentorial CMs (0.4% per patient-year).[25] After analyzing superficial malformations against CMs located in the brainstem, thalamus, or basal ganglia, they reported a hemorrhage risk of 0% per patient-year versus 4.1%, respectively. Multiple retrospective case series focused on brainstem CMs have documented an elevated hemorrhage risk rate of 2.5%–5% per patient-year and a rate of hemorrhage of 5.1%–30% per patient-year after an initial bleeding event.[10,12,26,27] Note, however, that a retrospective analysis by Tarnaris et al.[30] revealed a very low rate of rehemorrhage, 0.05% per patient-year. Deep CMs may have a greater risk for hemorrhage or instead are more likely to have an identified symptomatic event as a result of

their eloquent location. Several studies have also demonstrated an elevated risk of hemorrhage in females. Kupersmith et al.[15] reported an increased rate of rehemorrhage in women (5.9%) compared with that in men (3.3%). Anecdotally, an increase in the size of CMs is thought to occur with frequent microhemorrhages, causing fibrosis and calcification. However, there is no evidence to correlate size with hemorrhagic risk.

Seizure Development

Seizures are the most common presentation in patients with symptomatic CMs and are thought to develop based on the ionic effects of iron deposition.[4] Seizures are found to occur in 4.3% of patients after the initial diagnosis and in about 2.4% per patient-year. Seizures are thought to develop from microhemorrhages and formations of gliosis that surround the CM. Despite this theoretical etiology, seizures have not been shown to be a risk factor for subsequent hemorrhage.[33]

Surgical Risks and Outcomes

Many surgical series on CMs have demonstrated good results with operative management, with minimal surgical morbidity or mortality among patients with lesions in the cerebral hemispheres. Amin-Hanjani et al.[2] reported no deaths, a 20.6% rate of transient neurological deficits, and a permanent morbidity rate of 6.2% following the treatment of all 97 CMs in 94 patients. The rate of permanent disability was diminished to 3.2% among patients with lesions in the cerebral hemispheres compared with 14.2% among those with brainstem CMs. Similarly, among patients with lobar CMs, only 4.8% suffered a neurological decline. The authors also reported their experience with CMs in which total resection was complicated by the elevated risk of permanent deficit and low potential for restoring function.

Several studies have reported favorable results, that is, complete freedom from seizures, after complete resection of CMs in patients who had presented with seizures. Amin-Hanjani et al.[2] reported that 97% of their patients who had presented with or later demonstrated epilepsy were seizure free at an average of 1.5 years of clinical follow-up.

Brainstem CMs

Approximately 20%–35% of CMs are found in the brainstem.[1] The risk of symptomatic hemorrhage for nonfamilial brainstem CMs has been prospectively studied and reported as 0.25%–6.5% per patient-year.[1,35] As is the case with more superficial CMs, an increase in the annual hemorrhagic risk in the context of prior bleeding ranges from 3.8% to 35%.[1,12] Other studies use "clinical event rates" as an end point to presume hemorrhage despite radiographic findings, which Porter et al.[26] note as 10.6% per patient-year for deep CMs. This higher rate is emblematic of the location of and close association that brainstem CMs have with adjacent cranial nerve nuclei as well as motor and sensory tracts. Among brainstem CMs, 60% of all hemorrhages were found to be symptomatic.[19]

A very high initial postoperative morbidity rate (29%–67%) is related to postoperative edema and surgical manipulation.[1] Several series have reported a tracheostomy and/or gastrostomy rate of approximately 10%.[16,26,36] Moreover, permanent morbidity and mortality have been estimated to be around 10%–36% and 1.1%–2%, respectively, in large case series.[12] The surgical approach is carefully selected depending on the anatomical location of the lesion and surgeon preference. Recurrence rates on follow-up MR imaging after surgical extirpation are as high as 3.4%–3.5%.[18,28]

Mathiesen et al.[18] attained complete resection of brainstem CMs in only 25 of 69 patients who had undergone surgical treatment, with a 69% incidence of transient neurological worsening. However, other studies have shown some promise in achieving a higher rate of complete resection with low morbidity. A series of 137 patients who underwent surgery for brainstem CMs demonstrated a 72% rate of stability or improvement.[32] The indications for treatment in patients with lesions were presentation with neurological deterioration, grave presentation, overt hemorrhage, and a lesion location at the surface of the brainstem. Clearly, CMs that reach the pial surface are the most accessible and lead to the most favorable results. More recently, other groups would offer resection to all patients with symptomatic lesions that are surgically accessible, including intrinsic ones not abutting the pial surface.[1] Only if lesions are deep-seated and causing mild symptoms are they treated conservatively.

Radiosurgery

In several series radiosurgery has been advocated as a treatment option for CMs; however, its efficacy has been heavily debated. When advocated, its use is generally recommended only for deep or eloquent CMs with 2 symptomatic hemorrhages and when the operative risk carries increased morbidity, effectively making the lesions surgically inaccessible. The option for the patient and treating neurosurgeon is between radiosurgery and the natural history of the lesion. Regardless of the lesion location, reported postradiation rebleeding rates have been from 4% to 15.2% per patient-year. Morbidity and mortality from radiation injury or rebleeding have been 7%–21% and 0%–13%, respectively.[3,27,33] Liscák et al.[17] had noted improvement in neurological deficits attributed to CMs in 43% of isolated brainstem lesions; edema and rebleeding in the first 6 months was noted in 28%.

Role of Surgery

No clear consensus has been reached regarding the role of surgical treatment for CMs. Incidental lesions that carry no history of neurological deficits have traditionally been observed. In the absence of symptoms the morbidity associated with surgery argues for conservative management. These guidelines are supported almost exclusively by modest case series (Level 4 evidence;[23] Table 1), and no Level 1 evidence exists on the management of this disease entity. However, asymptomatic CMs must be closely monitored for either clinical symptomatology or a change in radiographic appearance. Many originally asymptomatic patients may experience symptomatic hemorrhage

TABLE 1: Factors promoting or contraindicating resection of CMs

Factors Promoting Surgical Intervention
medically intractable seizures
progressive neurological decline
clinically significant hemorrhage in noneloquent cortex
2nd clinically significant hemorrhage in eloquent cortex
patient risk adversity
young patient age
female sex
Relative Contraindications
asymptomatic
multiple incidental or familial lesions
brainstem CM

(0.2%–3.8% per patient-year) or seizures (2.4% per patient-year).

Even utilizing the most conservative risk of bleeding, such a risk is not trivial over a lifetime, especially in younger patients. For certain people, depending on their lifestyle, occupation, or mindset, an incidental lesion often cannot be ignored and carries an intrinsic psychological burden that may outweigh the risk of surgical morbidity once the lesion is diagnosed. For truly solitary lesions discovered incidentally, an easily accessible one in a young patient presents an opportunity for a cure, obviating regular follow-up, preventing even a small chance of serious sequelae from the lesion, and even simplifying pregnancy management in women or any anticoagulation management that may be needed later in life.

For the majority of patients with known CMs at our institutions, annual MR imaging is undertaken to determine the development of de novo CMs, any lesion growth, or new microhemorrhages. A careful neurological history and physical examination are performed to determine whether a newly discovered CM is truly asymptomatic or whether a patient has a history of seizures or an undiagnosed neurological deficit. Similarly, based on the imaging and genetic criteria mentioned above along with a family history, patients with multiple familial cavernomas are closely monitored both clinically and radiographically. For most patients with multiple familial cavernomas that are incidentally discovered, resection is not offered given its risk, as well as the morbidity associated with multiple surgical corridors or even craniotomies to access the multiple cavernomas. At the point of neurological decline, we would generally advocate surgical intervention for CMs in noneloquent cortex because of the increased risk of further symptomatology, which is 2.5%–5% per patient-year. For patients with CMs in eloquent areas, we would recommend surgical intervention after a second hemorrhage, particularly for cavernomas that occur at the pial surface. However, if the first hemorrhage is particularly disabling or if the lesion is easily accessible surgically (that is, an exophytic fourth ventricular lesion, a cerebellar lesion, or a lesion accessible via a transsulcal approach in the primary hand area), then surgical intervention is considered after symptomatic presentation or the first hemorrhagic event. Conversely, in some locations (that is, the central pons or ventral medulla), even 3 or more nondisabling bleeds would not warrant a disabling surgery, and further observation or radiosurgery may be considered even after 2 bleeds. At our center, we generally manage these lesions conservatively through observation and do not offer radiosurgery. As stated above, we emphasize that these are only general guidelines based on surgical experience and that they must be tempered by the individual patient and lesion considerations.

Conclusions

Cavernomas are being increasingly detected as incidental lesions on noninvasive imaging studies. Patients with CMs may also present with seizures or hemorrhage. Purely incidental CMs should be managed conservatively and followed-up with annual MR imaging. The treatment of symptomatic CMs is generally image-guided resection. If a venous abnormality is associated, we do not recommend excising the developmental venous anomaly, as doing so would pose an unnecessary risk of venous infarction. We recommend treating CMs only in the following situations: in the context of intractable seizures or progressive significant neurological deficit, after the first clinically significant hemorrhage in noneloquent areas, and after the second clinically significant hemorrhage in eloquent areas including the brainstem. Note, however, that these are only general guidelines. The best management at present relies on a surgeon's personal experience and clinical judgment.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References

1. Abla AA, Lekovic GP, Turner JD, de Oliveira JG, Porter R, Spetzler RF: Advances in the treatment and outcome of brainstem cavernous malformation surgery: a single-center case series of 300 surgically treated patients. **Neurosurgery 68:** 403–415, 2011
2. Amin-Hanjani S, Ogilvy CS, Ojemann RG, Crowell RM: Risks of surgical management for cavernous malformations of the nervous system. **Neurosurgery 42:**1220–1228, 1998
3. Asaad WF, Walcott BP, Nahed BV, Ogilvy CS: Operative management of brainstem cavernous malformations. **Neurosurg Focus 29(3):**E10, 2010
4. Awad I, Jabbour P: Cerebral cavernous malformations and epilepsy. **Neurosurg Focus 21(1):**e7, 2006
5. Barker FG II, Amin-Hanjani S, Butler WE, Lyons S, Ojemann RG, Chapman PH, et al: Temporal clustering of hemorrhages from untreated cavernous malformations of the central nervous system. **Neurosurgery 49:**15–25, 2001
6. Batra S, Lin D, Recinos PF, Zhang J, Rigamonti D: Cavernous

malformations: natural history, diagnosis and treatment. **Nat Rev Neurol 5:**659–670, 2009
7. Campbell PG, Jabbour P, Yadla S, Awad IA: Emerging clinical imaging techniques for cerebral cavernous malformations: a systematic review. **Neurosurg Focus 29(3):**E6, 2010
8. D'Angelo VA, De Bonis C, Amoroso R, Cali A, D'Agruma L, Guarnieri V, et al: Supratentorial cerebral cavernous malformations: clinical, surgical, and genetic involvement. **Neurosurg Focus 21(1):**e9, 2006
9. Del Curling O Jr, Kelly DL Jr, Elster AD, Craven TE: An analysis of the natural history of cavernous angiomas. **J Neurosurg 75:**702–708, 1991
10. Fritschi JA, Reulen HJ, Spetzler RF, Zabramski JM: Cavernous malformations of the brain stem. A review of 139 cases. **Acta Neurochir (Wien) 130:**35–46, 1994
11. Gault J, Sarin H, Awadallah NA, Shenkar R, Awad IA: Pathobiology of human cerebrovascular malformations: basic mechanisms and clinical relevance. **Neurosurgery 55:**1–17, 2004
12. Gross BA, Batjer HH, Awad IA, Bendok BR: Brainstem cavernous malformations. **Neurosurgery 64:**E805–E818, 2009
13. Kim DS, Park YG, Choi JU, Chung SS, Lee KC: An analysis of the natural history of cavernous malformations. **Surg Neurol 48:**9–18, 1997
14. Kondziolka D, Lunsford LD, Kestle JR: The natural history of cerebral cavernous malformations. **J Neurosurg 83:**820–824, 1995
15. Kupersmith MJ, Kalish H, Epstein F, Yu G, Berenstein A, Woo H, et al: Natural history of brainstem cavernous malformations. **Neurosurgery 48:**47–54, 2001
16. Lapras C, Lapras C, Deruty R, Patet JD, Mottolèse C: [Surgical treatment of intracerebral cavernomas.] **Neurochirurgie 35:**120–125, 1989 (Fr)
17. Liscák R, Vladyka V, Simonová G, Vymazal J, Novotny J Jr: Gamma knife radiosurgery of the brain stem cavernomas. **Minim Invasive Neurosurg 43:**201–207, 2000
18. Mathiesen T, Edner G, Kihlström L: Deep and brainstem cavernomas: a consecutive 8-year series. **J Neurosurg 99:**31–37, 2003
19. Mizoi K, Yoshimoto T, Suzuki J: Clinical analysis of ten cases with surgically treated brain stem cavernous angiomas. **Tohoku J Exp Med 166:**259–267, 1992
20. Moriarity JL, Wetzel M, Clatterbuck RE, Javedan S, Sheppard JM, Hoenig-Rigamonti K, et al: The natural history of cavernous malformations: a prospective study of 68 patients. **Neurosurgery 44:**1166–1173, 1999
21. Mottolese C, Hermier M, Stan H, Jouvet A, Saint-Pierre G, Froment JC, et al: Central nervous system cavernomas in the pediatric age group. **Neurosurg Rev 24:**55–73, 2001
22. New PF, Ojemann RG, Davis KR, Rosen BR, Heros R, Kjellberg RN, et al: MR and CT of occult vascular malformations of the brain. **AJR Am J Roentgenol 147:**985–993, 1986
23. OCEBM Levels of Evidence Working Group: **The Oxford 2011 Levels of Evidence.** Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653) [Accessed September 27, 2011]
24. Otten P, Pizzolato GP, Rilliet B, Berney J: [131 cases of cavernous angioma (cavernomas) of the CNS, discovered by retrospective analysis of 24,535 autopsies.] **Neurochirurgie 35:**82–83, 128–131, 1989 (Fr)
25. Porter PJ, Willinsky RA, Harper W, Wallace MC: Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. **J Neurosurg 87:**190–197, 1997
26. Porter RW, Detwiler PW, Spetzler RF, Lawton MT, Baskin JJ, Derksen PT, et al: Cavernous malformations of the brainstem: experience with 100 patients. **J Neurosurg 90:**50–58, 1999
27. Raychaudhuri R, Batjer HH, Awad IA: Intracranial cavernous angioma: a practical review of clinical and biological aspects. **Surg Neurol 63:**319–328, 2005
28. Robinson JR, Awad IA, Little JR: Natural history of the cavernous angioma. **J Neurosurg 75:**709–714, 1991
29. Steiner L, Karlsson B, Yen CP, Torner JC, Lindquist C, Schlesinger D: Editorial: Radiosurgery in cavernous malformations: anatomy of a controversy. **J Neurosurg 113:**16–22, 2010
30. Tarnaris A, Fernandes RP, Kitchen ND: Does conservative management for brain stem cavernomas have better long-term outcome? **Br J Neurosurg 22:**748–757, 2008
31. Voigt K, Yaşargil MG: Cerebral cavernous haemangiomas or cavernomas. Incidence, pathology, localization, diagnosis, clinical features and treatment. Review of the literature and report of an unusual case. **Neurochirurgia (Stuttg) 19:**59–68, 1976
32. Wang CC, Liu A, Zhang JT, Sun B, Zhao YL: Surgical management of brain-stem cavernous malformations: report of 137 cases. **Surg Neurol 59:**444–454, 2003
33. Washington CW, McCoy KE, Zipfel GJ: Update on the natural history of cavernous malformations and factors predicting aggressive clinical presentation. **Neurosurg Focus 29(3):**E7, 2010
34. Yadla S, Jabbour PM, Shenkar R, Shi C, Campbell PG, Awad IA: Cerebral cavernous malformations as a disease of vascular permeability: from bench to bedside with caution. **Neurosurg Focus 29(3):**E4, 2010
35. Zabramski JM, Wascher TM, Spetzler RF, Johnson B, Golfinos J, Drayer BP, et al: The natural history of familial cavernous malformations: results of an ongoing study. **J Neurosurg 80:**422–432, 1994
36. Ziyal IM, Ozgen T: Natural history of brainstem cavernous malformations. **Neurosurgery 49:**1023–1024, 2001

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Address correspondence to: Pascal Jabbour, M.D., Department of Neurosurgery, Thomas Jefferson University Hospital, 909 Walnut Street, 2nd Floor, Philadelphia, Pennsylvania 19107. email: Pascal.Jabbour@jefferson.edu.

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Discovery of asymptomatic moyamoya arteriopathy in pediatric syndromic populations: radiographic and clinical progression

Ning Lin, M.D., Lissa Baird, M.D., McKenzie Koss, B.S., Kimberly E. Kopecky, B.S., Evelyne Gone, B.A., Nicole J. Ullrich, M.D., Ph.D., R. Michael Scott, M.D., and Edward R. Smith, M.D.

Department of Neurosurgery, Children's Hospital, Harvard Medical School, Boston, Massachusetts

Object. Limited data exist to guide management of incidentally discovered pediatric moyamoya. Best exemplified in the setting of unilateral moyamoya, in which the unaffected side is monitored, this phenomenon also occurs in populations undergoing routine surveillance of the cerebral vasculature for other conditions, such as sickle cell disease (SCD) or neurofibromatosis Type 1 (NF1). The authors present their experience with specific syndromic moyamoya populations to better characterize the natural history of radiographic and clinical progression in patients with asymptomatic moyamoya.

Methods. The authors performed a retrospective review of the clinical database of the neurosurgery department at Children's Hospital Boston, including both nonoperative referrals and a consecutive series of 418 patients who underwent surgical revascularization for moyamoya disease between 1988 and 2010.

Results. Within the period of time studied, 83 patients were asymptomatic at the time of radiographic diagnosis of moyamoya, while also having either unilateral moyamoya or moyamoya in association with either SCD or NF1. The mean age at presentation was 9.1 years (range 1–21 years), and there were 49 female (59%) and 34 male (41%) patients. The mean follow-up duration was 5.4 ± 3.8 years (mean ± SD), with 45 patients (54%) demonstrating radiographic progression and 37 (45%) becoming symptomatic within this period. Patients with SCD had the highest incidence of both radiographic (15 patients [75%]) and clinical (13 patients [65%]) progression, followed by NF1 (20 patients [59%] with radiographic progression and 15 patients [44%] with clinical progression) and patients with unilateral moyamoya (10 patients [35%] with radiographic progression and 9 patients [31%] with clinical progression).

Conclusions. Radiographic progression occurred in the majority of asymptomatic patients and generally heralded subsequent clinical symptoms. These data demonstrate that moyamoya is a progressive disorder, even in asymptomatic populations, and support the rationale of early surgical intervention to minimize morbidity from stroke.
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Key Words • **asymptomatic moyamoya** • **sickle cell disease** • **neurofibromatosis Type 1** • **stroke** • **pediatric moyamoya** • **pial synangiosis**

The role for surgical revascularization for symptomatic moyamoya in children has been well established, with multiple studies demonstrating a clear benefit to patients, with reduced rates of ischemic injury when compared with the natural history.[5,13,16,17] Less clear, however, is the natural history and appropriate course of action to take in the case of children found to have the arteriopathy of moyamoya who are asymptomatic. Whereas a sound rationale has been proposed for revascularization in patients with asymptomatic moyamoya based on the premise that long-term outcome is largely dependent on neurological status at the time of surgery, there are few data on the natural history of incidentally discovered moyamoya, with almost no data specific to children.[13,17]

One of the major limitations to the study of asymptomatic moyamoya in children is the rarity of incidentally discovered cases. The majority of pediatric moyamoya is idiopathic moyamoya disease (bilateral, presumably genetic, arteriopathy), which is found only after presentation with ischemic symptoms.[5,16,17] However, there are populations of pediatric patients who have medical conditions known to be associated with moyamoya (moyamoya syndrome) who undergo periodic screening studies of the brain and cerebral vasculature and are thus more likely to have an incidental diagnosis. In particular, if one excludes idiopathic moyamoya disease, children with NF1 and SCD comprise the most common subgroups of syndromic moyamoya.[16] Patients with NF1 may receive surveillance MR images to monitor tumor status, and patients with SCD routinely undergo TCD studies to ascertain the need for exchange transfusions, which are frequently corroborated with MR images.[15,18,22] In addition, patients with unilateral

Abbreviations used in this paper: NF1 = neurofibromatosis Type 1; SCD = sickle cell disease; TCD = transcranial Doppler; TIA = transient ischemic attack.

moyamoya syndrome are frequently followed with serial imaging, because approximately one-third of unaffected hemispheres will ultimately progress to develop moyamoya.[10,19]

This study exploits the availability of serial imaging studies in select populations of pediatric patients—those with NF1, SCD, or the unaffected hemisphere in children with unilateral moyamoya—to characterize the radiographic and clinical progression of incidentally found, asymptomatic moyamoya syndrome. The objectives of this work are to document the incidence of radiographic and clinical progression in previously asymptomatic children found to have moyamoya. A clear demonstration that asymptomatic, incidentally discovered moyamoya can progress—both radiographically and clinically—along with data identifying general rates of progression and at-risk populations would aid clinicians involved with the care of these children.

Methods

We performed a review of the clinical database from the Boston Pediatric Neurosurgical Foundation to identify all patients referred to either of the senior authors (R.M.S. and E.R.S.) for the diagnosis of moyamoya and who had the coexisting diagnosis of either NF1 or SCD. This series thus included both surgically and nonsurgically treated patients, with the surgically treated cases obtained from clinical records of a consecutive series of 418 patients with moyamoya syndrome who underwent surgical revascularization performed by the senior authors at the Children's Hospital, Boston, between 1988 and 2010. All patients ultimately received a diagnosis of moyamoya arteriopathy as defined by the ICD and outlined in the guidelines from the Japanese Ministry of Health.[4] All patients also had a concomitant diagnosis of NF1, SCD, or unilateral moyamoya. A total of 83 patients met these criteria.

We determined patient age, sex, length of follow-up, radiographic findings, and clinical symptoms. All patients had undergone multiple MR imaging sessions, including at least 1 individual with no evident arteriopathy. Radiographic progression was defined as the following: 1) worsening of arteriopathy, with development of collateral vessels and/or greater narrowing of the anterior cerebral, middle cerebral, or internal carotid arteries on MR imaging or catheter angiogram (per the cited guidelines); 2) development of FLAIR hyperintensity in the sulci on MR imaging—the "ivy sign"—as a marker of slow cerebral blood flow; and 3) evidence of radiographic infarction, as determined by MR imaging and reported by neuroradiologists.[3,4,23]

Although all patients were by definition asymptomatic at the time of the initial radiographic diagnosis of moyamoya, we collected data on the number of patients in whom clinical symptoms occurred after development of the arteriopathy. Clinical progression was defined as the new onset of any of the following symptoms: TIA, stroke, headache, seizure, or symptomatic hemorrhage.[16] In addition, the number of patients who ultimately underwent surgical revascularization was analyzed, along with the time interval between diagnosis of the arteriopathy and the revascularization procedure.

Special note should be made of the patients with unilateral moyamoya. Although these individuals had radiographic evidence of moyamoya in the initial, ipsilateral, affected hemisphere (with or without symptoms), the patients selected for this study had no evident disease—radiographically or clinically—on the contralateral, unaffected hemisphere. They are included here as a population that had no disease contralaterally at the time of diagnosis of the ipsilateral hemisphere, but who are known to be at risk for potential involvement of the contralateral hemisphere, and are thus followed carefully with serial imaging and office visits in the practice of the senior authors.

This work was performed with approval of the Children's Hospital Boston's institutional review board.

Results

Demographic Information and Clinical Characteristics at Diagnosis

A total of 83 patients were included in this study, with demographic and summary data reviewed in Table 1. The majority of the children were female (49 patients, 59%), and the mean age was 9.1 years (range 1–21 years). Of the 83 patients, 34 had NF1, 20 had SCD, and 29 had unilateral disease. Differences in age and sex were noted between these groups (see Table 1), but all had comparable overall lengths of follow-up (5.4 ± 3.8 years; mean ± SD).

Radiographic Progression

Radiographic data are summarized in Table 2. Overall, 45 patients (54%) had evidence of radiographic progression within a mean of 5.4 years of follow-up. Differences in the incidence of progression were present, with the SCD subgroup having the greatest number of patients who worsened (75%), followed by NF1 (59%) and patients with unilateral moyamoya (35%). Radiographic data collected included the following: 1) the interval between the date of the first diagnosis of the clinical syndrome (NF1, SCD, or the first affected hemisphere in unilateral moyamoya) and the date of the first radiographic study (MR imaging or angiogram) in which the diagnosis of moyamoya was recognized; 2) the interval between the last MR imaging study with no reported moyamoya (that is, the last "normal" scan) and the first radiographic study

TABLE 1: Demographic information and clinical characteristics on admission in 83 patients with asymptomatic moyamoya*

Characteristic	NF1	SCD	Unilat Moyamoya	All Pts
no. of pts	34	20	29	83
mean age in yrs	7.3 ± 3.9	9.0 ± 4.9	11.7 ± 7.4	9.1 ± 5.7
sex (%)				
F	22 (65)	13 (65)	14 (48)	49 (59)
M	12 (35)	7 (35)	15 (52)	34 (41)
mean FU in yrs	5.5 ± 4.3	5.3 ± 3.9	5.5 ± 2.7	5.4 ± 3.8

* Unless otherwise indicated, values are expressed as the mean ± SD.
Abbreviations: FU = follow-up; pts = patients.

TABLE 2: Radiographic progression in 83 patients with asymptomatic moyamoya*

Feature	NF1	SCD	Unilat Moyamoya	All Pts
no. of pts	34	20	29	83
any radiographic progression (%)	20 (59)	15 (75)	10 (35)	45 (54)
mean FU in yrs	5.5 ± 4.3	5.3 ± 3.9	5.5 ± 2.7	5.4 ± 3.8
time interval measurements in yrs				
interval btwn diagnosis of syndromic disease & arteriopathy	5.9 ± 3.7	8.3 ± 5.1	1.8 ± 2.4	5.8 ± 4.7
interval btwn last normal scan & arteriopathy	1.5 ± 0.9	2.4 ± 2.4	2.0 ± 1.6	1.9 ± 1.6
interval btwn arteriopathy & slow cortical blood flow ("ivy sign")	0.4 ± 0.4	1.1 ± 1.4	NA	0.7 ± 1.1
interval btwn arteriopathy & stroke	0.5 ± 0.4	1.3 ± 1.9	0.5 ± 0.7	1.0 ± 1.6

* Unless otherwise indicated, values are expressed as the mean ± SD. Abbreviation: NA = not available.

(MR imaging or angiogram) in which the diagnosis of moyamoya was recognized; and, for the subset of patients in whom the findings developed, 3) the interval between the first scan in which the diagnosis of moyamoya was identified and the first scan that demonstrated "ivy sign" on FLAIR imaging; and 4) the interval between the first scan in which the moyamoya was diagnosed and the presence of a stroke on MR imaging.

Clinical Progression

Clinical progression is defined as the new onset of any of the following symptoms; TIA, stroke, headache, seizure, or symptomatic hemorrhage.[16] It is important to note that individual patients could experience more than 1 symptom, making the total number of reported findings greater than the total number of patients. Results are reported in Table 3, with 37 patients (45%) developing at least 1 new symptom following the diagnosis of moyamoya. Overall, any ischemic symptoms including TIA or stroke (clinically persistent neurological deficit) were the most common, followed by headache, then seizure, with no symptomatic hemorrhages. These relative frequencies were conserved across all 3 subgroups.

Discussion

This study seeks to better inform the clinician faced with the scenario of a child presenting with asymptomatic, incidentally discovered moyamoya. Although the natural history of the symptomatic patient generally supports the use of surgical revascularization, there are few data to guide decision-making in the asymptomatic pediatric population.[5,13,16,17] However, reports from the literature on adult patients, coupled with isolated pediatric papers (or individual patients within larger series), lend support to the hypothesis that asymptomatic moyamoya is not a benign entity, and—although variable in rate and severity—often progresses to affect individuals adversely.

Patient Population

The overall demographic composition of the patient population in this report was reflective of larger series reported by us and others.[5,17] Female sex predominated in a roughly 2:1 ratio overall, although the percentages for unilateral cases were nearly evenly split between the sexes, at 48:52. The composite mean age was 9.1 years, slightly older than in other reported series (including the previously reported series from our institution, in which the mean age was 6.5 years).[17] The older age at diagnosis may correlate with the absence of symptoms or with referral patterns from subspecialists who may think it unnecessary to send outwardly healthy patients for neurosurgical evaluation.

There was a clear age division by subgroup: the patients with NF1 were the youngest, at 7.3 years; those with SCD were in between, at 9 years; and the patients with uni-

TABLE 3: Clinical progression in 83 patients with asymptomatic moyamoya

Feature	NF1	SCD	Unilat Moyamoya	All Pts
no. of pts	34	20	29	83
any clinical progression (%)	15 (44)	13 (65)	9 (31)	37 (45)
mean FU in yrs	5.5 ± 4.3	5.3 ± 3.9	5.5 ± 2.7	5.4 ± 3.8
symptoms				
headache	2	6	2	10
TIA	11	10	8	29
stroke	4	5	1	10
seizure	1	2	0	3
hemorrhage	0	0	0	0
op (%)	25 (74)	14 (70)	10 (35)	49 (59)
interval btwn arteriopathy & op in yrs	0.6 ± 0.4	1.9 ± 1.5	0.6 ± 1.2	1.1 ± 1.2

lateral moyamoya were the oldest, at 11.7 years. Although difficult to assess from the relatively small numbers, it is interesting to note that the group with the youngest age is also the one that most commonly starts screening with MR imaging soonest, with the attendant risk of tumors in children with NF1. It is tempting to speculate that the younger age of detection in this study might be related to the earlier use of imaging, although subsequent studies will need to address this question more formally.

Radiographic Progression

More than half of all patients (45 [54%]) demonstrated radiographic progression after being diagnosed with moyamoya within the mean 5.4 years of follow-up, suggesting that this is a dynamic process that is particularly likely to have an impact on pediatric patients, given their expected long life spans. When children are born or first diagnosed with genetic conditions, such as NF1 or SCD, it can take a long time (5.9–8.3 years) for moyamoya arteriopathy to first develop, but once started, the disease often moves quickly. Following the first-ever development of asymptomatic evidence of radiographically confirmed arteriopathy, the mean time to then develop radiographic evidence of ischemia (as manifested by the "ivy" sign) is 0.4 and 1.1 years for NF1 and SCD patients, respectively. It is then only 1–3 months longer, on average, until the first radiographic evidence of infarction appears for the one-third of patients who develop strokes. These data suggest that any evidence of progression of the arteriopathy on serial scans in asymptomatic patients may herald precipitous changes in cerebral perfusion, with a concomitantly increased risk of ischemic injury. Although further study of this interesting finding is warranted, it provides additional justification to consider revascularization in this asymptomatic population.

Clinical Progression

Of the 83 patients in whom incidentally discovered, asymptomatic moyamoya was found in this series, 37 (45%) went on to develop clinical symptoms referable to the arteriopathy within the mean 5.4 years of follow-up. As outlined in Table 3, the most common symptoms in the 37 patients with clinical progression were directly related to cerebral ischemia, including TIA (29 patients, 78%) and stroke (10 patients, 27% [manifesting clinically as fixed neurological deficits]). These symptoms were followed in frequency by headache (10 patients, 27%) and seizure (3 patients, 8%). No patient had clinically evident hemorrhage. Interestingly, these symptomatic presentations were essentially unchanged in order of frequency, regardless of whether the patient had NF1, SCD, or unilateral moyamoya. The overwhelming preponderance of ischemic symptoms is concordant with many other series of pediatric patients with moyamoya and suggests that the natural history of these children—once they become symptomatic—will probably become indistinguishable from patients with symptomatic moyamoya in any population.[5,16]

Comparisons With Previous Reports, Including Adult Series, With Rationale for Surgical Intervention

Similar to what we have reported here, there is evidence in the adult literature that substantial numbers of patients with asymptomatic moyamoya can experience radiographic and clinical progression. One group reported that 24% of 63 adults with idiopathic moyamoya exhibited radiographic progression within a 6-year period, with more than 50% of these patients manifesting ischemic or hemorrhagic infarction during this time.[12] In a more recent series from Japan, a group of asymptomatic adults and children who were followed without undergoing surgery demonstrated a 7% mortality rate from cerebral infarction/hemorrhage over a mean of 3.7 years.[24] Other adult case reports reveal that untreated, asymptomatic moyamoya can present with catastrophic stroke or death, adding further support to the premise that this disorder can be rapidly progressive, and that preemptive treatment in asymptomatic patients may be warranted.[1,2,7]

The findings in these reports, coupled with our data in this series, are important because the practice of performing surgical revascularization in asymptomatic patients—including populations of syndromic children (those with Down syndrome, SCD, NF1, unilateral cases, and brain tumor survivors postirradiation)—demonstrates minimal operative morbidity and, in contrast to the natural history reported above, durable protection from ischemic symptoms in long-term outcomes.[6,8–10,16–19,22] Surgery has been successfully used in adults who were found to have asymptomatic progression of their moyamoya, with evidence of improved perfusion and absence of ischemic symptoms postoperatively, despite the radiographic progression.[9] The protective effect of surgery against stroke in this population was further highlighted in another study of 34 asymptomatic adults, in which 20% of untreated patients became symptomatic within approximately 3.5 years, with an overall 3.2% annual stroke rate; this contrasts with a 0% stroke rate in surgically treated patients.[11]

In the series described here, 49 (59%) of the 83 patients elected to undergo surgical treatment with pial synangiosis, a technique of indirect revascularization developed by one of the senior authors (R.M.S.).[17,20] With the exception of the SCD patients (in whom had a mean of 1.9 years elapsed between the development of radiographic arteriopathy and surgical intervention), most patients were treated within 7 months of the scan on which radiographic progression of the moyamoya was seen. As with other series, the surgical treatment was offered to provide protection from stroke but did not halt the ongoing radiographic progression of the arteriopathy.[14,18,19]

Operative Indications and Technique, Follow-Up

It is the practice in our institution to offer surgical revascularization with pial synangiosis to patients in whom moyamoya is diagnosed, including asymptomatic patients. Although individual review occurs with each case, we will generally proceed with surgery in children with radiographically documented moyamoya (Suzuki Stage 2 or greater), barring medical contraindications to craniotomy or a recent stroke (< 6 weeks). In patients with bilateral disease, we have routinely performed surgery on both sides during a single anesthetic session; we have used this method for nearly a decade. For greater detail on the operative technique, along with specific protocols

for subpopulations of syndromic patients (such as children with SCD), readers are referred to other reports from our group.[17,18,20,21]

For those patients who are observed (unclear diagnosis, Suzuki Stage 1, medically unstable—or patients with unilateral disease undergoing monitoring of the unaffected hemisphere), we will commonly perform surveillance imaging with MR imaging/MR angiography on an annual basis. In cases with the onset of new symptoms or in infants (< 3 years of age), we will consider more frequent studies and offer surgical treatment if moyamoya is confirmed. In surgically treated patients we typically obtain an MR imaging/angiography study at 6 months and then imaging at 1 year postoperatively, with annual MR imaging/angiography for at least 5 years thereafter.

Study Limitations

There are obvious limitations to this type of study, including its retrospective nature, limited number of patients, and the inherent variability in defining many of the measures used in the evaluations (progression of arteriopathy, "ivy" sign, clinical manifestations of cerebral ischemia). The selection of specific subgroups of patients with syndromic moyamoya was based on availability of data and relatively homogeneous patient populations. It would be beneficial to expand this work to include other groups, such as patients with brain tumor postirradiation and children with Down syndrome, among others.

It is also important to note that the population in this study is derived from a center that has a high volume of moyamoya referrals. This may introduce a bias, because it is likely that asymptomatic patients in other locations may not be referred for evaluation and treatment. Our center has a bias toward offering treatment—even to asymptomatic patients—and it would be potentially useful to understand the natural history better in untreated individuals. However, data from Japan and the US suggest that the natural history in moyamoya is highly likely to be progressive, with a substantial risk of stroke, as reviewed previously in the discussion. Therefore, although we acknowledge that a bias probably exists at our institution and appreciate that further study would certainly be of interest, we would contend that our aggressive approach to offering treatment can be justified.

Although we acknowledge that further study is certainly warranted, we hope that this work will provide some preliminary observational data to assist in the clinical practice of physicians involved in the care of children with these syndromes and with moyamoya.

Conclusions

Incidentally discovered asymptomatic moyamoya in children has the potential to progress, both radiographically and clinically. Once started, development of signs and symptoms referable to cerebral ischemia can present in rapid fashion, sometimes within months, with the potential for permanent deficits. These data support the practice of continued monitoring in at-risk syndromic populations and early referral to neurosurgeons once evidence of arteriopathy develops, and they provide additional justification to consider revascularization in asymptomatic patients with moyamoya.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Smith, Ullrich, Scott. Acquisition of data: Lin, Koss, Kopecky, Gone. Analysis and interpretation of data: Smith, Lin. Drafting the article: Smith. Critically revising the article: Smith, Baird. Reviewed submitted version of manuscript: Smith, Baird. Study supervision: Smith.

References

1. Calviere L, Catalaa I, Frugier CG, Viguier A, Albucher JF, Delisle MB, et al: [Clinical course and outcome in French adults with Moyamoya disease.] **Rev Neurol (Paris) 165:**709–717, 2009 (Fr)
2. Fujimura M, Mugikura S, Shimizu H, Tominaga T: Asymptomatic moyamoya disease subsequently manifesting as transient ischemic attack, intracerebral hemorrhage, and subarachnoid hemorrhage in a short period: case report. **Neurol Med Chir (Tokyo) 50:**316–319, 2010
3. Fujiwara H, Momoshima S, Kuribayashi S: Leptomeningeal high signal intensity (ivy sign) on fluid-attenuated inversion-recovery (FLAIR) MR images in moyamoya disease. **Eur J Radiol 55:**224–230, 2005
4. Fukui M: Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis ('moyamoya' disease). Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare, Japan. **Clin Neurol Neurosurg 99 (Suppl 2):**S238–S240, 1997
5. Fung LW, Thompson D, Ganesan V: Revascularisation surgery for paediatric moyamoya: a review of the literature. **Childs Nerv Syst 21:**358–364, 2005
6. Golby AJ, Marks MP, Thompson RC, Steinberg GK: Direct and combined revascularization in pediatric moyamoya disease. **Neurosurgery 45:**50–60, 1999
7. He Y, Zhou Q, He M: An asymptomatic Moyamoya disease: autopsy case and literature review. **Am J Forensic Med Pathol 31:**77–79, 2010
8. Jea A, Smith ER, Robertson R, Scott RM: Moyamoya syndrome associated with Down syndrome: outcome after surgical revascularization. **Pediatrics 116:**e694–e701, 2005
9. Kawai K, Kuroda S, Kawabori M, Nakayama N, Terasaka S, Iwasaki Y: [Revascularization surgery for asymptomatic adult moyamoya disease presenting silent disease progression: report of two cases.] **No Shinkei Geka 38:**825–830, 2010 (Jpn)
10. Kelly ME, Bell-Stephens TE, Marks MP, Do HM, Steinberg GK: Progression of unilateral moyamoya disease: a clinical series. **Cerebrovasc Dis 22:**109–115, 2006
11. Kuroda S, Hashimoto N, Yoshimoto T, Iwasaki Y: Radiological findings, clinical course, and outcome in asymptomatic moyamoya disease: results of multicenter survey in Japan. **Stroke 38:**1430–1435, 2007
12. Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y: Incidence and clinical features of disease progression in adult moyamoya disease. **Stroke 36:**2148–2153, 2005
13. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al: Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. **Stroke 39:**2644–2691, 2008
14. Robertson RL, Burrows PE, Barnes PD, Robson CD, Pous-

saint TY, Scott RM: Angiographic changes after pial synangiosis in childhood moyamoya disease. **AJNR Am J Neuroradiol 18:**837–845, 1997
15. Rosser TL, Vezina G, Packer RJ: Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. **Neurology 64:**553–555, 2005
16. Scott RM, Smith ER: Moyamoya disease and moyamoya syndrome. **N Engl J Med 360:**1226–1237, 2009
17. Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA: Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. **J Neurosurg 100 (2 Suppl Pediatrics):**142–149, 2004
18. Smith ER, McClain CD, Heeney M, Scott RM: Pial synangiosis in patients with moyamoya syndrome and sickle cell anemia: perioperative management and surgical outcome. **Neurosurg Focus 26(4):**E10, 2009
19. Smith ER, Scott RM: Progression of disease in unilateral moyamoya syndrome. **Neurosurg Focus 24(2):**E17, 2008
20. Smith ER, Scott RM: Surgical management of moyamoya syndrome. **Skull Base 15:**15–26, 2005
21. Soriano SG, Sethna NF, Scott RM: Anesthetic management of children with moyamoya syndrome. **Anesth Analg 77:**1066–1070, 1993
22. Ullrich NJ, Robertson R, Kinnamon DD, Scott RM, Kieran MW, Turner CD, et al: Moyamoya following cranial irradiation for primary brain tumors in children. **Neurology 68:**932–938, 2007
23. Yamada I, Suzuki S, Matsushima Y: Moyamoya disease: diagnostic accuracy of MRI. **Neuroradiology 37:**356–361, 1995
24. Yamada M, Fujii K, Fukui M: [Clinical features and outcomes in patients with asymptomatic moyamoya disease—from the results of nation-wide questionnaire survey.] **No Shinkei Geka 33:**337–342, 2005 (Jpn)

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Address correspondence to: Edward R. Smith, M.D., Department of Neurosurgery, Children's Hospital Boston, Hunnewell 2, 300 Longwood Avenue, Boston, Massachusetts 02115. email: edward.smith@childrens.harvard.edu.

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Clinical considerations in the management of asymptomatic carotid artery stenosis

Philipp Taussky, M.D.,[1,2] Ricardo A. Hanel, M.D., Ph.D.,[2] and Fredric B. Meyer, M.D.[1]

[1]Department of Neurosurgery, Mayo Clinic College of Medicine, Rochester, Minnesota; and [2]Department of Neurosurgery, Mayo Clinic, Jacksonville, Florida

Incidental findings pose considerable management dilemmas for the treating physician and psychological burden for the respective patient. With an aging population, more patients will be diagnosed with asymptomatic internal carotid artery stenosis. Patients will have to be counseled with regard to treatment options according to their individual risk profile and according to professionals' knowledge of evidence-based data derived from large randomized control trials. Treatment consensus has long been lacking for patients with asymptomatic carotid artery stenosis prior to any randomized controlled trials. Additionally, an individual's risk profile may be hard to assess according to knowledge gained from randomized controlled trials. Moreover, while earlier studies compared carotid endarterectomy and medical therapy, in the past years, a new therapeutic modality, carotid artery angioplasty and stenting, has emerged as a possible alternative. This has been evaluated in a recent randomized controlled trial, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which compared carotid endarterectomy with angioplasty and stenting in both symptomatic and asymptomatic patients. The following review summarizes current knowledge of the natural history, diagnosis, and treatment strategies to counsel patients with asymptomatic carotid artery stenosis. *(DOI: 10.3171/2011.9.FOCUS11222)*

Key Words • stroke • revascularization • carotid occlusive disease • evidence-based medicine

Since the advent of modern neuroradiological imaging, incidental findings have become common, with clinically significant findings present in about 2%–8% of patients undergoing MR imaging of the brain.[69] The management of these incidental findings poses considerable treatment dilemmas and psychological burden for the patient because there is no widespread agreement of treatment concepts.[66] Treatment dilemmas have traditionally been particularly pronounced in patients with incidental or asymptomatic cerebrovascular pathological entities.[66] This dilemma partly stems from the fact that, while most cerebrovascular pathological entities may cause catastrophic events, their proposed surgical treatment is not without important risks. The risk of treatment may further be accentuated in the mind of the patients because they are asymptomatic when the lesion is incidentally found and any intervention carries only a hypothetical benefit in the future.

Careful consideration of the natural history and possible benefit of various management options is particularly necessary in cases of asymptomatic carotid artery stenosis, for which treatment consensus has been lacking, prior to any randomized controlled trials.[50,51] Given that roughly 2 million Americans may be harboring an asymptomatic carotid artery stenosis, the optimum treatment is of considerable public health interest.[57] In the following review, we discuss the prevalence, natural history, progression rate, diagnostic modalities, and the results of randomized controlled trials highlighting our current understanding of the management of asymptomatic internal carotid artery stenosis.

Abbreviations used in this paper: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CREST = Carotid Revascularization Endarterectomy versus Stenting Trial.

Prevalence of Carotid Occlusive Disease

Carotid artery stenosis is one of the main causes of ischemic stroke, which remains a major public health issue with a high burden of disease in the US. To put the current epidemiology of stroke in perspective: stroke is the third leading cause of death in the US, with more than 143,579 people dying from strokes each year (http://www.strokecenter.org/patients/stats.htm). It is also the main cause of serious, long-term disability. Each year, about 795,000 people suffer a stroke. About 600,000 of these are first attacks and 185,000 are recurrent attacks.[57] About 15%–20% of these strokes are estimated to be the result of carotid

artery occlusive disease, with nearly 80% of these strokes occurring in asymptomatic patients without a history of stroke or transient ischemic attacks.[2,16]

The estimated prevalence of asymptomatic carotid artery stenosis varies significantly depending on the population studied. The overall prevalence of asymptomatic carotid artery stenosis ≥ 50% in the general population is estimated at 2%–9%.[47] A higher prevalence of 5%–9% is anticipated in patients older than 65 years of age, which is of public health relevance because it means that 1.3–2.4 million Americans in this age group are being affected by carotid artery occlusive disease (http://www.strokecenter.org/patients/stats.htm).[18,57] The prevalence is even higher in patients who harbor additional atherosclerotic lesions. An estimated 11%–26% of patients with coronary artery disease and 25%–49% with peripheral artery disease have asymptomatic carotid artery stenosis.[47] Table 1 summarizes the findings of some of the large studies assessing the prevalence of asymptomatic carotid artery stenosis in different populations.

A number of risk factors have been established for the development and presence of asymptomatic carotid artery stenosis.[7,13,31,47,58] Among these factors, age appears to be the most consistent. This may be due to a combination of factors, mostly inherent changes related to aging of the arterial wall but also prolonged exposure to risk factors with increasing age.[7,33] Male sex is another significant risk factor, with men exhibiting a 2-fold higher prevalence than women in some studies and with a gradual increase in both males and females with increasing age.[13,31,41] Large population-based studies in numerous countries have also established traditional modifiable cardiovascular risk factors, such as diabetes, hypertension, smoking, and dyslipidemia, as being consistently associated with carotid artery occlusive disease.[38,41,70]

Progression of Carotid Artery Occlusive Disease

The progression rate of asymptomatic carotid artery stenosis is important to the clinician because higher grades of stenosis are associated with a higher stroke risk, while the progression of carotid artery stenosis itself is a predictor of increased stroke risk.[48,60] Numerous studies have analyzed the rate and severity of carotid artery occlusive progression, but the results show considerable differences.[11,25,49] Table 2 summarizes the results of some of these studies.

In the first prospective study of its kind, Roederer and colleagues[62] performed follow Doppler/duplex ultrasonography in 167 patients with carotid bruits. Of these patients, 31% exhibited stenotic progression unilaterally and 7% exhibited progression bilaterally. After 3 years, disease in one-third of the patients progressed to carotid artery stenosis of ≥ 50% and 3 of 5 studied arteries progressed to a more severe category of stenosis.

In the largest prospective study, Muluk and coauthors[48] followed 1004 asymptomatic patients with serial duplex ultrasonography for a mean 28-month follow-up period at the Pittsburgh Veterans Administration Medical Center. Progression was defined as a minimum increase in internal carotid artery stenosis of 50%, with a baseline of less than 50%, or as an increase to a higher category of stenosis if the baseline stenosis was ≥ 50%. The authors found a substantial and steady increase of stenosis at an annualized risk of progression of 9.3%. A multivariate analysis identified 4 variables affecting progression: baseline ipsilateral internal carotid artery stenosis ≥ 50% (relative risk 3.34), baseline ipsilateral external carotid artery stenosis ≥ 50% (relative risk 1.51), baseline contralateral internal carotid artery stenosis ≥ 50% (relative risk 1.41), and systolic pressure > 160 mm Hg (relative risk 1.37). By the 7th year of follow-up, more than 50% of patients studied showed some degree of disease progression.[48]

Depending on the population studied, the rate of progression may even be higher. Liapsis and colleagues[37] showed a 15% progression rate in a large cohort of asymptomatic patients with a large prevalence of significant risk factors, including coronary artery disease. Cinà and colleagues[7] studied a Canadian cohort of asymptomatic patients with peripheral vascular disease. They found

TABLE 1: Selection of large studies reporting prevalence rates of asymptomatic carotid artery disease in different populations*

Authors & Year	Screening Population	No. of Pts	Age (yrs)†	Male/Female Ratio	Diagnostic Tool	% Stenosis	Prevalence	Risk Factors Identified
Hennerici et al., 1981	cardiovascular disease	2009	58	1647:362	Doppler	≥50	9.1%	peripheral vascular disease
Hennerici et al., 1987	vascular risk factors	3225	62	NS	Doppler	≥40	50–99: 7.5%; occlusion: 1.7%	
Ellis et al., 1992	peripheral vascular disease	1196	68	826:370	duplex	50–99	13.8%	
O'Leary et al., 1992	age >65 yrs	5116	NS	2210:2906	duplex	50–99	M 7.6%/F 5.1%; occlusion M 1.0%/F 0.6%	male, hypertension, smoking, CAD, wall thickness
Fine-Edelstein et al., 1994	general	1116	66–93	441:675	duplex	≥50	M 9%/F 7%	age, smoking, hypertension, hypercholesterolemia
Qureshi et al., 2001	general	1331	66	439:892	duplex	≥60	18%	age >65 yrs, smoking, CAD, hypercholesterolemia

* CAD = coronary artery disease; NS = not stated; Pts = patients.

† Age reflects the mean, except for the Fine-Edelstein et al. value, which represents the age range.

TABLE 2: Studies analyzing the percentage of carotid artery stenosis progression over time*

Authors & Year	% of CAS Progression	Time Period
Javid et al., 1970	22	1–9 yrs
Roederer et al., 1984	31	36 mos
Lewis et al., 1997	21.3	5.6 yrs
Olin et al., 1998	15.5	60 mos
Muluk et al., 1999	22.6	10 yrs
Liapis et al., 2000	18.6	10 yrs
Sabeti et al., 2007	5	6–9 mos
Hirt, 2011	5.2	≥5 yrs

* CAS = carotid artery stenosis.

progression from one class of stenosis to a more severe class in 15% of patients and progression from a lower degree of 50% to 99% stenosis in 6.5% of patients during a follow-up period of 6–9 months.

In summary, the risk of progression of an asymptomatic carotid artery stenosis increases with time and varies from 4% to 29% annually, mainly depending on the population studied. Numerous studies have addressed the question of predictors of stenotic progression to identify asymptomatic patients in need of regular follow-up and possible early intervention.[7,23,37,48] Carotid artery disease progression appears to be associated with diabetes, smoking, hypertension, and, in patients with more severe stenosis, heterogeneous plaque and contralateral disease.[6,11,37,48,60] Moreover, the severity of the stenosis is a risk factor for progression, with moderate stenosis being 5-fold more likely to progress than mild or no stenosis.[40,48]

Diagnostic Studies

Traditionally, asymptomatic carotid artery stenosis was identified on hearing a carotid bruit during physical examination or on carotid artery ultrasound screening. While carotid artery auscultation is a consistent part of a routine physical examination, its accuracy in detecting carotid artery stenosis depends on the severity of the stenosis. In a large cohort of 1486 patients in whom 1555 carotid artery investigations were performed, Johanson and Wester[32] demonstrated a sensitivity for carotid artery bruits of 55% for stenosis of 50%–69% and 77% sensitivity for stenosis of 70%–99%. Specificity was 52% for stenosis of 50%–69% and 71% sensitivity for stenosis of 70%–99%, as measured by carotid artery ultrasonography. Table 3 summarizes some of the medical statistical terms used here.

Ultrasonography has been the most commonly used diagnostic modality to screen for carotid artery stenosis because of the modality's noninvasive nature, lack of radiation exposure, and widespread availability. Its limitations in carotid artery stenosis include its association with the operator's skill, experience, and large interpersonal variability. Two meta-analyses examined the accuracy of ultrasonography to detect carotid artery stenosis. A meta-analysis by Nederkoorn and colleagues[54] included studies published from 1993 through 2001 and estimated the accuracy of carotid duplex ultrasonography using digital subtraction angiography as the reference standard. The authors found that carotid duplex ultrasonography had an estimated sensitivity of 86% and a specificity of 87% for detecting carotid artery stenosis of 70%–99%.[54] In a meta-analysis by Jahromi and colleagues,[29] the authors reported comparable results for sensitivity and specificity. Using their analysis, a sensitivity of 94% was estimated, as was a specificity of 92% for carotid artery stenosis of 60% or greater.[29,72] The reliability of carotid artery duplex ultrasonography, however, has significant limitations with important differences in the measurement properties applied by different ultrasound laboratories, which may result in clinically relevant differences.[29]

More commonly, with the advent of modern neuroimaging modalities, MR angiography and CT angiography have become common noninvasive screening tools. While similar in many aspects, MR angiography and CT

TABLE 3: Definition of commonly used statistical terms*

Statistical Term	Definition
sensitivity	the probability that the test says a person has the disease when in fact he/she does have the disease
specificity	the probability that the test says a person does not have the disease when in fact he/she is disease free
95% CI	indicates the range of values w/in which the value would fall 95% of the time if the researcher were to calculate the value from an infinite no. of samples of the same size, drawn from the same population
absolute risk	the probability that an individual will experience the specified outcome during a specified period; it lies in the range 0–1, or is expressed as a percentage
relative risk	the no. of times more likely (relative risk >1) or less likely (relative risk <1) an event is to happen in one group compared w/ another; the ratio of the risk in the treated group to the risk in the control group
absolute risk reduction	the absolute difference in risk btwn the treated & control groups in a trial; this value does not give any idea of the proportional reduction btwn the 2 groups: for this, relative risk reduction is needed
relative risk reduction	the proportional reduction in risk btwn treated & control participants in a trial; it is the percentage reduction in events in treated patients vs controls
hazard ratio	compares 2 treatments: if the hazard ratio is 2.0, then the rate of deaths in one treatment group is twice the rate in the other group

* CI = confidence interval.

angiography exhibit differences not only because CT angiography is radiation based and uses contrast cleared by the kidneys, but because these diagnostic options show different sensitivity and specificity profiles, which are summarized in Table 4.

Nederkoorn and colleagues[53] examined 203 consecutive patients in whom there was suspicion of carotid artery stenosis, using MR angiography and conventional angiography. The sensitivity and specificity of the MR angiography with projection that showed the maximal stenosis on angiography were 92.6% (95% CI, 85.3%–97.0%) and 82.7% (95% CI, 78.1%–87.3%), respectively. The mean difference between maximal stenosis on MR angiography and angiography was 7.5% (95% CI, 5.2%–9.9%).[53] A meta-analysis by the same research group showed a pooled sensitivity of 95% (95% CI, 92%–97%) and a pooled specificity of 90% (95% CI, 86%–93%) for stenosis of 70%–99%. For occlusions, MR angiography yielded a sensitivity of 98% (95% CI, 94%–100%) and a specificity of 100% (95% CI, 99%–100%).[54]

More recently, CT angiography has been introduced as a diagnostic tool to evaluate carotid artery stenosis. While it exposes the patient to radiation and iodine-based contrast medium, many clinicians prefer this modality because it is based on tomography scanning and thought to depict the pathoanatomical features more directly than MR angiography. Disadvantages include the possible overlap with bone and venous structures, as well as its inaccuracy in the presence of calcified plaque.[9] A recent systematic review analyzing CT angiography and standard angiography found a pooled sensitivity and specificity for detection of a 70%–99% stenosis were 85% (95% CI, 79%–89%) and 93% (95% CI, 89%–96%), respectively.[35] For detection of an occlusion, the sensitivity and specificity were 97% (95% CI, 93%–99%) and 99% (95% CI, 98%–100%), respectively.[35] This compares favorably with the sensitivity and specificity found in MR angiography.

The gold standard, against which all diagnostic modalities are compared, remains conventional angiography. The degree of carotid artery stenosis was determined by angiography in the ACAS, ECST (European Carotid Surgery Trial), and NASCET (North American Symptomatic Carotid Endarterectomy Trial), but most centers currently do not use angiography as a regular diagnostic tool. The main disadvantages of angiography are its invasiveness, associated costs, and infrastructural needs, as well as the reported 1.3% neurological complication rate.[71] As a result, cerebral angiography is used by most clinicians only in selected patients in whom noninvasive diagnostics were not conclusive, or when MR angiography cannot be performed due to claustrophobia or the presence of metal implants.

TABLE 4: Representation of sensitivity and specificity in the diagnosis of carotid occlusion expressed in percentage, as represented in the literature*

Extent of Stenosis/Diagnostic Modality	Sensitivity	Specificity
stenosis ≥70		
duplex	86	87
MRA	93	83
CTA	85	93
occlusion		
duplex	96	100
MRA	98	100
CTA	97	99

* Data were derived from studies by Koelemay et al., Nederkoorn and Brown, 2009, and Nederkoorn et al., 2003. Abbreviations: CTA = CT angiography; MRA = MR angiography.

Natural History

Several short- and long-term cohort studies have analyzed the natural history of asymptomatic carotid artery stenosis to define risk factors, or predictors, for stenosis progression by multiple linear regression analysis and also to evaluate stroke risk and predictors of stroke risk.[5,25,39,61] Depending on the population studied, most short-term follow-up studies report an annual risk of unheralded ipsilateral stroke of approximately 1%–3%; within this group, higher degrees of stenosis are associated with higher risks of stroke.[5,18,26,28,39] Conversely, some studies report higher stroke rates in patients with clinically manifest atherosclerotic disease: In the Dutch Smart Study, a large prospective cohort study, 2684 consecutive patients with clinical manifestations of arterial vascular disease or Type 2 diabetes mellitus were followed after undergoing baseline carotid artery ultrasonography.[18] Asymptomatic carotid artery stenosis of 50% or greater was present in 221 patients (8%). During a mean follow-up period of 3.6 years, a first vascular event occurred in 253 patients (9%). The cumulative incidence for the composite of subsequent vascular events after 5 years was 12.3% (95% CI, 10.7%–13.9%), for cerebral infarction 2.2% (95% CI, 1.4%–2.8%), and for myocardial infarction 8.0% (95% CI, 6.6%–9.4%). Adjusted for age and sex, asymptomatic carotid artery stenosis of 50% or greater was associated with a higher risk of subsequent vascular events (hazard ratio 1.5, 95% CI, 1.1%–2.1%).[18] Longer follow-up studies show 10- and 15-year risks of ipsilateral stroke to be 5.7% (95% CI, 0%–12%) and 8.7% (95% CI, 1%– 17%), respectively, in patients with 0%–49% stenosis, and 9.3% (95% CI, 1%–18%) and 16.6% (95% CI, 1%–32%), respectively, in patients with a stenosis of 50%–99%.[49]

Despite the clear association shown in these studies between asymptomatic carotid artery stenosis and stroke risk, our ability to predict stroke risk in any individual patient is limited.[47] While large cohort studies demonstrate a higher stroke risk with a higher degree of stenosis, and patients with classic cardiovascular risk factors are at a higher risk of experiencing cerebrovascular events, individualized data remain difficult to obtain because of the multifactorial etiology of ischemic events.[18,28,49] Uncertainty in interpreting the current data in an individualized fashion stems, in part, from the following factors. Inzitari and colleagues[28] showed that, while the stroke risk increases with a higher degree of stenosis, it actually decreases again in asymptomatic patients whose stenosis is between 94% and 99%. Moreover, in the same study, approximately 80% of the first strokes were not heralded by a prior transient ischemic attack. A large number of

actual cerebral ischemic events may have been unrelated to the carotid artery stenosis and were of a cardioembolic nature or related to lacunar infarcts, further complicating any true risk assessment.[28] A complex interaction of both patient factors and lesion factors turn an asymptomatic stenosis into a symptomatic one, but these factors are poorly understood.[47]

Treatment Evidence

Finally, the question needs to be addressed of whether patients with asymptomatic carotid artery stenosis benefit from any particular treatment option. Historically, studies on this issue compared maximal medical management and carotid endarterectomy. Later studies compared these treatment modalities with carotid artery angioplasty and stenting.[57]

The earliest studies analyzing the role of surgery in asymptomatic carotid artery disease was provided by the CASANOVA trial (Carotid Artery Stenosis with Asymptomatic Narrowing Operation Versus Aspirin)[4] and the MACE trial (Mayo Asymptomatic Carotid Endarterectomy).[44,45] These studies have been regarded as suboptimal.[14] The MACE trial was prematurely stopped after enrollment of only 71 patients due to a high rate of myocardial infarction (22%) in the surgical group. This may have been a direct result of the trial policy of withholding aspirin from the surgical group. For the CASANOVA study, a total of 410 patients with 50%–90% stenosis were enrolled. A total of 17% of the surgical patients never underwent a carotid endarterectomy, and in 20% of the medical patients, a unilateral or bilateral carotid endarterectomy was performed. This high rate of crossovers made the final interpretation of this study problematic.

The Veterans Affairs Trial included 444 asymptomatic men with angiographically demonstrated stenosis of 50%–99%; the patients were randomly assigned to 1 of 2 groups: the best medical management or the best medical management with carotid endarterectomy. The primary end points after 48 months were incidence of transient ischemic attack, transient monocular blindness, and stroke. The combined incidence of ipsilateral neurological events was 8.0% in the surgical group and 20.6% in the medical group ($p < 0.001$), given a relative risk of 0.38 (95% CI, 0.22–0.67) for the surgical group compared with the medical group.[42] The incidence of ipsilateral stroke alone was 4.7% in the surgical group and 9.4% in the medical group. An analysis of stroke and death combined within the first 30 postoperative days showed no significant differences between groups in terms of all strokes and deaths (surgical group 41.2%, medical group 44.2%; relative risk 0.92; 95% CI, 0.69–1.22).[24] Overall mortality, including postoperative deaths, was primarily due to coronary artery disease.

The ACAS is considered the first modern well-designed and conducted study to examine the role of carotid endarterectomy in asymptomatic patients for stroke prevention.[12] Its results were reported in 1995. A total of 1662 patients with asymptomatic carotid artery stenosis of 60% were randomized to either medical management alone or medical management with carotid endarterectomy. The study was halted by the Data Safety and Monitoring Board 2.7 years after it began because of a projected 5.9% absolute risk reduction at 5 years favoring carotid endarterectomy. The 5-year projected rate of ipsilateral stroke was 11.0% for the medically treated patients and 5.1% for the surgically treated patients. This translated into a 47% relative risk reduction of stroke or perioperative death in the surgical group. The perioperative stroke rate was 2.3%, which is lower than that in more contemporary studies and is most probably due to accepting only surgeons with an excellent safety record. The ACAS calculated that 17 carotid endarterectomies need to be performed to prevent 1 stroke, but a 1000 endarterectomies need to be performed to prevent 59 strokes by 5 years.[50]

At the time of its publication, ACAS was the largest and methodologically best study of its kind. However, the study also produced some controversial findings.[50,57] Its results provided no evidence that the incidence of disabling stroke was reduced. Reduction seemed to be only in nondisabling stroke, although this may have been a chance finding.[50] While men benefited significantly from surgery at 5 years (absolute risk reduction 8%, relative risk reduction 66%), women derived no advantage (absolute risk reduction 1.4% at 5 years, relative risk reduction 17%).[50] Another controversial issue was there appeared to be no association between stenosis severity and long-term stroke risk.

Many of these uncertainties could be settled once the results of the ACST were published.[20] The ACST enrolled 3120 patients with greater than 60% stenosis documented on ultrasonography and assigned groups to immediate carotid endarterectomy (88% by the 1st year) or indefinite deferral of carotid endarterectomy with a 5-year follow-up at 1 of 126 centers in 30 countries. Eligibility included carotid artery diameter reduction of at least 60% on ultrasound and no symptoms within the last 6 months. Enrollment began in 1993 and continued until 2003. A total of 3120 patients were randomized (1560 in each group). The study included 2044 men and 1076 women. Combining the perioperative events (stroke and death within 30 days) and the non-perioperative strokes, the net 5-year risks were 6.4% (immediate carotid endarterectomy) compared with 11.8% (deferred carotid endarterectomy) for all strokes ($p < 0.0001$) and 3.5% compared with 6.1% for fatal or disabling strokes ($p = 0.004$). Subgroup analyses demonstrated significant benefits for patients younger than 65 years and those between 65 and 74 years, but uncertain benefits for those older than 75 years. Both men and women benefited from carotid endarterectomy. The 5-year benefit of carotid endarterectomy appeared to be as great for those with about 70%, 80%, and 90% carotid artery stenosis on ultrasonography. The results showed no significant difference in patients who were never symptomatic (7.1% absolute 5-year gain) compared with those with symptoms greater than in the previous 6 months (4.6% absolute 5-year gain). And finally, surgery was performed very safely with a low operative risk of 2.8%.[20]

With ACST largely supporting and extending the results of ACAS, there now exists Level I evidence demonstrating a net benefit of surgery for asymptomatic patients with stenosis ≥ 60% in reducing disabling or fatal strokes.[63]

Even with the advent of endovascular techniques, carotid artery angioplasty and stenting has been considered an alternative to carotid endarterectomy in both studies of symptomatic and asymptomatic patients.[3,10] Thus, with the established benefit in stroke reduction for asymptomatic patients, questions were raised with regard to optimal treatment. While the first large modern study in which carotid endarterectomy was compared with carotid angioplasty and stenting, the ICSS study (International Carotid Stenting Study), included only symptomatic patients; the later CREST enrolled both symptomatic and asymptomatic patients.[3,10]

The CREST study enrolled 2502 patients at 117 centers in the US and Canada. The trial included 1321 symptomatic and 1181 asymptomatic patients who were randomized to undergo either stenting with the same stent and distal protection devices (Acculink and Accunet devices) or carotid endarterectomy. Inclusion criteria were as follows: patients with symptomatic stenosis had 50% or greater stenosis documented by angiography, 70% or greater by ultrasonography, or 70% or greater by CT or MR angiography. In asymptomatic patients lesions were identified by angiography (≥ 60%), ultrasonography (≥ 70%), or CT/MR angiography (≥ 80%). The primary end point for the study was any periprocedural stroke, myocardial infarction, death, or postprocedural ipsilateral stroke up to 4 years after intervention. A rigorous training and credentialing process for interventionalists was required prior to participation.[27] In short, there was no significant difference in the rates of the primary end points between carotid angioplasty with stenting and carotid endarterectomy (7.2% vs 6.8%, respectively; hazard ratio with stenting 1.11; p = 0.51) at a mean follow-up of 2.5 years.[3] No modification of a treatment effect was detected with respect to symptomatic status or sex, but an interaction with age was established (p = 0.02). Surprisingly, outcomes were slightly better with carotid artery stenting in patients aged younger than 70 years, with greater benefit the younger the patient; outcomes were also better with endarterectomy in patients older than 70 years of age, with an increase in age demonstrating an increase in benefit. Overall, the periprocedural (30-day incidence) end point did not differ for carotid artery stenting and endarterectomy, but there were statistically significant differences in the components for stent- and endarterectomy-treated patients (stroke 4.1% vs 2.3%, respectively [p = 0.012], and myocardial infarction 1.1% vs 2.3%, respectively [p = 0.032]). The CREST showed endarterectomy to be superior to carotid angioplasty and stenting with respect to the outcomes of ischemic stroke, perioperative stroke, or death in both asymptomatic and symptomatic patients. However, addressing the primary end point of any stroke, myocardial infarction, or death up to 4 years after intervention, both procedures proved equal.[3]

The inclusion of asymptomatic myocardial infarction as a primary end point in CREST has been criticized by a number of commentators.[1] The clinical relevance of including silent cardiac events is questionable because results from the SF-36 (36-Item Short Form Health Survey) in CREST showed no adverse effects on the quality of life as a result of cardiac events, whereas the occurrence of a stroke significantly affected the patient's quality of life in a negative manner. Without inclusion of asymptomatic cardiac ischemia in CREST as a primary end point, endarterectomy would be a safer procedure because of a greater incidence of perioperative strokes and death in the angioplasty and stenting group. This difference is still significant at 4 years.[1,8] A post hoc analysis of outcome and safety according to patients' symptomatic status included an analysis of 1181 asymptomatic patients. For these asymptomatic patients, the stroke and mortality rates were 2.5% and 0.6% for carotid artery stenosis and 1.4% and 0.5% for carotid endarterectomy (hazard ratio, 1.88; 95% CI, 0.79–4.42; p = 0.15).[65]

Individualized Decision-Making Strategies

The assessment of an individual patient's risk based on our knowledge from large randomized controlled trials remains challenging. An individual's risk profile depends on many factors and may not be easily interpolated from clinical trials because of differences in the individual's clinical factors or anatomical characteristics. While both carotid endarterectomy and carotid artery stenting have been proven to be safe and effective treatment options in the context of asymptomatic carotid artery stenosis, a number of different patients' characteristics need to be considered when choosing the optimal treatment modality for any single patient. Table 5 summarizes the clinical and anatomical features favoring either endarterectomy or stenting.

Discussion and Outlook Into the Future

With increasing prevalence due to an aging population, asymptomatic carotid artery stenosis is a significant

TABLE 5: Clinical and anatomical factors influencing decision making for either carotid endarterectomy or carotid stenting*

Factor	Favoring Endarterectomy	Favoring Stenting
age >69 yrs	X	
female sex	X	
severe plaque calcification	X	
severe common or internal carotid artery tortuosity	X	
cardiac disease (CHF, CAD)		X
kidney disease	X	
complex aortic arch	X	
carotid bifurcation above C-2		X
tandem stenosis		X
contralat laryngeal palsy		X
contralat carotid occlusion		X
prior radiotherapy		X
prior neck op		X
prior endarterectomy		X

* CHF = congestive heart failure.

cause of stroke morbidity and mortality;[17] prevention and treatment remain major public health concerns. Although large randomized controlled trials on carotid endarterectomy for symptomatic patients have provided impressive results in terms of stroke risk reduction, uncertainties about the optimum treatment of asymptomatic patients persist.[34,46,67] These uncertainties are mainly related to a lack of data on prevalence, progression rates, and the natural history of patients suffering from asymptomatic carotid artery stenosis.[43] In the meantime, 2 large randomized controlled trials, ACAS and ACST, with a combined population of 4782, established a net benefit of carotid endarterectomy for asymptomatic patients with a stenosis exceeding 60%. Moreover, surgery was shown to be safe, with a perioperative neurological complication rate of less than 3%.[12,20] In a recent 10-year update on the findings of the ACST, Halliday and colleagues[19] reported a sustained benefit with carotid endarterectomy in stroke risk reduction. Half of this reduction has been in disabling or fatal strokes.

Clearly, the treatment benefit for any patient diagnosed with an asymptomatic carotid artery stenosis needs to be weighed against the natural history of the disease and treatment risks. Determination of any patient's individual risk for future cerebrovascular events is an equivocal task. Ideally, stroke risks and best treatment options may be predicted and individualized according to a number of different factors evaluating a patient's individual risk profile. Such factors may include an analysis of plaque characteristics and plaque instability, fludeoxyglucose-based PET scanning of brain metabolism, and transcranial Doppler monitoring of high-intensity transient signals.[68] Indeed, some researchers have hypothesized that in the future, 3 subgroups of patients will benefit from surgical interventions: patients with plaque instability; patients with insufficient collateral circulation demonstrated on transcranial Doppler ultrasonography and/or MR angiography; and patients with severe metabolic compromise, characterized by increased oxygen-extraction fraction on PET.[61] Other patients may best be treated by medical management. While improvements in medical management may change the future risk profile, the outcome impact remains to be seen. In fact, in the 10-year follow-up study of ACST, 80% of patients received aggressive modern medical management, including lipid-lowering medications. Carotid endarterectomy, however, reduced the stroke risk by about one-third of patients. By 10 years, the overall risk of stroke (including perioperative events) was 13.4% for those undergoing early operation compared with 17.9% with delayed or no carotid endarterectomy.[19] Currently, carotid endarterectomy remains the gold standard for asymptomatic patients with an incidental asymptomatic carotid artery stenosis of 60% or greater.

Disclosure

Dr. Hanel is a consultant for Neurovasx.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Taussky. Analysis and interpretation of data: Taussky. Drafting the article: Taussky, Hanel. Critically revising the article: all authors. Reviewed submitted version of manuscript: Taussky.

References

1. Amarenco P, Labreuche J, Mazighi M: Lessons from carotid endarterectomy and stenting trials. **Lancet 376:**1028–1031, 2010
2. Bogousslavsky J, Van Melle G, Regli F: The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. **Stroke 19:**1083–1092, 1988
3. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, et al: Stenting versus endarterectomy for treatment of carotid-artery stenosis. **N Engl J Med 363:**11–23, 2010
4. CASANOVA Study Group: Carotid surgery versus medical therapy in asymptomatic carotid stenosis. **Stroke 22:**1229–1235, 1991
5. Chambers BR, Norris JW: Outcome in patients with asymptomatic neck bruits. **N Engl J Med 315:**860–865, 1986
6. Cina CS, Clase CM, Haynes RB: Carotid endarterectomy for symptomatic carotid stenosis. **Cochrane Database Syst Rev (2):**CD001081, 2000
7. Cinà CS, Safar HA, Maggisano R, Bailey R, Clase CM: Prevalence and progression of internal carotid artery stenosis in patients with peripheral arterial occlusive disease. **J Vasc Surg 36:**75–82, 2002
8. Davis SM, Donnan GA: Carotid-artery stenting in stroke prevention. **N Engl J Med 363:**80–82, 2010
9. Dodick DW, Meissner I, Meyer FB, Cloft HJ: Evaluation and management of asymptomatic carotid artery stenosis. **Mayo Clin Proc 79:**937–944, 2004
10. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, et al: Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. **Lancet 375:**985–997, 2010 (Erratum in **Lancet 376:**90, 2010)
11. Ellis MR, Franks PJ, Cuming R, Powell JT, Greenhalgh RM: Prevalence, progression and natural history of asymptomatic carotid stenosis: is there a place for carotid endarterectomy? **Eur J Vasc Surg 6:**172–177, 1992
12. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study: Endarterectomy for asymptomatic carotid artery stenosis. **JAMA 273:**1421–1428, 1995
13. Fabris F, Zanocchi M, Bo M, Fonte G, Poli L, Bergoglio I, et al: Carotid plaque, aging, and risk factors. A study of 457 subjects. **Stroke 25:**1133–1140, 1994
14. Fazel P, Johnson K: Current role of medical treatment and invasive management in carotid atherosclerotic disease. **Proc (Bayl Univ Med Cent) 21:**133–138, 2008
15. Fine-Edelstein JS, Wolf PA, O'Leary DH, Poehlman H, Belanger AJ, Kase CS, et al: Precursors of extracranial carotid atherosclerosis in the Framingham Study. **Neurology 44:**1046–1050, 1994
16. Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB: The Stroke Data Bank: design, methods, and baseline characteristics. **Stroke 19:**547–554, 1988
17. Goessens BM, Visseren FL, Algra A, Banga JD, van der Graaf Y: Screening for asymptomatic cardiovascular disease with noninvasive imaging in patients at high-risk and low-risk according to the European Guidelines on Cardiovascular Disease Prevention: the SMART study. **J Vasc Surg 43:**525–532, 2006
18. Goessens BM, Visseren FL, Kappelle LJ, Algra A, van der Graaf Y: Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. **Stroke 38:**1470–1475, 2007
19. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al: 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. **Lancet 376:**1074–1084, 2010
20. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al: Prevention of disabling and fatal strokes by successful

carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. **Lancet 363:**1491–1502, 2004
21. Hennerici M, Aulich A, Sandmann W, Freund HJ: Incidence of asymptomatic extracranial arterial disease. **Stroke 12:**750–758, 1981
22. Hennerici M, Hülsbömer HB, Hefter H, Lammerts D, Rautenberg W: Natural history of asymptomatic extracranial arterial disease. Results of a long-term prospective study. **Brain 110:** 777–791, 1987
23. Hirt LS: Progression rate and ipsilateral neurological events in asymptomatic carotid stenosis. **Stroke** [epub ahead of print], 2011
24. Hobson RW II, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, et al: Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. **N Engl J Med 328:**221–227, 1993
25. Hollander M, Hak AE, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, et al: Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. **Stroke 34:** 2367–2372, 2003
26. Hollander M, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, Breteler MM: Incidence, risk, and case fatality of first ever stroke in the elderly population. The Rotterdam Study. **J Neurol Neurosurg Psychiatry 74:**317–321, 2003
27. Hopkins LN, Roubin GS, Chakhtoura EY, Gray WA, Ferguson RD, Katzen BT, et al: The Carotid Revascularization Endarterectomy versus Stenting Trial: credentialing of interventionalists and final results of lead-in phase. **J Stroke Cerebrovasc Dis 19:**153–162, 2010
28. Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, et al: The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. **N Engl J Med 342:**1693–1700, 2000
29. Jahromi AS, Cinà CS, Liu Y, Clase CM: Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid artery stenosis: a systematic review and meta-analysis. **J Vasc Surg 41:**962–972, 2005
30. Javid H, Ostermiller WE Jr, Hengesh JW, Dye WS, Najafi H, Julian OC: Natural history of carotid bifurcation atheroma. **Surgery 67:**80–86, 1970
31. Joakimsen O, Bonaa KH, Stensland-Bugge E, Jacobsen BK: Age and sex differences in the distribution and ultrasound morphology of carotid atherosclerosis: the Tromsø Study. **Arterioscler Thromb Vasc Biol 19:**3007–3013, 1999
32. Johansson EP, Wester P: Carotid bruits as predictor for carotid stenoses detected by ultrasonography: an observational study. **BMC Neurol 8:**23, 2008
33. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al: Prevalence of conventional risk factors in patients with coronary heart disease. **JAMA 290:**898–904, 2003
34. Kita MW: Carotid endarterectomy in symptomatic carotid stenosis: NASCET comparative results at 30 months of follow-up. **J Insur Med 24:**42–46, 1992
35. Koelemay MJ, Nederkoorn PJ, Reitsma JB, Majoie CB: Systematic review of computed tomographic angiography for assessment of carotid artery disease. **Stroke 35:**2306–2312, 2004
36. Lewis RF, Abrahamowicz M, Côté R, Battista RN: Predictive power of duplex ultrasonography in asymptomatic carotid disease. **Ann Intern Med 127:**13–20, 1997
37. Liapis C, Kakisis J, Papavassiliou V, Ntanou A, Kontopoulou S, Kaperonis E, et al: Internal carotid artery stenosis: rate of progression. **Eur J Vasc Endovasc Surg 19:**111–117, 2000
38. Mannami T, Konishi M, Baba S, Nishi N, Terao A: Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. **Stroke 28:**518–525, 1997
39. Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR: Short-term predictors of incident stroke in older adults. The Cardiovascular Health Study. **Stroke 27:**1479–1486, 1996
40. Martin-Conejero A, Reina-Gutierrez T, Serrano-Hernando FJ, Sanchez-Hervas L, Blanco-Cañibano E, Ponce-Cano AI, et al: Disease progression in the contralateral carotid artery after endarterectomy. **Ann Vasc Surg 19:**662–668, 2005
41. Mathiesen EB, Joakimsen O, Bønaa KH: Prevalence of and risk factors associated with carotid artery stenosis: the Tromsø Study. **Cerebrovasc Dis 12:**44–51, 2001
42. Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, et al: Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. **JAMA 266:**3289–3294, 1991
43. Mayberg MR, Winn HR: Endarterectomy for asymptomatic carotid artery stenosis. Resolving the controversy. **JAMA 273:** 1459–1461, 1995
44. Mayo Asymptomatic Carotid Endarterectomy Study Group: Effectiveness of carotid endarterectomy for asymptomatic carotid stenosis: design of a clinical trial. **Mayo Clin Proc 64:** 897–904, 1989
45. Mayo Asymptomatic Carotid Endarterectomy Study Group: Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. **Mayo Clin Proc 67:**513–518, 1992
46. Moneta GL, Edwards JM, Chitwood RW, Taylor LM Jr, Lee RW, Cummings CA, et al: Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. **J Vasc Surg 17:**152–159, 1993
47. Moussa ID, Rundek T, Mohr JP: **Asymptomatic Carotid Artery Stenosis: Risk Stratification and Management.** London: Informa Healthcare, 2007
48. Muluk SC, Muluk VS, Sugimoto H, Rhee RY, Trachtenberg J, Steed DL, et al: Progression of asymptomatic carotid stenosis: a natural history study in 1004 patients. **J Vasc Surg 29:** 208–216, 1999
49. Nadareishvili ZG, Rothwell PM, Beletsky V, Pagniello A, Norris JW: Long-term risk of stroke and other vascular events in patients with asymptomatic carotid artery stenosis. **Arch Neurol 59:**1162–1166, 2002
50. Naylor AR: The Asymptomatic Carotid Surgery Trial: bigger study, better evidence. **Br J Surg 91:**787–789, 2004
51. Naylor AR: Interventions for carotid artery disease: time to confront some 'inconvenient truths.' **Expert Rev Cardiovasc Ther 5:**1053–1063, 2007
52. Nederkoorn PJ, Brown MM: Optimal cut-off criteria for duplex ultrasound for the diagnosis of restenosis in stented carotid arteries: review and protocol for a diagnostic study. **BMC Neurol 9:**36, 2009
53. Nederkoorn PJ, Elgersma OE, Mali WP, Eikelboom BC, Kappelle LJ, van der Graaf Y: Overestimation of carotid artery stenosis with magnetic resonance angiography compared with digital subtraction angiography. **J Vasc Surg 36:**806–813, 2002
54. Nederkoorn PJ, van der Graaf Y, Hunink MG: Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: a systematic review. **Stroke 34:**1324–1332, 2003
55. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK Jr, et al: Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. **Stroke 23:**1752–1760, 1992
56. Olin JW, Fonseca C, Childs MB, Piedmonte MR, Hertzer NR, Young JR: The natural history of asymptomatic moderate internal carotid artery stenosis by duplex ultrasound. **Vasc Med 3:**101–108, 1998
57. Perkins WJ, Lanzino G, Brott TG: Carotid stenting vs endar-

terectomy: new results in perspective. **Mayo Clin Proc 85:** 1101–1108, 2010
58. Prati P, Vanuzzo D, Casaroli M, Di Chiara A, De Biasi F, Feruglio GA, et al: Prevalence and determinants of carotid atherosclerosis in a general population. **Stroke 23:**1705–1711, 1992
59. Qureshi AI, Janardhan V, Bennett SE, Luft AR, Hopkins LN, Guterman LR: Who should be screened for asymptomatic carotid artery stenosis? Experience from the Western New York Stroke Screening Program. **J Neuroimaging 11:**105–111, 2001
60. Raman KG, Layne S, Makaroun MS, Kelley ME, Rhee RY, Tzeng E, et al: Disease progression in contralateral carotid artery is common after endarterectomy. **J Vasc Surg 39:**52–57, 2004
61. Rijbroek A, Wisselink W, Vriens EM, Barkhof F, Lammertsma AA, Rauwerda JA: Asymptomatic carotid artery stenosis: past, present and future. How to improve patient selection? **Eur Neurol 56:**139–154, 2006
62. Roederer GO, Langlois YE, Lusiani L, Jäger KA, Primozich JF, Lawrence RJ, et al: Natural history of carotid artery disease on the side contralateral to endarterectomy. **J Vasc Surg 1:**62–72, 1984
63. Rothwell PM, Goldstein LB: Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. **Stroke 35:**2425–2427, 2004
64. Sabeti S, Schlager O, Exner M, Mlekusch W, Amighi J, Dick P, et al: Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. **Stroke 38:**2887–2894, 2007
65. Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al: Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). **Stroke 42:**675–680, 2011
66. Steiger HJ: Preventive neurosurgery: population-wide check-up examinations and correction of asymptomatic pathologies of the nervous system. **Acta Neurochir (Wien) 148:**1075–1083, 2006
67. Strandness DE Jr: Carotid endarterectomy: current status, and effects of clinical trials. **Cardiovasc Surg 1:**311–316, 1993
68. U-King-Im JM, Young V, Gillard JH: Carotid-artery imaging in the diagnosis and management of patients at risk of stroke. **Lancet Neurol 8:**569–580, 2009
69. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al: Incidental findings on brain MRI in the general population. **N Engl J Med 357:**1821–1828, 2007
70. Willeit J, Kiechl S: Prevalence and risk factors of asymptomatic extracranial carotid artery atherosclerosis. A population-based study. **Arterioscler Thromb 13:**661–668, 1993
71. Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera W: Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. **Radiology 227:**522–528, 2003
72. Wolff T, Guirguis-Blake J, Miller T, Gillespie M, Harris R: Screening for carotid artery stenosis: an update of the evidence for the U.S. Preventive Services Task Force. **Ann Intern Med 147:**860–870, 2007

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Address correspondence to: Fredric B. Meyer, M.D., Department of Neurosurgery, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. email: meyer.fredric@mayo.edu.

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Spinal injury patterns among skiers and snowboarders

Molly E. Hubbard, B.S.,[1] Ryan P. Jewell, M.D.,[2] Travis M. Dumont, M.D.,[2] and Anand I. Rughani, M.D.[2]

[1]College of Medicine, and [2]Division of Neurosurgery, University of Vermont, Burlington, Vermont

Object. Skiing and snowboarding injuries have increased with the popularity of these sports. Spinal cord injuries (SCIs) are a rare but serious event, and a major cause of morbidity and mortality for skiers and snowboarders. The purpose of this study is to characterize the patterns of SCI in skiers and snowboarders.

Methods. The authors queried the Nationwide Inpatient Sample for the years 2000–2008 for all patients admitted with skiing or snowboarding as the mechanism of injury, yielding a total of 8634 patients. The injury patterns were characterized by the ICD-9 diagnostic and procedure codes. The codes were searched for those pertaining to vertebral and skull fracture; spinal cord, chest, abdominal, pelvic, and vessel injuries; and fractures and dislocations of the upper and lower extremity. Statistical analysis was performed with ANOVA and Student t-test.

Results. Patients were predominantly male (71%) skiers (61%), with the average age of the skiers being older than that of snowboarders (39.5 vs 23.5 years). The average length of stay for patients suffering from spine trauma was 3.8 days and was increased to 8.9 days in those with SCI. Among hospitalized patients, SCI was seen in 0.98% of individuals and was equally likely to occur in snowboarders and skiers (1.07% vs 0.93%, $p < 0.509$). Cervical spine trauma was associated with the highest likelihood of SCI (19.6% vs. 10.9% of thoracic and 6% of lumbar injuries, $p < 0.0001$). Patients who were injured skiing were more likely to sustain a cervical spine injury, whereas those injured snowboarding had higher frequencies of injury to the lumbar spine. The most common injury seen in tandem with spine injury was closed head injury, and it was seen in 13.4% of patients. Conversely, a spine injury was seen in 12.9% of patients with a head injury. Isolated spine fractures were seen in 4.6% of patients.

Conclusions. Skiers and snowboarders evaluated at the hospital are equally likely to sustain spine injuries. Additionally, participants in both sports have an increased incidence of SCI with cervical spine trauma.
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Key Words • **epidemiological study** • **skiing** • **snowboarding** • **spine injury**

Skiing and snowboarding are commonly enjoyed as winter sports and are growing in popularity, which has coincided with an increase in injuries in both sports.[2] With injury rates ranging from 2 to 6 per 1000 days of skiing or snowboarding, both sports are considered to be fairly safe. Despite the low incidence, there tends to be high morbidity associated with these injuries, because they typically occur at high speeds. Accidents involving collision with trees or other obstacles are the most common causes of injury and death seen in skiers,[7,11] whereas intentional jumping over obstacles higher than 2 m is consistently reported as the most frequent cause of injury in snowboarders.[1,13] Most injuries in skiers occur in the lower extremities, most commonly as a tibial fracture or anterior cruciate ligament strain.[2,7,13] Snowboarding accidents lead to fewer lower-extremity injuries, but to more wrist fractures and a higher incidence of splenic injuries.[1]

Although SCIs are a relatively rare event,[12] they result in significant morbidity and mortality when they do occur. One study suggested that snowboarders had a higher risk of spine injuries.[1] The inherent differences in skiing and snowboarding, such as stance, preferred terrain, and maximum speeds attained, probably account for the differences in severity and patterns of injury. A later study suggests that the risk of SCI is approximately equal in both skiers and snowboarders.[12]

In the present study, the NIS was used to attain a large study population, and our investigation aimed to describe SCI patterns in those who suffer a vertebral column fracture while skiing or snowboarding. This study is a descriptive analysis of spinal column injuries and SCIs seen in skiers and snowboarders who sustained trauma requiring hospital evaluation.

Methods

The NIS was obtained from the Agency for Healthcare Research and Quality for the years 2000–2008. The NIS represents the largest database of hospital admissions

Abbreviations used in this paper: NIS = Nationwide Inpatient Sample; SCI = spinal cord injury; SCIWORA = SCI without radiographic abnormality.

in the US, includes all payers, and with approximately 8 million entries per year, it accounts for a stratified sample of approximately 20% of all inpatient admissions. For the year 2008, the NIS contains data obtained from 1056 hospitals in 42 states. The authors queried the NIS for the years 2000–2008 for all patients admitted with skiing or snowboarding as the mechanism of injury, yielding a total of 8634 patients. Patient sex, age, in-hospital death, and the day of the week and month of injury were recorded. The injury patterns were characterized using the ICD-9 diagnostic and procedure codes. The codes were searched for those pertaining to vertebral and skull fracture; spinal cord, chest, abdominal, pelvic, and vessel injuries; and fractures and dislocations of the upper and lower extremity. Procedure codes for fusion of any vertebral level, laminectomy, or any surgical spine repair were extracted from the sample set (Table 1). The length of stay, need for repeat surgery, and presence of thromboembolic complication were assessed for each patient. Statistical software (SPSS, Inc.) was used to search the database for each of the above-mentioned codes. Statistical analysis was completed using the Fisher exact, chi-square, ANOVA, and Student t-tests in GraphPad Prism (GraphPad Software, Inc.).

Results

Patient Demographic Data

Patients were predominantly male (71%) skiers (61%), with the average age of the skiers being older than that of snowboarders (39.5 vs 23.5 years). Nine (25%) of 36 snowboarders with an SCI were younger than 18 years of age, compared with 9 (18.3%) of 49 skiers (Table 2). The

TABLE 1: List of ICD-9 codes queried for injuries, procedures, and complications related to ski and snowboard accidents

Description of Injury	ICD-9 Injury Codes
cause of injury	
fall from skis	E885.3
fall from snowboard	E885.4
closed head injury	
concussion, contusion, intracranial bleed	850–854
skull fracture	
skull vault	800
skull base	801
facial fracture	802
other skull fracture	803, 804
nervous system injury	
SCI	806
cranial nerve injury	950, 951
peripheral nerve injury	955, 956
SCIWORA	952
spine fracture	
cervical vertebrae/dislocation	805.0, 805.1, 806.0, 806.1, 839.0, 839.1
thoracic vertebrae/dislocation	805.2, 805.3, 806.2, 806.3, 839.21, 839.31
lumbar vertebrae/dislocation	805.4, 805.5, 806.4, 805.5, 839.20, 839.30
sacral	805.6, 805.7, 806.6, 806.7
pelvic fracture	
anywhere in pelvis	808
limb injury	
upper extremity	810–819, 880–887, 840–842
lower extremity	820–829, 890–897, 843–846
dislocations	830–838
chest injury	
internal chest injuries	860–862
rib fracture	807
abdominal injury	
internal injuries	863–868
vessel injury	
carotid artery	900

TABLE 2: Demographic data for patients with ski and snowboard injuries obtained from the NIS

Characteristic	No. (%)		
	Total	Skiers	Snowboarders
no. of patients	8634 (100)	5277 (61)	3357 (39)
sex			
M	6096 (71)	3423 (65)	2673 (80)
F	2538 (29)	1854 (35)	684 (20)
average age in yrs	33.3	39.5	23.5
range	2–99	2–99	2–97
no. of injuries			
vertebral	510 (5.9)	433 (8.2)	77 (2.3)
SCI	85 (0.98)	49 (0.93)	36 (1.07)

majority of injuries occurred in February, followed by March and January (23.1%, 21.8%, and 21.2%, respectively; $p < 0.002$). Among hospitalized patients, SCI was seen in 0.98% of the patient sample and was equally prevalent in snowboarders and skiers treated in the hospital (1.07% vs 0.93%; $p < 0.509$ [not significant]). Of the subset of patients who suffered an SCI, 57.6% were injured while skiing and 42.4% were injured while snowboarding.

Surgical Intervention

Isolated spine injuries were seen in 4.6% of patients. Skiers had higher rates of fracture or dislocation in the cervical spine, followed by thoracic and lumbar spine (3%, 2.7%, and 2.5%, respectively; $p < 0.0001$ between cervical and lumbar spine). Snowboarders were more likely to suffer lumbar or thoracic injury than trauma in the cervical spine (4.9% lumbar, 3.9% thoracic, 2.6% cervical; $p < 0.0001$). In the analysis of patients who suffered a spine injury with or without SCI, skiers were more likely to injure the cervical spine (40.7% in skiers vs 25.3% in snowboarders; $p < 0.0001$), whereas snowboarders were more likely to injure the lumbar spine (47.6% in snowboarders vs 35.2% in skiers; $p < 0.0007$). However, in both groups, cervical spine trauma was associated with the highest likelihood of SCI (19.6%, vs 10.9% of thoracic and 6.0% of lumbar injuries; $p < 0.0001$) (Fig. 1 upper). This held true when analyzed according to sport as well, as seen in Fig. 1 lower.

Of those who sustained a cervical SCI, 66.6% underwent surgical fixation compared with 56.7% of those with a thoracic injury and 55.6% of those with a lumbar injury. Patients with SCI associated with a thoracic fracture were more likely to undergo surgical fusion than those without SCI (OR 11.93, 95% CI 5.171–27.54). Similarly, in patients with a lumbar spine fracture, there was a significantly increased tendency to undergo spinal fusion if there was an associated SCI (OR 13.4, 95% CI 4.847–37.25). Patients with cervical spine injuries were equally likely to have fusion with and without SCI (OR 1.3, 95% CI 0.707–2.540) (Fig. 2).

Of note, SCIWORA, although rarely occurring, was seen almost twice as frequently in skiers as in snowboarders (1.17% vs 0.54%, $p < 0.0001$).

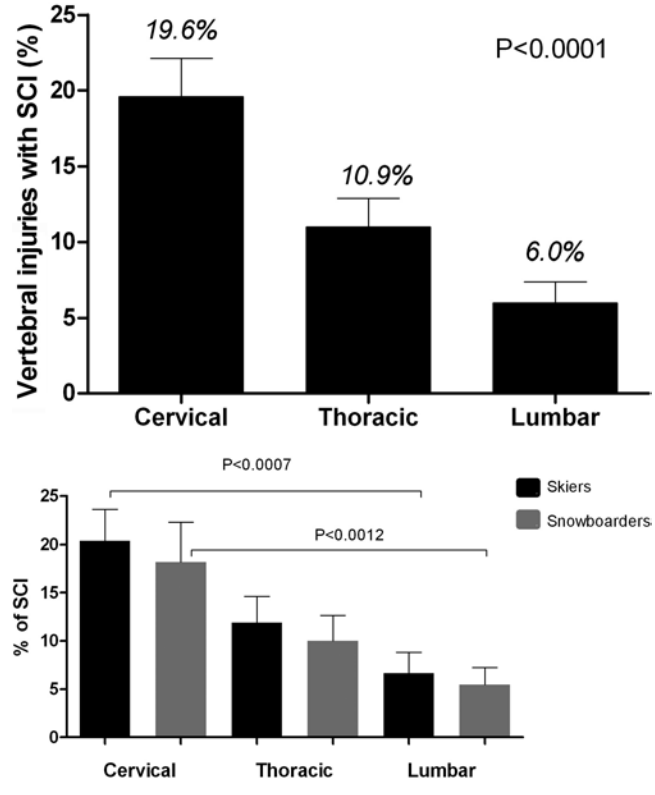

Fig. 1. Bar graphs showing associations between trauma level and SCI. **Upper:** The SCI level among injured skiers and snowboarders was significantly correlated with the vertebral level of the trauma. Cervical spine trauma had the highest incidence of SCI, at 19.6%, compared with 10.9% in thoracic, and 6.0% in lumbar spine fractures ($p < 0.0001$). **Lower:** The association between higher vertebral level and increased likelihood of SCI was maintained across both skiers and snowboarders.

Multiply Injured Patients

The most common injury seen in tandem with spine injury was closed head injury, and it was seen in 13.4% of patients. Conversely, a spine injury was seen in 12.9% of patients with a head injury. Among those with spine injuries, snowboarders had almost twice as many closed head injuries compared with their skiing counterparts (14.0% and 7.8%, $p < 0.0001$).

Excluding head injuries, skiers who had thoracic and lumbar vertebral injury were more likely to have multiorgan trauma than skiers who had cervical spine injuries (48% for thoracic and 46% for lumbar vs 19% for cervical; $p < 0.004$). A similar trend was seen in snowboarders; 24% with thoracic trauma, 27% with lumbar trauma, and 14% with cervical trauma had multiple injuries ($p < 0.06$).

In general, snowboarders were more likely to have injuries to their upper extremities, (48% vs 13% of skiers, $p < 0.0001$), whereas skiers had significantly more lower-extremity injuries (58.6% vs 22.3% of snowboarders, $p < 0.0001$). Patients who had an SCI were more likely to be discharged to a rehabilitation facility than those with injuries not including SCI (OR 17.02, 95% CI 11.02–26.30).

Length of Stay and Hospital Charges

On average, patients who suffered an SCI stayed 5.8

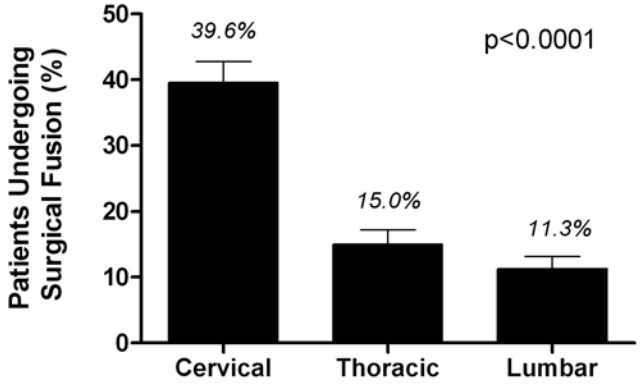

Fig. 2. Bar graph showing that operative stabilization was performed most frequently among skiers and snowboarders with cervical fractures (39.6%) compared with thoracic (15.0%) and lumbar spine injuries (11.3%), with or without SCI.

days longer than their counterparts without SCI (8.8 days vs 3.0 days, $p < 0.0001$). Patients who suffered an SCI also had higher costs associated with their hospitalizations ($94,795 vs $29,479; $p < 0.0001$). Patients with SCI were more than 8 times as likely to be discharged to a rehabilitation facility versus home or self-care after their hospital stay (53% of patients with SCI vs 6.2% patients without SCI, $p < 0.0001$). Skiers and snowboarders had similar length of hospital stays and charges accrued (2.9 vs 3.2 days and $20,175 vs $22,824, respectively).

Discussion

As skiing and snowboarding become more popular sports, with growing numbers of occasional participants, the rates of injuries are increasing.[3,6,7] Two studies suggested that the rates of spinal column (vertebral) injury and SCI are decreasing in overall frequency, but have changed in regard to the level injured.[5,7] The rates of neurological injury are typically in the range of 1 in 100,000 skier days, and complications leading to death are as low as 1 in 2 million skier days.[5,11–13] This study aimed to examine, on a large scale, how spinal column injuries and SCIs differed in participants in these 2 sports. As with other studies, minor injuries may not have been brought to the attention of the ski patrol or may not have required evaluation in an emergency department.[10]

Using the dataset, we calculated an estimate of the national burden of spine injuries among skiers and snowboarders. Because the NIS represents a rotating sample of approximately one-fifth of hospitalizations in the US annually, we performed an approximation of the annual injury burden by calculating the mean injury rate within the NIS for the years in question and then estimating a national average of the types of injuries in patients admitted to hospital. Between the years 2000 and 2008, there was a mean of 81.3 (range 18–126) spine injuries, leading to an estimate of 406.5 spine fractures sustained nationally by skiers and snowboarders each year. Of these spine injuries, an estimated 105.5 required surgical treatment each year nationwide.

In this population, SCI was not seen more frequently in skiers or snowboarders, which is divergent from the study by Tarazi et al.,[13] but mirrors the results seen by Sacco et al.[12] The difference may be due a deficiency in our study due to inability to calculate the total number of skiing participants or because of the substantially larger patient population in this study.

Cervical injuries were seen more frequently in skiers than in snowboarders, which is congruent with the mechanism of injury previously described for each sport.[1,7,11] The majority of injuries sustained while skiing occur due to falls or collision and have been associated with cervical injuries, whereas snowboarding injuries are more likely to occur as a result of intentional jumping and subsequent landing on the buttocks or with increased force on the legs.[4,6,9,11,13,14,16] This is contrary to what was seen in an analysis of injuries treated in a Utah hospital,[15] where the most frequent level injured was the thoracic and lumbar spine. As stated above, our data suggest that cervical spine injuries lead to more SCI and that skiers more frequently injure their cervical spine. However, it did not show statistically significantly more SCIs in skiers. We reported a higher surgical intervention rate than in previous studies[5] and noted that SCI substantially increased the incidence of fusion in lumbar and thoracic injury. Cervical fusion rates were not dependent on SCI. The high occurrence of fusion in cervical injuries without SCI could be due to surgeons' comfort level with cervical fusions compared with the thoracic spine. In our study, the exact vertebral injury level was not assessed, nor was injury to the thoracolumbar junction, which was noted to be the most common location by other authors.[4,13] Also, the type of fracture could not be assessed in this study due to the inability to review patient charts.

The proximal cause of death was not available because charts were not reviewed. However, the number of deaths in patients admitted to the hospital with ski or snowboard injuries is extremely low. Other authors have quoted the incidence of fatal ski or snowboarding injury to be as low as 1 in 2 million skier days.[5] Also, similarly to Sacco et al.,[12] a higher number of fatal injuries was seen in primarily male skiers.

The younger age of snowboarders is a trend that has been noted in several other studies.[6,8,12,14–16] Although in this study we were not able to assess skill levels in the injured participants, others have noted that most injuries occurred while patients were skiing or snowboarding at their skill level, and individuals sustaining injuries were typically intermediate or expert skiers.[11,14] This has been attributed to the higher likelihood of "jump failure" in the expert groups; these individuals are taking more risks than those in the beginner groups.

The most common mechanism of injury in snowboarders is associated with jumping.[1,16] With aerial maneuvers being cited as the culprit for increased SCIs in snowboarders,[16] it is not unreasonable to believe that more skiers will sustain injuries as they begin pushing vertical boundaries. The addition of more extreme skiing and snowboarding into the Olympics and other international competitions will serve to push those limits further.

The increased incidence of SCIWORA in skiers is interesting, because it is typically associated with pediatric injuries due to the laxity of the spinal ligaments.[8] This

differs from what would be expected when the younger population typically consists of more snowboarders than skiers. It is likely that the flexion and extension injuries seen in skiers accounts for this difference.

We did not find a difference in length of hospital stay between skiers and snowboarders, unlike others.[13,15] Length of hospital stay was dictated more by the presence of SCI, which is probably reflective of the more severe nature of the injury. The overall cost of hospitalization was not different between sports, which is expected if the length of stay is primarily determined by other variables. Similar to what was found by Sacco et al.,[12] February was the month most associated with injuries.

Limitations of the Study

As a retrospective study, there may have been some information that was not included in the initial collection of data. Coding for similar injuries may have been inconsistent because the patient population was formed using a nationwide database. In such a large, heterogeneous population, there is no way to know the total number of ski/snowboard days, and thus there is no true denominator. Also, the use of protective equipment was not recorded in the database.

Skiers and snowboarders who suffered injuries that did not necessitate an emergency room workup were not part of this study group, thus eliminating less severe injuries from this cohort. To counteract this, those who died while still at the resorts were also not included, which leads to an underestimation of fatalities in this study.

Conclusions

The prevalence of SCIs is similar among skiers and snowboarders evaluated in hospital. Additionally, participants of both sports have an increased incidence of SCI with cervical spine trauma. The most predominant difference between the groups is at what level the fracture occurred; snowboarders had more lumbar fractures and skiers had more cervical injuries. This is probably attributed to the mechanism of injury, which has been described in other studies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References

1. Abu-Laban RB: Snowboarding injuries: an analysis and comparison with alpine skiing injuries. **CMAJ 145:**1097–1103, 1991
2. Ackery A, Hagel BE, Provvidenza C, Tator CH: An international review of head and spinal cord injuries in alpine skiing and snowboarding. **Inj Prev 13:**368–375, 2007
3. Chissell HR, Feagin JA Jr, Warme WJ, Lambert KL, King P, Johnson L: Trends in ski and snowboard injuries. **Sports Med 22:**141–145, 1996
4. Deady LH, Salonen D: Skiing and snowboarding injuries: a review with a focus on mechanism of injury. **Radiol Clin North Am 48:**1113–1124, 2010
5. Floyd T: Alpine skiing, snowboarding, and spinal trauma. **Arch Orthop Trauma Surg 121:**433–436, 2001
6. Franz T, Hasler RM, Benneker L, Zimmermann H, Siebenrock KA, Exadaktylos AK: Severe spinal injuries in alpine skiing and snowboarding: a 6-year review of a tertiary trauma centre for the Bernese Alps ski resorts, Switzerland. **Br J Sports Med 42:**55–58, 2008
7. Hagel BE, Goulet C, Platt RW, Pless IB: Injuries among skiers and snowboarders in Quebec. **Epidemiology 15:**279–286, 2004
8. Legome E, Shockley LW: **Trauma: A Comprehensive Emergency Medicine Approach.** Cambridge: Cambridge University Press, 2011
9. Levy AS, Smith RH: Neurologic injuries in skiers and snowboarders. **Semin Neurol 20:**233–245, 2000
10. Macnab AJ, Cadman R: Demographics of alpine skiing and snowboarding injury: lessons for prevention programs. **Inj Prev 2:**286–289, 1996
11. Prall JA, Winston KR, Brennan R: Spine and spinal cord injuries in downhill skiers. **J Trauma 39:**1115–1118, 1995
12. Sacco DE, Sartorelli DH, Vane DW: Evaluation of alpine skiing and snowboarding injury in a northeastern state. **J Trauma 44:**654–659, 1998
13. Tarazi F, Dvorak MF, Wing PC: Spinal injuries in skiers and snowboarders. **Am J Sports Med 27:**177–180, 1999
14. Wakahara K, Matsumoto K, Sumi H, Sumi Y, Shimizu K: Traumatic spinal cord injuries from snowboarding. **Am J Sports Med 34:**1670–1674, 2006
15. Wasden CC, McIntosh SE, Keith DS, McCowan C: An analysis of skiing and snowboarding injuries on Utah slopes. **J Trauma 67:**1022–1026, 2009
16. Yamakawa H, Murase S, Sakai H, Iwama T, Katada M, Niikawa S, et al: Spinal injuries in snowboarders: risk of jumping as an integral part of snowboarding. **J Trauma 50:**1101–1105, 2001

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Address correspondence to: Anand I. Rughani, M.D., Division of Neurosurgery, University of Vermont, 111 Colchester Avenue, Fletcher 507, Burlington, Vermont 05401. email: anand.rughani@mail.mcgill.ca.

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Strategies for asymptomatic carotid artery stenosis

Christopher Doe, B.S.,[1] Pinakin R. Jethwa, M.D.,[1] Chirag D. Gandhi, M.D.,[1,2] and Charles J. Prestigiacomo, M.D.[1–3]

Departments of [1]Neurological Surgery, [2]Radiology, and [3]Neurology and Neuroscience, University of Medicine & Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey

The treatment of asymptomatic carotid artery stenosis (ACAS) has continued to evolve for the past 3 decades. With rapidly advancing technology, the results of old trials have become obsolete. While there has been little change in the efficacy of carotid endarterectomy, there have been vast improvements in both medical management and carotid angioplasty with stenting. Finding the best therapy for a given patient can therefore be difficult. In this article, the authors review the current literature regarding treatment options for ACAS and the methods available for stratifying patients who would benefit from surgical versus medical treatment. *(DOI: 10.3171/2011.9.FOCUS11206)*

Key Words • asymptomatic carotid artery stenosis • treatment • endarterectomy • carotid stent

Carotid artery stenosis commonly refers to a narrowing of the common carotid artery or the ICA due to atherosclerosis and is most commonly seen in the geriatric population. It is associated with an increased risk of ischemic stroke.[35] In some patients, the stenosis is discovered as a result of transient ischemic attacks or amaurosis fugax (transient blindness in one eye). In these patients, the likelihood of suffering an ischemic stroke in the near future is increased.[41] Surgical intervention, either CEA or CAS, is generally accepted in symptomatic patients.[37]

Given advances in imaging of the cerebral vasculature and the more widespread use of such studies, the frequency of incidentally discovered carotid stenosis is increasing.[14] The severity of stenosis and the development of symptoms are not necessarily directly related, due to collateral circulation from the contralateral carotid artery and the posterior circulation. The management of ACAS has been debated since the late 1970s and early 1980s when clinical trials were performed to compare the best medical treatment at the time and CAE.[72] The controversy continued in the early 1980s when some physicians believed that conservative medical management was warranted until severe stenosis or symptoms appeared[60] versus others who advocated more aggressive prophylactic surgery.[72]

Current American Heart Association and American Stroke Guidelines indicate that endarterectomy and aggressive management of risk factors is the best course of treatment for ACAS in patients with ≥ 60% stenosis if surgery is not otherwise contraindicated due to comorbidities and other risk factors.[27] Polling in the US indicates that about 47% of patients are treated medically, 36% with CEA, and the remainder with CAS.[40] International statistics are similar regarding treatment choice.[40] The clinical reasoning behind the predominance of medical management is that many physicians are treating individuals with atherosclerotic disease in other areas of the body and are uncomfortable with the risks of surgery, despite the proven long-term success of endarterectomy.[40] However, the choice of aggressive medical management alone may not necessarily be incorrect given the recent advances and emerging evidence.

Multiple trials have been performed to help elucidate the best treatment strategy for ACAS.[9] In the 1980s and 1990s, trials were designed to examine CEA and medical management. Examples of these trials include the NASCET and the ECST. Although focused on symptomatic stenosis, both NASCET and ECST included information regarding the nonsymptomatic artery. These data have been used for analyses of the efficacy of CEA in asymptomatic stenosis; however, the data cannot be generalized to the truly asymptomatic population as these trials involved patients who were symptomatic in the contralateral artery.[35]

Abbreviations used in this study: ACAS = asymptomatic carotid artery stenosis; CAE = carotid endarterectomy; CAS = carotid angioplasty with stenting; ECST = European Carotid Surgery Trial; hs-CRP = high-sensitivity C-reactive protein; ICA = internal carotid artery; NASCET = North American Symptomatic Carotid Endarterectomy Trial; TCD = transcranial Doppler.

In the 1990s and early 2000s, trials specifically focused on asymptomatic patients were conducted, the most notable being the Asymptomatic Carotid Atherosclerosis Study and the Asymptomatic Carotid Surgery Trial.[57] These studies examined ACAS directly by following the long-term effects of medical management and CEA; however, these trials were performed at a time when medical management consisted mainly of aspirin. Therefore, these trials may now be outdated due to improvements in medical management, including lipid-lowering medications, antihypertension medications, and antiplatelet agents.

In the early 2000s, CAS became a viable treatment option for patients with carotid stenosis. Percutaneous angioplasty and stenting gained popularity due to the less invasive nature of endovascular procedures. Carotid angioplasty with stenting was believed to be a particularly good option for patients with a high surgical risk. Specific trials investigating the efficacy and safety of CAS were organized, including the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial and the Stent-Protected Angioplasty in Asymptomatic Carotid Stenosis (SPACE) trials. These trials have led to little consensus as to where CAS should fall in the treatment paradigm for patients with ACAS. Additionally, these trials examined CAS against CEA and rarely included a branch for medical management alone. An ongoing trial, SPACE-2, has an arm for CEA, CAS, and purely medical treatment, making it unique.

The management of ACAS remains debatable due to the inherent risks posed by surgical procedures, both CEA and CAS, and the improvements in medical management. A consensus on the prognosis for ACAS needs to be developed to properly stratify patients who would benefit from either surgical intervention or medical management.

Diagnosis

It is estimated that 15%–30% of all ischemic strokes are related to carotid atherosclerotic disease, highlighting the importance of early diagnosis.[67] A thorough history and physical examination are the initial steps in evaluating a patient with potential ACAS. Risk factors for carotid stenosis are similar to those for coronary artery disease and include hypertension, diabetes mellitus, smoking, and elevated blood cholesterol levels, but may include patient age and sex as well.[14] A carotid bruit is an often overlooked sign that can easily be identified on routine physical examination; although it is not necessarily indicative of carotid stenosis, its presence should raise suspicion. A carotid bruit should be followed up with TCD, which is currently the most cost-effective means of diagnosing carotid stenosis. Doppler ultrasonography is also capable of determining the degree of stenosis, which is a major factor in determining the risks associated with carotid stenosis.[41] The NASCET and ECST trials were important in helping to establish the methods by which stenosis is measured for consistency among observers. Both trials used the formula: percent stenosis = $(1 - D/N) \times 100$, where D is the diameter of the vessel at the most stenotic segment and N is the normal diameter of the vessel. The difference between the 2 trials is how the normal diameter was measured. According to NASCET criteria the normal diameter was measured in the ICA distal to the stenosis, whereas according to ECST criteria the normal diameter was measured at the predicted outline of the carotid bulb.[23,56,61] Figure 1 illustrates the differences in these methodologies. Although the methods are different, they both have been effective in minimizing interobserver variability.[61]

Patients with significant findings on Doppler ultrasonography should undergo further workup with advanced imaging of the cerebral vasculature using conventional angiography, CT angiography, or MR angiography. The greater definition of the anatomy, collateral circulation, and plaque morphology is helpful in designing treatment options, particularly if an intervention is being considered.

Depending on the degree of stenosis, the 7-year risk of an ipsilateral stroke varies from 8% to 35%.[55] In an earlier study, patients with moderate to severe stenosis of

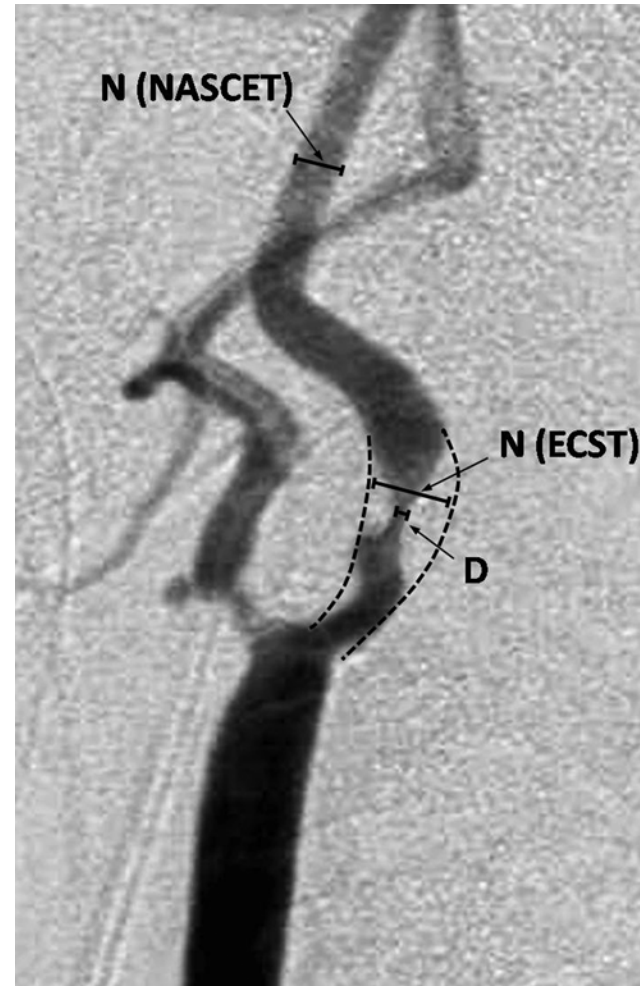

Fig. 1. Lateral cervical angiogram showing the anatomical sites used in calculating percent stenosis. Diameter of the vessel at the site of maximal stenosis is indicated by D, and normal vessel diameter is indicated by N. Note that N is measured distal to the stenosis according to the NASCET criteria, while the ECST criteria measured N using the predicted outline of the carotid bulb.

more than 50% had a 9.3% risk of ipsilateral stroke at 10 years.[51] Since a significant proportion of strokes can be attributed to carotid stenosis, some physicians believe that screening for ACAS in the general population could be beneficial.[14] In the general population, the prevalence of moderate (≥ 50%) and severe (≥ 70%) stenosis ranges from 0% to 7.5% and 0% to 3.1%, respectively, depending on patient age and sex.[14,49] Accounting for the time and costs associated with screening using TCD, it has been estimated that the prevalence of severe ACAS would need to surpass 20% to be cost-effective.[14] Given these figures, it seems that screening the general population is not warranted; however, some authors have pointed out that there may be a cost-benefit to screening populations with multiple risk factors.[31]

Medical Management

The medical treatment of ACAS has evolved greatly since the major trials of the 1980s.[67] At that time, aspirin was the only major component of medical management.[34] However, medical management now involves lipid-lowering drugs, a greater variety of antihypertension medications, and antiplatelet agents.[67] Clinical trials indicate that statins may even go so far as to decrease atherosclerotic plaques in individuals who do not yet have significant stenosis.[24,63] Maintenance of adequate high-density lipoprotein levels is also important since they help to reduce plaque volume.[39] Antiplatelet drugs have also been developed to decrease the risk of thromboembolic events, which could lead to ischemic stroke. When CEA was followed by antiplatelet therapy, there was a decreased stroke risk as compared with CEA alone.[21] It would be expected that antiplatelet medications would similarly decrease stroke risk within a strictly medical management option as well. The increase in the quality of these drugs is cause enough to perform new trials comparing their efficacy to that of CEA and CAS.[67]

Hemodynamic studies provide some evidence that medical therapy is becoming more effective in preventing adverse events in ACAS. Transcranial Doppler ultrasonography is capable of detecting the presence microemboli due to carotid stenosis.[73] Microemboli are fragments from emboli from the heart or arteries. It has been shown that these microemboli are extravasated through tissues in a normal perfusion model; however, in the case of hypoperfusion, they are not as readily cleared from the vascular system.[73] This is relevant since stenosis of the carotid artery would affect perfusion of the ipsilateral anterior circulation of the brain and could hinder clearance of these microemboli, eventually leading to stroke. Aged mice were also shown to have delayed removal of microemboli.[73] Since most patients with ACAS are 50 years of age or older, this finding may be relevant. With more widespread use of increasingly effective medical treatment, the presence of microemboli has decreased in patients with ACAS.[69] The rate of plaque progression in treated patients has also significantly decreased.[69] While this provides some evidence that medical treatment is becoming more successful, a clinical trial would be required to validate this claim.

Strokes that occur in patients with carotid stenosis may not necessarily be caused by the stenosis itself. Inzitari et al.[35] suggested that 45% of strokes ipsilateral to carotid stenosis are either lacunes or cardioembolic in origin. These statistics have not been used in the methodology of clinical trials for carotid stenosis. Since ACAS is a predictor of cardiovascular disease elsewhere in the body, aggressive medical treatment is beneficial for the long-term health of these patients independent of the carotid artery disease.[26,49]

The risk of stroke due to carotid stenosis is lower than previously believed according to recent studies.[47,51] Some physicians believe that medical management should be the mainstay of ACAS therapy and that invasive techniques should only be used in specific cases.[41] There is growing support in the literature for reevaluating the efficacy of medical treatments due to the aforementioned improvements. Some authors believe that no patients with asymptomatic disease warrant surgery due to the generally poor vascular health in this population.[2] In a recent analysis by Abbott,[1] medical management was determined to be the best option for patients with ACAS due to the high costs of surgical intervention and associated complications.

Surgical Treatment

Carotid Endarterectomy

In the early 1950s CEA was developed as a method of removing plaque in the carotid artery and thus decreasing the risk of stroke in patients by improving cerebral perfusion.[72] Carotid endarterectomy is associated with a periprocedural risk of myocardial infarction, cranial nerve injury, and stroke.[8] It is generally accepted that CEA provides an absolute risk reduction in stroke of approximately 1% over the moderate to long term.[51] Based on estimates from older data on medical management, CEA is advocated if the periprocedural risk is 3% or lower.[37,66,74] Accordingly, the skill and experience of the surgeon are significant and should be included in the decision regarding CEA.[37] Earlier studies have indicated that CEA should only be considered in patients with a hemodynamically significant stenosis.[72]

Several classification systems exist for risk stratification in patients undergoing CEA. In 1978 Moore et al.[50] developed a classification system based on the extent of plaque ulceration. Grade A indicates a smooth and shallow ulcer; Grade B, a smooth but large and deep ulcer; and Grade C, an irregular, large, and deep ulcer.[15,50] A more thorough system for stratifying risk in carotid stenosis was introduced by Sundt et al.[71] in 1986. Table 1 shows the essential features of this classification system.[17,71] Only patients in Groups 1–3 are relevant to the discussion of ACAS, as those in Group 4 are by definition symptomatic. Patients in higher groups have a greater incidence of postoperative neurological complications and death following CEA.[71]

Restenosis following CEA is another consideration when evaluating a patient for endarterectomy[67] and has been reported in up to 15% of cases.[48] Patients experiencing restenosis after CEA have an increased risk of stroke.[64] Several techniques have been developed to reduce the incidence of restenosis. One of these is eversion CEA, in which a transverse incision is made in the artery

TABLE 1: Sundt classification system*

Group	Description
1	neurologically stable w/ no major medical or angiographic risks w/ unilat or bilat carotid disease
2	neurologically stable w/ no major medical factor but significant angiographic risks
3	major medical risks regardless of angiographic findings
4	neurologically unstable

* Medical risk factors: angina pectoris, myocardial infarction within 6 months, congestive heart failure, obesity, chronic obstructive pulmonary disease, or age > 70 years. Neurological risk factors: progressive deficit, deficit within 24 hours, crescendo transient ischemic attacks, and multiple cerebral infarcts associated with deficits. Angiographic risk factors: contralateral ICA occlusion, coexisting carotid siphon stenosis, high bifurcation, long plaque length, or evidence of thrombus from an ulcer.

as opposed to a standard longitudinal arteriotomy. Eversion CEA has been reported to have a lower restenosis rate compared with a traditional technique while maintaining similar perioperative mortality and morbidity.[38] Another technique is patch angioplasty, which involves the use of a venous or synthetic patch to close the arteriotomy, as opposed to the primary closure utilized in the standard technique. In a recent review by Rerkasem and Rothwell,[58] the incidences of periprocedural stroke and restenosis were both decreased with patch angioplasty as compared with the standard technique, although the sample size was relatively small in the study. Despite the lack of conclusive data regarding the efficacy of patch angioplasty with CEA, it is still commonly used, with the choice of patch material being unimportant.[13]

Although it is recognized that performing CEA in all patients with moderate to severe stenosis is not cost-effective, there are clinicians who would still recommend it to all patients with ACAS as long as a skilled surgeon is available.[6,63] Small studies done in single centers have demonstrated that endarterectomy is still superior to medical management. Lutz et al.[44] studied data from patients receiving lipid-lowering medications and antiplatelet agents, as well as treatment for diabetes and hypertension. The sample size of this study was small, and a larger scale, multicenter clinical trial is needed to determine whether CEA is truly superior to current medical management. It is also important to note that although it is easy to argue for medical management as a better possible option, there is no Level I evidence to indicate that this is necessarily true.[65] Without further trials to prove otherwise, CEA should be accepted as the standard of care in patients with moderate to severe ACAS.

Figure 2 shows representative images from a patient with asymptomatic stenosis of the right ICA and near-complete occlusion of the left ICA that was treated with right-sided endarterectomy.

Carotid Angioplasty With Stenting

Carotid angioplasty with stenting is a newer option in the treatment of ACAS, and due to its less invasive nature

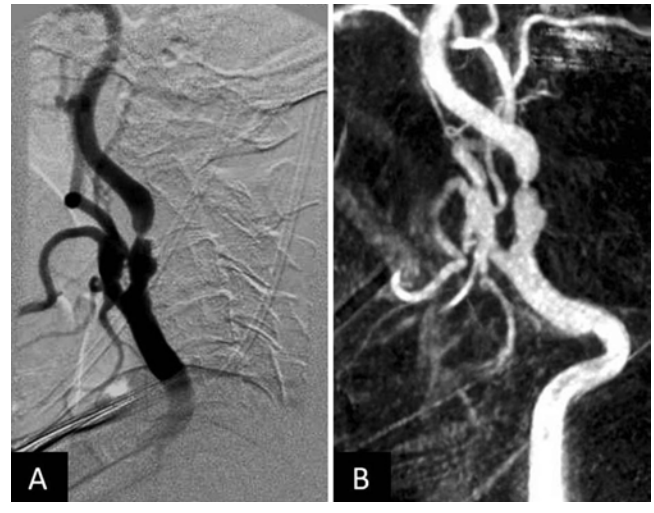

Fig. 2. Images obtained in a 77-year-old woman who was found to have near-occlusion of the left ICA and severe stenosis of the right cervical ICA on MR imaging of the cervical spine for neck pain. **A:** Lateral view angiogram showing focal stenosis in the proximal cervical ICA. **B:** A 3D reconstruction of a rotational angiogram further highlighting the stenosis. The patient was treated with CEA.

it has garnered a great deal of interest. Several trials, such as the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), have been designed to compare the efficacy of CAS as compared with CEA.[52] Patient selection for the CAS trials was aimed at patients with a high surgical risk. It is important to note that although the Sundt classification is often used to stratify patients for CAS, the system was not designed with this application in mind and may not be applicable. The trials comparing CAS and CEA suggest that CAS is at best equal to CEA in patients with ACAS in terms of efficacy.[28,30,36,52] There is common agreement that CAS has a decreased risk of myocardial infarction and cranial nerve injury and an increased risk of perioperative stroke.[8,11,73] However, there is little consensus beyond that. A lack of consensus occurs even when the same data are analyzed because of the use of different statistical strategies.[18] Even within a single meta-analysis of CAS, there are few conclusions that can be made given the heterogeneity of the data.[20] The use of a distal protection device during a CAS procedure has shown questionable benefit, although it is still a common practice when placing a carotid stent.[20] The CREST was the first trial to evaluate the efficacy of CEA and CAS in a similar population and showed that the prognosis following the 2 procedures was similar, although they had different periprocedural risks, as previously mentioned.[11] Moreover, it was concluded that older patients (age ≥ 70 years) encountered worse outcomes with CAS.[73] In another study, which focused on patients 80 years of age or older, CAS results approached those of the natural history (approximately 3%).[74]

Much like with CEA, patients who have undergone CAS are at risk for restenosis; however, the rates are typically lower than those seen with CEA. In a study by González et al.[28] restenosis occurred in 4.3% of patients. Even in patients with a high surgical risk, restenosis after CAS occurs less frequently than after CEA.[64]

Economically, CAS has a much greater material cost as compared with CEA.[74] Although there is a decreased hospital stay for those undergoing CAS, the high cost of equipment from the procedure itself offsets the savings.[36,45] There also appears to be an age-linked benefit to CAS that should be factored in, as perioperative risks of CAS are reduced in younger patients.[19]

Operator experience is a factor that has led to inconsistency in interpreting data from these trials. The entry criteria for surgeons performing CEA were more stringent than for those performing CAS. This may help to explain the lack of consensus and disagreement found in the carotid stenting literature.[20] Furthermore, the stratification of patients recommended for either CAS or CEA is significant. Since many patients with a high surgical risk undergo CAS, they should be considered inherently riskier. Because of this bias, it may be hard to objectively compare CEA and CAS.[43] The early CAS trials did not include these factors in their designs and thus are flawed.[29,53] These trials also had issues with patient recruitment as well as trial suspensions due to risks, ultimately leading to debate of their validity.[53] Although CEA is equal or better in long-term benefit depending on the trial, even the proponents of CEA recognize the situational benefit of CAS for those who are at a particular risk for surgery.[19] Carotid angioplasty with stenting is currently used in high risk surgical patients with asymptomatic disease and > 80% stenosis; however, in May 2011 the FDA approved CAS for standard surgical risk patients with > 60% stenosis. Table 2 illustrates various factors that should be considered when deciding between CEA and CAS for a patient with ACAS.

Figure 3 illustrates a patient with complete right ICA occlusion and severe stenosis of the left ICA that was treated with carotid stent placement, with subsequent improvement in cerebral blood flow.

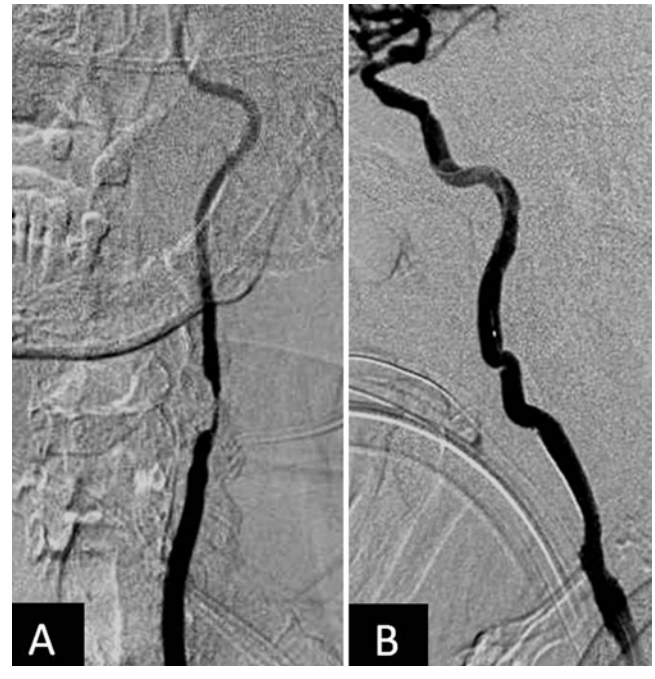

Fig. 3. Images obtained in a 55-year-old woman who was found to have complete occlusion of the right ICA and severe stenosis (> 80%) of the left ICA during medical clearance for femur fixation. The patient was deemed high risk for surgery and was treated with carotid stenting. **A:** Preintervention lateral angiogram showing flow-limiting stenosis of the left ICA and complete occlusion of the left ECA from an atherosclerotic plaque. **B:** Poststenting lateral angiogram showing improvement in vessel diameter as well as blood flow.

Risk Stratification

Identifying patients who would benefit from an intervention and those who can be treated with medical treatment alone is likely more useful than classifying any one treatment method as superior.[41] The importance of identifying asymptomatic patients who are at particularly high risk has been realized since the 1970s.[72] If patients can be risk stratified using noninvasive and cost-effective tests, then patients with ACAS can remain on medical treatment and undergo surgery only when there is a specific need.

TABLE 2: Factors favoring a type of intervention in ACAS*

Carotid Endarterectomy	Carotid Artery Stenting
focal lesions	long-segment stenosis
calcified	noncalcified
tight	EDP-friendly
robust collateral circulation	poor collateral circulation
poor stent candidate	medical comorbidities
average bifurcation	high bifurcation
tortuous aortic arch	favorable aortic arch
male	prior neck op or radiation
age <70 yrs	age >70 yrs

* EDP = embolic distal protection device.

Transcranial Doppler ultrasonography can be used to identify the presence of microemboli. Their presence is a positive marker for future stroke.[70] Patients positive for embolic signals are 5.6 times more likely to experience ipsilateral stroke compared with those without the embolic signals.[46] Patients without the signals have a low absolute risk of stroke.[46] Based on detection of microemboli, it is estimated that as few as 5% of patients with ACAS stand to benefit from surgical revascularization.[66,70] In utilizing TCD ultrasonography to better understand the hemodynamics of the cerebral vasculature and the affected carotid artery, patient selection for surgery can be improved.[59] Patients with ACAS who have microemboli on TCD ultrasonography are more likely to benefit from surgery, whereas those without microemboli can be maintained on medical treatment.

Ultrasonography has also been used in stratifying patients with ACAS. It has been observed that patients with progressively increasing stenosis are at highest risk for adverse events affecting not only the cerebral, but also the coronary and peripheral vasculature.[42,62] Ultrasonography can also be useful in understanding the histology of the plaque. Echolucent plaques are indicative of high lipid levels with more inflammatory cells and thin cap, whereas echogenic plaques are indicative of fibrous struc-

tures.[10] Patients with echolucent plaques are therefore at increased risk for neurological events.[42] It is also possible to determine the homo- or heterogeneity of a plaque with ultrasonography. Heterogeneous plaques have been shown to be more unstable than plaques that are more homogeneous.[5]

Thrombin production is associated with inflammation, which is helpful in understanding the utility of another test. Increased levels of hs-CRP have been identified as being indicative of plaque instability since it marks the presence of macrophages and T lymphocytes.[7] If hs-CRP is monitored in patients with ACAS, the need for surgical intervention could be identified earlier in those most at risk for thromboembolic events from the atherosclerotic plaque.[67]

Another factor when considering an intervention for asymptomatic patients is cerebral hemodynamics. Single photon emission computed tomography with an acetazolamide challenge is a common method for measuring a patient's cerebral reserve. A radioisotope (technetium-99) that is conjugated to a compound capable of crossing the blood-brain barrier (hexamethylpropyleneamine oxime) is injected intravenously. The isotope then gives off gamma rays, which can be detected by CT and translated to a map of cerebral blood flow. Administration of acetazolamide causes vasodilation and can help to determine cerebral reserve in the areas of interest after obtaining a baseline scan. Patients with diminished cerebral reserve may benefit from an interventional procedure over those with adequate reserve.[25] At our institution, we are investigating the use of SPECT data when it is unclear on imaging alone whether a patient should undergo an intervention or remain on medical therapy. Figure 4 shows a flow diagram of our institutional protocol for caring for patients with ACAS.

Patient compliance and costs are important considerations when weighing the different treatment options. Medication can be expensive and must be maintained for long periods.[74] At the same time, myocardial infarction is more common in patients with ACAS than stroke. This is due to atherosclerosis present elsewhere in the vasculature.[68] Thus, patients who undergo CEA or CAS are generally asked to maintain these medications for cardiac protective reasons. Carotid angioplasty with stenting is more expensive initially due to the high material input

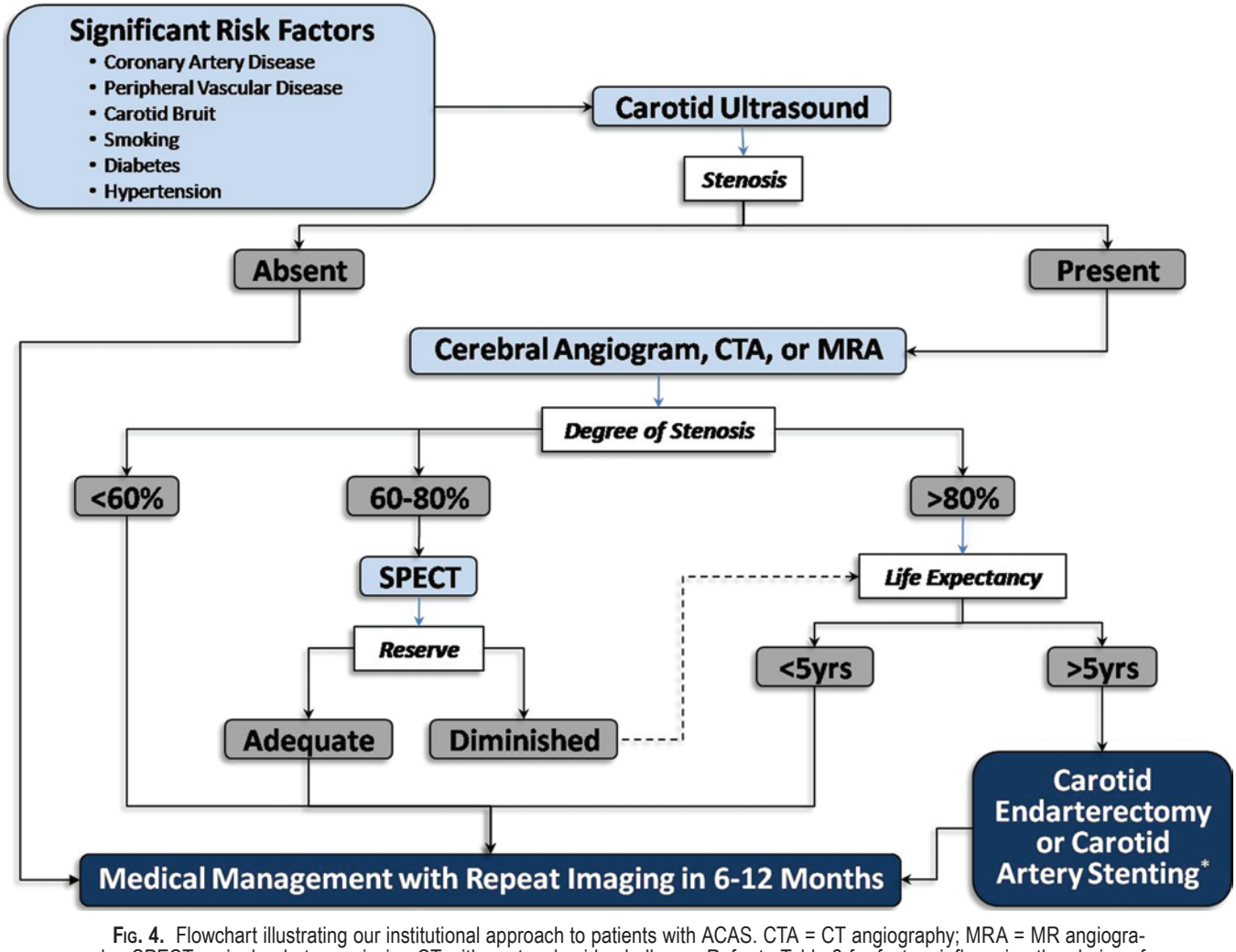

Fig. 4. Flowchart illustrating our institutional approach to patients with ACAS. CTA = CT angiography; MRA = MR angiography; SPECT = single-photon emission CT with acetazolamide challenge. Refer to Table 2 for factors influencing the choice of CEA or carotid artery stenting.

required relative to CEA. Long-term follow-up in patients both undergoing surgical intervention and receiving medical treatment is crucial. Restenosis occurs in a significant proportion of the population and is associated with an increased risk of stroke.[64] Monitoring the contralateral carotid artery is also important since stenosis can develop following surgical treatment.[3]

When deciding on treatment, it is important to consider all risk factors. Manageable cardiovascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and smoking, should be controlled.[51] Patient age and sex are both important when considering treatment options.[16] Several studies have noted an apparent surgical benefit for younger cohorts as opposed to older ones, especially in the case of CAS.[19] Men are also more likely to have ACAS and garner a greater benefit from surgery.[14,16,66] The contralateral carotid artery should also be observed since patients with even moderate stenosis have been shown to have a significantly increased risk of stroke if the other carotid is occluded.[4] Specific surgical risks are also important to consider. It has been recognized that although CEA does reduce stroke risk, this reduction must be measured carefully against procedural risks, as these patients are generally high-risk surgical candidates.[32] The Asymptomatic Carotid Surgery Trial suggests that surgery is only beneficial to patients with an age < 75 years due to life expectancy.[33] A life expectancy of approximately 3–5 years is necessary to warrant surgical intervention in all cases; patients who have a generally decreased life expectancy due to age or comorbidities should be treated with medical management.[22,33,64] In a Cochrane-based meta-analysis of the ACAS trials from the 1990s, the perioperative stroke and death rate was 2.9% and the absolute reduction of stroke risk was about 1%.[12] In these trials, the enrollment of patients was highly selective and centers were specialized in the care of these patients. Thus, the 2.9% is not likely to be reproducible at less specialized hospitals, which may exceed the numbers observed in separate trials and in Medicare records.[68]

Conclusions

Since there is no definitive evidence that CEA has become inferior to medical treatment or CAS, it should remain the standard for treatment. Physicians and patients alike can find it difficult to manage ACAS, especially given the current evidence.[65] This is further complicated by the fact that there is some evidence in support of current medical management as a better and more cost-effective method of treating ACAS.[47] Since medical treatment has improved over the past 3 decades while CEA has had little change in efficacy and operative risk, medical treatment must be compared again in more updated trials. The role of CAS remains uncertain in this patient population, but the recent FDA approval for patients with a standard surgical risk may result in increased acceptance.

Creating effective strategies for identifying those who would benefit from surgery is another area of development. If hs-CRP, TCD ultrasonography, SPECT, and carotid ultrasonography can be used to identify patients at high risk for stroke, medical treatment can become the initial treatment choice, with surgical intervention used strictly for those who would gain the most benefit from it.[66] There has been a general trend toward this style of care. This strategy may have the secondary benefit of decreasing the number of strokes attributable to surgery.[54] Although the best treatment for ACAS is still debated, it is generally accepted that aggressive medical therapy and risk management are warranted in all cases, regardless of the decision to intervene surgically or not.[40] Since ACAS is almost entirely seen in the elderly population, it is important to take into account all risk factors for cardiovascular disease and surgical risk, as well as the anticipated lifespan in deciding a treatment plan. Doctors must learn to help patients make judgments based on circumstances and experience.

The therapies available for treating ACAS continue to evolve. Trials evaluating CAS and current medical management against CEA are underway and will help to elucidate the best treatment strategy for patients with asymptomatic carotid disease. Additionally, there are diagnostic studies capable of identifying patients with ACAS who are at higher risk for stroke. Physicians treating patients with ACAS must understand these factors, as well as the natural history of the disease and procedural risks to better select patients for either surgical or medical treatment.

Disclosure

Dr. Prestigiacomo is a consultant for Aesculap, Inc., Thermopeutix, Inc., and Edge Therapeutics, Inc., and is a board member of the International Brain Research Foundation, Inc.

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References

1. Abbott AL: Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. **Stroke 40:**e573–e583, 2009
2. Abbott AL, Donnan GA: Does the 'high risk' patient with asymptomatic carotid stenosis really exist? **Eur J Vasc Endovasc Surg 35:**524–533, 2008
3. AbuRahma AF, Cook CC, Metz MJ, Wulu JT Jr, Bartolucci A: Natural history of carotid artery stenosis contralateral to endarterectomy: results from two randomized prospective trials. **J Vasc Surg 38:**1154–1161, 2003
4. AbuRahma AF, Metz MJ, Robinson PA: Natural history of > or =60% asymptomatic carotid stenosis in patients with contralateral carotid occlusion. **Ann Surg 238:**551–562, 2003
5. Aburahma AF, Thiele SP, Wulu JT Jr: Prospective controlled study of the natural history of asymptomatic 60% to 69% carotid stenosis according to ultrasonic plaque morphology. **J Vasc Surg 36:**437–442, 2002
6. Ailawadi G, Stanley JC, Rajagopalan S, Upchurch GR Jr: Carotid stenosis: medical and surgical aspects. **Cardiol Clin 20:** 599–609, 2002
7. Alvarez Garcia B, Ruiz C, Chacon P, Sabin JA, Matas M: High-sensitivity C-reactive protein in high-grade carotid stenosis: risk marker for unstable carotid plaque. **J Vasc Surg 38:**1018–1024, 2003

8. Bangalore S, Kumar S, Wetterslev J, Bavry AA, Gluud C, Cutlip DE, et al: Carotid artery stenting vs carotid endarterectomy: meta-analysis and diversity-adjusted trial sequential analysis of randomized trials. **Arch Neurol 68:**172–184, 2011
9. Biggs KL, Moore WS: Current trends in managing carotid artery disease. **Surg Clin North Am 87:**995–1016, vii, 2007
10. Borissoff JI, Spronk HMH, ten Cate H: The hemostatic system as a modulator of atherosclerosis. **N Engl J Med 364:**1746–1760, 2011
11. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, et al: Stenting versus endarterectomy for treatment of carotid-artery stenosis. **N Engl J Med 363:**11–23, 2010
12. Chambers BR, Donnan GA: Carotid endarterectomy for asymptomatic carotid stenosis. **Cochrane Database Syst Rev(4):**CD001923, 2005
13. Cikrit DF, Larson DM, Sawchuk AP, Thornhill C, Shafique S, Nachreiner RD, et al: Discretionary carotid patch angioplasty leads to good results. **Am J Surg 192:**e46–e50, 2006
14. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, et al: Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. **Stroke 41:**1294–1297, 2010
15. Diaz FG, Velardo B, Johnson R, Malik GM: Carotid endarterectomy: indications and surgical technique. **J Clin Neurosci 1:**98–105, 1994
16. Dick P, Sherif C, Sabeti S, Amighi J, Minar E, Schillinger M: Gender differences in outcome of conservatively treated patients with asymptomatic high grade carotid stenosis. **Stroke 36:**1178–1183, 2005
17. Ecker RD, Levy EI, Hopkins LN: Carotid artery stenting: evidence-based treatment. **Clin Neurosurg 53:**217–222, 2006
18. Economopoulos KP, Sergentanis TN: Methodological remarks concerning the recent meta-analysis of carotid artery stenting vs carotid endarterectomy. **Arch Neurol 68:**543–544, 2011
19. Economopoulos KP, Sergentanis TN, Tsivgoulis G, Mariolis AD, Stefanadis C: Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. **Stroke 42:**687–692, 2011
20. Ederle J, Featherstone RL, Brown MM: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. **Cochrane Database Syst Rev (4):**CD000515, 2007
21. Engelter S, Lyrer P: Antiplatelet therapy for preventing stroke and other vascular events after carotid endarterectomy. **Cochrane Database Syst Rev (3):**CD001458, 2003
22. Erzurum VZ, Littooy FN, Steffen G, Chmura C, Mansour MA: Outcome of nonoperative management of asymptomatic high-grade carotid stenosis. **J Vasc Surg 36:**663–667, 2002
23. European Carotid Surgery Trialists' Collaborative Group: MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. **Lancet 337:**1235–1243, 1991
24. Furberg CD, Adams HP Jr, Applegate WB, Byington RP, Espeland MA, Hartwell T, et al: Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. **Circulation 90:**1679–1687, 1994
25. Gao DY, Varcoe RL, Niesche JW, Lennox AR, Haindl W, Frawley JE: Association of carotid artery atheromatous plaque types with cerebral perfusion. **ANZ J Surg 79:**824–828, 2009
26. Goessens BMB, Visseren FLJ, Kappelle LJ, Algra A, van der Graaf Y: Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. **Stroke 38:**1470–1475, 2007
27. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al: Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. **Circulation 113:**e873–e923, 2006 (Erratum in **Circulation 114:**e617, 2006)
28. González A, Gil-Peralta A, Mayol A, Gonzalez-Marcos JR, Moniche F, Aguilar M, et al: Internal carotid artery stenting in patients with near occlusion: 30-day and long-term outcome. **AJNR Am J Neuroradiol 32:**252–258, 2011
29. Grunwald IQ, Kühn AL: Controversies around carotid stenting. **Acta Chir Belg 111:**63–67, 2011
30. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al: Long-term results of carotid stenting versus endarterectomy in high-risk patients. **N Engl J Med 358:**1572–1579, 2008
31. Hadjiev DI, Mineva PP: Which patients having asymptomatic carotid artery stenosis might benefit from screening? **Stroke 41:**e587–e588, 2010
32. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al: 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. **Lancet 376:**1074–1084, 2010
33. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al: Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. **Lancet 363:**1491–1502, 2004
34. Hobson RW II, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, et al: Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. **N Engl J Med 328:**221–227, 1993
35. Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, et al: The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. **N Engl J Med 342:**1693–1700, 2000
36. Janssen MP, de Borst GJ, Mali WP, Kappelle LJ, Moll FL, Ackerstaff RG, et al: Carotid stenting versus carotid endarterectomy: evidence basis and cost implications. **Eur J Vasc Endovasc Surg 36:**258–266, 2008
37. Karp HR, Flanders WD, Shipp CC, Taylor B, Martin D: Carotid endarterectomy among Medicare beneficiaries: a statewide evaluation of appropriateness and outcome. **Stroke 29:**46–52, 1998
38. Katras T, Baltazar U, Rush DS, Sutterfield WC, Harvill LM, Stanton PE Jr: Durability of eversion carotid endarterectomy: comparison with primary closure and carotid patch angioplasty. **J Vasc Surg 34:**453–458, 2001
39. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, et al: Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. **N Engl J Med 364:**127–135, 2011
40. Klein A, Solomon CG, Hamel MB: Clinical decisions. Management of carotid stenosis—polling results. **N Engl J Med 358:**e23, 2008
41. Lanzino G, Tallarita T, Rabinstein AA: Internal carotid artery stenosis: natural history and management. **Semin Neurol 30:**518–527, 2010
42. Liapis CD, Kakisis JD, Kostakis AG: Carotid stenosis: factors affecting symptomatology. **Stroke 32:**2782–2786, 2001
43. Longmore RB, Yeh RW, Kennedy KF, Anderson HV, White CJ, Longmore LS, et al: Clinical referral patterns for carotid artery stenting versus carotid endarterectomy: results from the Carotid Artery Revascularization and Endarterectomy Registry. **Circ Cardiovasc Interv 4:**88–94, 2011
44. Lutz HJ, Sacuiu RD, Gahl B, Savolainen H: Best medical therapy or wishful thinking in carotid disease? A single-centre audit in Germany. **Eur J Vasc Endovasc Surg 41:**501–506, 2011
45. Mahoney EM, Greenberg D, Lavelle TA, Natarajan A, Berezin R, Ishak KJ, et al: Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at increased surgi-

cal risk: results from the SAPPHIRE trial. **Catheter Cardiovasc Interv 77:**463–472, 2011
46. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al: Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. **Lancet Neurol 9:**663–671, 2010
47. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM: Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. **Stroke 41:**e11–e17, 2010
48. McDonnell CO, Legge D, Twomey E, Kavanagh EG, Dundon S, O'Donohoe MK, et al: Carotid artery angioplasty for restenosis following endarterectomy. **Eur J Vasc Endovasc Surg 27:**163–166, 2004
49. Mineva PP, Manchev IC, Hadjiev DI: Prevalence and outcome of asymptomatic carotid stenosis: a population-based ultrasonographic study. **Eur J Neurol 9:**383–388, 2002
50. Moore WS, Boren C, Malone JM, Roon AJ, Eisenberg R, Goldstone J, et al: Natural history of nonstenotic, asymptomatic ulcerative lesions of the carotid artery. **Arch Surg 113:**1352–1359, 1978
51. Nadareishvili ZG, Rothwell PM, Beletsky V, Pagniello A, Norris JW: Long-term risk of stroke and other vascular events in patients with asymptomatic carotid artery stenosis. **Arch Neurol 59:**1162–1166, 2002
52. Naylor AR: Riding on the CREST of a wave! **Eur J Vasc Endovasc Surg 39:**523–526, 2010
53. Naylor AR: Where next after SPACE and EVA-3S: 'the good, the bad and the ugly!' **Eur J Vasc Endovasc Surg 33:**44–47, 2007
54. Naylor AR, Ricco JB: Just when we thought we knew all the answers, someone changed the questions! **Eur J Vasc Endovasc Surg 41:**150–152, 2011
55. Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T, et al: Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. **Eur J Vasc Endovasc Surg 30:**275–284, 2005
56. North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. **N Engl J Med 325:**445–453, 1991
57. Reiff T, Böckler D, Böhm M, Brückmann H, Debus ES, Eckstein HH, et al: Ongoing randomized controlled trials comparing interventional methods and optimal medical treatment in the treatment of asymptomatic carotid stenosis. **Stroke 41:**e605–e607, 2010
58. Rerkasem K, Rothwell PM: Systematic review of randomized controlled trials of patch angioplasty versus primary closure during carotid endarterectomy. **Stroke** [epub ahead of print], 2009
59. Rijbroek A, Wisselink W, Vriens EM, Barkhof F, Lammertsma AA, Rauwerda JA: Asymptomatic carotid artery stenosis: past, present and future. How to improve patient selection? **Eur Neurol 56:**139–154, 2006
60. Roederer GO, Langlois YE, Jager KA, Primozich JF, Beach KW, Phillips DJ, et al: The natural history of carotid arterial disease in asymptomatic patients with cervical bruits. **Stroke 15:**605–613, 1984
61. Saba L, Mallarini G: A comparison between NASCET and ECST methods in the study of carotids: evaluation using Multi-Detector-Row CT angiography. **Eur J Radiol 76:**42–47, 2010
62. Sabeti S, Schlager O, Exner M, Mlekusch W, Amighi J, Dick P, et al: Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. **Stroke 38:**2887–2894, 2007
63. Sacco RL: Clinical practice. Extracranial carotid stenosis. **N Engl J Med 345:**1113–1118, 2001
64. Safian RD: Treatment strategies for carotid stenosis in patients at increased risk for surgery. **Prog Cardiovasc Dis 54:**22–28, 2011
65. Schneider PA, Naylor AR: Transatlantic debate. Asymptomatic carotid artery stenosis—medical therapy alone versus medical therapy plus carotid endarterectomy or stenting. **Eur J Vasc Endovasc Surg 40:**274–281, 2010
66. Selim MH, Molina CA: Medical versus surgical treatment of asymptomatic carotid stenosis: the ever-changing nature of evidence-based medicine. **Stroke 42:**1156–1157, 2011
67. Shields RC: Medical management of carotid stenosis. **Perspect Vasc Surg Endovasc Ther 22:**18–27, 2010
68. Sila CA, Higashida RT, Clagett GP: Clinical decisions. Management of carotid stenosis. **N Engl J Med 358:**1617–1621, 2008
69. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al: Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. **Arch Neurol 67:**180–186, 2010
70. Spence JD, Tamayo A, Lownie SP, Ng WP, Ferguson GG: Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. **Stroke 36:**2373–2378, 2005
71. Sundt TM Jr, Ebersold MJ, Sharbrough FW, Piepgras DG, Marsh WR, Messick JM Jr: The risk-benefit ratio of intraoperative shunting during carotid endarterectomy. Relevancy to operative and postoperative results and complications. **Ann Surg 203:**196–204, 1986
72. Thompson JE, Patman RD, Talkington CM: Asymptomatic carotid bruit: long term outcome of patients having endarterectomy compared with unoperated controls. **Ann Surg 188:** 308–316, 1978
73. Wang CJ, Wang CX, Zhang L, Wang YL, Wang YJ: Advances in stroke care and research in 2010. **Clin Exp Pharmacol Physiol 38:**562–569, 2011
74. Young KC, Jahromi BS: Does current practice in the United States of carotid artery stent placement benefit asymptomatic octogenarians? **AJNR Am J Neuroradiol 32:**170–173, 2011

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Address correspondence to: Charles J. Prestigiacomo, M.D., Department of Neurological Surgery, UMDNJ–New Jersey Medical School, 90 Bergen Street, Suite 8100, Newark, New Jersey 07103. email: c.prestigiacomo@umdnj.edu.

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Incidental os odontoideum: current management strategies

Paul Klimo Jr., M.D., M.P.H.,[1] Valerie Coon, M.D.,[2] and Douglas Brockmeyer, M.D.[2]

[1]Semmes-Murphey Neurologic & Spine Institute, Memphis, Tennessee; and [2]Department of Neurosurgery, Primary Children's Medical Center, University of Utah, Salt Lake City, Utah

Os odontoideum was first described in the late 1880s and still remains a mystery in many respects. The genesis of os odontoideum is thought to be prior bone injury to the odontoid, but a developmental cause probably also exists. The spectrum of presentation is striking and ranges from patients who are asymptomatic or have only neck pain to those with acute quadriplegia, chronic myelopathy, or even sudden death. By definition, the presence of an os odontoideum renders the C1–2 region unstable, even under physiological loads in some patients. The consequences of this instability are exemplified by numerous cases in the literature in which a patient with os odontoideum has suffered a spinal cord injury after minor trauma. Although there is little debate that patients with os odontoideum and clinical or radiographic evidence of neurological injury or spinal cord compression should undergo surgery, the dispute continues regarding the care of asymptomatic patients whose os odontoideum is discovered incidentally. The authors' clinical experience leads them to believe that certain subgroups of asymptomatic patients should be strongly considered for surgery. These subgroups include those who are young, have anatomy favorable for surgical intervention, and show evidence of instability on flexion-extension cervical spine x-rays. This recommendation is bolstered by the fact that surgical fusion of the C1–2 region has evolved greatly and can now be done with considerable safety and success. When atlantoaxial instrumentation is used, fusion rates for os odontoideum should approach 100%.
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Key Words • **incidental os odontoideum** • **atlantoaxial instability** • **atlantoaxial fusion** • **screw fixation**

Os odontoideum is an anatomical abnormality in which the tip of the odontoid process lacks continuity with the body of C-2. It appears as a smooth-margined, apical osseous segment separated from the base of the odontoid process by an obvious gap. Os odontoideum may be discovered as part of a workup for neck pain and/or neurological symptoms, but it is also often found incidentally. Most spine surgeons agree that patients with signs or symptoms of neurological dysfunction should undergo stabilization, but the role for surgical stabilization in asymptomatic patients and those with neck pain alone remains controversial.

In an article in the "Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries" supplement published in 2002 jointly by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, the authors reviewed the available literature on os odontoideum and found no Class I or Class II data to generate treatment standards or guidelines.[1] The following management option was given for patients with incidental os odontoideum based on the available Class III data: "Patients with os odontoideum, either with or without C1–2 instability, who have neither symptoms nor neurological signs may be managed with clinical and radiographic surveillance." Even so, the authors acknowledged that patients with C1–2 instability are at risk for future spinal cord damage and that surgical stabilization and fusion of C1–2 is "meritorious." In fact, the literature regarding the management of os odontoideum remains limited to Class III data. Here we present the case of a patient with an incidentally discovered os odontoideum and review the embryological aspects and relevant upper cervical spinal anatomy and literature. We conclude by presenting a management strategy that we believe is rational given our experience, along with data from the available literature.

Abbreviation used in this paper: VA = vertebral artery.

Illustrative Case

Clinical Presentation

This 14-year-old girl was admitted to the hospital after having possible seizures, intermittent headaches, and dizziness. She underwent MR imaging of her brain, which showed a mild Chiari I malformation with approximately 6 mm of tonsillar herniation, but also a dysplastic odontoid. On her cervical spine MR images there was no spinal cord signal change or syringohydromyelia, and the VA anatomy was normal (Fig. 1A). A CT scan confirmed the presence of an os odontoideum. The os fragment was

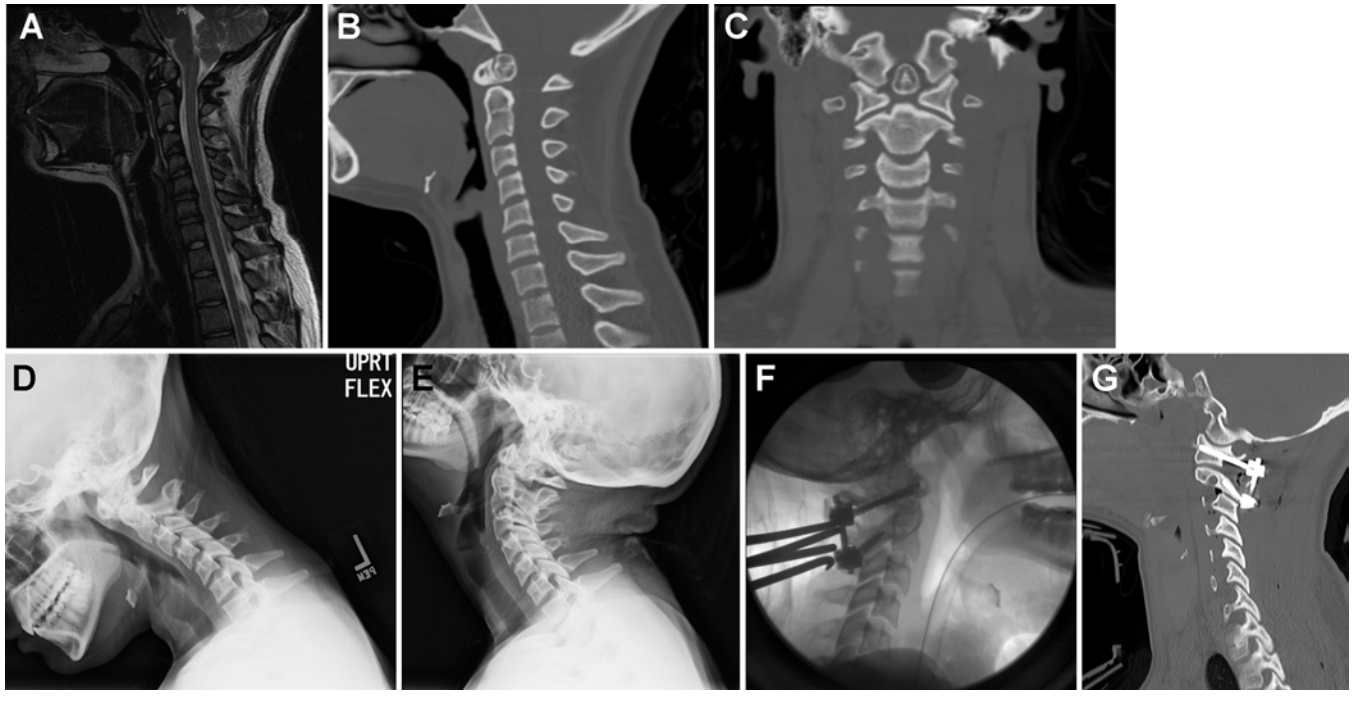

Fig. 1. Sagittal T2-weighted MR image **(A)** and sagittal **(B)** and coronal **(C)** CT scans showing a dystopic-type os odontoideum in a 14-year-old girl. On the coronal image, it is clear that the gap between the ossicle and the remainder of the odontoid is above the superior articulating facet of C-2. Flexion radiograph **(D)** shows no sign of instability, but with extension **(E)**, there is almost 10 mm of subluxation. The patient underwent placement of a Harms construct with bilateral pars interarticularis screws at C-2 coupled to lateral mass screws at C-1. The intraoperative radiograph **(F)** and postoperative sagittal CT **(G)** show the position of the hardware. An iliac crest autograft was harvested and secured between C-1 and C-2 after the surfaces were well decorticated.

fused to the posterior aspect of C-1, consistent with a dystopic os odontoideum (Fig. 1B and C). There was no abnormal atlantoaxial motion on flexion, but with extension, the patient had posterior subluxation of 9–10 mm (posterior instability, Fig. 1D and E). We concluded that although her os odontoideum was discovered incidentally, surgical fusion was indicated because she showed evidence of instability.

Treatment and Postoperative Follow-Up

After approximately 1 month in a collar, the patient underwent a posterior C1–2 fusion performed using C-1 lateral mass screws coupled to C-2 pars interarticularis screws (Fig. 1F and G). Posterior iliac crest autograft was fashioned and secured between C-1 and C-2. We elected not to perform a posterior fossa decompression for her mild Chiari malformation because we believed it was asymptomatic. A CT scan obtained 4 months after surgery showed a solid fusion.

Embryological Development and Pathogenesis

During normal embryological development, the odontoid process is derived from somites 4 (fourth occipital sclerotome, "C0"); 5 (first cervical sclerotome, "C1"); and 6 (second cervical sclerotome, "C2"). The body of the odontoid begins as part of the centrum of the first cervical vertebra, but becomes separated from the atlas to fuse with the remainder of the axis between the 6th and 7th weeks of gestation. The apex of the odontoid is derived from the fourth occipital sclerotome, commonly known as the proatlas. At birth, there is an epiphyseal growth plate called the neurocentral synchondrosis that separates the body of the axis (C-2) from the dens (C-1). This synchondrosis is not located at the base of the dens, but is well below the level of the superior articulating facet of the axis and into its body. The blood supply to the odontoid is also unique. The VA provides both an anterior and a posterior ascending artery, but the neurocentral synchondrosis prevents further rostral supply by these arteries. Therefore, the odontoid is supplied by a descending supply superiorly called the apical arcade.

The cause of os odontoideum remains the subject of debate. It was once believed to be a congenital lesion caused by a failure of fusion between the first and second sclerotomes (that is, across the neurocentral synchondrosis). A familial form of the condition and os odontoideum found in identical twins have been reported in patients with no preceding history of trauma, supporting the congenital hypothesis;[18,26,36] however, this theory has been questioned because, as previously stated, the neurocentral synchondrosis is located below the level of the superior articulating facet, whereas the gap in os odontoideum is frequently located above the plane of the superior articulating facet. Nonetheless, some authors still believe that a congenital mechanism is plausible. Currarino[5] proposed that os odontoideum represents an abnormal complete or partial embryonic segmentation of the midportion of the odontoid between chondrification segments X and Y.

Most physicians now believe that the ossicle rep-

resents a posttraumatic phenomenon resulting from a nonhealed odontoid synchondrosis fracture. In essence, the odontoid fragment fails to remodel and unite with the body of C-2. This scenario is supported by the observation that many patients with os odontoideum have a history of remote trauma, particularly in early childhood.[23] The most commonly cited theory was proposed by Fielding et al.,[9] who suggested that with a fracture or disruption through the neurocentral synchondrosis, the alar ligaments that attach to the apex of the odontoid may gradually distract the fragment away from the base. The apex and base of the odontoid continue to have adequate perfusion, but the midportion suffers from lack of blood supply and thus contributes to poor healing.

The "traumatic cause" hypothesis is supported by case reports of patients with a previously documented intact C-2 who later were found to have os odontoideum after remote trauma. Schuler et al.[31] reported on a 2-year-old patient who fell out of her crib and complained of neck pain; her initial cervical x-ray was normal. After continued neck pain, repeat cervical x-rays were obtained 13 months after her injury, which demonstrated os odontoideum with atlantoaxial instability. A recent case report by Zygourakis et al.[41] supports the delayed formation of an os odontoideum through a combination of trauma and vascular compromise. Their patient was a 2-year-old girl who sustained a C1–2 ligamentous injury but no bone injury. Four years later an os odontoideum was found, and 10 years after trauma the child had developed mild atlantoaxial hypermobility that continued to be managed nonoperatively. It is likely that os odontoideum most commonly arises as a result of remote trauma, but some cases are also probably due to faulty embryogenesis. Os odontoideum needs to be differentiated from a persistent ossiculum terminale. The latter represents congenital nonunion of the odontoid body from a terminal ossicle located above the transverse atlantal ligament. Thus, atlantoaxial instability is usually not associated with an ossiculum terminale.

Presentation and Imaging Features

Rowland et al.[29] categorized symptoms of os odontoideum into 4 groups: Group 1, local symptoms only (for example, neck pain, headaches) and no signs of myelopathy; Group 2, posttraumatic transient myelopathy; Group 3, persistent myelopathy; and Group 4, cerebral symptoms suggestive of posterior circulation ischemia. Patients with symptoms in Group 2 classically have transient complete tetraplegia immediately after a traumatic event, which is often minor in nature. Those with symptoms in Group 3 have chronic, often progressive myelopathy because of repeated trauma to the spinal cord as a result of excessive motion of the ring of C-1 and the ossicle. Patients with posterior circulation symptoms are quite rare, but have been reported.[10,34] Asymptomatic patients, by definition, have incidentally discovered os odontoideum. This group comprised 15% of patients in our recent series.[19]

Os odontoideum is a rare radiographic diagnosis. Two types of os odontoideum have been defined based on the position of the dens tip: orthotopic and dystopic.[8] In the orthotopic type, the dens is in an anatomical position. In dystopic os odontoideum, the dens tip is in any other position. Most commonly, the fragment is located near the foramen magnum, where it may fuse with the clivus, or it may be fixed to the anterior ring of the atlas. Plain cervical x-rays are often sufficient to suggest the diagnosis of an os odontoideum, but a high-resolution multiplanar CT scan is necessary to provide the detailed anatomy of the os odontoideum and any associated cervical or skull base anomalies for surgical planning. Dynamic flexion and extension lateral radiographs may be obtained to determine whether there is any abnormal atlantoaxial motion and, if so, in which direction is the subluxation: anterior, posterior, or both.

In our series, a subset of 60 patients with os odontoideum who underwent dynamic imaging had predominantly anterior instability (70%), with almost equal posterior instability (10%) or combined anterior/posterior instability (13%). No motion was seen in 7% of the patients. Although many spine surgeons believe that a patient with normal mentation can undergo volitional flexion and extension imaging without risking neurological injury, particularly in those who are without symptoms, these studies should be ordered with caution in those who have had recent neurological injury or chronic myelopathy. An MR imaging study should also be done to evaluate for any intrinsic spinal cord signal change at the level of os odontoideum that would indicate prior or continuing spinal cord trauma. Rarely, synovial cysts may develop as a result of the abnormal motion, and these are best evaluated using MR imaging.[17,27] Careful evaluation of the regional vascular anatomy is necessary because anomalies have been reported in association with an os odontoideum, particularly the presence of an anomalous VA[38,39] or persistent fetal anterior-posterior circulation connection.[21]

Biomechanics and Stability

The stability of the C1–2 joint is determined by the integrity of the odontoid process, the transverse ligament, and to a lesser extent, the alar ligaments. Thus, the biomechanical principles of C1–2 stability are inherently violated with os odontoideum. With an incompetent odontoid process, the spinal cord may be compressed posteriorly during flexion by the posterior ring of C-1 or on extension by posterior translation of the os itself (Fig. 2). In the absence of an intact odontoid process, we believe that the existing stabilizing structures—the thinner vertical portion of the cruciate ligament (an extension of the posterior longitudinal ligament), the thin anterior longitudinal ligament, and the lax capsular ligaments—are insufficient to provide the necessary spinal stability and protection of the spinal cord. An os odontoideum is biomechanically analogous and in some cases difficult to distinguish from a chronic nonunited Type 2 odontoid fracture. Although it is well accepted among most spine surgeons that Type 2 fractures, whether acute or chronic but not healed, are unstable and require treatment, there continues to be a significant difference of opinion among surgeons regarding the treatment of an incidental os odontoideum.

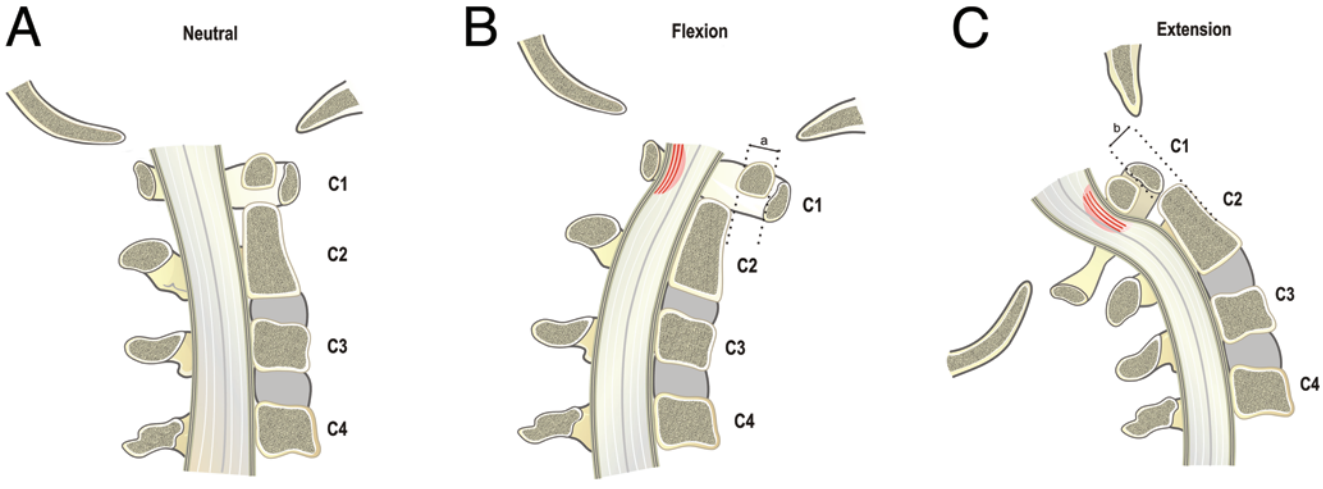

Fig. 2. Diagrams depicting an os odontoideum in neutral **(A)**, flexed **(B)**, and extended **(C)** positions. With an os odontoideum (A), abnormal motion may occur anteriorly, posteriorly, or both. Flexion (B) can cause translation of the C-1 ring and ossicle complex to the point that it may impinge on the dorsal aspect of the cord. On extension (C), the anterior ring with the ossicle can strike the ventral aspect of the cord. Reproduced with permission from Klimo P Jr, Kan P, Rao G, et al: Os odontoideum: presentation, diagnosis, and treatment in a series of 78 patients. Clinical article. **J Neurosurg Spine 9:**332–342, 2008.

Natural History and Risk of Injury

Descriptions of the natural history of os odontoideum are very limited and dated. Several reports have presented evidence of patients who were treated conservatively without further incident. Fielding et al.[9] reported a series of 35 patients, 8 of whom had no radiographic evidence of C1–2 instability and underwent conservative management. Each of them remained without symptoms at follow-up evaluation. Similarly, all 5 of the asymptomatic patients with os odontoideum in whom the condition was managed without surgical intervention by Dai et al.[6] remained stable at follow-up. Spierings and Braakman[32] analyzed 37 patients with os odontoideum, in 20 of whom the condition was managed conservatively. The authors found that patients with a minimal sagittal diameter (defined as the distance between the posterior border of the body of C-2 and the posterior atlantal arch on flexion) of < 13 mm had the greatest risk of developing permanent or progressive cord signs. This suggests that incidental os odontoideum may be managed without surgical intervention unless the minimum sagittal diameter is < 13 mm or there is progressive neurological decline. Although these studies suggest that in some patients with incidental os odontoideum the condition can be safely managed conservatively, in sum the studies provide less than definitive evidence as to the natural history and risks associated with untreated os odontoideum.

Sudden death[7,25,30] and significant neurological morbidity[20,24,33] with minor trauma have both been reported as the initial presentation of patients with a previously undiagnosed os odontoideum. Choit et al.[4] reported on 2 children who each had an os odontoideum that had not been appreciated on initial imaging and that caused subsequent morbidity. One of the children sustained a severe high spinal cord injury after a minor accident. We previously presented 3 case examples of patients in whom an os odontoideum was initially diagnosed but who never received treatment and who subsequently developed a spinal cord injury.[19] More recently, Zhang et al.[40] reported on 10 patients with atlantoaxial instability from os odontoideum, including 3 who were asymptomatic, who later suffered a spinal cord injury. The mechanism was a fall in 6 patients, a minor motor vehicle accident in 3, and assault in 1. Based on this experience, the authors advocated fusion and instrumentation for all patients with radiographically unstable os odontoideum, whether they were symptomatic or not.

White and Panjabi[37] defined clinical instability as "the loss of the ability of the spine under physiological loads to maintain its pattern of displacement so that there is no initial or additional neurological deficit, no major deformity, and no incapacitating pain." For some patients with os odontoideum, everyday physiological loads are well tolerated and supported by the accessory structures described previously. Given the numerous reports of patients suffering neurological injury from minor trauma, however, we believe that the ability to tolerate physiological loads or minor trauma cannot be assumed, because the potential loss of that gamble could be catastrophic.

For some patients, particularly young children and teenagers, it is difficult or even impossible to limit day-to-day activity to "physiological" loading, without severely restricting their activity and thus negatively impacting the quality of their life. This includes the normal day-to-day episodes of ground-level falls in toddlers or, for example, falls from playground equipment in older children. For teenagers, giving up contact or collision sports may be relatively easy, but the pushing and shoving that goes on in school hallways, as another example, may not be so easy to avoid. Conversely, it is relatively easy for most young adults with os odontoideum to modify their activities to reduce the risk of spinal cord injury. Their greatest risk obviously lies in the possibility of a motor vehicle accident, which is a risk shared by almost everyone. That

is why we choose to use the patient's age as a surgical selection criterion for an incidentally discovered os odontoideum; we believe that young patients are more likely to need protection than older ones.

Management of Incidental Os Odontoideum

We believe that all patients with neurological symptoms or significant neck pain due to os odontoideum should undergo surgical stabilization. Patients with incidentally discovered os odontoideum should be considered for surgery on a case-by-case basis. Those patients who show evidence of radiographic instability at the atlantoaxial level, who are relatively young (< 20 years old), and who have bone anatomy favorable for screw fixation should be strongly considered for surgery. Asymptomatic patients who do not meet the criteria given above may be monitored with serial radiographs and clinical evaluations to detect whether instability or significant symptoms are developing. Arvin et al.[2] presented similar recommendations, arguing that patients with a stable os odontoideum without evidence of spinal cord compression should be evaluated annually with dynamic plain x-rays, repeat MR imaging in 5 years, and avoidance of all contact sports.

Surgery

Excellent clinical results and high rates of fusion (> 90%) for both adults and children who have undergone instrumentation of the C1–2 level have been demonstrated in numerous series.[12,14,15,22,28,35] Surgical techniques and fusion technology have evolved tremendously over the last several decades. Screw fixation techniques have largely replaced the stand-alone graft/wiring procedures such as the Gallie and Brooks techniques of the past, leading to excellent results.[3,11] Placement of transarticular C1–2 screws was the main method of screw fixation of the C1–2 joint, but this technique involved a risk of injuring the VA.[13] The surgeon now has available other types of screws, including C-1 lateral mass screws, C-2 pedicle or pars screws, C-1 hooks, and C-2 laminar screws, to minimize the chance of injuring the VA. Consequently, the use of transarticular screws has become less popular. Hardware can now be placed with minimal risk of neurological or vascular injury. Although harvested autograft, typically from the patient's posterior iliac crest, is still the main grafting substrate, there is now evidence that allograft may work just as well, thus eliminating donor site-related issues, particularly pain.[16] Although there is a loss of approximately 40%–50% of rotation with fusion of C1–2, we have found that older adults seem to adapt well to this loss of motion. Younger adults and children often have little, if any, limitation to motion after atlantoaxial fusion, because other spinal levels assume more rotatory function. It is our opinion that the loss of rotation after a C1–2 fusion seems to be a small price to pay for securing spinal stability and avoiding potentially catastrophic cord compression.

Conclusions

The incomplete odontoid process found in os odontoideum results in weakness of the C1–2 joint. It is potentially dangerous to assume that the remaining supporting structures are strong enough to sustain physiological loads and forces from even minor trauma. Patients with an incidentally discovered os odontoideum should be considered carefully for surgery, taking into account their age, activity level, and radiographic findings, including evidence of atlantoaxial instability and anatomy favorable for surgical instrumentation. Surgery can be done safely, with minimal risk of complications, and with an excellent chance of achieving optimal clinical results.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Brockmeyer. Acquisition of data: Coon. Drafting the article: Klimo, Coon. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Klimo. Study supervision: Brockmeyer.

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References

1. Anonymous: Os odontoideum. **Neurosurgery 50 (3 Suppl):** S148–S155, 2002
2. Arvin B, Fournier-Gosselin MP, Fehlings MG: Os odontoideum: etiology and surgical management. **Neurosurgery 66 (3 Suppl):**22–31, 2010
3. Brooks AL, Jenkins EB: Atlanto-axial arthrodesis by the wedge compression method. **J Bone Joint Surg Am 60:**279–284, 1978
4. Choit RL, Jamieson DH, Reilly CW: Os odontoideum: a significant radiographic finding. **Pediatr Radiol 35:**803–807, 2005
5. Currarino G: Segmentation defect in the midodontoid process and its possible relationship to the congenital type of os odontoideum. **Pediatr Radiol 32:**34–40, 2002
6. Dai L, Yuan W, Ni B, Jia L: Os odontoideum: etiology, diagnosis, and management. **Surg Neurol 53:**106–109, 2000
7. Dempster AG, Heap SW: Fatal high cervical spinal cord injury in an automobile accident complicating os odontoideum. **Am J Forensic Med Pathol 11:**252–256, 1990
8. Fielding JW, Griffin PP: Os odontoideum: an acquired lesion. **J Bone Joint Surg Am 56:**187–190, 1974
9. Fielding JW, Hensinger RN, Hawkins RJ: Os odontoideum. **J Bone Joint Surg Am 62:**376–383, 1980
10. Fukuda M, Aiba T, Akiyama K, Nishiyama K, Ozawa T: Cerebellar infarction secondary to os odontoideum. **J Clin Neurosci 10:**625–626, 2003
11. Gallie WE: Fractures and dislocations of the cervical spine. **Am J Surg 46:**495–499, 1939
12. Gluf WM, Brockmeyer DL: Atlantoaxial transarticular screw fixation: a review of surgical indications, fusion rate, complications, and lessons learned in 67 pediatric patients. **J Neurosurg Spine 2:**164–169, 2005
13. Gluf WM, Schmidt MH, Apfelbaum RI: Atlantoaxial transarticular screw fixation: a review of surgical indications, fusion rate, complications, and lessons learned in 191 adult patients. **J Neurosurg Spine 2:**155–163, 2005
14. Goel A, Desai KI, Muzumdar DP: Atlantoaxial fixation using

plate and screw method: a report of 160 treated patients. **Neurosurgery 51:**1351–1357, 2002
15. Harms J, Melcher RP: Posterior C1-C2 fusion with polyaxial screw and rod fixation. **Spine (Phila Pa 1976) 26:**2467–2471, 2001
16. Hillard VH, Fassett DR, Finn MA, Apfelbaum RI: Use of allograft bone for posterior C1-2 fusion. Clinical article. **J Neurosurg Spine 11:**396–401, 2009
17. Kirk HJ, Pik JH: A novel operative technique to manage a symptomatic synovial cyst associated with an os odontoideum. **J Clin Neurosci 16:**822–824, 2009
18. Kirlew KA, Hathout GM, Reiter SD, Gold RH: Os odontoideum in identical twins: perspectives on etiology. **Skeletal Radiol 22:**525–527, 1993
19. Klimo P Jr, Kan P, Rao G, Apfelbaum R, Brockmeyer D: Os odontoideum: presentation, diagnosis, and treatment in a series of 78 patients. Clinical article. **J Neurosurg Spine 9:**332–342, 2008
20. Kuhns LR, Loder RT, Farley FA, Hensinger RN: Nuchal cord changes in children with os odontoideum: evidence for associated trauma. **J Pediatr Orthop 18:**815–819, 1998
21. Lee SH, Kim ES, Eoh W: Posterior C1-2 fusion using a polyaxial screw/rod system for os odontoideum with bilateral persistence of the first intersegmental artery. Case report. **J Neurosurg Spine 14:**10–13, 2011
22. Leonard JR, Wright NM: Pediatric atlantoaxial fixation with bilateral, crossing C-2 translaminar screws. Technical note. **J Neurosurg 104 (1 Suppl):**59–63, 2006
23. Menezes AH: Pathogenesis, dynamics, and management of os odontoideum. **Neurosurg Focus 6(6):**e2, 1999
24. Minderhoud JM, Braakman R, Penning L: Os odontoideum, clinical, radiological and therapeutic aspects. **J Neurol Sci 8:**521–544, 1969
25. Mixter SJ, Osgood RB: IV. Traumatic lesions of the atlas and axis. **Ann Surg 51:**193–207, 1910
26. Morgan MK, Onofrio BM, Bender CE: Familial os odontoideum. Case report. **J Neurosurg 70:**636–639, 1989
27. Ogata T, Kawatani Y, Morino T, Yamamoto H: Resolution of intraspinal retro-odontoid cyst associated with os odontoideum after posterior fixation. **J Spinal Disord Tech 22:**58–61, 2009
28. Reilly CW, Choit RL: Transarticular screws in the management of C1-C2 instability in children. **J Pediatr Orthop 26:** 582–588, 2006
29. Rowland LP, Shapiro JH, Jacobson HG: Neurological syndromes associated with congenital absence of the odontoid process. **AMA Arch Neurol Psychiatry 80:**286–291, 1958
30. Schiller F, Nieda I: Malformation of the odontoid process—report of a case and clinical survey. **Calif Med 86:**394–398, 1957
31. Schuler TC, Kurz L, Thompson DE, Zemenick G, Hensinger RN, Herkowitz HN: Natural history of os odontoideum. **J Pediatr Orthop 11:**222–225, 1991
32. Spierings EL, Braakman R: The management of os odontoideum. Analysis of 37 cases. **J Bone Joint Surg Br 64:**422–428, 1982
33. Stevens JM, Chong WK, Barber C, Kendall BE, Crockard HA: A new appraisal of abnormalities of the odontoid process associated with atlanto-axial subluxation and neurological disability. **Brain 117:**133–148, 1994
34. Takakuwa T, Hiroi S, Hasegawa H, Hurukawa K, Endo S, Shimamura T: Os odontoideum with vertebral artery occlusion. **Spine (Phila Pa 1976) 19:**460–462, 1994
35. Wang MY: Transarticular screws and C1 hooks fixation for os odontoideum with atlantoaxial dislocation. **World Neurosurg 75:**440, 2011
36. Wang S, Wang C: Familial dystopic os odontoideum: a report of three cases. **J Bone Joint Surg Am 93:**e44, 2011
37. White AA III, Panjabi MM: The problem of clinical instability in the human spine: a systematic approach, in **Clinical Biomechanics of the Spine, ed 2.** Philadelphia: JB Lippincott, 1990, pp 277–378
38. Yamazaki M, Koda M, Aramomi MA, Hashimoto M, Masaki Y, Okawa A: Anomalous vertebral artery at the extraosseous and intraosseous regions of the craniovertebral junction: analysis by three-dimensional computed tomography angiography. **Spine (Phila Pa 1976) 30:**2452–2457, 2005
39. Yamazaki M, Koda M, Yoneda M, Aiba A, Moriya H: Anomalous vertebral artery at the craniovertebral junction in a patient with Down syndrome. Case report. **J Neurosurg Spine 1:**338–341, 2004
40. Zhang Z, Zhou Y, Wang J, Chu T, Li C, Ren X, et al: Acute traumatic cervical cord injury in patients with os odontoideum. **J Clin Neurosci 17:**1289–1293, 2010
41. Zygourakis CC, Cahill KS, Proctor MR: Delayed development of os odontoideum after traumatic cervical injury: support for a vascular etiology. Case report. **J Neurosurg Pediatr 7:**201–204, 2011

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Address correspondence to: Paul Klimo Jr., M.D., M.P.H., Semmes-Murphey Neurologic & Spine Institute, 6325 Humphreys Boulevard, Memphis, Tennessee 38120. email: pklimo@semmes-murphey.com.

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Incidental findings on cranial imaging in nonagenarians

Wajd N. Al-Holou, M.D.,[1] Adam Khan, B.S.,[1] Thomas J. Wilson, M.D.,[1] William R. Stetler Jr., M.D.,[1] Gaurang V. Shah, M.D.,[2] and Cormac O. Maher, M.D.[1]

Departments of [1]Neurosurgery and [2]Radiology, University of Michigan, Ann Arbor, Michigan

Object. The aim of this article was to report on the nature and prevalence of incidental imaging findings in a consecutive series of patients older than 90 years of age who underwent intracranial imaging for any reason.

Methods. The authors retrospectively reviewed the electronic medical and imaging records of consecutive patients who underwent brain MR imaging at a single institution over a 153-month interval and were at least 90 but less than 100 years of age at the time of the imaging study. The prevalence of lesions by type in this consecutive series of MR imaging evaluations was calculated for all patients. The authors reviewed the medical record to evaluate whether a change in management was recommended based on MR imaging findings. They evaluated patient age at the time of death and the time interval between MR imaging and death.

Results. The authors identified 177 patients who met the study criteria. The group included 119 women (67%) and 58 (33%) men. Their mean age was 92.3 ± 1.8 years. Evidence of acute ischemic changes or cerebrovascular accident (CVA) was found in 36 patients (20%). Fifteen patients (8%) had an intracranial tumor. Intracranial aneurysms were incidentally identified in 6 patients (3%). Chronic subdural hematomas were found in 3 patients (2%). Overall, 25 patients (14%) had some change in medical management as a result of the MR imaging findings. The most common MR imaging finding that resulted in a change in medical management was an acute CVA ($p < 0.0001$). The mean time to death from date of MR imaging was 2.5 ± 2.3 years.

Conclusions. Intracranial imaging is rarely performed in patients older than 90 years. In cases of suspected stroke, MR imaging findings may influence treatment decisions. Brain MR imaging studies ordered for other indications in this age group rarely influence treatment decisions. Incidentally discovered lesions in this age group are generally not treated. *(DOI: 10.3171/2011.9.FOCUS11205)*

Key Words • **incidental findings** • **magnetic resonance imaging** • **nonagenarians**

With the increasing use of diagnostic intracranial imaging, the incidental discovery of lesions on MR imaging is becoming an increasingly frequent cause of referral to specialists.[29] Prior reports on incidental findings from brain MR imaging have included very few individuals older than 90 years of age. Awad et al.[5] reported on 86 adults undergoing brain MR imaging and found that adults older than 60 years of age were more likely to have incidental lesions discovered on images. Vernooij et al.[42] studied the MR imaging studies of 2000 older adults in the Netherlands to examine the prevalence of incidental findings on neuroimaging. In that report, 257 patients were included who were older than 75 years of age, but the nonagenarian age group was not examined separately. Yue et al.[46] reported on 3672 patients older than 65 years of age who were enrolled in a longitudinal study of cardiovascular and cerebrovascular disease. They found clinically important incidental abnormalities on 64 scans (2%). Katzman et al.[21] studied brain MR images obtained in 1000 healthy adults and found incidental abnormal findings in 18% of this group. No nonagenarians were included in that analysis. No patients older than 90 years of age were included in several other recent analyses of incidental findings,[2,26,29,32,41,43] and no prior study has focused on patients in this age group. The aim of this article is to report on the nature and prevalence of incidental imaging findings in a consecutive series of patients older than 90 years of age who underwent intracranial imaging for any reason.

Abbreviations used in this paper: CVA = cerebrovascular accident; SDH = subdural hematoma.

Methods

Data Collection

Following approval from the University of Michigan institutional review board, we retrospectively reviewed the electronic records of all patients who underwent brain MR imaging at the University of Michigan Health System from January 1, 1997, through September 30, 2009, and

were at least 90 but less than 100 years of age at the time of the study. All MR imaging studies were performed with either a 1.5- or 3-T MR imaging device. During the study period, 62,933 patients of all ages underwent intracranial imaging at our center. Of these patients, 177 (0.3%) were in the 10th decade of life at time of the MR imaging. We reviewed the electronic medical record of each of these patients to collect data regarding patient demographic characteristics, including date of birth and sex, as well as clinical information such as the indication given for ordering the brain MR imaging, records of any previous intracranial imaging, neurological symptoms, and neurological examination findings. Any lesion that was not considered symptomatic by the treating physician was considered incidental, even if the patient had symptoms that were attributed to a different cause. The MR imaging findings were reviewed and categorized as either symptomatic or asymptomatic and incidental. The prevalence of lesions by type in this consecutive series of MR imaging evaluations was calculated for all patients. The finding of acute ischemic changes was defined as any acute or subacute parenchymal diffusion abnormality identified on MR imaging. We also reviewed the medical record to evaluate whether a change in management was recommended based on the MR imaging findings. We defined a change in management as any recommendation that would not have been made without the results of the MR imaging study. For example, in patients identified with acute ischemia, a change in management took place if a patient was placed on antiplatelet or anticoagulation therapy, such as high-dose aspirin, aspirin/dipyridamole (Aggrenox), clopidogrel sulfate, or warfarin, or underwent an intervention for the treatment or prevention of further acute ischemic events, such as administration of tissue plasminogen activator or carotid endarterectomy. We also evaluated patient age at the time of death and the time interval between MR imaging and death. For patients in whom the date of death was not recorded in our electronic medical record, the date of death, when applicable, was obtained from the Social Security Death Index.

Data Analysis

Categorical data points were compared using the Fisher exact test. Data were analyzed using PASW version 18.0 software (SPSS, Inc.).

Results

We identified 177 patients who underwent brain MR imaging during the period from January 1, 1997, through September 30, 2009, and were at least 90 but less than 100 years of age at the time of the imaging study (Table 1). Of these patients, 119 (67%) were women and 58 (33%) were men. Their mean age was 92.3 ± 1.8 years. The most common indication for imaging was an acute neurological change concerning for acute CVA in 65 patients (37%) (Table 2). Other common indications for imaging were dementia evaluation in 29 patients (16%) and mental status changes in 22 patients (12%). Eleven patients (6%) underwent MR imaging for evaluation of a known head or neck malignancy. Magnetic resonance angiography of the brain or neck was performed in conjunction with brain MR imaging in 47 patients (27%). In 96 patients (54%), a CT scan of the head had been performed in the month prior to the brain MR imaging.

TABLE 1: Age distribution of 177 consecutive nonagenarians undergoing brain MR imaging

Patient Age (yrs)	No. of MRIs
90	54
91	39
92	29
93	26
94	13
95	7
96	6
97	2
98	1
99	0

The MR images were evaluated to identify intracranial findings (Table 3). All patients had evidence of chronic ischemic changes. Evidence of acute ischemic changes or CVA was found in 36 patients (20%), and 12 (7%) had evidence of severe carotid artery or vertebrobasilar artery stenosis. Of the 12 patients with vascular stenosis, 11 had significant cervical carotid artery disease (> 70% stenosis). In 7 cases, the stenosis was identified incidentally and in 4 cases the stenosis was considered symptomatic. None of the patients with incidentally discovered carotid artery stenosis underwent treatment for the condition. One patient had significant vertebral artery stenosis, but this was considered an incidental finding and no treatment was recommended.

Fifteen patients (8%) had an intracranial tumor on MR imaging. Based on imaging appearance, 7 of these tumors were meningiomas, 3 were consistent with metastatic disease from a known primary carcinoma, 3 were suspected intraparenchymal glial tumors, and 2 were pituitary tumors. Of the 7 patients identified with meningiomas, 1 had a known history of a meningioma; in the other 6 patients the meningiomas were newly identified. Of these 7 meningiomas, 6 were asymptomatic, incidentally discovered, and were not treated (Fig. 1). One patient with a newly diagnosed posterior fossa meningioma presented with mass effect related to the meningioma; however, this patient did not receive any treatment. Three patients presented with an intracranial glial tumor; each of these patients had symptoms due to the tumor. Three patients had a presentation consistent with intracranial metastatic disease from a known primary carcinoma; the finding of intracranial disease was not included in any of these 3 patients. Head and neck malignancies were seen on MR images obtained in 13 additional patients. None of the head or neck cancers were incidental discoveries.

Intracranial aneurysms were incidentally identified in 6 patients (3%) (Fig. 2). None of these patients were symptomatic and none were treated. Five patients had anterior circulation aneurysms ranging in size from 2 to 9

TABLE 2: Indications for imaging in 177 nonagenarians as recorded on the MR imaging requisition form

Indication	Frequency (%)	Patients w/ Head CT Prior to MRI (% w/in indication)	Patients w/ Changes in Management Following MRI (% w/in indication)
acute neurological deficits/concern for CVA	65 (37)	56 (86)	17 (26)
dementia	29 (16)	0 (0)	0 (0)
nonfocal mental status changes	22 (12)	19 (86)	2 (9)
dizziness/vertigo	17 (10)	9 (53)	2 (12)
concern for seizure	8 (5)	4 (50)	0 (0)
headache	6 (3)	3 (50)	1 (17)
hearing loss	6 (3)	0 (0)	0 (0)
trigeminal neuralgia	3 (2)	0 (0)	0 (0)
history of head or neck tumor	11 (6)	2 (18)	6 (55)
evaluation for metastatic disease	7 (4)	3 (43)	0 (0)
other	3 (2)	0 (0)	0 (0)

mm, and 1 patient had a small basilar apex aneurysm. One patient had 2 incidentally identified aneurysms: a right-sided posterior communicating artery aneurysm and a left-sided middle cerebral artery aneurysm. No patients were identified with cavernous malformations or arteriovenous malformations. Chronic SDHs were found in 3 patients (2%). In 2 patients, the SDH was found incidentally; the remaining patient was symptomatic and underwent bur hole evacuation. In 1 patient (0.6%), a small asymptomatic acute SDH was identified. Four patients (2%) had other symptomatic intracranial hemorrhages. No pineal cysts were identified. Intracranial findings did not significantly differ between male and female patients.

Clinical records were reviewed to determine if the medical management for a patient was altered on the basis of the MR imaging findings (Table 2). Overall, 25 patients (14%) had some change in medical management as a result of the MR imaging findings, whereas 152 patients had no change in management. No patient in this series underwent surgical treatment for an incidentally discovered lesion. The most common MR imaging finding that resulted in a change in medical management was an acute CVA ($p < 0.0001$). In the 36 patients with a CVA on MR imaging, 18 (50%) had a change in management; in 10 patients the dose of antiplatelet medication was increased, 7 were treated with anticoagulant medication, and 2 underwent carotid endarterectomy. Five patients (3%) with head and neck cancers had a change in management as a result of the imaging findings relating to the malignancy; 4 of these patients were treated with radiation and 1 patient was offered resection. No patients with incidentally discovered intracranial aneurysms were offered surgical or endovascular treatment. Of the 81 patients who did not undergo previous head CT scans, only 4 (5%) had some change in management as result of MR imaging findings, and this was a significantly smaller proportion than in patients who had a prior head CT (22%) ($p = 0.001$).

TABLE 3: Imaging findings in 177 consecutive nonagenarians undergoing intracranial MR imaging for any indication

Finding	Frequency (%)	Incidental	Symptomatic
intracranial tumor	15 (8)	8	7
glioma	3	0	3
meningioma	7	6	1
pituitary adenoma	2	2	0
intracranial metastasis	3	0	3
head & neck malignancy	13 (7)	0	13
intracranial aneurysm	6 (3)	6	0
intracranial stenosis	12 (7)	8	4
chronic SDH	3 (2)	2	1
acute SDH	1 (0.6)	1	0
other intracranial hemorrhage	4 (2)	0	4
developmental venous anomaly	2 (1)	2	0
cavernous malformation	0	0	0
arteriovenous malformation	0	0	0
arachnoid cyst	1 (0.6)	1	0
pineal cyst	0	0	0
xanthogranuloma	1 (0.6)	1	0
cavum septum pellucidum & cavum vergae	1 (0.6)	1	0

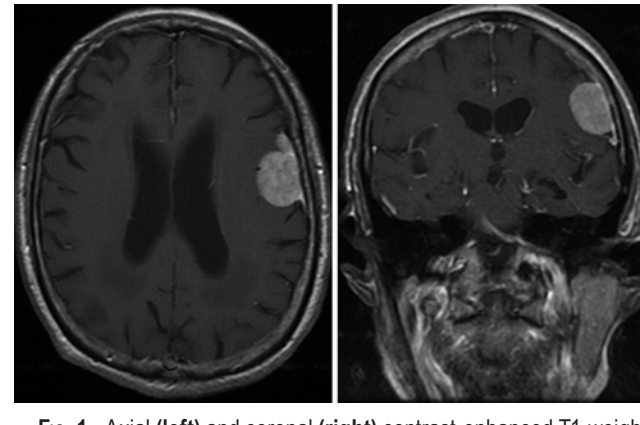

Fig. 1. Axial **(left)** and coronal **(right)** contrast-enhanced T1-weighted MR images obtained in a 93-year-old woman who presented with a 2-week history of severe headaches. The images demonstrate a left frontal meningioma. The headaches resolved spontaneously and no treatment was recommended.

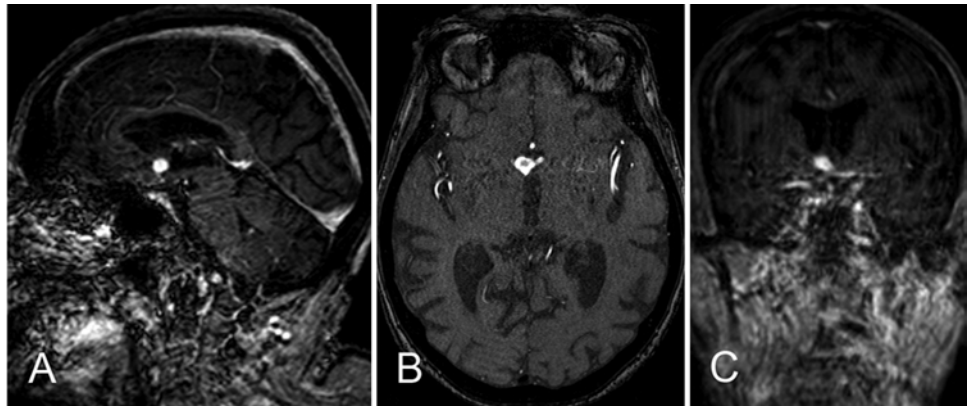

Fig. 2. Sagittal **(A)**, axial **(B)**, and coronal **(C)** contrast-enhanced T1-weighted images obtained in a 94-year-old woman who presented with acute mental status changes following a fall. The images show an incidentally discovered anterior communicating artery aneurysm. No treatment was recommended.

We evaluated the indication for imaging as recorded on the MR imaging requisition (Table 2). Of the 29 patients who underwent MR imaging as part of the workup for dementia, no patient underwent a head CT scan prior to the MR imaging study, and no patient had any change in management as a result of the MR imaging. Overall, of these 29 patients, 1 had significant carotid artery stenosis and 1 had a possible intracranial xanthogranuloma. Of the 22 patients who underwent MR imaging because of nonfocal mental status changes, 2 (9%) patients had a change in management and in both cases the change was due to the finding of a cerebral infarction. Of these 22 patients, 3 (14%) did not have preceding head CT scans.

At the completion of this study, 132 patients were deceased (75%). The mean age at death for this population was 94.9 ± 2.8 years. The mean time to death from the date of the MR imaging was 2.5 ± 2.3 years. Twenty-nine patients (16%) died within 4 months of completion of the MR imaging.

Discussion

The increasing prevalence of small-vessel disease and leukomalacia in older age groups is well established.[3,4,18,29,42] White matter lesions in the elderly are frequently asymptomatic but have been associated with a decline in cognitive or neurobehavioral ability in some studies, even when controlling for patient age.[18,28] Our finding that every nonagenarian in this group had some evidence of leukomalacia is consistent with the known natural progression of leukomalacia with advancing age.[4,20,29,42] In addition to evidence of small-vessel disease, 36 of our patients had evidence of a larger cerebral infarction. Advancing age is a risk factor for cerebral infarction.[37] Vernooij et al.[42] found MR imaging evidence of asymptomatic cerebral infarction in 18% of patients older than 75 years. When even small (> 3 mm) infarcts were considered, Price et al.[37] found cerebral infarcts in a higher percentage (31%) of individuals older than 65 years.

In our study, 15 patients had evidence of an intracranial tumor on MR imaging and 8 of these lesions were incidental findings. Although 3 patients in this series had an intrinsic brain tumor consistent with a glioma, none of these tumors were incidental findings. Meningiomas, however, were most often found incidentally. In 6 of the 7 patients with a diagnosis of meningioma, the lesions were asymptomatic. Vernooij et al.[42] found that 1.6% of individuals older than 75 years had incidental meningiomas. Our own detection rate in an older population was even higher. Fortunately, older age at the time of meningioma diagnosis has been associated with slower rates of growth.[30,33] For this reason, it is unusual for patients in this age group to undergo surgery for the treatment of meningioma. Nevertheless, several groups have found that meningioma resection can be performed safely in well-selected elderly individuals.[9,16,27] None of the patients in our own series that presented with asymptomatic meningiomas required treatment.

Incidental pituitary tumors ("incidentalomas") are known to occur in adults of all ages but are especially prevalent in the elderly. Prevalence estimates of pituitary incidentalomas in adults have ranged from less than 1% to over 20% and vary by age of the population studied and the screening method used.[10,19,34,40] Autopsy series have resulted in higher prevalence estimates than imaging studies.[25] In our group, 2 patients had pituitary lesions that, by imaging appearance, were most consistent with incidentally discovered pituitary tumors. Asymptomatic, incidentally discovered pituitary lesions are associated with a generally benign natural history and should not be treated in the elderly unless symptoms arise.[19,31] Neither of our patients with an incidentaloma was treated.

Arachnoid cysts have previously been reported in older individuals,[8,11,12,23,45] but there are no prior published reports of an arachnoid cyst in a nonagenarian. One patient in our group had an arachnoid cyst. None of the patients in our series had a pineal cyst. This finding is consistent with results of prior analyses of age-related changes in the prevalence of pineal cysts.[1] We previously found that cysts of the pineal gland became less prevalent with advancing age, becoming extremely rare in older age groups.[1]

In 6 patients (3%), intracranial aneurysms were incidentally discovered on brain MR imaging. Although this imaging prevalence is higher than that of cerebral aneurysms in the general population,[7,44] the prevalence of these lesions is believed to increase over time. Winn et al.[44] re-

ported on a consecutive series of 3684 arteriograms from a single institution. They found unruptured aneurysms in 0.6%–1.1% of patients younger than 75 years, but in 1.5% of those patients aged 75–84 years. No nonagenarians were included in that report. Similarly, Vernooij et al.[42] found that 1.6% of individuals older than 75 years in their study harbored an incidental cerebral aneurysm. None of the patients in our series with an incidentally discovered intracranial aneurysm were offered surgical or endovascular treatment. This is consistent with treatment guidelines for unruptured intracranial aneurysms, in which patient age is considered an important factor with respect to evaluation of candidates for treatment.[24]

Decreasing brain volume and increased size of the extraaxial spaces places the elderly at increased risk for SDH.[14,15,17,35] We found chronic SDH in 3 patients, only one of whom presented with symptoms of the condition. Symptomatic SDHs in the elderly should generally be treated with surgical drainage.[38]

In general, surgeons should exercise extreme caution and follow evidence-based guidelines if recommending surgical treatment for incidental discoveries. Most incidental lesions will not require surgical treatment. This principle is especially true for treating nonagenarians who may have a short life expectancy and are likely to have significant medical comorbidities. Surgical risk increases with advancing age.[6,13,36,39] In many cases, patients in our series were not surgically treated for lesions that were discovered on imaging. If a lesion becomes symptomatic, resection may be well tolerated in individuals who are highly functional, lack significant comorbidities, and have a lesion in a noncritical location.[38,39] Even symptomatic tumor resection may not be indicated in very elderly individuals if the Karnofsky Performance Scale score is less than 70, if there are significant medical comorbidities (American Society of Anesthesiologists Grade 4 or 5), or if the lesion is located in eloquent or deep areas of the brain.[16,38,39] Magnetic resonance imaging findings are more likely to affect medical management of the stroke patient. Surgical or endovascular treatment of carotid artery disease may be indicated for symptomatic stenosis in some cases.[22]

There are several limitations to our analysis. This is a retrospective review evaluating a series of patients at a large referral center. Therefore, there is a selection bias, since patients who are referred for brain MR imaging evaluation may have a higher rate of intracranial findings than is expected in the general population. Patients were included in this cohort because they underwent brain MR imaging at our institution. Although there are many reasons to obtain a brain MR imaging study, the population undergoing brain MR imaging is different from the general population. Therefore, the prevalence estimates that were found should be properly termed MR imaging prevalence rather than true population prevalence. It is possible that this MR imaging prevalence is an overestimate of lesion prevalence in the population. To obtain a true population prevalence of intracranial findings in nonagenarians, screening normal nonagenarians with MR imaging would be preferable to reviewing a cohort for whom scanning was thought to be medically necessary. Referral bias may affect our results, as physicians may be more likely to refer patients with neurological symptoms for evaluation. The impact of this bias is mitigated by the lack of symptoms resulting from many of these lesions.

Conclusions

Intracranial imaging is rarely performed in patients older than 90 years. In cases of suspected stroke, MR imaging findings may influence treatment decisions. Brain MR imaging studies ordered for other indications in this age group rarely influence treatment decisions. Incidentally discovered lesions in this age group are generally not treated.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Maher. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Maher, Shah. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Maher. Statistical analysis: Maher, Al-Holou, Wilson, Stetler. Study supervision: Maher.

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References

1. Al-Holou WN, Terman SW, Kilburg C, Garton HJL, Muraszko KM, Chandler WF, et al: Prevalence and natural history of pineal cysts in adults. Clinical article. **J Neurosurg** [epub ahead of print July 22, 2011. DOI: 10.3171/2011.6.JNS11506]
2. Alphs HH, Schwartz BS, Stewart WF, Yousem DM: Findings on brain MRI from research studies of occupational exposure to known neurotoxicants. **AJR Am J Roentgenol 187:**1043–1047, 2006
3. Awad IA, Johnson PC, Spetzler RF, Hodak JA: Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. **Stroke 17:**1090–1097, 1986
4. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R: Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. I. Correlation with age and cerebrovascular risk factors. **Stroke 17:**1084–1089, 1986
5. Awad IA, Spetzler RF, Hodak JA, Awad CA, Williams F Jr, Carey R: Incidental lesions noted on magnetic resonance imaging of the brain: prevalence and clinical significance in various age groups. **Neurosurgery 20:**222–227, 1987
6. Bateman BT, Pile-Spellman J, Gutin PH, Berman MF: Meningioma resection in the elderly: nationwide inpatient sample, 1998-2002. **Neurosurgery 57:**866–872, 2005
7. Berenstein A, Flamm ES, Kupersmith MJ: Unruptured intracranial aneurysms. **N Engl J Med 340:**1439–1442, 1999
8. Boomkens HR, van der Cammen TJ, Mattace-Raso FU: Primary arachnoid cyst mimicking depressive symptoms in an elderly woman. **Int Psychogeriatr 22:**832–833, 2010
9. Buhl R, Hasan A, Behnke A, Mehdorn HM: Results in the operative treatment of elderly patients with intracranial meningioma. **Neurosurg Rev 23:**25–29, 2000

10. Burrow GN, Wortzman G, Rewcastle NB, Holgate RC, Kovacs K: Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. **N Engl J Med 304:**156–158, 1981
11. Caruso R, Salvati M, Cervoni L: Primary intracranial arachnoid cyst in the elderly. **Neurosurg Rev 17:**195–198, 1994
12. Clavel M, Taborga FG, Onzain I: Arachnoid cysts as a cause of dementia in the elderly. **Acta Neurochir (Wien) 78:**28–32, 1985
13. Cohen JR, Johnson H, Eaton S, Sterman H, Wise L: Surgical procedures in patients during the tenth decade of life. **Surgery 104:**646–651, 1988
14. Cook IA, Leuchter AF, Morgan ML, Conlee EW, David S, Lufkin R, et al: Cognitive and physiologic correlates of subclinical structural brain disease in elderly healthy control subjects. **Arch Neurol 59:**1612–1620, 2002
15. Cook IA, Leuchter AF, Morgan ML, Dunkin JJ, Witte E, David S, et al: Longitudinal progression of subclinical structural brain disease in normal aging. **Am J Geriatr Psychiatry 12:** 190–200, 2004
16. D'Andrea G, Roperto R, Caroli E, Crispo F, Ferrante L: Thirty-seven cases of intracranial meningiomas in the ninth decade of life: our experience and review of the literature. **Neurosurgery 56:**956–961, 2005
17. Drayer BP: Imaging of the aging brain. Part I. Normal findings. **Radiology 166:**785–796, 1988
18. Garde E, Mortensen EL, Krabbe K, Rostrup E, Larsson HB: Relation between age-related decline in intelligence and cerebral white-matter hyperintensities in healthy octogenarians: a longitudinal study. **Lancet 356:**628–634, 2000
19. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH: Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. **Ann Intern Med 120:**817–820, 1994
20. Horikoshi T, Yagi S, Fukamachi A: Incidental high-intensity foci in white matter on T2-weighted magnetic resonance imaging. Frequency and clinical significance in symptom-free adults. **Neuroradiology 35:**151–155, 1993
21. Katzman GL, Dagher AP, Patronas NJ: Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. **JAMA 282:**36–39, 1999
22. Killeen KL, Wagner WH, Cossman DV, Cohen JL, Rao RK, Woo K: Carotid reconstruction in nonagenarians: is surgery a viable option? **Ann Vasc Surg 22:**190–194, 2008
23. Koga H, Mukawa J, Miyagi K, Kinjo T, Okuyama K: Symptomatic intraventricular arachnoid cyst in an elderly man. **Acta Neurochir (Wien) 137:**113–117, 1995
24. Komotar RJ, Mocco J, Solomon RA: Guidelines for the surgical treatment of unruptured intracranial aneurysms: the first annual J. Lawrence Pool memorial research symposium—controversies in the management of cerebral aneurysms. **Neurosurgery 62:**183–194, 2008
25. Koppelmans V, Schagen SB, Poels MM, Boogerd W, Seynaeve C, Lugt AV, et al: Incidental findings on brain magnetic resonance imaging in long-term survivors of breast cancer treated with adjuvant chemotherapy. **Eur J Cancer** [epub ahead of print], 2011
26. Lee WJ, Chang LB, Lee YC: Incidental findings on brain MRI. **N Engl J Med 358:**853–855, 2008
27. Mastronardi L, Ferrante L, Qasho R, Ferrari V, Tatarelli R, Fortuna A: Intracranial meningiomas in the 9th decade of life: a retrospective study of 17 surgical cases. **Neurosurgery 36:** 270–274, 1995
28. Matsubayashi K, Shimada K, Kawamoto A, Ozawa T: Incidental brain lesions on magnetic resonance imaging and neurobehavioral functions in the apparently healthy elderly. **Stroke 23:**175–180, 1992
29. Morris Z, Whiteley WN, Longstreth WT Jr, Weber F, Lee YC, Tsushima Y, et al: Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. **BMJ 339:**b3016, 2009
30. Nakamura M, Roser F, Michel J, Jacobs C, Samii M: The natural history of incidental meningiomas. **Neurosurgery 53:** 62–71, 2003
31. Nishizawa S, Ohta S, Yokoyama T, Uemura K: Therapeutic strategy for incidentally found pituitary tumors ("pituitary incidentalomas"). **Neurosurgery 43:**1344–1350, 1998
32. Onizuka M, Suyama K, Shibayama A, Hiura T, Horie N, Miyazaki H: Asymptomatic brain tumor detected at brain checkup. **Neurol Med Chir (Tokyo) 41:**431–435, 2001
33. Oya S, Kim SH, Sade B, Lee JH: The natural history of intracranial meningiomas. Clinical article. **J Neurosurg 114:** 1250–1256, 2011
34. Parent AD, Bebin J, Smith RR: Incidental pituitary adenomas. **J Neurosurg 54:**228–231, 1981
35. Peress NS, Kane WC, Aronson SM: Central nervous system findings in a tenth decade autopsy population. **Prog Brain Res 40:**473–483, 1973
36. Pirracchio R, Resche-Rigon M, Bresson D, Basta B, Welschbillig S, Heyer L, et al: One-year outcome after neurosurgery for intracranial tumor in elderly patients. **J Neurosurg Anesthesiol 22:**342–346, 2010
37. Price TR, Manolio TA, Kronmal RA, Kittner SJ, Yue NC, Robbins J, et al: Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. **Stroke 28:**1158–1164, 1997
38. Roger EP, Butler J, Benzel EC: Neurosurgery in the elderly: brain tumors and subdural hematomas. **Clin Geriatr Med 22:** 623–644, 2006
39. Sacko O, Sesay M, Roux FE, Riem T, Grenier B, Liguoro D, et al: Intracranial meningioma surgery in the ninth decade of life. **Neurosurgery 61:**950–955, 2007
40. Teramoto A, Hirakawa K, Sanno N, Osamura Y: Incidental pituitary lesions in 1,000 unselected autopsy specimens. **Radiology 193:**161–164, 1994
41. Tsushima Y, Taketomi-Takahashi A, Endo K: Prevalence of abnormal findings on brain magnetic resonance (MR) examinations in adult participants of brain docking. **BMC Neurol 5:**18, 2005
42. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al: Incidental findings on brain MRI in the general population. **N Engl J Med 357:**1821–1828, 2007
43. Weber F, Knopf H: Incidental findings in magnetic resonance imaging of the brains of healthy young men. **J Neurol Sci 240:**81–84, 2006
44. Winn HR, Jane JA Sr, Taylor J, Kaiser D, Britz GW: Prevalence of asymptomatic incidental aneurysms: review of 4568 arteriograms. **J Neurosurg 96:**43–49, 2002
45. Yamasaki F, Kodama Y, Hotta T, Taniguchi E, Eguchi K, Yoshioka H, et al: Interhemispheric arachnoid cyst in the elderly: case report and review of the literature. **Surg Neurol 59:**68–74, 2003
46. Yue NC, Longstreth WT Jr, Elster AD, Jungreis CA, O'Leary DH, Poirier VC: Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. **Radiology 202:**41–46, 1997

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Address correspondence to: Cormac O. Maher, M.D., Department of Neurosurgery, University of Michigan, 1500 East Medical Center Drive, Room 3552, Taubman Center, Ann Arbor, Michigan 48109-5338. email: cmaher@med.umich.edu.

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The management of incidental low-grade gliomas using magnetic resonance imaging: systematic review and optimal treatment paradigm

Ashish H. Shah, B.S.,[1] Karthik Madhavan, M.D.,[1] Deborah Heros, M.D.,[2] Daniel M. S. Raper, M.B.B.S.,[4] J. Bryan Iorgulescu, B.S.,[5] Brian E. Lally, M.D.,[3] and Ricardo J. Komotar, M.D.[1]

Departments of [1]Neurological Surgery, [2]Neurology, and [3]Radiation Oncology, University of Miami, Florida; [4]Royal North Shore Hospital, Sydney, Australia; and [5]Department of Neurosurgery, Memorial Sloan–Kettering Cancer Center, New York, New York

Object. The discovery of incidental low-grade gliomas (LGGs) on MR imaging is rare, and currently there is no existing protocol for management of these lesions. Various studies have approached the dilemma of managing patients with incidental LGGs. While some advocate surgery and radiotherapy, others reserve surgery until there is radiological evidence of growth. For neurosurgeons and radiologists, determining the course of action after routine brain imaging poses not only a medical but also an ethical dilemma. The authors conducted a systematic review of case reports and case series in hopes of enhancing the current understanding of the management options for these rare lesions.

Methods. A PubMed search was performed to include all relevant MR imaging studies in which management of suspected incidental LGG was reported. Comparisons were made between the surgical treatment arm and the active surveillance arm in terms of outcome, mode of discovery, reasons for treatment, and histology.

Results. Nine studies with 72 patients were included in this study (56 in the surgical arm and 16 in the active surveillance arm). Within the surgical arm, 49% remained deficit free after treatment, 25% showed evidence of tumor progression, 13% underwent a second treatment, and 7% died. The active surveillance group resulted in no unanticipated adverse events, with serial imaging revealing no tumor growth in all cases. Lesion regression was reported in 31% of this group. The surgical arm's mortality rate was 7% compared with 0% in the active surveillance arm.

Conclusions. Treatment decisions for incidental LGG should be individualized based on presenting symptoms and radiological evidence of growth. The asymptomatic patient may be monitored safely with serial MR imaging and occasionally PET scanning before treatment is initiated. In patients presenting with nonspecific symptoms or concurrent symptomatic lesions, treatment may be initiated earlier to reduce potential morbidity. All treatment decisions must be tempered by patient factors and expectations of anticipated benefit. *(DOI: 10.3171/2011.9.FOCUS11219)*

Key Words • **incidental finding** • **low-grade glioma** • **magnetic resonance imaging** • **management protocols** • **systematic review**

Incidental abnormal findings on MR imaging are occasionally noted in asymptomatic individuals. In the case of LGGs, the reported occurrence of incidental findings is extremely rare, with an incidence rate of 0.04%–0.2% within the general asymptomatic population.[19,26] Although seizures are often the presenting symptoms in most LGGs, incidental LGGs lack associated specific symptoms and remain undetected until the patient obtains radiological imaging for an unrelated reason. The majority of incidental findings are a consequence of general radiological screening of an asymptomatic population;[26] they may also be discovered as a result of imaging for trauma[34] or from investigation of other neurological or nonspecific conditions.[38]

With the increasing use of MR imaging of the brain by clinicians and investigators, the occurrence of these incidental findings has increased.[17,20,23,24] Typically, the objective of preventative screening using CNS imaging is to identify any abnormalities that may pose significant future risk. For gliomas in particular, the goal is early identification and intervention before anaplastic dedifferentiation to potentially thwart progression and improve survival. Patients with incidental gliomas may have longer overall survival from radiological diagnosis than patients with symptomatic gliomas.[29] Incidental gliomas potentially represent an early step in the histopathologi-

Abbreviations used in this paper: ^{18}F-FET = fluorine-18–labeled fluoroethyl-l-tyrosine; KPS = Karnofsky Performance Scale; LGG = low-grade glioma; SAH = subarachnoid hemorrhage.

cal progression of high-grade gliomas.[8] Detecting and treating incidental gliomas may therefore yield a better prognosis, limiting active treatment to symptomatic gliomas; however, no long-term prospective analysis has been conducted to provide confirmation.

On the other hand, several studies have questioned the validity of glioma screening. According to Steiger,[37] screening for gliomas is unjustified given their rarity and the lack of evidence corroborating the prognostic value of early intervention. In addition, long-term studies hint at the inevitability of glioma progression even with early diagnosis and treatment.[35] Because of the ubiquity of brain imaging for a wide variety of unrelated complaints, the occurrence of incidental LGG is likely to continue to increase, furthering the need for an appropriate management paradigm for these lesions.

Various studies have approached the dilemma of managing patients with incidental LGG. Although some studies advocate surgery and radiotherapy, other studies suggest that deferral of surgery until tumor progression may be more appropriate for asymptomatic patients. For neurosurgeons and radiologists, determining the course of action after routine brain imaging poses not only a medical but also an ethical dilemma. On the one hand, surgical intervention carries the risk of harm without benefit in terms of symptomatic relief; on the other hand, passively allowing tumor progression carries the potential for preventable harm. These questions have been only rarely addressed in the literature on this topic.[17] In this paper, we analyze all relevant published data on the management of incidental LGGs and determine whether there is a consensus on their management.

Methods

Study Selection

Our study used the MeSH database system within the PubMed search engine to perform our literature search. Within the MeSH system, we searched between 1990 and 2011 for the phrases "incidental findings" and "glioma." Because of the low number of matches, we expanded our search to a general PubMed search of the following phrases singly: "incidental astrocytoma," "incidental oligodendroglioma," "asymptomatic astrocytoma," and "asymptomatic oligodendroglioma." To ensure that all possible studies were included, another PubMed search was conducted using the terms "magnetic resonance imaging AND (incidental finding* OR incidental discover* AND brain)." Articles were limited to those in English, and humans were defined as the subjects for this study.

To examine the controversial management issues of gliomas, we limited our study to the main spectrum of incidental LGGs: low-grade (WHO Grade I or II) astrocytomas and oligodendrogliomas. To meet the inclusion criteria for this paper, each article must have had at least 1 case of an incidental/asymptomatic LGG (astrocytoma or oligodendroglioma) found based on MR imaging. Case reports and large asymptomatic screenings were included, and editorials and commentaries were excluded. Articles that did not describe methods of treatment/management for the incidental tumor were excluded. No studies were found to be duplicates. The last search was performed July 1, 2011.

Data Extraction

The included studies were carefully analyzed based on the patient population, methodology, reasoning for MR imaging, treatment modality, outcome, and follow-up time. Articles were separated into 2 main groups based on treatment: active surveillance and surgical treatment. Included in the surgery group were patients who underwent surgery or biopsies, including patients who delayed treatment until symptomatic progression. Patients who waited until malignant transformation for treatment were placed in the surgical group. Patients who were originally diagnosed with incidental LGG but were found to have malignant tumors were excluded. The outcome of these patients was reported in reference to the author's postoperative outcome and follow-up description.

Data for all patients were reported when available in the literature. We note that the literature search yielded very few articles, and from those articles, only a few contained full data sets for our study. No formal statistical analysis was performed due to the small sample size and intrinsic selection bias.

Results

Study Selection

Six case series (4 retrospective analyses and 2 prospective studies) and 3 case reports met the criteria for our study (Table 1). Seventy-two patients were included, with a mean age of 37.0 years (range 3–63 years). The male-to-female ratio was 0.68. Two papers formed the majority of cases with 17[11] and 47[29] patients, comprising 88.9% of the total study population. Within specific papers, certain patient data sets with incidental LGG were excluded because the reported information was pooled with other patient populations, and management information specific to patients with incidental LGG was not specified.[27] In addition, cases involving findings of incidental LGG with CT scans were not included due to the lack of diagnostic certainty (gliomas may be isodense on CT) and the implausibility of using CT scans in asymptomatic research studies due to radiation risks.[6,9,10,30,31] Four cases that were originally believed to be incidental LGG (based on radiological evidence) were excluded because histological examination revealed malignant WHO Grade III and IV astrocytomas.[11] Incidental LGG was most often diagnosed due to investigation of nonspecific or unrelated symptoms (69.4%), through workup of concurrent CNS lesions (13.9%), through MR imaging screening of healthy volunteers (11.1%), and following trauma (5.6%). The most common presenting symptom was headache (50%), followed by dizziness (22%) and mood disorders (8%; Table 2). Other reported nonspecific or unrelated symptoms included amenorrhea (6%), blurred vision (4%), fainting (4%), hearing deficiencies (4%), and lower-limb paresthesias (2%). All nonspecific or unrelated symptoms were not found to be related to the functional location of the incidental LGG. The 10 symptomatic lesions diagnosed

TABLE 1: Study characteristics of incidental LGGs*

Authors & Year	Study Design	No. of Pts (male)	Mean Age (yrs)	Mode of Discovery	Histology	Type of Initial Treatment			Outcome	Mean FU (mos)	Recurr	Notes
						None	Op	Type				
Shah et al., 2007	CR	1 (1)	11	trauma	cerebellar oligo	NA	1	GTR	no neurological deficits	16	none	boy fell from tree
Katzman et al., 1999	retro	2 (UK)	UK	screening	low-grade oligo & pilocytic astro	NA	2	resection	UK	UK	UK	none
Onizuka et al., 2001	retro	1 (1)	60	screening	low-grade astro	NA	1	GTR	no szs	12	none	pt deferred op (2 yrs) until szs
Vernooij et al., 2007	prosp	1 (UK)	UK	screening	low-grade glioma	1	NA	NA	UK	UK	UK	referral center denied op
Pallud et al., 2010	retro	47 (20)	36.6	nonspecific Sx	astro (7), oligo (31), & mixed (9)	0	47	biopsy (6), op (33; alone 28, & RT 3, & chemo 1, both 1)	tumor progression 14 (8 untreated & 6 treated), 7 needed 2nd treatment, 4 died a mean 8.9 yrs postop	91.2	7	8 pts deferred treatment until malignant transformation; 13 pts (surgical) waited until clinical Sx (mean 55.0 mos)
Suslu & Bozbuga, 2011	CR	1 (1)	39	SAH (ACoA aneurysm	Grade II oligo	NA	1	resection	healthy	22	none	aneurysm & oligo unrelated
Duffau et al., 2011	CR	1 (1)	31	FU MRI after CM	Grade II oligo	NA	1	STR	mild language deficit (resolved)	6	none	MRI demonstrated tumor growth necessitating op
Floeth et al., 2008	prosp	17 (4)	38.4	nonspecific Sx/ screening	low-grade astro (2), unproven (15)	15	2	resection	no treatment: tumor regression (5), stable (10); op: unremarkable, no neurological deficits/szs	12–72	none	op was not indicated until tumor growth was demonstrated (2 pts), no treatment (15 pts, no or negative tumor growth)
Stark et al., 2005	retro	1 (1)	3	trauma	Grade II astro	NA	1	resection & shunt, & ETV	unremarkable; PFST = 11 yrs, KPS Score 90 at last FU	132	none	tectal glioma

* ACoA = anterior communicating artery; astro = astrocytoma; chemo = chemotherapy; CM = Chiari malformation; CR = case report; ETV = endoscopic third ventriculostomy; FU = follow-up; GTR = gross-total resection; NA = not applicable; oligo = oligodendroglioma; PFST = progression-free survival time; prosp = prospective; pt = patient; Recurr = recurrence; retro = retrospective; RT = radiation therapy; szs = seizures; UK = unknown.

TABLE 2: Mode of incidental LGG discovery

Mode of ILGG Discovery	No. (%)
nonspecific symptoms	50 (69.4)
headache	25 (50)
dizziness	11 (22)
mood disorders	4 (8)
amenorrhea	3 (6)
fainting	2 (4)
hearing deficiencies	2 (4)
blurred vision	2 (4)
lower-limb paresthesia	1 (2)
other symptomatic lesions	10 (13.9)
glioma	2 (20)
schwannoma	2 (20)
cerebellar atrophy	1 (10)
SAH	1 (10)
Chiari malformation	1 (10)
meningioma	1 (10)
pituitary adenoma	1 (10)
arteriovenous malformation	1 (10)
trauma	4 (5.6)
asymptomatic screenings	8 (11.1)
total	72 (100)

that led to the discovery of an incidental LGG were additional symptomatic gliomas (2), schwannomas (2), meningioma (1), pituitary adenoma (1), arteriovenous malformation (1), cerebellar atrophy (1), SAH of the anterior communicating artery (1), and surveillance imaging of a postoperative Chiari malformation (1).

Reasons for Treatment

Within the study group, 4 patients (5.6%) did not mention a reason for treatment distinct from the standard of protocol for LGGs and were treated immediately. For the rest of the patients (Table 3), reasons for treatment included 24 of the 56 patients with radiological evidence of growth (42.9%), 15 with manifestations of physical symptoms (26.8%), 8 with radiological evidence of malignant transformation (14.3%), 4 with the need for histological diagnosis (7.1%), and 1 with patchy enhancement (1.8%). Two reports measured the volumetric diameter expansion with MR imaging and determined the necessity of treatment based on models of predicted LGG growth of 3.5 mm per year.[8,29] Another study used ^{18}F-FET PET analysis in conjunction with MR imaging to determine the prognosis of incidental LGG and subsequent treatment.[11] If there was radiological evidence of continuous slow growth (2–3 mm per year) and a negative ^{18}F-FET PET scan, patients were referred to surgery, and histological confirmation was performed. Included in the patients who were treated as a result of physical symptoms was a case of symptomatic SAH anatomically close to an incidental LGG in the frontal lobe, which facilitated tumor removal with a single craniotomy.[38] Eight patients underwent biopsies, which revealed incidental LGGs, but these patients refused further treatment after histological diagnosis until MR imaging demonstrated a suspected malignant transformation.

TABLE 3: Reasons for treatment

Reason for Treatment	No. (%)
radiological evidence of growth	24 (42.9)
development of clinical symptoms	15 (26.8)
evidence of malignant transformation	8 (14.3)
need for histological diagnosis	4 (7.1)
patchy enhancement	1 (1.8)
unknown	4 (7.1)
total	56 (100)

Patient Management

Patients were divided into 2 categories: those who underwent resection/biopsies and those who did not. In the surgery category, 56 patients were treated at a mean of 21.4 months (range 0–171 months) after radiological diagnosis. At least partial resection was achieved in 40 patients (71.4%), with 16 undergoing biopsy only (28.6%; Table 4). Fourteen patients delayed surgery until evidence of physical symptoms and were treated similarly to standard LGG patients (with resection). One patient with an SAH from a ruptured anterior communicating artery aneurysm in the same anatomical location as a glioma was treated surgically by a single craniotomy.

Stereotactic biopsies were obtained prior to treatment in 16 patients (Table 4).[29] Of these 16 patients, 8 did not receive oncological treatment until malignant transformation, whereas 1 received radiotherapy and 5 received chemotherapy. The mode of treatment was unspecified in the 8 patients who had radiological evidence of malignant transformation and in 2 patients who received a stereotactic biopsy alone because of pooling of information within the article. Histological confirmation was made by either stereotactic biopsy primarily (16 patients) or surgical removal (40 patients; Table 5).

TABLE 4: Surgical management

Surgical Management	No. (%)
biopsy	16 (28.6)
no treatment until malignant transformation	8 (14.3)
& chemo	5 (8.9)
& RT	1 (1.8)
only	2 (3.6)
resection	40 (71.4)
partial	1 (1.8)
subtotal	13 (23.2)
GTR	20 (35.7)
unspecified	6 (10.7)
& RT	4 (7.14)
& chemo	1 (1.8)
& both	1 (1.8)

TABLE 5: Histological diagnosis

Histological Diagnosis	No. (%)
oligodendroglioma	35 (48.6)
pilocytic astrocytoma	1 (1.4)
low-grade astrocytoma	11 (15.3)
mixed oligodendroglioma/astrocytoma	9 (12.5)
unspecified/unknown	16 (22.2)

A total of 16 patients underwent active surveillance after radiological diagnosis of incidental LGG, without histological confirmation. Fifteen patients demonstrated negative results on the study's prognostic tests (negative growth on serial MR imaging and negative ^{18}F-FET PET scan), so no treatment was required. These patients underwent clinical and radiological follow-up examinations. In 1 case a patient was referred to a tertiary center where treatment was believed to be unwarranted.[39]

Outcomes

The mean follow-up among all 72 patients was 74.8 months (range 0–29.7 years; data available for 69 patients). Outcomes were reported for the surgical group and the active surveillance group. Within the surgical group of 56 patients, 49% did not have any neurological deficits and remained stable with no events over the course of the follow-up period (Fig. 1). Twenty-five percent of the patients in the surgical group had radiological or histological confirmation of tumor progression to a higher WHO grade (mean follow-up postdiscovery using radiology was 5.4 years). This also included 8 patients who waited for oncological treatment until malignant transformation. Approximately 13% of the surgical group underwent a second treatment, and 7% died during the course of follow-up.

The outcome of 10 patients was complicated by the existence of other symptomatic lesions and tumors that were diagnosed simultaneously to the incidental LGG. Individual survival rates for this specific patient population were not calculable because several papers reported grouped data instead of individual data sets. In fact, 80% of the symptomatic lesions that justified an initial radiological screening were from a single paper, which also had the highest reported complication rates.[29] It is likely that the patients with coexisting symptomatic lesions and incidental LGGs may have had worse outcomes, although individual data were not reported in any included study.

Asymptomatic patients from large screening trials without previous surgery or neurological impairment who underwent surgery did not have any reported complications.[19,28] Among the patients whose incidental LGGs were discovered due to trauma, there were no reported recurrences, and only 1 patient with a tectal glioma had a KPS score < 100 at follow-up.[36]

Among the 16 patients with no interventional treatment, radiological evidence of lesion regression (at least 30% of original diameter) occurred in 5 patients; in 4 of these patients the lesion completely resolved within 6 months, and 1 slowly regressed over 1 year. For patients with lesion regression, clinical and radiological examinations with MR imaging were performed at 4-month intervals for 1–2 years after radiological diagnosis.[11] Ten patients did not demonstrate any growth and remained stable during the course of follow-up examinations for 3 years. The MR imaging findings of these patients were inconclusive, although they suggested the presence of an incidental LGG. Both those with lesion regression and those with stable lesions had negative prognostic indicators of malignancy, with negative ^{18}F-FET PET scans and no growth on MR imaging. No complications were reported for this patient population, although Floeth et al.[11] mentioned the possibility that a thromboembolic event may have been attributable to a radiological lesion in 1 patient. There was no evidence of poor outcomes at follow-up for the untreated patients (Fig. 2).

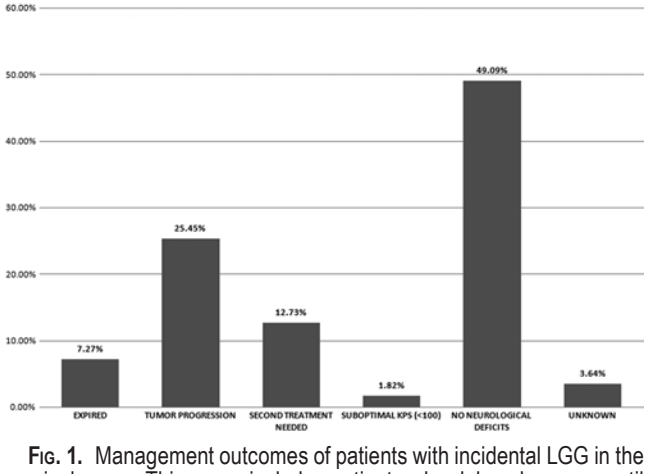

Fig. 1. Management outcomes of patients with incidental LGG in the surgical group. This group includes patients who delayed surgery until radiological progression and/or clinical manifestations.

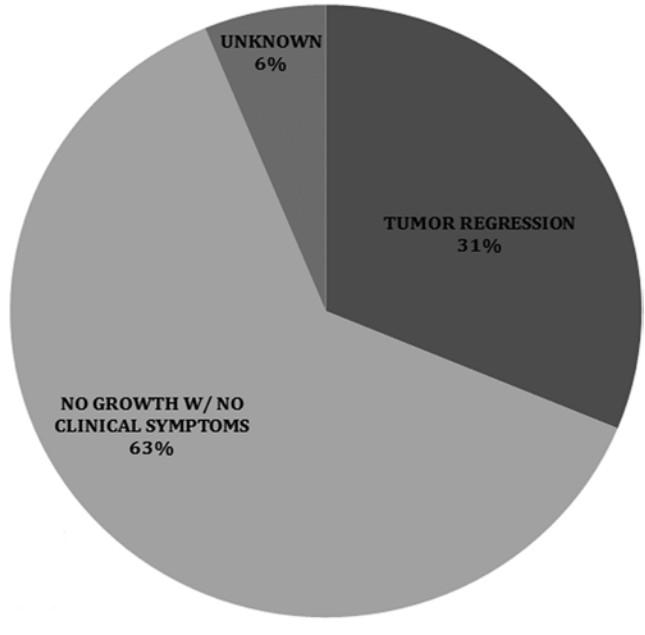

Fig. 2. Management outcomes of patients with incidental LGG in the active surveillance group. This group includes patients who were determined to have incidental LGG based on radiological findings alone. Follow-up MR imaging found no tumor growth and showed negative ^{18}F-FET PET uptake in 15 patients.

Discussion

Incidental LGGs account for roughly 3%–5% of all LGGs.[1,18] As neuroimaging technology advances and thus incidence increases, the controversial issues surrounding treatment of incidental findings will become increasingly relevant. This holds true for incidental LGG, as well as many other radiological findings of incidental pathology elsewhere in the body. Although some authors propose a uniform policy toward managing incidental findings,[3] many investigators do not comment on management options and usually adhere to a similar approach to that applied to symptomatic patients.[34] Because of these discrepancies in the management of these lesions, and even in the recognition of incidental LGG as a distinct entity, understanding the natural history and response to treatment of these lesions is extremely important.

Symptomatic Versus Incidental LGG: Is There a Difference?

Duffau and colleagues[8] proposed that incidental LGG may be an earlier step in the pathological progression of LGG. Their data extrapolated the genesis of a Grade II glioma using repeated surveillance MR images of a 31-year-old patient after decompression for a Chiari malformation. Using these repeat scans, the volumetric diameter expansion was established, dating the inception of the glioma and providing critical insight into the pathogenesis of LGG. Pallud et al.[29] provided supplemental data to distinguish between the traditional symptomatic LGG and incidental LGG. The incidental 47 patients in the LGG group in this study had a lower age at diagnosis, a significantly smaller tumor volume, and a significantly lower rate of midline shift at the time of radiological diagnosis, which gives credence to the theory that incidental LGG may represent a premature step in the natural course of LGG. In addition, 13 patients developed clinical symptoms when no treatment was initiated. Of significance, the study also reported an increased survival rate among the incidental LGG group, although this may be attributable to lead-time bias from early diagnosis. The question of whether survival is affected by early treatment of incidental LGG is, as yet, unanswered.

Does the Mode of Discovery of Incidental LGG Matter?

Within our study, incidental LGGs were discovered due to a variety of reasons including research studies, nonspecific symptoms, trauma, and other symptomatic lesions. There are 2 categories of patients that must be considered fundamentally differently based on the ethical considerations of further investigation and treatment. The first is the group of healthy, asymptomatic volunteers among whom incidental LGG is discovered through participation in a research study or preventative screening program. The second is the group of patients who receive MR imaging for other neurological or nonspecific complaints. The treatment approach to these 2 groups is fundamentally different, as outlined below.

Healthy Volunteers. Studies with healthy volunteers comprised 11.1% of our review's patient population. Although not the majority of patients, intervention in this group is controversial. Because many healthy volunteers are enrolled in brain MR imaging screenings, occasionally for research or for occupational screening, the protocols that govern treatment and management of these lesions should be defined clearly.[15,16,39,40] Due to the potential impact on quality of life and occupation from a diagnosis of glioma, the following questions should be explicitly addressed prior to enrolling patients in research studies that carry the potential for revealing an incidental LGG: 1) is the patient fully aware of the potential implications of brain MR imaging and the possibility of an incidental finding; 2) who should supervise the follow-up care for these patients in the event that an incidental LGG is found; 3) who will provide the neurosurgical care for these patients; and 4) what is the accepted guideline for treating a lesion that produces no clinical symptoms?

Floeth et al.[11] outlined a potential treatment paradigm for patients enrolled as healthy volunteers who are radiologically diagnosed with incidental LGG, with active surveillance by MR imaging every 3–4 months with a concurrent PET scan (used to discover possible malignant gliomas). Pallud et al.[29] followed a similar regimen without the addition of the PET scan. Most of the patients in this study underwent oncological treatment after radiological progression with few receiving treatment due to patchy enhancement on MR imaging or the need to confirm histology. In this manner, exploratory surgery may be avoided and additional MR imaging investigation can be used to confirm growth by volumetric diameter expansion. However, once symptomatic progression occurs or radiological evidence of growth or malignant transformation is found, the need for resection becomes more pressing. In cases in which a needle biopsy has been performed and histology confirms an incidental LGG, the optimal management approach remains to be elucidated.

Nonspecific or Unrelated Symptoms. There may be considerable debate as to whether a particular patient's symptoms are, in fact, related to the incidental LGG. Although symptoms such as headaches, mood disorders, and amenorrhea may not be functionally related to incidental LGG, the correlation between presentation and pathology can be difficult to attribute to coincidence alone.[12,25] In these cases, the patient's preferences are instrumental in guiding therapeutic decisions. In general, management in these patients tends to be more aggressive due to the uncertain cause of their symptoms;[29] however, as before, radiological evidence of growth before initiation of treatment can be a prerequisite for any intervention. In the study by Floeth et al.,[11] most (14/15) of the patients with nonspecific symptoms did not show any radiological evidence of growth, and treatment was avoided. At the end of the follow-up period, patients remained healthy and had no evidence of seizures. Nevertheless, these patients remain challenging to manage because their symptomatology is unclear, and the definite need for surgery is yet to be established. For any patient who desires surgical intervention for resection of an incidental LGG in the setting of vague or not functionally related symptoms, the risk that surgery will not relieve their chief complaint must be explicitly and carefully outlined.

Incidental LGG in Patients With Concurrent CNS Disease. In the few cases in which symptomatic CNS lesions were the main reason for radiological imaging, management of a coincidental incidental LGG can be difficult. In the 10 cases reported in the analyzable literature, resection was performed in all cases; however, the justification for surgery has not always been readily apparent.[29] The decision to perform a biopsy/resection may be justified in this population due to increased morbidity associated with multiple lesions, although there is no specific evidence for this in the published literature. Furthermore, the clinical decision to operate in these cases may be influenced by the neurosurgical protocol for treatment of the symptomatic lesion. For example, if a meningioma necessitates surgical intervention, it may be prudent to resect a nearby incidental LGG in the same surgery.[5,7,13]

Age-Dependent Classification

When determining treatment for incidental LGG, the neurosurgeon may be compelled to alter his or her decisions based on the age of the patient at diagnosis. For example, younger patients may be more prone to receive surgery earlier due to parent's anxiety of "observing" children with incidental LGG. Furthermore, for the middle-age group of patients, surgery may be a viable option given no previous history of comorbidities. Considering evidence of an age-dependent increase in anaplastic transformation of incidental LGG, operative decisions may be made depending on the age of the patient at diagnosis.[4,32,33] For example, studies by Shafqat et al.[33] demonstrated that patients older than 45 years of age have a mean time to dedifferentiation of 7.5 months after radiological diagnosis, compared with 44.2 months in patients younger than 45 years. However, the elderly population may benefit from active observation given that neurosurgery on elderly patients may have an increased risk for complications and poor outcomes. Regardless, age must be factored together with the mode of discovery and other confounding factors into the decision for treatment of incidental LGG.

Treatment Paradigm. The management of incidental LGG may be portrayed as a continuum of care due to the interplay between the active surveillance group and the surgical group. Many patients (24) in the surgical group initially were actively observed and underwent resection at a later time. Therefore, understanding the transition between active surveillance and surgery may be an important tool in creating a treatment paradigm. Based on our review of analyzable literature, we have established the safety of active surveillance, and have therefore proposed the following diagram (Fig. 3) illustrating the management of incidental LGG.

Limitations. This interpretation of the literature on the topic of incidental LGG is subject to a number of limitations. Taken together, the case series and case reports of incidental LGG comprise Level III evidence and should not be used as a definitive guide for clinical practice, but rather as an indication of the viability of different treatment approaches for different patients.

The surgical group was the only group that reported negative outcomes. Although surgery is associated with inherent risks, there may be other risks attributable to the active surveillance group. Patients who are being observed without treatment may progress to anaplastic transformation or present with clinical symptoms, which could increase the overall morbidity and mortality in this group. However, because these patients may eventually receive some form of treatment, they transition to the surgical group. Therefore, a portion of the surgical group may be a reflection of an acute cohort of the active surveillance group.

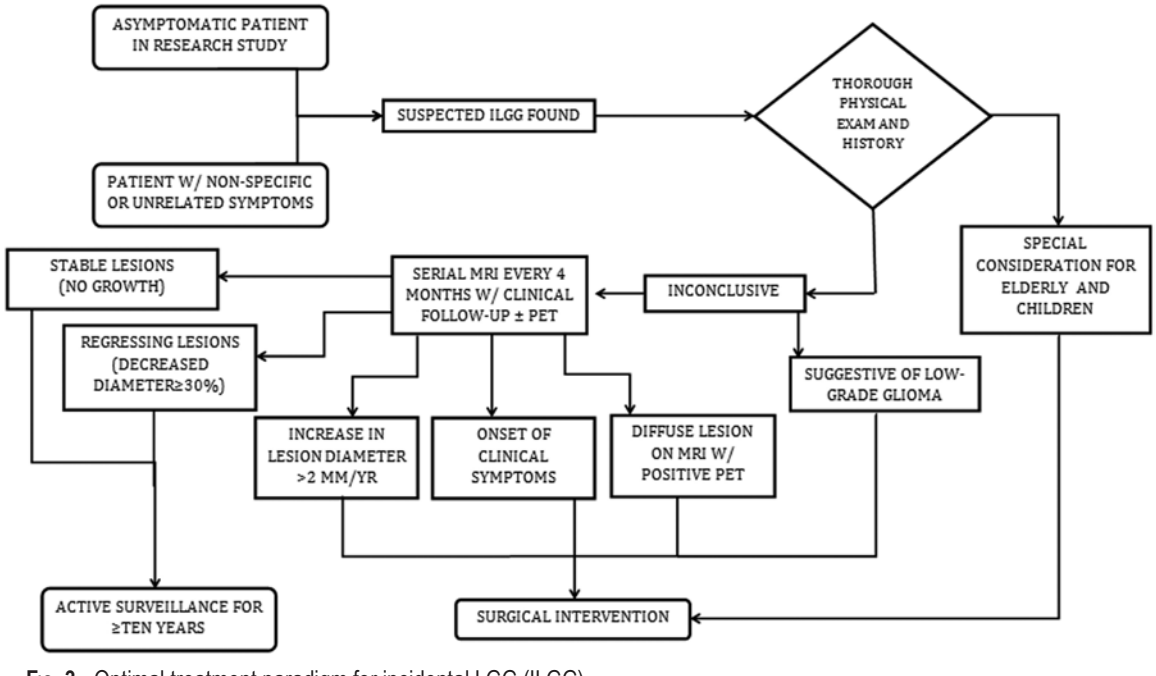

Fig. 3. Optimal treatment paradigm for incidental LGG (ILGG).

Because all the patients underwent biopsies/surgeries (retrospectively screened for incidental LGG confirmed by histology), it was difficult to eliminate this paper's negative outcome bias within the surgical group. Regardless, the outcomes of the surgical patients included deceased patients, the need for second treatment, and tumor progression (Fig. 1). It is important to note that 8 patients diagnosed with radiological or histological evidence of tumor progression only underwent biopsy and were not fully treated until malignant transformation. Excluding the paper by Pallud et al.,[29] it appears that the surgical group did not have many complications and that resection for incidental LGG remains relatively safe, although there may be a publication bias that excludes negative outcomes. In addition, suspected cases of incidental LGG that underwent resection that confirmed a different unsuspected lesion were not included in this study; therefore, it remains unknown how many diagnostically erroneous surgeries are performed.

Among the active surveillance group, incidental LGG was only suspected and not definitively diagnosed. This makes direct comparison between the 2 groups impossible, and outcomes should be used as a guide only rather than a definitive comparison for statistical analyses. Nevertheless, patients in this group who have been reported in the literature had extremely good outcomes, with no evidence of growth, malignant transformation, or clinical symptomatology. The majority of lesions remained stable throughout follow-up and demonstrated no growth on MR imaging.

It is important to recognize that although this paper provides insight into the management of incidental LGG, the authors of this paper are not offering evidence that supports the use of asymptomatic healthy patient screenings. Previously, it has been shown that these screenings can lead to misdiagnosis of patients with no underlying pathology,[2] increasing anxiety in patients by unmasking abnormalities that are not clinically relevant,[14,22] or giving patients the false impression that their brain MR imaging is negative. Previous publications have provided insight into the necessity to tailor brain MR imaging for asymptomatic patients in specific at-risk populations instead of generalized screenings.[21] Patients at risk for cerebrovascular disease might benefit from brain imaging that could possibly identify asymptomatic cerebral infarctions and reduce future risk. However, for patients not at risk or enrolled in healthy volunteer research studies, the need for brain MR imaging screenings may not be clinically worthwhile as it would exaggerate negligible findings with very few clinically significant diagnoses.

Ethical Issues. The decision to treat patients without symptomatology is certainly an ethical predicament. In the case of incidental LGG, decisions to operate or intervene must be weighed with a careful examination of the clinical symptoms, history, and radiological findings. Without sufficient evidence, intervening in cases of incidental LGG may have significant ethical implications because it is unclear whether the decision to treat earlier improves overall survival rates. Also, surgical intervention must be weighed against the uncertainty of diagnosis, inadequate clinical history, or evidence of growth. In addition, intervening in suspected incidental LGG cases that do not necessitate immediate removal may disrupt the quality of life of asymptomatic patients or create increased pre- and postoperative anxiety, yet the decision not to operate can also be viewed as an ethical dilemma as well. Patients may not understand the rationale for withholding treatment until sufficient evidence is uncovered, and the neurosurgeon must be prepared to address all possible concerns about management in these cases. In all circumstances, precise care must be taken to maintain physician's values while respecting the patient's wishes.

Decisions to manage incidental LGG nonoperatively hold considerable legal implications in countries in which malpractice litigation is prevalent. Justifying active surveillance on a patient may result in increased litigation if there is sufficient evidence to demonstrate negligence. Currently, neurosurgeons must practice defensively in countries where medical malpractice lawsuits are prevalent, and considerable precaution must be taken into account before a decision to not operate is made. In other countries with more malpractice reform, nonsurgical intervention may be facilitated.

Conclusions

For the neurosurgeons responsible for the care of patients with incidental LGG, understanding the ethical responsibilities of treating asymptomatic lesions is critical as we address this problem in the future. Urgent surgery is not always indicated in cases of suspected incidental LGG, and each patient's treatment must be individualized based on the context, circumstances, and characteristics of the diagnosed lesion. Recognizing that incidental LGG is a precursor to symptomatic LGG may just be the first step in the process of elucidating a unified therapeutic approach for these lesions. Based on the continuum between surveillance and treatment, our treatment paradigm may be clinically useful in asymptomatic patients; however, these decisions for an incidental LGG in settings of concurrent lesions may be different. It is likely that serial clinical examination and MR imaging is a safe option for most asymptomatic patients, with the option of intervention based on certain criteria that are, as yet, to be elucidated fully.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Komotar, Shah, Madhavan. Acquisition of data: Shah. Analysis and interpretation of data: Shah, Madhavan, Raper. Drafting the article: Shah, Raper. Critically revising the article: all authors. Reviewed submitted version of manuscript: Komotar, Shah, Heros, Iorgulescu, Raper, Lally. Approved the final version of the manuscript on behalf of all authors: Komotar. Study supervision: Komotar.

References

1. Bauchet L, Rigau V, Mathieu-Daudé H, Figarella-Branger D,

Hugues D, Palusseau L, et al: French brain tumor data bank: methodology and first results on 10,000 cases. **J Neurooncol 84:**189–199, 2007
2. Baum KA, Schulte C, Girke W, Reischies FM, Felix R: Incidental white-matter foci on MRI in "healthy" subjects: evidence of subtle cognitive dysfunction. **Neuroradiology 38:** 755–760, 1996
3. Brown DA, Hasso AN: Toward a uniform policy for handling incidental findings in neuroimaging research. **AJNR Am J Neuroradiol 29:**1425–1427, 2008
4. Brown PD: Low-grade gliomas: the debate continues. **Curr Oncol Rep 8:**71–77, 2006
5. Chen G, Gao X, Liao Y, Xu B: A glioblastoma adjacent to a meningioma. **Br J Neurosurg 24:**718–719, 2010
6. Davis F, Il'yasova D, Rankin K, McCarthy B, Bigner DD: Medical diagnostic radiation exposures and risk of gliomas. **Radiat Res 175:**790–796, 2011
7. Davis GA, Fabinyi GC, Kalnins RM, Brazenor GA, Rogers MA: Concurrent adjacent meningioma and astrocytoma: a report of three cases and review of the literature. **Neurosurgery 36:**599–605, 1995
8. Duffau H, Pallud J, Mandonnet E: Evidence for the genesis of WHO grade II glioma in an asymptomatic young adult using repeated MRIs. **Acta Neurochir (Wien) 153:**473–477, 2011
9. Eskandary H, Sabba M, Khajehpour F, Eskandari M: Incidental findings in brain computed tomography scans of 3000 head trauma patients. **Surg Neurol 63:**550–553, 2005
10. Fayngersh V, Passero M: Estimating radiation risk from computed tomography scanning. **Lung 187:**143–148, 2009
11. Floeth FW, Sabel M, Stoffels G, Pauleit D, Hamacher K, Steiger HJ, et al: Prognostic value of 18F-fluoroethyl-L-tyrosine PET and MRI in small nonspecific incidental brain lesions. **J Nucl Med 49:**730–737, 2008
12. Franges EZ: When a headache is really a brain tumor. **Nurse Pract 31:**47–51, 2006
13. Giannopoulos S, Kyritsis AP: Diagnosis and management of multifocal gliomas. **Oncology 79:**306–312, 2010
14. Hinton VJ: Ethics of neuroimaging in pediatric development. **Brain Cogn 50:**455–468, 2002
15. Illes J: 'Pandora's box' of incidental findings in brain imaging research. **Nat Clin Pract Neurol 2:**60–61, 2006
16. Illes J, Kirschen MP, Karetsky K, Kelly M, Saha A, Desmond JE, et al: Discovery and disclosure of incidental findings in neuroimaging research. **J Magn Reson Imaging 20:**743–747, 2004
17. Illes J, Rosen AC, Huang L, Goldstein RA, Raffin TA, Swan G, et al: Ethical consideration of incidental findings on adults brain MRI in research. **Neurology 62:**888–890, 2004
18. Kamiguchi H, Shiobara R, Toya S: Accidentally detected brain tumors: clinical analysis of a series of 110 patients. **Clin Neurol Neurosurg 98:**171–175, 1996
19. Katzman GL, Dagher AP, Patronas NJ: Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. **JAMA 282:**36–39, 1999
20. Kim BS, Illes J, Kaplan RT, Reiss A, Atlas SW: Incidental findings on pediatric MR images of the brain. **AJNR Am J Neuroradiol 23:**1674–1677, 2002
21. Komotar RJ, Starke RM, Connolly ES: Brain magnetic resonance imaging scans for asymptomatic patients: role in medical screening. **Mayo Clin Proc 83:**563–565, 2008
22. Kumra S, Ashtari M, Anderson B, Cervellione KL, Kan L: Ethical and practical considerations in the management of incidental findings in pediatric MRI studies. **J Am Acad Child Adolesc Psychiatry 45:**1000–1006, 2006
23. Lucignani G, Nappi G: Neuroimaging technology and philosophy: a coming of age? **Funct Neurol 22:**181–183, 2007
24. Mamourian A: Incidental findings on research functional MR images: should we look? **AJNR Am J Neuroradiol 25:**520–522, 2004
25. Mignogna MD, Adamo D, Falleti J, Fortuna G: Dysgeusia: an atypical and neglected psychiatric symptom induced by fibrillary astrocytoma. **Am J Med 124:**e1–e2, 2011
26. Morris Z, Whiteley WN, Longstreth WT Jr, Weber F, Lee YC, Tsushima Y, et al: Incidental findings on brain magnetic resonance imaging: systemic review and meta-analysis. **BMJ 339:**b3016, 2009
27. Olson JD, Riedel E, DeAngelis LM: Long-term outcome of low-grade oligodendroglioma and mixed glioma. **Neurology 54:**1442–1448, 2000
28. Onizuka M, Suyama K, Shibayama A, Hiura T, Horie N, Miyazaki H: Asymptomatic brain tumor detected at brain checkup. **Neurol Med Chir (Tokyo) 41:**431–435, 2001
29. Pallud J, Fontaine D, Duffau H, Mandonnet E, Sanai N, Taillandier L, et al: Natural history of incidental World Health Organization grade II gliomas. **Ann Neurol 68:**727–733, 2010
30. Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, et al: Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. **J Natl Cancer Inst 94:**1555–1563, 2002
31. Ron E, Modan B, Boice JD Jr, Alfandary E, Stovall M, Chetrit A, et al: Tumors of the brain and nervous system after radiotherapy in childhood. **N Engl J Med 319:**1033–1039, 1988
32. Schomas DA, Laack NN, Brown PD: Low-grade gliomas in older patients: long-term follow-up from Mayo Clinic. **Cancer 115:**3969–3978, 2009
33. Shafqat S, Hedley-Whyte ET, Henson JW: Age-dependent rate of anaplastic transformation in low-grade astrocytoma. **Neurology 52:**867–869, 1999
34. Shah S, Schelper RL, Krishnamurthy S, Chang HT: An 11-year-old boy with an incidental mass in the left lateral cerebellum. **Neuropathology 27:**95–97, 2007
35. Ständer M, Peraud A, Leroch B, Kreth FW: Prognostic impact of TP53 mutation status for adult patients with supratentorial World Health Organization Grade II astrocytoma or oligoastrocytoma: a long-term analysis. **Cancer 101:**1028–1035, 2004
36. Stark AM, Fritsch MJ, Claviez A, Dörner L, Mehdorn HM: Management of tectal glioma in childhood. **Pediatr Neurol 33:**33–38, 2005
37. Steiger HJ: Preventive neurosurgery: population-wide checkup examinations and correction of asymptomatic pathologies of the nervous system. **Acta Neurochir (Wien) 148:**1075–1083, 2006
38. Suslu HT, Bozbuga M: Primary brain tumors associated with cerebral aneurysm: report of three cases. **Turk Neurosurg 21:**216–221, 2011
39. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al: Incidental findings on brain MRI in the general population. **N Engl J Med 357:**1821–1828, 2007
40. Weber F, Knopf H: Incidental findings in magnetic resonance imaging of the brains of healthy young men. **J Neurol Sci 240:**81–84, 2006

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Address correspondence to: Ricardo J. Komotar, M.D., University of Miami School of Medicine, 1095 NW 14th Terrace, Room 2-06, Miami, Florida 33136. email: rkomotar@med.miami.edu.

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Natural history of untreated syringomyelia in pediatric patients

Ash Singhal, M.D., F.R.C.S.C.,[1] Tim Bowen-Roberts, B.A.,[1] Paul Steinbok, M.B.B.S.,[1] Doug Cochrane, M.D.,[1] Angela T. Byrne, M.B.,[2] and John M. Kerr, B.Sc.[1]

Departments of [1]Surgery (Division of Pediatric Neurosurgery) and [2]Radiology, British Columbia's Children's Hospital and University of British Columbia, Vancouver, British Columbia, Canada

Object. The natural history of syringomyelia in pediatric patients remains uncertain. Although symptomatic and operative cases of syringomyelia are well studied, there are fewer articles in the literature on the nonoperative syrinx and its clinical and radiological course. The purpose of this research was to analyze the natural history of untreated syringomyelia in pediatric patients presenting with minimal neurological symptoms.

Methods. A review of the neurosurgery database at British Columbia's Children's Hospital identified all pediatric patients (< 18 years of age) with syringes identified on MR imaging. Patients were included in this study if they had at least 2 MR images of the spine, at least 1 year apart, while receiving nonoperative treatment. Magnetic resonance imaging was used to determine changes in the size of the syrinx over time. Clinic notes were analyzed to establish demographic and clinical features and to determine any clinical changes over time.

Results. A total of 17 patients were included in the study. Symptoms at presentation were often mild and included limb numbness (3 cases), headaches (2 cases), mild sensory deficits (2 cases), mild motor deficits (3 cases), and intermittent incontinence (7 cases). The consultant neurosurgeon believed that the syrinx was not contributing to the symptoms in these 17 patients. The syrinx either remained unchanged (7 cases) or diminished in size (8 cases) in a total of 15 patients (88%). In the remaining 2 patients the authors noted an increase in syrinx size, in 1 of whom the clinical course also worsened. Both of these patients had a Chiari malformation and subsequently underwent craniocervical decompression. Overall, the mean change was –0.7 mm of maximal axial diameter (range –2.6 to +2.7 mm). Sixteen patients (94%) exhibited no worsening of symptoms over time.

Conclusions. Syringomyelia often remains stable in patients receiving nonoperative treatment. However, given that 2 (12%) of 17 syringes in this series enlarged, it is likely appropriate to include periodic imaging in the follow-up of these cases. *(DOI: 10.3171/2011.9.FOCUS11208)*

Key Words • syringomyelia • conservative management • magnetic resonance imaging

The natural history of syringomyelia in nonoperatively treated patients remains unclear. With its pathogenesis not well defined,[13] ambiguity exists with regard to managing this condition, especially when syringomyelia is identified incidentally on MR imaging. Most neurosurgeons would choose to operate when a syrinx is progressing in size or deemed symptomatic.[7] There is no accepted strategy, however, for the management of syringes found on MR images when symptoms are subtle or not thought to be related to the syrinx. Although some other studies have emphasized purely idiopathic syringes,[9] our institution has some cases of Chiari malformation–associated syringes managed without surgery, and the patients are included in the present study.

Many pediatric patients presenting with a syrinx at BCCH also present with a Chiari malformation. Surgical correction of the latter condition often leads to reduction in size of the syrinx.[2,14] For this reason, many neurosurgeons elect to intervene surgically when a syrinx with tonsillar herniation is present.[1] In idiopathic cases (that is, those unrelated to Chiari Type I malformation), syrinx management is less clear. Management options are dependent on the clinical circumstances and include posterior fossa decompression, syrinx shunting, tethered cord release, or serial imaging observation.[3,4]

Pediatric case studies have demonstrated that syringomyelia can spontaneously resolve if left untreated.[10] As a consequence of these observations, some authors have advocated nonoperative management.[5,10] This is a sentiment anecdotally shared by many others,[2] and we have generally been following our cases asymptomatic syringes without undertaking surgery.

Abbreviations used in this paper: AP = anteroposterior; BCCH = British Columbia's Children's Hospital.

Other cases of syringomyelia, while the lesion has not diminished in size, have shown no progress over time. One study analyzing the natural history of syringomyelia in 14 adult patients found disease progression to be slowly progressive or clinically arrested in most clinical cases.[11] Another study in adults reported no neurological deterioration in 8 of 9 asymptomatic patients with syringomyelia. These patients had an associated Chiari malformation and were followed up nonoperatively for 10 years.[12] The natural history of syringomyelia in the pediatric population, however, remains poorly characterized.

At BCCH, our pediatric neurosurgery service advocates nonoperative management when patients are asymptomatic or when patients' symptoms are deemed to be unrelated to the syrinx.

Patients/families frequently have questions regarding the likelihood that the syrinx will enlarge or diminish or become symptomatic in the future—in short, questions about the natural history of the condition. The research study in the present study focuses on this issue by evaluating the clinical and radiological history of these syringes in the pediatric population.

Methods

Ethics approval for the study was obtained from the University of British Columbia and Children's and Women's Health Center of British Columbia research ethics board. A review of the prospectively maintained neurosurgery database at BCCH was conducted, and all pediatric patients (< 18 years of age) diagnosed with syringomyelia were identified, with syrinx defined as a central canal 1 mm or greater in axial size and extending a minimum of 2 vertebral levels.[9] Patients were included in the study if they had a follow-up MR imaging of the spine (at least 1 year from initial imaging study) while being managed with observation for a minimum of 1 year.

A chart review was performed to ascertain clinical signs and symptoms. Clinical status was compared at presentation and at last follow-up to determine any changes in symptoms over time.

A review of all MR imaging studies was conducted to evaluate the change in size of the syrinx in relation to time. Two authors (A.B. and T.B.R.) reviewed all images, blinded to clinical information at presentation and follow-up. Axial MR images were used to measure both the AP and the transverse diameters of the syrinx. The maximum diameter of these 2 measurements was then recorded. Other information obtained included location and length of the syrinx. The location of the syrinx was determined in relation to the level of the spinal cord. The length of the syrinx was measured on sagittal T2-weighted images.

Comparison of measurements was made between initial MR images and most recent follow-up images to determine the change in maximum syrinx diameter. For consistency, initial AP values and initial transverse values were compared with AP and transverse measurements at follow-up. Depending on the image available (digital or film), digital calipers or rulers (appropriate to the magnification scale on film images) were used for measurements.

For the purposes of this study, any difference in syrinx greater than 1 mm was considered a change in size. This number was chosen because of the potential error in measuring small syringes, both using digital calipers and mechanical ruler measurements.

Results

Syringomyelia was identified in 103 patients in the neurosurgery database. Seventeen patients met the inclusion criteria for the study. The relatively small number of patients eligible for the study was reflective of many patients in our database who underwent surgery, had an associated spinal cord lesion (for example tumor or myelomeningocele), or had no follow-up information (clinical or radiological) available. The ratio of males to females was 10:7. The average age at initial imaging assessment was 8.7 years (range 10 months–16 years). The mean follow-up duration was 3.2 years and the median was 2.3 years (range 1–12.8 years, interquartile range 1.2–4.2 years).

In all cases of syringomyelia in the present population, the lesions were discovered on MR imaging, with the earliest investigation dating to 1997. Syringes were found in 4 patients while ruling out tethered spinal cord. Three patients underwent imaging for scoliosis investigation. Headaches, dizziness, and episodes of syncope led to studies in 3 patients whereas in 2 additional patients imaging was performed for physical injuries. The remaining 5 patients underwent imaging for seizures, cerebral palsy, possible Chiari malformation, and work-up VACTERL syndrome (Vertebral anomalies, Anal or duodenal atresia, Cardiac defects, TracheoEsophageal fistula, Renal anomalies, and Limb malformations).

During the follow-up period, 28 MR imaging in the 17 patients studies were acquired in total, and the number of repeat scans per patient varied between 1 and 4. Ten of 17 patients had 1 follow-up MR imaging study at the time of investigation, whereas the other 7 patients had 2 or more repeat MR imaging studies. Other associated conditions identified on MR imaging included Chiari malformation (5 cases), scoliosis (3 cases), and abnormal vertebral fusion (3 cases). None of the 17 patients had an associated tethered cord.

The syringes were located at all levels of the spinal cord: the cervical (5 cases), cervicothoracic (3 cases), thoracic (8 cases), and thoracolumbar (1 case) spine. In 4 of the 5 patients with cervical syringes, we also documented a second syrinx in the thoracic region. The mean length of the syrinx was 80 mm. When compared against adjacent vertebrae, this corresponded to an average length of 7 vertebral levels.

Patients presented with minimal neurological symptoms, which included occasional numbness/tingling in limbs (3 cases), headaches (2 cases), pain (4 cases), subjective sensory deficits (2 cases), fine and gross motor difficulties (3 cases), bladder incontinence (5 cases), and bowel incontinence (2 cases). Two patients presented with toe-walking. Only 3 patients had no neurological symptoms at initial clinic visit. None of the syringes were believed to be contributing to the symptoms, based on the surgeon's judgment at the initial consultation. The pre-

senting symptoms and associated outcomes at the time of clinical follow-up are summarized in Table 1.

At most recent follow up, 16 of 17 patients showed either no change in symptoms (9 patients [53%]) or an improvement (7 patients [41%]). One patient exhibited a mild worsening of dysphagia, hand weakness, and incontinence. This patient had a cervical syrinx, and was 1 of 2 patients in whom the syrinx increased in size and who underwent surgery. These symptoms did not resolve after foramen magnum decompressive surgery (3-year follow-up period), and the syrinx has grown slightly in the postoperative period.

Eighty-eight percent of patients (15 of 17) had either no change (7 patients [41%]) in maximum axial diameter or reduction (8 [47%]) in syrinx size. In 2 patients (12%) imaging documented an increase in syrinx size (increase of 2.7 and 2.1 mm). Figures 1 and 2 highlight the radiological changes over time in syrinx morphology observed in 2 patients.

The average and median for the maximum diameter at initial investigation was 6.1 and 4.4 mm, respectively (range 3.1–13.3 mm). The median change in maximum diameter was –0.9 mm (range –2.6 to +2.7 mm). This means that the typical syrinx was smaller on follow-up than on the original MR image. The transverse measurement was found to be the maximum diameter in 12 (71%) of the 17 cases.

The results are summarized in Table 2.

Discussion

With the use of MR imaging as a tool for investigation, syringomyelia is increasingly being diagnosed. The majority of neurosurgeons consider surgery in cases involving symptomatic patients with syringes.[7] Debate exists among neurosurgeons as to the appropriate management of a syrinx when patients exhibit minimal symptoms or when the syrinx is detected serendipitously. Some

TABLE 1: Symptoms at presentation and at clinical follow-up*

Symptoms at Presentation (no. of patients)	Symptoms†		
	Worsened	Unchanged	Improved
pain (4)	0	1	3
headache (2)	0	0	2
toe-walking (2)	0	2	0
nausea & vomiting (1)	0	0	1
syncope (1)	0	0	1
numbness/tingling in limbs (3)	0	0	3
mild sensory deficits (2)	0	1	1
mild motor deficits (3)	1	2	0
dysphagia (1)	1	0	0
bladder incontinence (5)	1	1	3
bowel incontinence (2)	0	0	2
limited neck rotation (1)	0	1	0
no neurological symptoms (3)	0	3	NA

* NA = not applicable.
† Values represent the number of patients.

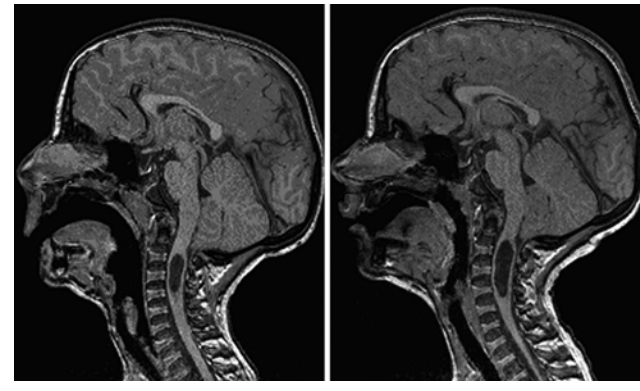

Fig. 1. Case 5. Sagittal T1-weighted MR images obtained in a patient with progressive syringomyelia and Chiari Type I malformation at initial **(left)** and 2-year follow-up **(right)** examination.

authors have argued that if a syrinx is relatively large, even if patient is asymptomatic, that intervention should be undertaken before symptoms progress.[12] Other authors have presented cases in which syringes may spontaneously resolve if left without surgical intervention.[5,10]

Our findings suggest that syringes tend to remain stable in the short term when patients present with minimal symptoms. In 15 (88%) of 17 patients there was no evidence that the syrinx increased in size (7 unchanged lesions, 8 reduced in size) from the initial imaging to follow-up, at least 1 year later. This is consistent with the findings of a recently published study of nonoperated syringes.[9]

The decreasing size of the syrinx in 8 patients is in keeping with the previous reports of spontaneous resolution.[5,10] Interestingly, one of these reported patients exhibited syrinx enlargement at the first follow-up, but nonoperative management was continued based on the clinical circumstance, and an overall reduction in size was noted after 5 further years of observation.

For the 2 remaining patients in whom the lesion neither remained the same size nor got smaller, the syrinx increased in size and surgical intervention was indicated after initial observation. These findings could be related to the fact that both of these patients had associated Chiari malformations and both had large syringes (> 12 mm, the largest 2 in our series) at initial presentation. With a small series, meaningful statistical analysis is challenging, but it is intriguing that both syringes that grew and required surgery were in the cervical spine, were associated with Chiari Type I malformation, appeared distended, and were the largest syringes in our series. In neither case did imaging initially exhibit a signal change above or below

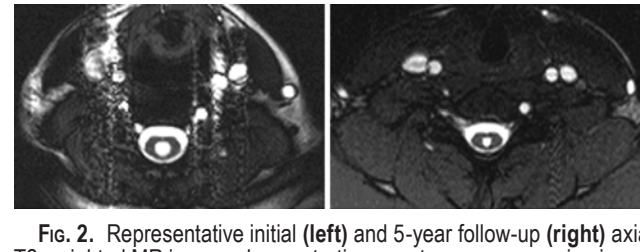

Fig. 2. Representative initial **(left)** and 5-year follow-up **(right)** axial T2-weighted MR images demonstrating spontaneous regression in syrinx size over time.

TABLE 2: Clinical and radiological outcome in 17 patients with nonsurgically treated syringes at follow-up imaging*

Case No.	Initial Syrinx Size (mm)	Location of Syrinx (initial)†	Time to FU MRI (yrs)	Change in Syrinx Size (mm)	Change in Syrinx Size‡	Reason for MRI	Presenting Symptoms	Change in Symptoms	Associated Findings
9	4.3	C4–7	5.3	−2.6	decreased	complex partial seizures	minor neck & upper thoracic pain	improved	CM
4	4.0	T5–9	4.2	−2.3	decreased	physical injury	bladder incontinence; numbness/tingling in toes & legs; abnormal swollen sensation in hands; upper thoracic pain	improved	–
14	6.9	T7–9	2.3	−1.9	decreased	headaches; syncope	headaches; syncope	improved	–
16	4.7	T8–12	1.0	−1.6	decreased	generalized/absence seizures	asymptomatic	unchanged	malformed hippocampi, bilat periventricular nodular heterotopia
12	9.5	C3–T5	4.9	−1.4	decreased	scoliosis investigation	mild sensory deficit on rt side of body	unchanged	scoliosis
8	3.1	C4–7	2.3	−1.4	decreased	physical injury	numbness/tingling in arms & legs	improved	–
17	5.7	C5–T9	1.2	−1.3	decreased	scoliosis investigation; possible CM	asymptomatic	unchanged	CM, scoliosis
3	4.2	T5–7	3.0	−1.1	decreased	atypical vertigo; headaches	headaches; nausea & vomiting; dizziness	improved	CM
15	4.0	C7–T9	12.8	−0.9	unchanged	scoliosis investigation	back & neck pain; bladder incontinence	unchanged	VFA, scoliosis
2	3.3	C6–7	2.3	−0.7	unchanged	R/O tethered cord	bladder & bowel incontinence; pain & numbness in lower limbs	improved	–
10	6.7	T6–12	4.5	−0.7	unchanged	R/O tethered cord	bladder & bowel incontinence	improved	–
11	3.7	T4–9	1.1	−0.6	unchanged	R/O tethered cord	toe-walking	unchanged	–
7	4.0	T4–12	1.2	0	unchanged	mild cerebral palsy, spastic diplegia	spastic diplegia; toe-walking	unchanged	–
1	4.4	T10–L2	1.4	0	unchanged	work-up for VACTERL syndrome	asymptomatic	unchanged	VFA
6	10.0	T4–9	1.0	0	unchanged	R/O tethered cord	spastic diplegia; ataxia	unchanged	malformation (hypoplasia) of lt cerebellar hemisphere, heterotopic gray matter involving both temporal lobes
5	12.3	C2–3	2.1	2.1	increased	global developmental delay; dizziness & headaches	dysphagia; fine & gross motor difficulties; dysarthria; dizziness; ataxic gait; bladder incontinence; hand weakness	worsened	CM, lt occipital condylar hypoplasia, assimilation of atlas
13	13.3	C2–5	3.1	2.7	increased	VFA	limited neck rotation	unchanged	CM, VFA
mean	6.1		3.2	−0.7					
med	4.4		2.3	−0.9					
range	3.1–13.3		1.0–12.8	−2.6 to 2.7					

* CM = Chiari malformation; FU = follow-up; med = median; R/O = rule out; VFA = vertebral fusion abnormality; – = no other associated findings.
† Vertebral level (based on initial MR imaging findings).
‡ Clinically significant change (> 1 mm).

the syrinx. It might be that the large, Chiari malformation–associated cervical syrinx, if not initially resected, deserves the closest clinical and radiological follow-up.

With 15 individuals (88%) harboring nongrowing syringes and 16 (94%) exhibiting no symptom progression, the clinician might need to consider the frequency and timing of follow-up MR imaging. A survey of pediatric neurosurgeons suggested that many would elect for follow-up MR imaging every 6–12 months to monitor syringomyelia in asymptomatic patients.[7] Magnetic resonance imaging, however, causes anxiety for children and their families[8] and are costly to the health care system.[6] Anesthesia/sedation may be necessary. Given that only 1 of our 17 patients harbored a growing syrinx in the absence of worsening symptoms, the need for frequent imaging could be reconsidered. This is particularly true of the smaller syringes (< 10 mm in greatest cross-sectional diameter), which in our study demonstrated no growth.

Limitations exist with respect to this study. The study relies on a retrospective review, even though it draws from a prospectively maintained database that minimizes ascertainment biases. With 17 individuals, meaningful comparative statistical analysis is challenging, and we rely largely on descriptive analysis. Measuring syrinx size is not perfectly precise, either by digital or manual means. An effort was made to determine the reliability of the measurements of the maximal syrinx diameter. Both a student (T.B.R.) and a neuroradiologist (A.B.) measured the syrinx diameter on MR images, and there was concordance between their measurements, as evidenced by an r value (line of best fit) of 0.94 between their measurements.

However, we only considered a syrinx to have changed if the change in maximum diameter was at least 1 mm.

Conclusions

In syringomyelia, the syrinx infrequently increases in size in conservatively and asymptomatic or minimally symptomatic patients during the early years following detection. Nonoperative management for asymptomatic or minimally symptomatic patients appears to be reasonable. Cervical syringes, associated with Chiari Type I malformation and measuring over 10 mm in greatest axial diameter, may benefit from regular annual follow-up. Less frequent imaging to detect changes in size seems appropriate in patients with small syringes

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Singhal, Steinbok, Cochrane. Acquisition of data: Bowen-Roberts, Byrne, Kerr. Analysis and interpretation of data: Singhal, Bowen-Roberts, Steinbok, Cochrane, Byrne. Drafting the article: Singhal, Bowen-Roberts. Critically revising the article: all authors. Reviewed submitted version of manuscript: Singhal, Kerr. Approved the final version of the manuscript on behalf of all authors: Singhal. Statistical analysis: Kerr. Administrative/technical/material support: Kerr. Study supervision: Singhal, Steinbok, Cochrane, Byrne.

References

1. Aitken LA, Lindan CE, Sidney S, Gupta N, Barkovich AJ, Sorel M, et al: Chiari type I malformation in a pediatric population. **Pediatr Neurol 40:**449–454, 2009
2. Albert GW, Menezes AH, Hansen DR, Greenlee JD, Weinstein SL: Chiari malformation Type I in children younger than age 6 years: presentation and surgical outcome. Clinical article. **J Neurosurg Pediatr 5:**554–561, 2010
3. Albright AL, Pollack IF, Adelson PD: **Principles and Practice of Pediatric Neurosurgery, ed 2.** New York: Thieme, 2008
4. Caird J, Flynn P, McConnell RS: Significant clinical and radiological resolution of a spinal cord syrinx following the release of a tethered cord in a patient with an anatomically normal conus medullaris. Case report. **J Neurosurg Pediatr 1:** 396–398, 2008
5. Guillen A, Costa JM: Spontaneous resolution of a Chiari I malformation associated syringomyelia in one child. **Acta Neurochir (Wien) 146:**187–191, 2004
6. Hailey D, Marshall D: The place of magnetic resonance imaging in health care. **Health Policy 31:**43–52, 1995
7. Haroun RI, Guarnieri M, Meadow JJ, Kraut M, Carson BS: Current opinions for the treatment of syringomyelia and chiari malformations: survey of the Pediatric Section of the American Association of Neurological Surgeons. **Pediatr Neurosurg 33:**311–317, 2000
8. Kotsoni E, Byrd D, Casey BJ: Special considerations for functional magnetic resonance imaging of pediatric populations. **J Magn Reson Imaging 23:**877–886, 2006
9. Magge SN, Smyth MD, Governale LS, Goumnerova L, Madsen J, Munro B, et al: Idiopathic syrinx in the pediatric population: a combined center experience. Clinical article. **J Neurosurg Pediatr 7:**30–36, 2011
10. Mallinger B, Marson F, Sévely A, Loubes-Lacroix F, Catalaa I, Manelfe C: [Spontaneous resolution of syringomyelia in a child with Chiari I malformation: a case report.] **J Radiol 85:**1943–1946, 2004 (Fr)
11. Mariani C, Cislaghi MG, Barbieri S, Filizzolo F, Di Palma F, Farina E, et al: The natural history and results of surgery in 50 cases of syringomyelia. **J Neurol 238:**433–438, 1991
12. Nishizawa S, Yokoyama T, Yokota N, Tokuyama T, Ohta S: Incidentally identified syringomyelia associated with Chiari I malformations: is early interventional surgery necessary? **Neurosurgery 49:**637–641, 2001
13. Sung WS, Chen YY, Dubey A, Hunn A: Spontaneous regression of syringomyelia—review of the current aetiological theories and implications for surgery. **J Clin Neurosci 15:**1185–1188, 2008
14. Wetjen NM, Heiss JD, Oldfield EH: Time course of syringomyelia resolution following decompression of Chiari malformation Type I. **J Neurosurg Pediatr 1:**118–123, 2008

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Address correspondence to: Ash Singhal, M.D., F.R.C.S.C., Division of Pediatric Neurosurgery, 4480 Oak Street, #K3-159, Vancouver, British Columbia V6H 3V4, Canada. email: ash.singhal @cw.bc.ca.

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Tarlov cysts: a controversial lesion of the sacral spine

Corrado Lucantoni, M.D.,[1] Khoi D. Than, M.D.,[2] Anthony C. Wang, M.D.,[2] Juan M. Valdivia-Valdivia, M.D.,[2] Cormac O. Maher, M.D.,[2] Frank La Marca, M.D.,[2] and Paul Park, M.D.[2]

[1]Institute of Neurosurgery, Università Cattolica del Sacro Cuore, Rome, Italy; and [2]Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan

The primary aim of our study was to provide a comprehensive review of the clinical, imaging, and histopathological features of Tarlov cysts (TCs) and to report operative and nonoperative management strategies in patients with sacral TCs. A literature review was performed to identify articles that reported surgical and nonsurgical management of TCs over the last 10 years. Tarlov cysts are often incidental lesions found in the spine and do not require surgical intervention in the great majority of cases. When TCs are symptomatic, the typical clinical presentation includes back pain, coccyx pain, low radicular pain, bowel/bladder dysfunction, leg weakness, and sexual dysfunction. Tarlov cysts may be revealed by MR and CT imaging of the lumbosacral spine and must be meticulously differentiated from other overlapping spinal pathological entities. They are typically benign, asymptomatic lesions that can simply be monitored. To date, no consensus exists about the best surgical strategy to use when indicated. The authors report and discuss various surgical strategies including posterior decompression, cyst wall resection, CT-guided needle aspiration with intralesional fibrin injection, and shunting. In operative patients, the rates of short-term and long-term improvement in clinical symptoms are not clear. Although neurological deficit frequently improves after surgical treatment of TC, pain is less likely to do so. *(DOI: 10.3171/2011.9.FOCUS11221)*

Key Words • Tarlov cyst • sacral perineural cyst • spine • incidental finding • surgery

Due to the wide availability of imaging, incidental lesions are increasingly found in patients undergoing neuroimaging studies. Tarlov cysts frequently present as multiple cystic lesions of the nerve root sheath in the lower spine. The first report of a TC was made by Tarlov[32] in 1938 as an incidental finding at autopsy, and the lesion was subsequently classified as a Type II meningeal cyst by Nabors et al.[20] Tarlov cysts are typically located at the junction of the dorsal ganglion and the posterior nerve root and usually develop between the endoneurium and perineurium of the nerve root.[6] Although the etiology is still unclear, microcommunication with the subarachnoid space at the dural sleeve of the nerve root may function as a valve, allowing CSF influx and restricting CSF efflux, causing formation of the cysts.[20,21]

We focus on a particular incidental lesion of the lumbosacral spine: sacral perineural (Tarlov) cysts. Tarlov cysts are rare lesions. According to the findings of previous studies, the lesions occur in about 1%–5% of patients.[23,26] Depending on their location, size, and relationship to the nerve roots, a subset of cysts may become symptomatic and cause sensory disturbances, motor deficits, or bowel/bladder dysfunction. This occurs in approximately 1% of patients.[26] The clinical significance of this lesion must be meticulously assessed before planning surgical treatment. There is no consensus on the best treatment of symptomatic sacral cysts, although various surgical strategies have been proposed.

Our goal is to provide a review focusing on the more commonly located sacral TC. The definition of a TC, as well as the clinical and operative management of this small subset of symptomatic cysts, is analyzed.

Methods

A thorough search of the PubMed database for English-language literature concerning sacral perineural cysts was conducted for the years 2000–2011. Studies were limited to this time period to emphasize the most current data. Search terms used were Tarlov cyst(s), perineural cyst(s), and sacral nerve root cyst(s). The bibliography of each article was reviewed for additional relevant articles. Each article was carefully analyzed and included in our study if details of treatment and outcome were reported. Pathogenesis, pathology, clinical presentation, neuroimaging, treatment options, and surgical indications were reviewed. In addition, case reports were included in this study to describe as many different treatment options as possible.

Results

Twelve studies published in the last 10 years were

Abbreviation used in this paper: TC = Tarlov cyst.

identified, each reporting treatment of more than 1 patient with a TC. After review of these 12 articles, 1 other relevant study was identified and included in the analysis. From these studies, a combined total of 251 patients were treated for symptomatic TCs. Data related to these series (> 2 patients/series) are summarized in Table 1. Table 2 summarizes the 11 single case reports of TC treatment to provide further insight into the surgical management of these lesions.

Discussion

In the practice of medicine, it is common to discover an incidental lesion, which is an asymptomatic lesion found while examining the patient for reasons unrelated to the incidentally found lesion. In many hospitals, the introduction of the picture archiving and communication system has led to an increasing number of incidental lesion discoveries.[34] Patients now undergo MR imaging of the lumbar spine for various symptoms including back pain, sciatica, and neurological dysfunction. These MR imaging studies of the lumbosacral spine often result in the discovery of benign lesions. The most common incidental lumbosacral lesions are vertebral hemangiomas, perineural cysts, fibrolipomas, synovial cysts, and sacral meningoceles.[23]

One recent report indicates an 8.4% rate of incidental findings on lumbar spine MR imaging for suspected disc herniation or lumbar stenosis.[23] The prevalence of different incidental findings in the lumbosacral spine seems to vary significantly for age and sex. Some authors describe a 1%–5% incidence of TCs (Table 3).[23,26,33] The incidence does not significantly differ between sexes but is more prevalent in younger people: 4.0% in people less than 50 years of age old versus 1.3% in people greater than 50 years of age.[23]

Definition, Anatomy, Pathophysiology, and Histology

After the first report by Tarlov[32] in 1938 as an incidental finding at autopsy, several authors described different types of spinal cysts. Spinal meningeal cysts have been recently classified by Nabors et al.[20] into 3 different types: Type I (extradural meningeal cysts without spinal nerve root fibers); Type II (extradural meningeal cysts with spinal nerve root fibers [that is, TCs]); and Type III (spinal intradural meningeal cysts).

Regardless of the classification system, the definition of a TC is histopathological, because it requires the presence of spinal nerve root fibers in the wall of the cyst or in its cavity. Tarlov cysts are defined as CSF-filled saccular lesions located in the extradural space of the sacral spinal canal and are formed within the nerve root sheath at the dorsal root ganglion. Cyst walls are composed of perineurium and neural tissue. The cysts show membranous tissue walls, with peripheral nerve fibers and ganglionic cells embedded into connective tissue.[6,21] Voyadzis et al.[33] found nerve fibers in the walls of the cysts in 75% of their cases.

Cysts created by the dilated sheaths usually have microconnections to the subarachnoid space. However, when pulsatile and hydrodynamic forces of CSF, through a ball-valve mechanism, cause these perineural cysts to fill and expand in size, they can begin to compress neighboring nerve fibers, resulting in neurological symptoms.[18] The ball-valve theory has been previously postulated as the reason why some large TCs cause symptoms that progress, whereas others cause only mild symptoms. The so-called un-valved cysts (that is, those in which

TABLE 1: Literature review of series in which patient were surgically treated for TCs*

Authors & Year	No. of Patients	Follow-Up (mos)	Surgical Technique	% w/ Symptom Improvement	Complications
Caspar et al., 2003	15	6–108	SL + CR	87	none
Guo et al., 2007	11	3–156	SL + CR + CI + FG + MP + Gelfoam	82	CSF leak, bladder dysfunction
Kunz et al., 1999	8	24–96	NA	38	NA
Langdown et al., 2005	3	6–12	SL + CR + MP	100	CSF leak, cauda syndrome by MP displacement
Lee et al., 2004	2	6	1) CT-NA; 2) SL + CR + NL + CI	100	none
Mummaneni et al., 2000	8	1–73	SL + CF + CI	88	none
Murphy et al., 2011	122	NA	1) CT-NA & FI; 2) SL + CF + FP	1) 65†; 2) 63	transient urticaria
Neulen et al., 2011	13	2.5–20	SL + CF + CR	54‡	CSF leak
Park et al., 2008	2	NA	SL + CR + FG + Gelfoam	100	none
Sajko et al., 2009	3	NA	CF + FG	100	none
Tanaka et al., 2006	12	6–52	SL + CR + CI	71	prostatitis, PF bleeding
Voyadzis et al., 2001	10	3–136	SL + CR + NL + FG + Gelfoam	70	urinary incontinence
Zhang et al., 2007	31	10–28	CT-NA & FI	80	fever, headache

* CF = cyst fenestration; CI = cyst imbrication; CR = cyst resection; CT-NA & FI = CT-guided needle aspiration and fibrin injection; FG = fibrin glue; FP = fat packing; MP = muscle patch; NA = not available; NL = (cyst) neck ligation; PF = posterior fossa; SL = sacral laminectomy.

† In 23% of improved patients, symptoms returned on average 7.3 months following the initial procedure.

‡ Includes 1 patient with initial improvement and pain relapse 2 months after surgery.

TABLE 2: Case reports of surgically treated TCs

Authors & Year	Follow-Up (mos)	Surgical Technique	Symptoms Improvement	Complications
Acosta et al., 2003	3	SL + CF + CR; FG + myofascial flap	yes	none
Chaiyabud & Suwanpratheep, 2006	9	SL + CF	yes	none
Hsu & Kuo, 2010	0.3	NL + FG + fat	yes	none
Ishii et al., 2007	NA	SL + NL + root section	yes	none
Kayali et al., 2003	3	SL + CF + CI	yes	none
Jain et al., 2002	NA	SL + CR	yes	none
Ju et al., 2009	6	cyst-subarachnoid shunt	yes	none
Landers & Seex, 2002	6	CT-NA + SL + CI + FG	yes	meningocele
Morio et al., 2001	24	cyst-subarachnoid shunt	yes	none
Prashad et al., 2007	9	SL + CR + CF	yes	none
Singh et al., 2009	12	SL + CR	yes	none

CSF can freely circulate in and out) are unlikely to cause symptoms. On the other hand, lesions in which CSF accumulates under gravitational pressure within the cyst in a valve-like way enlarge over time and can cause neural structure compression. The cysts are often multiple and can erode surrounding sacral bone structures, causing irritation of the periosteal pain fibers[21] and insufficiency fractures.[27]

Several hypotheses have been proposed to explain the etiologies of perineural cysts in the sacral region. The most important ones include inflammation of nerve root cysts followed by inoculation of fluid, arachnoidal proliferation along and around the sacral nerve root, breakage of venous drainage in the perineurium and epineurium secondary to hemosiderin deposition after trauma, and developmental or congenital origin.[6,18,33] Some authors have reported a 40% rate of association with trauma.[22] The presence of nerve fibers, ganglionic cells, or signs of old microhemorrhages in the form of hemosiderin has been related to fact that TCs may be in different stages of evolution.[24,33]

Based on their observations of 2 surgically treated cases of symptomatic sacral TCs in one family, Park et al.[24] suggested that a genetic origin could be an important factor involved in the pathogenesis of TCs.

Clinical Presentation

Most people with TCs are asymptomatic. The reported incidence of symptomatic TCs is approximately 1% or less (Table 3).[14,23,26] The clinical presentation of symptomatic cysts is nonspecific and similar to other disc or lumbar spine pathological entities. Symptoms that can be correlated to TCs include low-back pain, sacrococcygeal pain, perineal pain, sacral nerve root pain (sciatic pain), leg weakness, neurogenic claudication, bowel and bladder dysfunction, and sexual dysfunction.[1,6,35] The onset of symptoms can be sudden or gradual. Usually, patients report that their symptoms are exacerbated by coughing, standing, and change of position. This can be explained by the increase in CSF pressure, leading to an activation of the aforementioned ball-valve mechanism. Symptomatic relief can usually be achieved by recumbent positioning.

Neuroimaging

Magnetic resonance imaging is the gold-standard modality to detect sacral perineural cysts, to study their relationship with surrounding structures, and to plan surgical treatment (when indicated). On MR imaging, the cyst is a fluid-filled lesion showing a low signal on T1-weighted images and high signal on T2-weighted images (that is, CSF signal) (Fig. 1). Scalloping of the sacral vertebral body or posterior arches, caused by a slow increase in size of the cysts, can be seen on both MR and CT images. Computed tomography scans can also be useful for the treatment of the cysts by percutaneous aspiration, as has been reported.[15,19,26] Plain radiographs usually appear normal, but they may reveal characteristic bone erosion of the spinal canal or neural foramina.

Myelography is a more invasive imaging modality that can have a role in detecting communication of the TC with the subarachnoid space. The communication between the thecal sac and cysts functions as a valve. Thus, a delayed filling after intrathecal contrast administration helps to determine the "valved cysts," which are more likely to produce symptoms.

Surgical Indications and Treatment Options

Because TCs are often incidental, the finding can lead to 3 different diagnostic options: 1) another pathology is causing symptoms (that is, the TC is not related to symptoms); 2) another pathology is probably causing symptoms, but the TC could be a secondary cause of the symptoms; or 3) the TC is the only pathological finding that can explain the symptoms. Obviously, this requires

TABLE 3: Incidence of TCs in patients undergoing MR imaging for lumbosacral symptoms

Authors & Year	No. of Patients	Incidence of TC (%)	Incidence of Symptomatic TC (%)
Paulsen et al., 1994	500	23 (4.6)	5 (1.0)
Langdown et al., 2005	3535	54 (1.5)	7 (0.2)
Park et al., 2011	1268	27 (2.1)	0 (0)

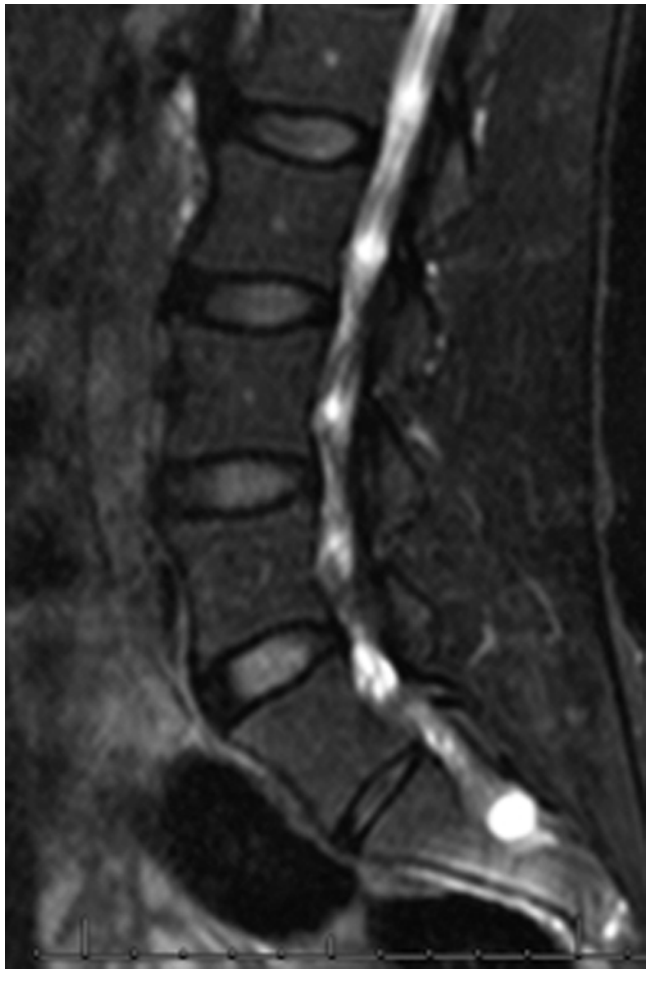

Fig. 1. Sagittal T2-weighted MR image showing an example of a small TC at S-2.

one to carefully evaluate the correlation between clinical and radiological findings.

In Option 1, the main goal is treatment of the primary cause. Some authors have reported cases related to Option 2, in which TCs can contribute to symptoms by virtue of their anatomical location, but they cannot be considered the primary cause because patients have other identified pathology. In those cases, surgical treatment of the associated problem (for example, disc prolapse or foraminal stenosis) can lead to symptomatic improvement.[5,14]

If the first 2 options can be excluded and the TC is considered the cause of patient's symptoms, treatment of the cyst is indicated. However, no consensus has been reached on the ideal treatment modality. There are very little published data regarding the natural history of TCs. Moreover, none of the available studies report significant numbers, and there seems to be no clearly defined criteria for surgical or conservative management of symptomatic TCs.

Conservative treatment, including medical therapy (with analgesic and nonsteroidal antiinflammatory medications) and physical therapy, is suggested as a first option. Mitra et al.[16] described 2 cases of symptomatic perineural cysts treated with conservative management. Symptomatic relief was obtained with oral steroids in a patient with a cervical (C-6) perineural cyst and in a patient with an L-5 perineural cyst, also obtaining in the latter case shrinkage of the cyst after epidural steroid injections. Langdown et al.[14] reported on 3 patients with symptomatic TCs who refused surgery and were able to tolerate their fluctuating symptoms. They did not describe the alternative treatment recommended to these patients, but in a median radiological follow-up of 3.3 years, no changes in cyst features were documented.

Reports in the literature thus far on different surgical options for TC can be divided in 2 subgroups: 1) diversion of CSF flow (CT-guided percutaneous aspiration and modifications, lumboperitoneal shunt, or cystosubarachnoid shunt); or 2) direct microsurgical approach.

The first reports on a percutaneous CT-guided sacral meningeal cyst aspiration described this technique as a potential treatment to alleviate symptoms,[26] but complications such as the tendency of the cysts to reaccumulate fluid and cause symptoms were noted. Subsequently, some authors suggested the use of percutaneous CT-guided fibrin glue injections in sacral meningeal cysts, reporting no recurrence of the cyst after 6 months, but there were 3 (of 4) cases of postprocedural aseptic meningitis.[25] In a more recent study of 31 patients treated with CT-guided percutaneous fibrin glue injections with or without previous cyst aspiration, the authors described an 80% symptom improvement.[35] There was statistically significant back and leg pain reduction and no recurrence of the treated cysts for during a mean follow-up of 23 months. Two cases of transitory aseptic meningitis were reported. Murphy et al.[19] retrospectively described a larger series of 122 patients treated by CT-guided fibrin glue cyst injection. This group showed symptomatic improvement in 65% of patients, 23% experienced symptom recurrence after 7 months. The authors recommended percutaneous CT-guided aspiration of the cyst and fibrin glue injection as a first treatment option, reserving open surgery only for patients not candidates for aspiration or for patients in whom this technique was unable to improve symptoms.

Assuming that a slit-like communication exists between the subarachnoid space and the cyst, functioning as a valve, pressure waves can enhance enlargement of the cyst. Thus, surgical strategies have been proposed with the aim of decreasing CSF pressure of the cephalad thecal sac. Lumboperitoneal shunt implant after a CSF lumbar drainage test has been proposed as a surgical option to lessen the hydrostatic pressure and dampen the CSF pressure waves, decreasing the pressure within the sacral nerve root cyst, as well as compression of the adjacent nerve root. Bartels and van Overbeeke[2] reported on 2 patients suffering from back/leg pain treated with a lumboperitoneal shunt. Symptom relief was achieved at a median of 10 months after shunt insertion. This option has been suggested for patients with multiple TCs, when it is difficult to determine which one is symptomatic. Its advantage is also that it avoids direct manipulation of the cyst by requiring a more technically demanding surgical procedure; however, the risks of every shunt procedure, such as malfunction or infection, are present.[2] In 2 single case reports,[10,17] the patients underwent placement of cys-

tosubarachnoid shunts. These systems were implanted following a direct surgical approach, aiming to equalize the pressure between the thecal sac and the cyst but avoiding the risk of cyst wall resection and potential neurological sequelae. The authors reported relief of symptoms without complication (Table 2).

Although some authors have not described good results in association with direct surgical treatment,[12] several authors have recommended it for selected symptomatic patients. Numerous strategies of direct surgical approaches have been proposed (Table 1). Simple posterior sacral bony decompression has low success rates and can have serious complications, such as dural or nerve lesions.[3] Microsurgical excision[3,6,18,21,33] consists of a sacral laminectomy or laminoplasty[31] followed by microsurgical resection of the wall of the cyst(s). Care must be taken in preserving nervous fibers of the parental nerve roots, which lie directly on the walls of the cyst.[3,6] Procedures including cyst imbrication by suturing the walls of the cyst;[31] neck ligation[7,33] to close communication of the cyst with the subarachnoid space; and cyst fenestration allowing free communication of the CSF between the thecal sac and the cyst[21] have been suggested as different technical options. Some authors[8] have proposed excising the cyst and sacrificing the parental root without significant neurological deficit.

Absorbable gelatin sponge and/or fibrin glue and muscle or fat patching can be used to fill the cyst cavity and cover the dural defects. Neurological worsening due to muscle patch displacement and subsequent cauda equina syndrome[14] has been reported. Leakage of CSF has been a reported complication in 1 of 11 patients reported by Guo et al.,[6] 1 of 3 by Langdown et al.,[14] and 1 of 13 by Neulen et al.[21] Prolonged lumbar drainage is the suggested treatment for CSF leakage. Some authors have recommended routine postoperative lumbar drainage for 3–7 days to prevent CSF leakage,[3,18] as well as the use of intraoperative electrophysiological monitoring to minimize damage to the sacral nerve roots during excision.[18]

Despite low rates of cyst recurrence (range 0%–10%[3,6,12,21]), different rates of symptomatic improvement have been reported in association with microsurgical treatment (Table 1), varying from 38% to 100%. These results should also be correlated to the patient's preoperative symptoms. Caspar et al.[3] noted an improvement in 87% of patients complaining of radicular pain, 90% of patients with sensory disturbances, and 100% of patients with a motor deficit or bowel/bladder dysfunction. Neulen et al.[21] suggested that radicular symptoms are less likely to benefit from surgery, probably because of the permanent impairment of the nerve itself, resulting in chronic pain due to deafferentation.

In statistical terms, the numbers in the present report are too small to draw any definitive conclusions. However, several authors have suggested some indications to identify the better responder to surgical treatment. Voyadzis et al.[33] observed that better results were achieved in patients with radicular symptoms or bladder/bowel dysfunction, and patient with cyst diameters exceeding 1.5 cm. Surgical treatment of multiple cysts, especially those larger than 1.5 cm, has been suggested.[6,18] Neulen et al.[21] suggested that a tendency to improve after surgery was present in patients with single or multiple perineural cysts > 1 cm in diameter and with delayed contrast filling on postmyelographic CT scanning. Patients who present with pain exacerbated by both postural changes and Valsalva maneuvers are also likely to benefit most from surgery.[18]

To our knowledge, only 1 study has reported on the results of surgical treatment compared with conservative management. Kunz et al.[12] did not observe significant differences in terms of symptomatic improvement between the 2 groups (total 16 patients). Due to unfavorable results in terms of pain relief observed after surgical treatment, they recommended surgery only for those patients with a short history and with a neurological deficit.[12]

Unfortunately, all these recommendations are based on results obtained from a small number of patients and, overall, from retrospective reviews.

Conclusions

Tarlov cysts are usually incidental findings on radiological examination performed in the lumbosacral spine. A small percentage of these lesions may be symptomatic. Meticulous care should be taken to clearly define the patient's symptoms and correlate them to radiological findings. What Tarlov stated in his seminal article more than 70 years ago still seems to be true today: "The clinical significance of these cysts remains to be determined."[32]

The results reported in the literature on the surgical treatment of symptomatic cysts, which can now be performed using different methods, have conflicting results, can be technically demanding and not without significant complications, and often do not provide lasting benefit. The best management option must be determined by the size and location of the patient's cyst, as well as the surgeon's skillset.

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References

1. Acosta FL Jr, Quinones-Hinojosa A, Schmidt MH, Weinstein PR: Diagnosis and management of sacral Tarlov cysts. Case

report and review of the literature. **Neurosurg Focus 15(2):** E15, 2003
2. Bartels RH, van Overbeeke JJ: Lumbar cerebrospinal fluid drainage for symptomatic sacral nerve root cysts: an adjuvant diagnostic procedure and/or alternative treatment? Technical case report. **Neurosurgery 40:**861–865, 1997
3. Caspar W, Papavero L, Nabhan A, Loew C, Ahlhelm F: Microsurgical excision of symptomatic sacral perineurial cysts: a study of 15 cases. **Surg Neurol 59:**101–106, 2003
4. Chaiyabud P, Suwanpratheep K: Symptomatic Tarlov cyst: report and review. **J Med Assoc Thai 89:**1047–1050, 2006
5. Dimitroulias AP, Stenner RC, Cavanagh PM, Madhavan P, Webb PJ: Multiple bilateral sacral perineural cysts unusually distal to the exit foramina. **Br J Neurosurg 21:**521–522, 2007
6. Guo D, Shu K, Chen R, Ke C, Zhu Y, Lei T: Microsurgical treatment of symptomatic sacral perineurial cysts. **Neurosurgery 60:**1059–1066, 2007
7. Hsu CH, Kuo MF: Unknown case/presacral mass: a presentation of a large Tarlov cyst. **Spine (Phila Pa 1976) 35:**1412–1413, 2010
8. Ishii K, Yuzurihara M, Asamoto S, Doi H, Kubota M: A huge presacral Tarlov cyst. Case report. **J Neurosurg Spine 7:**259–263, 2007
9. Jain SK, Chopra S, Bagaria H, Mathur PP: Sacral perineural cyst presenting as chronic perineal pain: a case report. **Neurol India 50:**514–515, 2002
10. Ju CI, Shin H, Kim SW, Kim HS: Sacral perineural cyst accompanying disc herniation. **J Korean Neurosurg Soc 45:** 185–187, 2009
11. Kayali H, Düz B, Gönül E: Symptomatic sacral Tarlov cyst: case report. **J Ankara Medical School 25:**103–106, 2003
12. Kunz U, Mauer UM, Waldbaur H: Lumbosacral extradural arachnoid cysts: diagnostic and indication for surgery. **Eur Spine J 8:**218–222, 1999
13. Landers J, Seex K: Sacral perineural cysts: imaging and treatment options. **Br J Neurosurg 16:**182–185, 2002
14. Langdown AJ, Grundy JR, Birch NC: The clinical relevance of Tarlov cysts. **J Spinal Disord Tech 18:**29–33, 2005
15. Lee JY, Impekoven P, Stenzel W, Löhr M, Ernestus RI, Klug N: CT-guided percutaneous aspiration of Tarlov cyst as a useful diagnostic procedure prior to operative intervention. **Acta Neurochir (Wien) 146:**667–670, 2004
16. Mitra R, Kirpalani D, Wedemeyer M: Conservative management of perineural cysts. **Spine (Phila Pa 1976) 33:**E565–E568, 2008
17. Morio Y, Nanjo Y, Nagashima H, Minamizaki T, Teshima R: Sacral cyst managed with cyst-subarachnoid shunt: a technical case report. **Spine (Phila Pa 1976) 26:**451–453, 2001
18. Mummaneni PV, Pitts LH, McCormack BM, Corroo JM, Weinstein PR: Microsurgical treatment of symptomatic sacral Tarlov cysts. **Neurosurgery 47:**74–79, 2000
19. Murphy KJ, Nussbaum DA, Schnupp S, Long D: Tarlov cysts: an overlooked clinical problem. **Semin Musculoskelet Radiol 15:**163–167, 2011
20. Nabors MW, Pait TG, Byrd EB, Karim NO, Davis DO, Kobrine AI, et al: Updated assessment and current classification of spinal meningeal cysts. **J Neurosurg 68:**366–377, 1988
21. Neulen A, Kantelhardt SR, Pilgram-Pastor SM, Metz I, Rohde V, Giese A: Microsurgical fenestration of perineural cysts to the thecal sac at the level of the distal dural sleeve. **Acta Neurochir (Wien) 153:**1427–1434, 2011
22. Nishiura I, Koyama T, Handa J: Intrasacral perineurial cyst. **Surg Neurol 23:**265–269, 1985
23. Park HJ, Jeon YH, Rho MH, Lee EJ, Park NH, Park SI, et al: Incidental findings of the lumbar spine at MRI during herniated intervertebral disk disease evaluation. **AJR Am J Roentgenol 196:**1151–1155, 2011
24. Park HJ, Kim IS, Lee SW, Son BC: Two cases of symptomatic perineural cysts (tarlov cysts) in one family: a case report. **J Korean Neurosurg Soc 44:**174–177, 2008
25. Patel MR, Louie W, Rachlin J: Percutaneous fibrin glue therapy of meningeal cysts of the sacral spine. **AJR Am J Roentgenol 168:**367–370, 1997
26. Paulsen RD, Call GA, Murtagh FR: Prevalence and percutaneous drainage of cysts of the sacral nerve root sheath (Tarlov cysts). **AJNR Am J Neuroradiol 15:**293–299, 1994
27. Peh WC, Evans NS: Tarlov cysts—another cause of sacral insufficiency fractures? **Clin Radiol 46:**329–330, 1992
28. Prashad B, Jain AK, Dhammi IK: Tarlov cyst: case report and review of literature. **Indian J Orthop 41:**401–403, 2007
29. Sajko T, Kovać D, Kudelić N, Kovac L: Symptomatic sacral perineurial (Tarlov) cysts. **Coll Antropol 33:**1401–1403, 2009
30. Singh PK, Singh VK, Azam A, Gupta S: Tarlov cyst and infertility. **J Spinal Cord Med 32:**191–197, 2009
31. Tanaka M, Nakahara S, Ito Y, Nakanishi K, Sugimoto Y, Ikuma H, et al: Surgical results of sacral perineural (Tarlov) cysts. **Acta Med Okayama 60:**65–70, 2006
32. Tarlov IM: Perineural cysts of the spinal nerve roots. **Arch Neurol Psychiatry 40:**1067–1074, 1938
33. Voyadzis JM, Bhargava P, Henderson FC: Tarlov cysts: a study of 10 cases with review of the literature. **J Neurosurg 95 (1 Suppl):**25–32, 2001
34. Wagner SC, Morrison WB, Carrino JA, Schweitzer ME, Nothnagel H: Picture archiving and communication system: effect on reporting of incidental findings. **Radiology 225:**500–505, 2002
35. Zhang T, Li Z, Gong W, Sun B, Liu S, Zhang K, et al: Percutaneous fibrin glue therapy for meningeal cysts of the sacral spine with or without aspiration of the cerebrospinal fluid. **J Neurosurg Spine 7:**145–150, 2007

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Address correspondence to: Paul Park, M.D., Department of Neurosurgery, University of Michigan, 1500 East Medical Center Drive, Room 3552, Taubman Center, Ann Arbor, Michigan 48109-5338. email: ppark@umich.edu.

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Idiopathic syringomyelia: retrospective case series, comprehensive review, and update on management

Anil K. Roy, B.S., Nicholas P. Slimack, M.D., and Aruna Ganju, M.D.

Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Object. A syrinx is a fluid-filled cavity within the spinal cord that can be an incidental finding or it can be accompanied by symptoms of pain and temperature insensitivity. Although it is most commonly associated with Chiari malformation Type I, the advancement of imaging techniques has resulted in more incidental idiopathic syringes that are not associated with Chiari, tumor, trauma, or postinfectious causes. The authors present a comprehensive review and management strategies for the idiopathic variant of syringomyelia.

Methods. The authors retrospectively identified 8 idiopathic cases of syringomyelia at their institution during the last 6 years. A PubMed/Medline literature review yielded an additional 38 articles.

Results. Two of the authors' patients underwent surgical treatment that included a combination of laminectomy, lysis of adhesions, duraplasty, and syrinx fenestration. The remaining 6 patients were treated conservatively and had neurologically stable outcomes. Review of the literature suggests that an etiology-driven approach is essential in the diagnosis and management of syringomyelia, although conservative management suffices for most cases. In particular, it is important to look at disturbances in CSF flow, as well as structural abnormalities including arachnoid webs, cysts, scars, and a diminutive posterior fossa.

Conclusions. The precise etiology for idiopathic syringomyelia (IS) is still unclear, although conceptual advances have been made toward the overall understanding of the pathophysiology of IS. Various theories include the cerebellar piston theory, intramedullary pulse pressure theory, and increased spinal subarachnoid pressure. For most patients with IS, conservative management works well. Continued progression of symptoms, however, could be approached using decompressive strategies such as laminectomy, lysis of adhesions, and craniocervical decompression, depending on the level of pathology. Management for patients with progressive neurological dysfunction and the lack of flow disturbance is unclear, although syringosubarachnoid shunting can be considered.
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Key Words • syringomyelia • idiopathic syringomyelia • syringomyelia pathophysiology

A syrinx is defined as a fluid-filled cavity that anatomically lies within the spinal cord parenchyma or the central canal.[10] Although syringomyelia is clinically associated with a centromedullary syndrome with predominantly sensory symptoms such as pain and temperature insensitivity,[34] in many cases it is an incidental finding. This entity is most frequently associated with a CM-I,[30] although other known causes include spinal cord tumor, trauma, and posttraumatic or infectious adhesive arachnoiditis.[18,22,36] With the increasing use of MR imaging, discovery of IS is more common.[31,34] Various terms have been used to refer to IS including hydromyelia, idiopathic localized hydromyelia, and syringohydromyelia.[15,26,34] Although not clearly defined, the general consensus seems to be that IS is not associated with any of the conditions mentioned previously.[3,28,31,34,37] The management and natural history of such idiopathic syringes remain unclear. Here, we present our experience with IS in a retrospective case series of 8 patients, and we provide a comprehensive review of the current evidence. We add to our previous study examining nontraumatic cervicothoracic syringes and include several cases that were observed conservatively.[33] We also formulate guidelines to assist neurosurgeons who encounter this pathological entity.

Abbreviations used in this paper: ACDF = anterior cervical discectomy and fusion; CM-I = Chiari malformation Type I; IS = idiopathic syringomyelia.

Methods

The study was approved by the institutional review board for patients seen in our neurosurgical clinic with

a diagnosis of syringomyelia. From this group, we retrospectively identified all patients who had been diagnosed with IS between 2005 and 2011. The patients had no evident etiology such as CM-I, tumor, trauma, or postlaminectomy adhesions. We did not have a minimal syrinx diameter for inclusion, given the overall paucity of syringes that were idiopathic. We also did not exclude patients with arachnoid webs, adhesions, or cysts, consistent with other studies on IS.[27,28]

PubMed/Medline searches using the key words "idiopathic syringomyelia," "pathophysiology of syringomyelia," "classification of syringomyelia," and "management of syringomyelia" resulted in 130 articles, which were independently analyzed by 2 authors (A.K.R. and N.P.S.). This group was further screened to include articles with a focus on IS; this process yielded 38 articles.

Results

A total of 8 patients were identified. The mean age was 39.3 years (25–61 years), and there were 7 men and 1 woman. Patient characteristics, type of surgery (if any), follow-up status, and duration are detailed in Table 1. Table 2 summarizes the evidence from key articles.

Symptoms and Signs

One patient (Case 1) presented with a history of worsening right arm pain and had myelopathic signs on examination that were evidenced by gait abnormalities, urinary urgency, and hyperreflexia in the lower extremities. Another patient (Case 2) presented with progressive difficulties in walking and also had myelopathic signs evidenced by hyperreflexia in the lower extremities.

Five patients (Cases 3–7) presented with milder symptoms that mostly included pain in different distributions. None of these patients had any abnormalities on examination. The patient in Case 8 had an initial diagnosis of cervical stenosis, which was treated by a C3–4 ACDF to which he responded well. Five years later, the patient presented with some recurrent radicular symptoms, which led to the diagnosis of a lower thoracic syrinx.

Imaging Studies

The patients in Cases 1 and 2 underwent extensive imaging, which revealed CSF flow abnormalities. In the patient in Case 1, initial MR imaging revealed a syrinx at the cervicothoracic junction. Further studies, including cine MR imaging and CT myelography, revealed abnormal flow at the T1–2 level and possible scarring/adhesions at the same level. Initial MR images obtained in the patient in Case 2 revealed a C5–T5 syrinx, and with the addition of cine MR imaging and CT myelography revealing abnormal flow at the C5–T1 levels and subarachnoid compartmentalization from T-4 to T-6.

The patients in Cases 3–8 were only investigated using MR imaging, given their mild symptoms and intact neurological examinations. All these patients had some evidence of degenerative changes apart from the syringes.

The combined mean syrinx diameter was 3.88 mm (range 0.78–8.39 mm), and the mean length was 97 mm (range 38.7–178.8 mm). A cursory analysis does reveal a larger mean diameter in the surgically versus conservatively treated cases (6.3 vs 3.08 mm); however, given the low case numbers, we have not run further statistical tests on these results. Most syringes spanned the cervicothoracic cord. The mean length was 78.9 mm for the surgical cases and 104.2 mm for the conservative cases. Only the imaging report was available for the initial scan in 1 patient (Case 3), which did not include the actual length of the syrinx.

Outcomes

Given the presence of myelopathic signs on examination with a demonstrable CSF flow abnormality, 1 patient (Case 1) underwent T1–3 laminectomy with lysis of adhesions. Figure 1 shows pre- and postoperative images of this case with collapse of the syrinx. At the 1-year postoperative visit, the patient had an intact neurological

TABLE 1: Summary of patients with IS*

Case No.	Age (yrs), Sex	Sx & Signs	Imaging Finding; Diameter (mm), Length (mm)	Treatment	Time/Outcomes
1	43, M	rt UE pain, urinary urgency, patellar hyperreflexia	C7–T2 syrinx; 7, 38.73	T1–3 laminectomy w/ lysis of adhesions	1 yr, collapse of syrinx & resolution of Sx
2	45, M	lt leg weakness	C5–T5 syrinx; 5.6, 119.25	T4–6 laminectomy w/ lysis of adhesions & fenestration of syrinx	5 yrs, initial resolution w/ LE pain at 5 yrs
3	27, M	mid-thoracic pain	T5–12 syrinx; 2, unclear	conservative	6 mos, stable syrinx & resolution of Sx
4	43, M	thoracic dysesthesia	T6–9 syrinx; 0.78, 76.86	conservative	no FU available
5	40, M	neck & thoracic pain	C5–T2 syrinx; 8.39, 128.13	conservative	10 yrs, stable syrinx & resolution of Sx
6	25, M	low-back & LE pain	T5–10 syrinx; 4.92, 178.81	conservative	2 yrs, stable syrinx & resolution of Sx
7	31, F	neck & shoulder pain	C4–T2 syrinx; 1.24, 61.84	conservative	no FU available
8	61, M	tingling in neck, low-back & LE pain	T8–11 syrinx; 1.16, 75.77	C3–4 ACDF at time of initial presentation	5 yrs, episodic radicular Sx

* Two patients underwent surgical intervention after signs of myelopathy were evident, which was progressive in nature. All other patients had a stable follow-up for different periods of time. Abbreviations: FU = follow-up; LE = lower extremity; UE = upper extremity.

TABLE 2: Summary of papers on IS patients including presentation, imaging findings, and outcomes*

Authors & Year	Type of Study	No. of Pts & Sex	Age (yrs)	Location	Sx	Treatment†	Outcome†	FU Period
Ataizi et al., 2007	case report	1 F	28	C5–T1	neck & back pain	conservative (pt refused op)	resolution of pain; spontaneous collapse of syrinx	16 mos
Bogdanov et al., 2004‡	cross-sectional: 17 idiopathic, 17 CM-I, 32 control	idiopathic: 2 F & 15 M	mean 49	cervical	segmental sensory loss, pyramidal signs, muscle atrophy	NA	NA	NA
Chen et al., 2004	case report	1 F	19	C2–6	proximal upper limb weakness, diminished pain & temperature	suboccipital craniectomy w/ C-1 and C3–5 laminectomy	improved motor strength but unchanged sensory deficit; syrinx reduced	12 mos
Chern et al., 2011	retrospective case series	15: 6 F & 9 M	mean 10.5	multiple	scoliosis, HA, neck pain	suboccipital craniectomy w/ C-1 laminectomy	resolved (4), improved (6), stable (3), worse (1), persistent HA (1)	12–75 mos
Holly & Batzdorf, 2002§	prospective study	32: 14 F & 18 M	mean 40	cervical (16), thoracic (12), cervicothoracic (4)	mechanical spinal pain, radicular pain, numbness	conservative (31), ACDF at C6–7 (1)	improved (6), worsened (7), unchanged (19)	6–110 mos (mean 38 mos)
Jinkins & Sener, 1999	case series	3: 2 F & 1 M	mean 27.3	lumbar, cervical, thoracic	low-back pain, HA, nonfocal back pain	conservative	stable w/ resolution of pain (2), migraines (1)	2–4 yrs (mean 3 yrs)
Kastrup et al., 2001	case report	1 F	61	C1–conus medullaris	burning pain	carbamazepine	subsequently collapsed syrinx but Sx did not change	8 yrs
Kyoshima et al., 2002¶	retrospective case series	4: 3 F & 1 M	mean 37.8	holocord (2), medulla–T12 (1), C1–T9 (1)	touch & pain impairment, weakness, hypalgesia	craniocervical decompression	all improved Sx & decreased syrinx except for 1	2.5–11 yrs (mean 8 yrs)
Lin et al., 2006	case report	1 M	35	T2–9	lt leg weakness over 5 yrs, decreased pinprick & touch below lt T-7	T6–8 laminectomy, SS shunt	JOA score improved from 10 preop to 14 on POD 30	5 yrs (30 days postop)
Magge et al., 2011	retrospective case series	48: 30 F & 18 M	mean 9.7	2–17 levels, mostly thoracic	scoliosis, cutaneous marker, LE or back pain, neurological Sx incidental	SS shunt (1), fenestration of syrinx (1), rest conservative	op (2), 1 w/ worsened gait & weakness, 1 w/ no change in clinical Sx	clinical: 3–56 mos (mean 15.5 mos); clinical + radiographic: 2–64 mos (mean 23.8 mos)
Mallucci et al., 1997	retrospective case series	10: 2 F & 8 M	mean 48	not described	sensory disturbance, less commonly weakness	laminectomy & excision of web, cyst, SP shunt (2)	all improved (Sx better & syrinx decreased) except for 2 who underwent shunting	not described
Mauer et al., 2008‡	prospective case series	125: 76 F & 49 M	mean 36	1–18 levels not clearly defined	w/o op: pain, sensory impairment; w/ op: bowel or bladder dysfunction, gait abnormalities, paralysis	arachnoid scar or web resection (10); conservative (115)	op: improvement (4), remaining pts showed no further progression; conservative: precise outcomes not described	pts selected over 3-yr period; FU not described

(continued)

TABLE 2: Summary of papers on IS patients including presentation, imaging findings, and outcomes* *(continued)*

Authors & Year	Type of Study	No. of Pts & Sex	Age (yrs)	Location	Sx	Treatment†	Outcome†	FU Period
Nakamura et al., 2009	retrospective case series	15: 4 F & 11 M	mean 45.1	localized C3–T2 (12), extended C1–T8 (3)	upper limb numbness, neck pain, extended (3): also progressive upper limb weakness	conservative (12), SS shunt (3)	conservative: no changes; op: decreased syrinx, mean JOA decreased from 11.8 to 11.2	7–20 yrs (mean 10 yrs)
Porensky et al., 2007	case report	2 M	43 & 44	T1–2, C5–5	ataxia, neck pain, progressive lt leg paresis, pinprick deficit rt leg	laminectomy, lysis of adhesions, duraplasty	asymptomatic, collapsed syrinx (Case 1); refilled syrinx, unchanged neurological exam (Case 2)	1 yr (Case 1), 7 mos (Case 2)
Roser et al., 2010	prospective case series	40: 25 F & 15 M	mean 36.7	cervical (23%), thoracic (51%), cervicothoracic (25%)	pain or dysesthesia of limbs	conservative	no radiological changes; neurologically stable	6–93 mos (mean 36.9 mos)
Struck & Haughton, 2009‡	retrospective case series	8: 4 F & 4 M	mean 12.1	lower cervical or thoracic	variable (scoliosis, HA, back pain, extremity numbness, family history, nausea & vomiting)	posterior fossa decompression (4); no op at time of study (4)	postop: decreased Sx (4); syrinx reduction (1)	pts selected over 7-yr period; FU not described

* HA = headache; JOA = Japanese Orthopaedic Association; POD = postoperative day; NA = not available; pt = patient; SP = syringopleural; SS = syringosubarachnoid.
† Numbers in parentheses indicate the number of patients.
‡ Findings from imaging studies.
§ Ten patients had a history of trauma.
¶ Technically these cases were not idiopathic since a tight cisterna magna is a definite lesion.

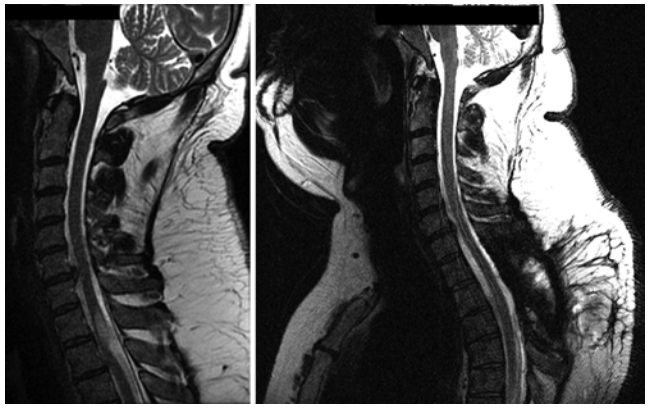

Fig. 1. Case 1. Preoperative **(left)** and 1-year postoperative **(right)** T2-weighted images.

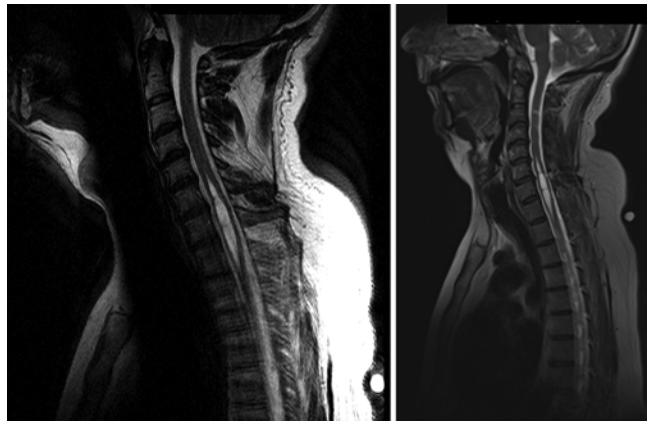

Fig. 2. Case 5. Sagittal T2-weighted images obtained at presentation **(left)** and at the 10-year follow-up **(right)**.

examination with resolution of symptoms. Under similar operative indications, another patient (Case 2) underwent a T4–6 laminectomy with lysis of adhesions. Although this patient did well for almost 2.5 years after surgery, he subsequently developed bilateral pain and weakness in his lower extremities. Cine MR imaging at this time revealed diminished dorsal and ventral flow from C5–T4, although we did not identify a clear pathology for surgery. In a subsequent 5-year follow-up, this patient has had some resolution of the pain.

The patients in Cases 3–8 were treated conservatively. The follow-up periods ranged from 6 months to 10 years. In 3 of these 6 patients, radiographic follow-up was also available and revealed no changes in syrinx size. Figure 2 shows images that were obtained at the initial visit and the 10-year follow-up in 1 patient (Case 5). All conservatively treated patients had resolution of their symptoms during follow-up visits, with the exception of the patient in Case 8 who had occasional radicular symptoms in his legs. This responded well to epidural steroid injections.

Discussion

Pathophysiology

There are few studies that directly address the pathophysiology behind IS. Most work in the field of syringomyelia comes from work done on CM-I. Here, we include a review of this evidence as background for possible similarities in mechanisms behind IS. Koyanagi and Houkin[19] divided the CM-I syringomyelia evidence into 3 categories depending on the source of origin: CSF entrance from the fourth ventricle, CSF entrance from the subarachnoid space, and extracellular fluid origin.

Previous evidence by Gardner and Angel[9] regarding CSF entrance from the fourth ventricle was supported by success of their procedure that involved closure of the obex along with a medial suboccipital craniectomy. The validity of this theory is now questioned by cine-mode MR imaging studies that did not demonstrate any CSF entrance from the fourth ventricle into the syrinx.[32] The procedure performed by Gardner and Angel has also been reported to work just as well without closure of the obex. In their review of pathological specimens, Milhorat et al.[29] reported that syringes that communicated with the fourth ventricle were mostly found in children with hydrocephalus. This included an association with postmeningitic and posthemorrhagic hydrocephalus along with CMs Type II and Dandy-Walker cysts.

Greitz[10] questioned the theory about increased subarachnoid pressure propelling CSF into the syrinx since such a pressure might actually compress the cavity. Moreover, most studies have not consistently identified a pressure gradient that would favor CSF flow into the syrinx from the subarachnoid space.[17,19] It has been noted that delayed CT myelography after intrathecal injection of metrizamide has demonstrated enhancement of syringomyelic cavities.[24] In their review, Koyanagi and Houkin[19] reported that these results are not specific to syringomyelia and that delayed clearance of the contrast from syrinx cavities may explain the delayed visualization on CT myelography. In an animal model of posttraumatic syringomyelia, Brodbelt et al.[5] showed increased perivascular flow at the level of the syrinx, although it is unclear if such flow actually causes the syrinx to develop or is simply a byproduct of localized inflammation and edema. Iwasaki et al.[14] demonstrated that syringosubarachnoid shunting is effective at collapsing CM-I syringes; this does not appear to be in concordance with the theory postulating CSF entrance from the subarachnoid space. The piston theory by Oldfield et al.[32] suggests that increased downward motion by cerebellar tonsils in CM-I causes increased CSF pressure, driving subarachnoid CSF into the central canal. This, however, has been questioned by the more recent studies mentioned above.

Papers that support an extracellular origin of CSF include those by Klekamp,[17] Levine,[23] Greitz,[10] and Koyanagi and Hougin.[19] The exact mechanism, however, is still debated. Greitz[10] described the concept of intramedullary pulse pressure causing cord distension and subsequent cavitation. Koyanagi and Hougin[19] argued that a reduced compliance of posterior spinal veins leads to reduced absorption of extracellular fluid and thus syringomyelia. The interested reader is referred to these reviews for an exhaustive coverage of these theories and historical evidence.

The intramedullary pulse pressure theory by Greitz[10]

synthesizes a unifying principle for all types of syringomyelia, regardless of cause. Future clinical evidence will demonstrate if this is indeed true, although it is not unreasonable that the theories outlined for the formation of syringomyelia in patients with CM-I may apply to those with IS. For example, in a study comparing patients with IS, those with CM-I, and controls, Bogdanov et al.[3] found similar morphometric abnormalities in patients with IS and those with CM-I. This included similar shortening of the posterior fossa and a reduction of ventral CSF space, although the dorsal CSF space was significantly smaller in CM-I patients. Syrinx diameter was found to be significantly larger in patients with CM-I (5.5 ± 4.7 vs 2.7 ± 1.9 mm). The study by Bogdanov et al.[3] posited that a posterior fossa with decreased compliance promotes the development of pulsatile CSF subarachnoid pressure waves, aiding in the development of syringomyelia.[11] Struck and Haughton[37] also reported abnormal CSF flow velocities in patients with IS and raised the possibility of similarities in flow patterns at the foramen magnum between patients with CM-I and those with IS. The idea of similar morphometric abnormalities in IS and CM-I seems to follow the reasoning by Klekamp,[17] who questioned whether a true idiopathic syrinx actually exists. Porensky et al.[33] reported on 2 patients with IS; the report postulated that subtle microtrauma may have been contributory.

Imaging and Classification

On imaging, it is critical to differentiate between a true syrinx and residual enlargement of the central canal. As we age, the central canal normally involutes, such that by adulthood it is often not easily seen on images.[38] Holly and Batzdorf[13] examined 32 patients with slitlike syrinx cavities, which they termed "asymptomatic persistent central canals." The authors found symmetrically enlarged central spinal cord cavities with a mean diameter of 2 mm (range 1–5 mm) with no enhancement after intravenous Gd injection. It was noted that 10 patients did have a history of trauma, although the study did not classify the syringes as posttraumatic. The study also found that 50% of the patients had alternate diagnoses for their symptoms. Holly and Batzdorf[13] argued that these slitlike syrinx cavities do not represent true syringomyelia and are possibly even different from a presyrinx-like state. In the literature, there is no uniformity regarding this opinion. For example, Roser et al.[34] differentiated hydromyelia as referring simply to a dilated central canal due to IS. These authors portended that IS is accompanied by different clinical and radiological signs. According to Roser et al.,[34] patients with hydromyelia have no neurological deficits and mainly present with pain that could be radicular, burning, or musculoskeletal. This constellation of symptoms is similar to those described by Holly and Batzdorf.[13] Roser et al.[34] suggested that hydromyelia is a congenital condition; in the setting of trauma, syringomyelia could develop.[10] Based on these studies, it is difficult to determine if slitlike syringes, hydromyelia, and IS are truly different entities or simply a continuum on a spectrum.

Classically, the idiopathic form of syringomyelia does not have an anatomical abnormality readily seen on imaging. Some of the evidence presented in the pathophysiology section earlier, however, raises the concern that this may be too simplistic of a definition. Struck and Haughton[37] have reported increased peak CSF flow velocities in IS. The study by Bogdanov et al.[3] also found a small posterior fossa and narrow CSF spaces in IS. Kyoshima et al.[20] described a series of 4 patients with IS but also documented all as having a "tight cisterna magna," referring to the cisterna magna being impacted by the tonsils. Mallucci et al.[27] evaluated 10 patients with apparent idiopathic syringomyelia, with subsequent CT myelography revealing CSF blockage in 9 of them. Patients who subsequently underwent laminectomy and adhesions of arachnoid webs performed much better than those who underwent shunt treatment. Clifton et al.[8] also reported on a patient with a T2–C5 syrinx along with a spinal intradural arachnoid cyst between T-6 and T-3 found by aqueous myelography. This patient improved after laminectomy and collapse of the cyst. A later study by Mauer et al.[28] evaluated 125 patients with IS using cardiac-gated phase-contrast CSF flow studies and found blockage of flow in 33 patients. The most common level of blockage was T-6. Fifteen of the 33 cases had a ventrally open circular shape syrinx cavity. In 8 of the 33 patients with unequivocal evidence of CSF flow blockage on MR imaging studies, Mauer et al.[28] also performed CT myelography, which revealed blockage in 2 patients. These authors concluded that conventional myelography is not a useful tool in diagnosis and that cardiac-gated CSF flow studies should suffice. According to this study, IS is not entirely idiopathic and a closer look at the anatomy may reveal structural problems.

Other descriptors of IS include a distinction of localized versus extended IS. In their retrospective case series on IS, Nakamura et al.[31] described localized IS as being fewer than 3 vertebrae and extended IS as 4 or more vertebrae. The localized variant had milder symptoms and was treated conservatively. Nakamura et al.[31] also referred to the localized syringomyelia variant as a possible congenital enlargement of the central canal. Kyoshima et al.[20] detailed the numerous classification systems to delineate terms such as hydromyelia, simple hydromyelia, syringomyelia, and syringohydromyelia. It is unclear if this aids in the diagnostic or management process.

Presentation

Symptoms that lead to the diagnosis of IS can fall into a variety of categories. In a population of 48 children with IS, Magge et al.[26] divided the presentation into the following 5 groups: scoliosis, cutaneous marker/developmental anomaly, pain, neurological findings, and screening/incidental finds. Chern et al.[7] also recently published their evidence on patients with CM Type 0 and syringomyelia, and the presenting symptoms included scoliosis, headaches, and neck, back, or leg pain.

Specifically, regarding the issue of pain, Magge et al.[26] noted that there does not appear to be any correlation between syrinx size or location and the symptom of pain. Although we did find an overall increased syrinx diameter in the 2 surgical cases, the relevance is unclear given the few cases we have. Nonspecific symptoms such

as pain may be a coincidental finding rather than a direct result of the syrinx. Even in our population of adults who were conservatively treated, it is difficult to localize the symptoms to the syrinx. Thus, it is critical to stress that IS is generally an incidental, asymptomatic finding. While the classically described centromedullary syndrome may accompany a syrinx, these are usually found in surgical cases.

In the few cases in which we can attempt to localize the symptoms to the syrinx, it is highly dependent on the location within the spinal cord. Patients may actually have comorbid symptoms from degenerative changes of the spine and musculoskeletal complaints, prompting medical evaluation. Although syringomyelia symptoms are classically described as pain and temperature insensitivity in a capelike distribution, few of our patients, and indeed few of the studies reviewed, actually demonstrated this. Mallucci et al.[27] discussed that while the most common presenting symptom is pain followed by paresthesias, numbness, and unnoticed hand injuries, it is not uncommon for patients to present with long tract signs. For noncommunicating syringes, symptoms can include spastic weakness of the lower extremities, paresthesias, or dysesthesias and segmental sensory loss.[29] Bogdanov and Mendelevich[4] reported that the pace of neurological deterioration in syringomyelia is initially rapid but slows down after neurological signs become well established.

Management

Table 2 provides a review of the key literature regarding idiopathic syringomyelia. The reader is cautioned that only some of the details for each study were included and that some of the patients were eventually found to have other structural anomalies. The studies discuss a large number of treatment options including posterior fossa and foramen magnum decompression, laminectomy, lysis of adhesions, syrinx fenestration, and syringosubarachnoid, syringoperitoneal, and syringopleural shunting. Most recent studies have reported on the importance of improving CSF flow dynamics regardless of the treatment strategy used.[3,20,21,31]

The management strategies outlined above should only be reserved for clearly symptomatic patients with progression on serial examinations. The majority of the patients in our series were conservatively treated, giving credence to the idea that serial imaging is an option for patients. The reader is especially cautioned in tying the symptoms to the syrinx and proceeding with surgical treatment, since the symptoms may be purely coincidental as mentioned earlier. In particular, a nonoperative approach is justified when a patient is either asymptomatic or experiences relatively mild symptoms. In their study on IS, Magge et al.[26] also suggested that surgical management of the syrinx may not offer much utility since both their surgical cases either worsened or showed no changes clinically. We routinely may obtain follow-up MR images on an annual basis or more frequently as dictated by symptoms.

Historically, shunting strategies have been used and have led to clinical and radiological improvement in the treatment of IS. However, some studies have reported a variety of complications including shunt failure, syrinx relapse, catheter tip migration, and comorbidities from mechanical damage to cord tissue.[2,35] Mallucci et al.[27] also discussed that shunts are not an effective solution in preventing the progress of syringomyelia given the subsequent gliosis that can follow within the cord. We believe that shunting should be used as a measure of last resort when no etiology is evident after repeated imaging studies and surgical exploration do not reveal any pathology around the site of the syrinx.

In cases in which the etiology is clearly evident such as a tight cisterna magna or small posterior fossa, craniocervical decompression is the best option for restoring CSF flow dynamics. Holly and Batzdorf,[12] however, have cautioned that too wide of a suboccipital craniectomy can lead to cerebellar ptosis. Kyoshima et al.[20] also mentioned that wider opening of the foramen magnum and not the posterior fossa is the key. If CSF flow obstruction originates from spinal subarachnoid pathology such as a cyst, web, or scar, treatment should be targeted toward decompressing the spinal subarachnoid space and reconstituting flow. This is illustrated by the 2 patients in our series who underwent surgical treatment. There is no clear evidence on precisely what such decompression and reconstruction should include. Laminectomy followed by scar, web, or cyst resection has been commonly used in other studies[8,21,27] and has been used with good results by the senior author (A.G.). In the event of no evidence of any anatomical abnormality in the setting of progressive neurological dysfunction attributable to a syrinx, surgical exploration is a reasonable option with a shunt as the last resort.

We have combined evidence on IS and our experience into an algorithm (Fig. 3) to assist in the decision-making process. In most cases of incidental, asymptomatic findings, annual imaging should be sufficient. For the more challenging symptomatic cases, the key focus is to resolve CSF flow problems since most of the evidence points to disrupted flow dynamics leading to the development of syringomyelia.

Conclusions

Idiopathic syringomyelia is a pathological entity in which no overt etiology is evident for a syrinx; numerous cases of IS are now attributed to CSF flow abnormalities. It is important to understand that most incidental cases of IS can be successfully managed using conservative approaches. Most patients in our series were treated conservatively. With regard to surgical options for continued progression of symptoms, syrinx shunting is generally a less favored approach as it does not resolve the underlying etiology and is associated with high failure rates. A particular challenge to the neurosurgeon is surgical treatment of syringes with no overt etiology and worsening symptoms even after a complete diagnostic workup including flow studies. While we recommend surgical exploration in these cases, future studies will hopefully reveal a more systematic approach for these patients. We have presented our institution's recent experience with IS management, and we have detailed the existing literature.

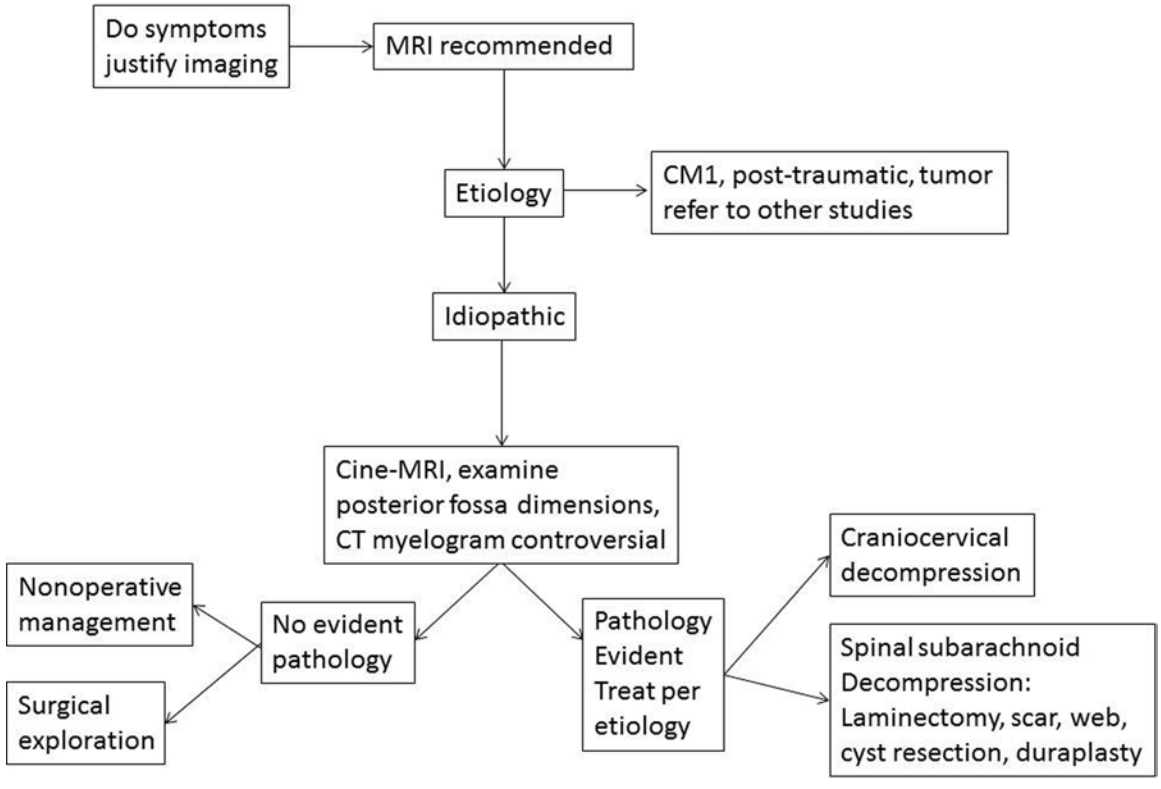

Fig. 3. Management algorithm for IS. Indications for imaging include progressive deterioration in signs or symptoms.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Roy, Slimack. Acquisition of data: Roy. Analysis and interpretation of data: all authors. Drafting the article: Roy, Slimack. Critically revising the article: all authors.

References

1. Ataizi S, Canakçi Z, Baloğlu M, Cerezci A: Spontaneously resorbed idiopathic syringomyelia: a case report. **Turk Neurosurg 17:**247–250, 2007
2. Batzdorf U, Klekamp J, Johnson JP: A critical appraisal of syrinx cavity shunting procedures. **J Neurosurg 89:**382–388, 1998
3. Bogdanov EI, Heiss JD, Mendelevich EG, Mikhaylov IM, Haass A: Clinical and neuroimaging features of "idiopathic" syringomyelia. **Neurology 62:**791–794, 2004
4. Bogdanov EI, Mendelevich EG: Syrinx size and duration of symptoms predict the pace of progressive myelopathy: retrospective analysis of 103 unoperated cases with craniocervical junction malformations and syringomyelia. **Clin Neurol Neurosurg 104:**90–97, 2002
5. Brodbelt AR, Stoodley MA, Watling AM, Tu J, Burke S, Jones NR: Altered subarachnoid space compliance and fluid flow in an animal model of posttraumatic syringomyelia. **Spine (Phila Pa 1976) 28:**E413–E419, 2003
6. Chen JK, Chen CH, Lee CL, Chen TW, Weng MC, Huang MH: Acute idiopathic syringomyelia: a case report. **Kaohsiung J Med Sci 20:**404–409, 2004
7. Chern JJ, Gordon AJ, Mortazavi MM, Tubbs RS, Oakes WJ: Pediatric Chiari malformation Type 0: a 12-year institutional experience. Clinical article. **J Neurosurg Pediatr 8:**1–5, 2011
8. Clifton AG, Ginsberg L, Webb WJ, Valentine AR: Idiopathic spinal arachnoid cyst and syringomyelia. **Br J Radiol 60:** 1023–1025, 1987
9. Gardner WJ, Angel J: The mechanism of syringomyelia and its surgical correction. **Clin Neurosurg 6:**131–140, 1958
10. Greitz D: Unraveling the riddle of syringomyelia. **Neurosurg Rev 29:**251–264, 2006
11. Heiss JD, Patronas N, DeVroom HL, Shawker T, Ennis R, Kammerer W, et al: Elucidating the pathophysiology of syringomyelia. **J Neurosurg 91:**553–562, 1999
12. Holly LT, Batzdorf U: Management of cerebellar ptosis following craniovertebral decompression for Chiari I malformation. **J Neurosurg 94:**21–26, 2001
13. Holly LT, Batzdorf U: Slitlike syrinx cavities: a persistent central canal. **J Neurosurg 97 (2 Suppl):**161–165, 2002
14. Iwasaki Y, Koyanagi I, Hida K, Abe H: Syringo-subarachnoid shunt for syringomyelia using partial hemilaminectomy. **Br J Neurosurg 13:**41–45, 1999
15. Jinkins JR, Sener RN: Idiopathic localized hydromyelia: dilatation of the central canal of the spinal cord of probable congenital origin. **J Comput Assist Tomogr 23:**351–353, 1999
16. Kastrup A, Nägele T, Topka H: Spontaneous resolution of idiopathic syringomyelia. **Neurology 57:**1519–1520, 2001
17. Klekamp J: The pathophysiology of syringomyelia—historical overview and current concept. **Acta Neurochir (Wien) 144:**649–664, 2002
18. Klekamp J, Batzdorf U, Samii M, Bothe HW: Treatment of syringomyelia associated with arachnoid scarring caused by arachnoiditis or trauma. **J Neurosurg 86:**233–240, 1997
19. Koyanagi I, Houkin K: Pathogenesis of syringomyelia associated with Chiari type 1 malformation: review of evidences and proposal of a new hypothesis. **Neurosurg Rev 33:**271–285, 2010

20. Kyoshima K, Kuroyanagi T, Oya F, Kamijo Y, El-Noamany H, Kobayashi S: Syringomyelia without hindbrain herniation: tight cisterna magna. Report of four cases and a review of the literature. **J Neurosurg 96 (2 Suppl):**239–249, 2002
21. Lee JH, Chung CK, Kim HJ: Decompression of the spinal subarachnoid space as a solution for syringomyelia without Chiari malformation. **Spinal Cord 40:**501–506, 2002
22. Lee TT, Alameda GJ, Camilo E, Green BA: Surgical treatment of post-traumatic myelopathy associated with syringomyelia. **Spine (Phila Pa 1976) 26 (24 Suppl):**S119–S127, 2001
23. Levine DN: The pathogenesis of syringomyelia associated with lesions at the foramen magnum: a critical review of existing theories and proposal of a new hypothesis. **J Neurol Sci 220:**3–21, 2004
24. Li KC, Chui MC: Conventional and CT metrizamide myelography in Arnold-Chiari I malformation and syringomyelia. **AJNR Am J Neuroradiol 8:**11–17, 1987
25. Lin JW, Lin MS, Lin CM, Tseng CH, Tsai SH, Kan IH, et al: Idiopathic syringomyelia: case report and review of the literature. **Acta Neurochir Suppl 99:**117–120, 2006
26. Magge SN, Smyth MD, Governale LS, Goumnerova L, Madsen J, Munro B, et al: Idiopathic syrinx in the pediatric population: a combined center experience. Clinical article. **J Neurosurg Pediatr 7:**30–36, 2011
27. Mallucci CL, Stacey RJ, Miles JB, Williams B: Idiopathic syringomyelia and the importance of occult arachnoid webs, pouches and cysts. **Br J Neurosurg 11:**306–309, 1997
28. Mauer UM, Freude G, Danz B, Kunz U: Cardiac-gated phase-contrast magnetic resonance imaging of cerebrospinal fluid flow in the diagnosis of idiopathic syringomyelia. **Neurosurgery 63:**1139–1144, 2008
29. Milhorat TH, Capocelli AL Jr, Anzil AP, Kotzen RM, Milhorat RH: Pathological basis of spinal cord cavitation in syringomyelia: analysis of 105 autopsy cases. **J Neurosurg 82:**802–812, 1995
30. Milhorat TH, Chou MW, Trinidad EM, Kula RW, Mandell M, Wolpert C, et al: Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. **Neurosurgery 44:**1005–1017, 1999
31. Nakamura M, Ishii K, Watanabe K, Tsuji T, Matsumoto M, Toyama Y, et al: Clinical significance and prognosis of idiopathic syringomyelia. **J Spinal Disord Tech 22:**372–375, 2009
32. Oldfield EH, Muraszko K, Shawker TH, Patronas NJ: Pathophysiology of syringomyelia associated with Chiari I malformation of the cerebellar tonsils. Implications for diagnosis and treatment. **J Neurosurg 80:**3–15, 1994
33. Porensky P, Muro K, Ganju A: Nontraumatic cervicothoracic syrinx as a cause of progressive neurologic dysfunction. **J Spinal Cord Med 30:**276–281, 2007
34. Roser F, Ebner FH, Sixt C, Hagen JM, Tatagiba MS: Defining the line between hydromyelia and syringomyelia. A differentiation is possible based on electrophysiological and magnetic resonance imaging studies. **Acta Neurochir (Wien) 152:**213–219, 2010
35. Sgouros S, Williams B: A critical appraisal of drainage in syringomyelia. **J Neurosurg 82:**1–10, 1995
36. Sgouros S, Williams B: Management and outcome of post-traumatic syringomyelia. **J Neurosurg 85:**197–205, 1996
37. Struck AF, Haughton VM: Idiopathic syringomyelia: phase-contrast MR of cerebrospinal fluid flow dynamics at level of foramen magnum. **Radiology 253:**184–190, 2009
38. Yasui K, Hashizume Y, Yoshida M, Kameyama T, Sobue G: Age-related morphologic changes of the central canal of the human spinal cord. **Acta Neuropathol 97:**253–259, 1999

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Address correspondence to: Anil K. Roy, B.S., Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, 676 North Clair Street, Suite 2210, Chicago, Illinois 60611. email: a-roy@fsm.northwestern.edu.

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Spontaneous resolution of an infantile hemangioma in a dorsal root ganglion

Shawn L. Hervey-Jumper, M.D.,[1] Paul E. McKeever, M.D., Ph.D.,[2] Stephen S. Gebarski, M.D.,[3] Karin M. Muraszko, M.D.,[1] and Cormac O. Maher, M.D.[1]

Departments of [1]Neurosurgery, [2]Pathology, and [3]Radiology, University of Michigan, Ann Arbor, Michigan

Infantile hemangiomas are tumors commonly seen in children. Few authors have reported infantile hemangiomas affecting the CNS, and there are no prior reports detailing spontaneous resolution of a histologically proven juvenile hemangioma within a dorsal root ganglion. The authors report the case of a newborn boy with a large cutaneous hemangioma in the midline of his back. Spinal MR images were obtained to rule out associated spinal cord tethering, and an intradural spinal lesion was unexpectedly discovered. Biopsy revealed an intradural infantile hemangioma within the dorsal root ganglion, and, based on this diagnosis, no resection was performed. Sixteen months following the biopsy, the cutaneous hemangioma had become involuted and the intradural hemangioma had completely resolved. The behavior of the intradural component in this case follows the natural history of many cutaneous infantile hemangiomas. *(DOI: 10.3171/2011.9.FOCUS11203)*

Key Words • **infantile hemangioma** • **natural history** • **vascular tumor**

Vascular tumors in childhood represent a number of distinct clinicopathological entities. Based on recommendations of the International Society for the Study of Vascular Anomalies, a biologically based classification system was adopted in 1996 that divided vascular anomalies into either malformations or tumors based on the presence of either endothelial cell mitotic activity or errors in vascular morphogenesis.[6,18] The vascular tumors that may present in children include infantile hemangiomas, congenital hemangiomas, hepatic hemangiomas, and Kasabach-Merritt lesions. Infantile hemangiomas are further classified into superficial, deep, or compound categories.[18] Although cutaneous hemangiomas are the most common tumor of infancy, affecting 3%–10% of all children,[20] intradural hemangiomas are much less common. There are multiple reports of spinal extradural[5,10,12] and intradural[8,9,14,15,17,22,23,26] hemangiomas in adults. We report the case of a newborn with a cutaneous hemangioma, as well as hemangiomas in the extradural space and a intradural space involving the DRG. Intradural infantile hemangiomas of the spine are very rare.[13] To the best of our knowledge, this is the first reported case documenting spontaneous resolution of a histologically proven infantile spinal hemangioma. The natural history mirrors the resolution that is often seen with cutaneous infantile type hemangiomas. This is also the first reported case of an infantile hemangioma infiltrating the DRG.

Abbreviation used in this paper: DRG = dorsal root ganglion.

Case Report

Presentation and Examination. This newborn boy presented to his pediatrician with a large cutaneous hemangioma on the midline of his lower back, from the level of the lumbosacral junction to the lower sacral levels (Fig. 1). Ultrasonography of the spine showed a low-lying conus medullaris, and MR imaging was recommended to determine if a tethered cord was present. Magnetic resonance images confirmed that the conus terminated below the L-3 level. Unexpectedly, a contrast-enhancing mass lesion was also seen within the spinal canal at the L5–S1 level (Fig. 2). Although the lesion was most obvious within the spinal canal, it extended through the neural foramen on the left and also had a paraspinal component extending to the psoas muscle (Fig. 2). The patient was referred for neurosurgical evaluation. At our initial examination of the patient, we observed a 7-cm, red, raised cutaneous hemangioma in the inferior midline portion of

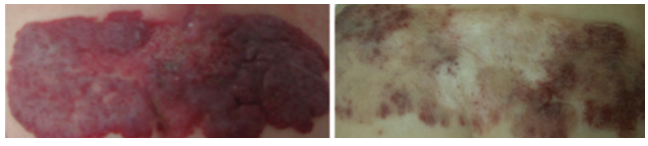

Fig. 1. Left: Photograph of the patient's back depicting a cutaneous hemangioma as it appeared 1 week following open biopsy. **Right:** Regression of the cutaneous hemangioma is seen at 17 months of age.

the patient's back. His neurological examination results were normal. In view of the imaging characteristics of the lesion, the differential diagnosis was thought to include neuroblastoma or, less likely, teratoma, lymphoma, or sarcoma.

Operation. A biopsy was performed. We made a midline incision 2 cm superior to the back hemangioma and extending less than 1 cm into the hemangioma itself. The spinal lesion was exposed via a 2-level laminoplasty. An epidural vascular mass was identified, removed, and sent for pathological analysis. The frozen section was thought to be consistent with a possible vascular tumor. We explored the left side of the spinal canal in the epidural space and found an enlarged L-5 nerve root sleeve. The dura mater was opened, and multiple samples of the red vascular tissue within the nerve root sleeve were sent for pathological analysis. The frozen-section analysis of this tissue sample was thought to be consistent with dorsal root ganglia without tumoral tissue, although we noted hypercellularity. Given the uncertain diagnosis, no resection of the mass lesion was carried out. The patient awoke from surgery in stable neurological condition and was dismissed from the hospital on the 3rd postoperative day.

Pathological Findings. On histological examination of the specimens, lobules of capillary-sized vessels were seen lined with flattened epithelium. Sheets of cells infiltrating the DRG were noted (Fig. 3). High-magnification microscopy of the epidural component showed endothelial cells with vacuolated cytoplasm, radially lined and resembling vascular lumens consistent with hemangioma. Immunohistochemistry for endothelial antigen CD31 was positive for both the epidural tumor and cells within the DRG. Cells positive for vimentin, CD31, CD34, factor VIII, muscle-specific actin, and smooth muscle actin were seen within the DRG, creating cellular density and swelling of the DRG. Type 4 collagen surrounded both the infiltrating cells and the DRG elements, but the collagen was noted to be much denser around the infiltrating cells. There were no mitoses, and the nuclei were bland with light chromatin. The MIB-1 proliferation index varied and was as high as 30% in some regions. Ganglion cells and satellite Schwann cells stained for neuron-specific enolase, CD57 and S100 protein; ganglion cells also stained for neurofilament and synaptophysin. A diagnosis of hemangioma infiltrating a DRG was made.

Postoperative Course. Given this diagnosis, the decision was made to follow the patient with serial MR imaging. On the first postoperative MR image, a significant amount of residual enhancing mass was seen, especially along the left L5–S1 foramen. Magnetic resonance images obtained 3 months later revealed further regression

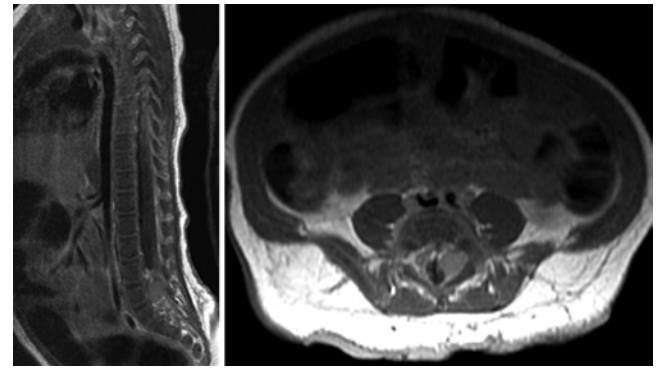

Fig. 2. Preoperative sagittal **(left)** and axial **(right)** T1-weighted MR images obtained after administration of Gd, showing an enhancing intradural mass lesion at L5–S1.

of the enhancing tissue with residual hemangioma along the cauda equina and nerve root sheaths. Sixteen months postoperatively, MR images showed no sign of a persistent spinal mass lesion (Fig. 4). The patient remains neurologically intact.

Discussion

Based on the International Society for the Study of Vascular Anomalies classification recommendations,[6,18] this infant's lesion may be categorized as a vascular tumor of the subtype infantile hemangioma. Infantile hemangiomas are benign tumors occurring in up to 10% of all infants.[4,27] Thirty percent of these hemangiomas are evident at birth. A small number of them may pose a risk by compressing vital structures. The vast majority, however, are solitary cutaneous lesions that have no serious consequences for the patient. Hemangiomas involving the head and neck area account for 40%–60% of cases, but the inferior portion of the back is also a common location.[27] Superficial hemangiomas are red and have well-defined borders. Deep hemangiomas, however, involve the dermal layer and appear as a red, purple, or blue subcutaneous mass. Those lesions displaying combined features of superficial and deep lesions are called compound hemangiomas. Infants with hemangiomas in the midline of the lower back are frequently referred for spinal imaging to rule out a tethered spinal cord and neural tube defect.[16,29] In our patient, spinal imaging led to the incidental discovery of an asymptomatic enhancing mass within the spinal canal.

Infantile hemangiomas involving the intradural spinal compartment in children are extremely rare. Fewer than 20 such cases have been reported.[8,31] Intradural hemangiomas in children are even less common, and there are no published reports reviewing the natural history of this lesion. Infantile hemangiomas of the CNS have been associated with both PHACE syndrome (Posterior fossa abnormalities and other structural brain abnormalities; Hemangioma(s) of the cervical facial region; Arterial cerebrovascular anomalies; Cardiac defects, aortic coarctation, and other aortic abnormalities; and Eye anomalies)[25,31] and tethered cord.[13,31] Our patient did not have any other features of PHACE syndrome, but the spinal cord

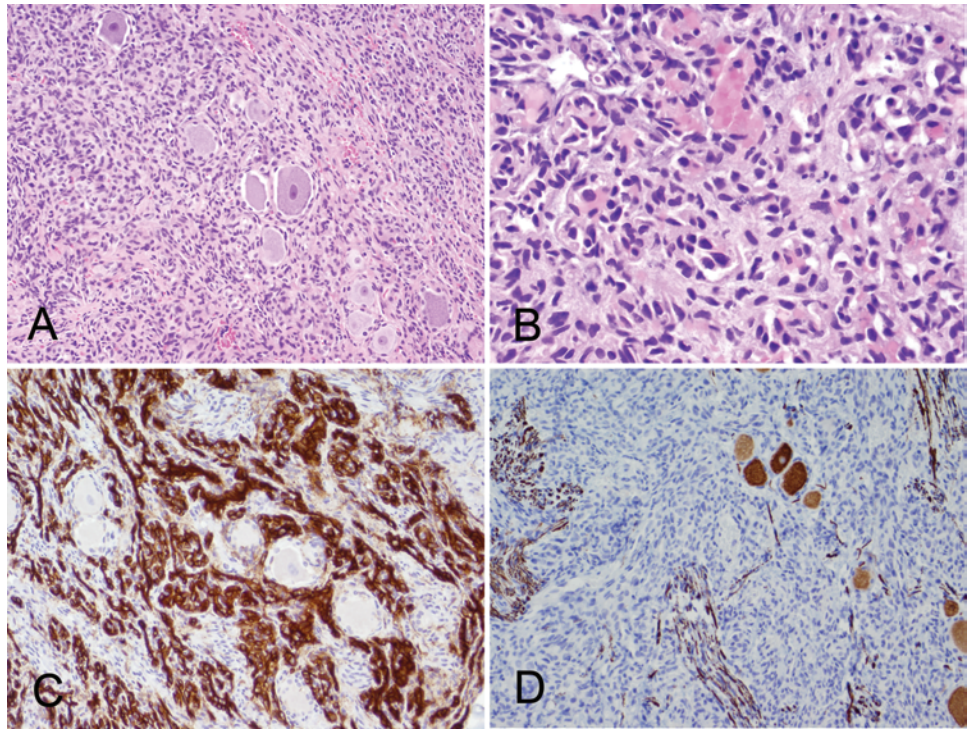

Fig. 3. Photomicrographs of tissue samples. **A:** Sheets of cells infiltrating the DRG containing nerve and ganglion cells. H & E, original magnification × 20. **B:** High magnification of a juvenile hemangioma showing plump endothelial cells resembling cells lining vascular lumens. The cytoplasm of the hemangioma cells is vacuolated. H & E, original magnification × 60. **C:** A classic immunohistochemical endothelial antigen stain, CD31, reveals juvenile hemangioma within DRG. Original magnification × 20. **D:** Neurofilament protein stain highlighting the long peripheral nerve axons and large round ganglion cells, spread apart by neurofilament-negative juvenile hemangioma cells. Original magnification × 20.

was tethered. Tethered cord has also been associated with cutaneous hemangioma of the lower back, even in the absence of an intradural lesion.[1] Our patient had a cutaneous hemangioma associated with hemangiomas in the DRG and the paraspinal musculature. To our knowledge, this is the first reported case of infantile hemangioma infiltrating a DRG and the first report detailing the spontaneous resolution of a histologically proven intradural hemangioma in an infant.

Infantile hemangiomas comprise a group of tumors exhibiting cellular proliferation with features including abnormal vascular lesions and extensive accumulations of blood vessels. Infantile hemangiomas may be distinguished from other types of hemangioma on the basis of their distinctive presentation and natural history. Infantile cutaneous hemangiomas characteristically appear within 2 weeks of birth, enlarge rapidly, stop growing before 1 year of age, and spontaneously involute over the next several years.[3,11,27] The natural history of cutaneous infantile hemangiomas is determined by 2 active clinical stages: proliferation and involution.[27] Proliferation occurs during the first 12 months of life, with periods of rapid growth within the first few weeks, and later between Months 4 and 6.[27,32,33] Cutaneous hemangioma involution is marked by a change in color from bright red to a darker red with a grayish hue. During this phase the lesion ceases growing and becomes soft, lobular, and compressible. During involution, infantile hemangiomas gradually flatten as inactive cells replace plump proliferating endothelial cells and vascular channels become more pronounced.

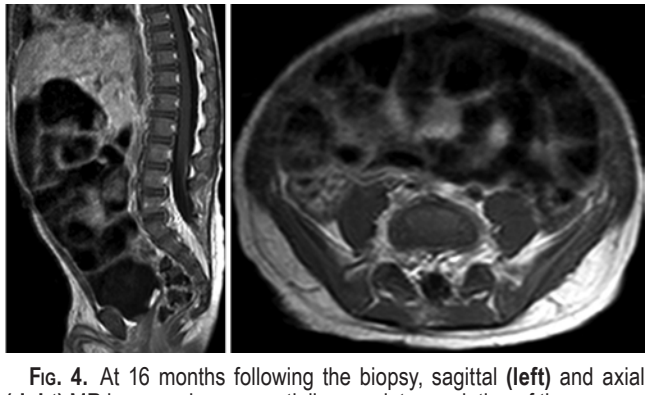

Fig. 4. At 16 months following the biopsy, sagittal **(left)** and axial **(right)** MR images show essentially complete resolution of the mass.

Given the usual clinical course, many cutaneous hemangiomas require no treatment. More severe cases of cutaneous hemangioma can be treated with corticosteroids, interferon, or vincristine.[31] In our case, the intradural component exhibited the natural history typical of cutaneous infantile hemangiomas. After 14 months of follow-up, the patient had near-complete resolution of the cutaneous portion and no evidence of residual intradural tumor. This parallel behavior should be remembered when determining the treatment for children with infantile hemangiomas that are associated with enhancing mass lesions within the intradural compartment. In cases with associated tethering of the spinal cord, the decision

to untether the spinal cord should be made according to the usual criteria for spinal cord untethering.

Infantile hemangiomas within the CNS are very rare. Most previously reported cases of infantile hemangioma in the CNS have been intracranial, including lesions found in the fourth ventricle, cerebellopontine angle, pineal region, hypothalamus, and hippocampus.[7,13,19,24,25,28,30,31] Balaci et al.[2] recently reported on a case that diffusely involved both the brain and the cervical spinal cord. Herman et al.[12] reported on a single infant with extradural extension of a mediastinal hemangioma. Karikari et al.[13] reported on 2 infantile cases involving the lumbar spine. Both patients underwent resection, precluding any analysis of the natural history.[13] In 2008 Viswanathan et al.[31] reviewed the literature and found 15 previously reported cases of true "infantile" hemangiomas that involved the neuronal axis, to which they added 15 of their own cases. Of their 15 new cases, 6 involved solitary intraspinal hemangiomas, and 9 were intracranial; 1 tumor involved both intracranial and intraspinal regions. Only 2 of the patients in the intraspinal cohort presented with neurological deficits and another 2 had cutaneous hemangiomas on the back. Viswanathan et al. found that none of their cases had spinal cord parenchymal involvement, in contrast to involvement of the DRG in our patient. While Viswanathan et al. reviewed the treatment, imaging, and histological features of infantile hemangiomas involving the neuronal axis, they did not report on natural history of the lesion in the absence of corticosteroid and interferon therapy. Nahed et al.[19] recently reported on a patient with a scalp hemangioma associated with a intracranial hemangioma that caused hydrocephalus and venous sinus thrombosis. The patient had a documented decrease in lesion size following treatment with prednisolone and low–molecular weight heparin. Although the lesion in their case was cranial rather than spinal, its behavior mimics that of our own case and reinforces our conclusion regarding the behavior of these lesions.

An important feature of most reported cases of infantile hemangioma involving the CNS is the overlying cutaneous hemangioma. Furthermore, many previously reported cases have had continuity between the superficial lesions and the lesions in the CNS.[31] In our patient, hemangiomas were present in the skin and epidural space, as well as the DRG, but the lesions did not appear continuous on either imaging or on surgical inspection.

The molecular analysis and histological observation of vascular tumors and malformations has been significantly clarified in recent years. Older reports frequently used identical terminology for lesions that are now considered to be different.[11] Capillary hemangiomas were once considered a subtype of infantile hemangiomas but are now considered a separate diagnostic entity, often renamed congenital nonprogressive hemangiomas.[8,20,21] These tumors typically display capillary lobules separated by fibrous tissue instead of the normal tissue that is seen in infantile hemangioma. In addition, these are not GLUT1-positive. Another subtype of hemangioma, the congenital hemangioma, is usually present and fully formed at birth, and variable periods of involution follow, further distinguishing it from classic infantile hemangioma.[20] Although pathological analysis will allow for the proper classification of a vascular lesion, we do not recommend biopsy sampling of a lesion that is considered likely to be an intramedullary hemangioma in an asymptomatic child. In cases that are not biopsied, follow-up MR imaging is necessary to document involution of the lesion.

Conclusions

Cutaneous vascular lesions are commonly found in infants and may very rarely be associated with enhancing lesions in the CNS. Although rare, infantile hemangioma should be included in the differential diagnosis of children with intradural extramedullary lesions, particularly when associated with an overlying cutaneous hemangioma. For CNS lesions with characteristics of infantile hemangioma of the CNS in neurologically intact children, close clinical observation rather than resection should be considered.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Maher. Acquisition of data: Maher, Hervey-Jumper, McKeever, Gebarski. Analysis and interpretation of data: all authors. Drafting the article: Maher, Hervey-Jumper. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Maher. Study supervision: Maher.

References

1. Albright AL, Gartner JC, Wiener ES: Lumbar cutaneous hemangiomas as indicators of tethered spinal cords. **Pediatrics 83:**977–980, 1989
2. Balaci E, Sumner TE, Auringer ST, Cox TD: Diffuse neonatal hemangiomatosis with extensive involvement of the brain and cervical spinal cord. **Pediatr Radiol 29:**441–443, 1999
3. Bowers RE, Graham EA, Tomlinson KM: The natural history of the strawberry nevus. **Arch Dermatol 82:**667–680, 1960
4. Chang E, Boyd A, Nelson CC, Crowley D, Law T, Keough KM, et al: Successful treatment of infantile hemangiomas with interferon-alpha-2b. **J Pediatr Hematol Oncol 19:**237–244, 1997
5. Doyle PM, Abou-Zeid A, Du Plessis D, Herwadkar A, Gnanalingham KK: Dumbbell-shaped intrathoracic-extradural haemangioma of the thoracic spine. **Br J Neurosurg 22:**299–300, 2008
6. Enjolras O, Mulliken JB: Vascular tumors and vascular malformations (new issues). **Adv Dermatol 13:**375–423, 1997
7. Ersoy S, Mancini AJ: Hemifacial infantile hemangioma with intracranial extension: a rare entity. **Pediatr Dermatol 22:** 309–313, 2005
8. Ganapathy S, Kleiner LI, Mirkin LD, Hall L: Intradural capillary hemangioma of the cauda equina. **Pediatr Radiol 38:** 1235–1238, 2008
9. Hanakita J, Suwa H, Nagayasu S, Suzuki H: Capillary heman-

gioma in the cauda equina: neuroradiological findings. **Neuroradiology 33:**458–461, 1991
10. Hasan A, Guiot MC, Torres C, Marcoux J: A case of a spinal epidural capillary hemangioma: case report. **Neurosurgery 68:**E850–E853, 2011
11. Hassanein AH, Mulliken JB, Fishman SJ, Greene AK: Evaluation of terminology for vascular anomalies in current literature. **Plast Reconstr Surg 127:**347–351, 2011
12. Herman TE, McAlister WH, Dehner LP: Posterior mediastinal capillary hemangioma with extradural extension resembling neuroblastoma. **Pediatr Radiol 29:**517–519, 1999
13. Karikari IO, Selznick LA, Cummings TJ, George TM: Capillary hemangioma of the fourth ventricle in an infant. Case report and review of the literature. **J Neurosurg 104 (3 Suppl):** 188–191, 2006
14. Kim KJ, Lee JY, Lee SH: Spinal intradural capillary hemangioma. **Surg Neurol 66:**212–214, 2006
15. Mastronardi L, Guiducci A, Frondizi D, Carletti S, Spera C, Maira G: Intraneural capillary hemangioma of the cauda equina. **Eur Spine J 6:**278–280, 1997
16. Maugans T, Sheridan RM, Adams D, Gupta A: Cutaneous vascular anomalies associated with neural tube defects: nomenclature and pathology revisited. **Neurosurgery 69:**112–118, 2011
17. Miri SM, Habibi Z, Hashemi M, Meybodi AT, Tabatabai SA: Capillary hemangioma of cauda equina: a case report. **Cases J 2:**80, 2009
18. Mulliken JB, Glowacki J: Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. **Plast Reconstr Surg 69:**412–422, 1982
19. Nahed BV, Ferreira M Jr, Babu MA, Terry AR, Walcott BP, Kahle KT, et al: Dural scalp and intracranial hemangiomas causing hydrocephalus and venous sinus thrombosis in an infant. **J Child Neurol 26:**777–781, 2011
20. North PE, Waner M, Buckmiller L, James CA, Mihm MC Jr: Vascular tumors of infancy and childhood: beyond capillary hemangioma. **Cardiovasc Pathol 15:**303–317, 2006
21. North PE, Waner M, James CA, Mizeracki A, Frieden IJ, Mihm MC Jr: Congenital nonprogressive hemangioma: a distinct clinicopathologic entity unlike infantile hemangioma. **Arch Dermatol 137:**1607–1620, 2001
22. Nowak DA, Gumprecht H, Stölzle A, Lumenta CB: Intraneural growth of a capillary haemangioma of the cauda equina. **Acta Neurochir (Wien) 142:**463–468, 2000
23. Nowak DA, Widenka DC: Spinal intradural capillary haemangioma: a review. **Eur Spine J 10:**464–472, 2001
24. Oza VS, Wang E, Berenstein A, Waner M, Lefton D, Wells J, et al: PHACES association: a neuroradiologic review of 17 patients. **AJNR Am J Neuroradiol 29:**807–813, 2008
25. Poindexter G, Metry DW, Barkovich AJ, Frieden IJ: PHACE syndrome with intracerebral hemangiomas, heterotopia, and endocrine dysfunction. **Pediatr Neurol 36:**402–406, 2007
26. Shin JH, Lee HK, Jeon SR, Park SH: Spinal intradural capillary hemangioma: MR findings. **AJNR Am J Neuroradiol 21:**954–956, 2000
27. Smith SP Jr, Buckingham ED, Williams EF III: Management of cutaneous juvenile hemangiomas. **Facial Plast Surg 24:** 50–64, 2008
28. Song JK, Niimi Y, Kupersmith MJ, Berenstein A: Postnatal growth and development of a cerebral arteriovenous malformation on serial magnetic resonance imaging in a child with hemangiomatosis. Case report. **J Neurosurg 106 (5 Suppl):** 384–387, 2007
29. Stockman A, Boralevi F, Taïeb A, Léauté-Labrèze C: SACRAL syndrome: spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization. **Dermatology 214:**40–45, 2007
30. Tortori-Donati P, Fondelli MP, Rossi A, Bava GL: Intracranial contrast-enhancing masses in infants with capillary haemangioma of the head and neck: intracranial capillary haemangioma? **Neuroradiology 41:**369–375, 1999
31. Viswanathan V, Smith ER, Mulliken JB, Fishman SJ, Kozakewich HP, Burrows PE, et al: Infantile hemangiomas involving the neuraxis: clinical and imaging findings. **AJNR Am J Neuroradiol 30:**1005–1013, 2009
32. Waner M, Suen JY (eds): A classification of congenital vascular lesions, in: **Hemangiomas and Vascular Malformations of the Head and Neck.** New York: Wiley-Liss, 1999, pp 1–12
33. Williams EF III, Stanislaw P, Dupree M, Mourtzikos K, Mihm M, Shannon L: Hemangiomas in infants and children. An algorithm for intervention. **Arch Facial Plast Surg 2:**103–111, 2000

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Address correspondence to: Cormac O. Maher, M.D., Department of Neurosurgery, University of Michigan, 1500 East Medical Center Drive, Room 3552, Taubman Center, Ann Arbor, Michigan 48109-5338. email: cmaher@med.umich.edu.

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Incidental vertebral lesions

Jean-Valery C. E. Coumans, M.D., and Brian P. Walcott, M.D.

Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

Incidental vertebral lesions on imaging of the spine are commonly encountered in clinical practice. Contributing factors include the aging population, the increasing prevalence of back pain, and increased usage of MR imaging. Additionally, refinements in CT and MR imaging have increased the number of demonstrable lesions. The management of incidental findings varies among practitioners and commonly depends more on practice style than on data or guidelines. In this article we review incidental findings within the vertebral column and review management of these lesions, based on available Class III data. *(DOI: 10.3171/2011.9.FOCUS11207)*

Key Words • **incidental finding** • **vertebra** • **congenital** • **os odontoideum**

Incidental lesions are commonly detected with imaging of the spine in asymptomatic individuals.[14,31] The advent or refinement of new imaging techniques carries with it the challenge of discerning these incidental findings from pathological lesions. Magnetic resonance images of the spine are obtained with increasing frequency, possibly because the incidence of back pain is increasing[20] and the population is aging.[10] Trauma patients are also increasingly undergoing evaluation with CT scanning, effectively replacing plain radiography.[7,11,29] Axial imaging also increases the amount of data to review and the probability of encountering an incidental lesion.[43] For the purpose of this review, incidental findings are defined as unexpected lesions that are unrelated to the original reason for obtaining the scan. There are two diagnostic pitfalls when dealing with incidental findings. At one end of the spectrum, failure to recognize a serious condition masquerading as an incidental finding can lead to a diagnostic delay. Also problematic is the failure to recognize a process as benign, and in the process exposing a patient to an unnecessary intervention such as a biopsy. As with any screening test, the lower the pretest probability, the higher the likelihood of a false positive finding. With the increasing use of spinal imaging, it is important to have an algorithm for managing incidental spine lesions.

In this article, we review the imaging characteristics and management of incidental findings in the osseous spine. Some incidental findings such as small hemangiomas and enostoses are asymptomatic and clinically insignificant. Others are potentially more serious than the original diagnosis prompting the study. The finding of anemia, or osteoporosis, for example, is incidental only in the sense that it may not relate to the indications for obtaining the scan in the first place. The term incidental should not be used to suggest that the findings are any less important.

The Normal Vertebral Body

Understanding the nuances of normal vertebral body anatomy is necessary to prevent mistaking normal anatomy as lesional. The normal vertebral body cancellous bone has the T1 and T2 signal characteristics of bone elsewhere. Cortical bone is hypointense to cancellous bone on T1- and T2-weighted imaging. The cartilage endplate is hypointense to marrow on T1- and T2-weighted imaging. With the normal aging process, bone marrow undergoes an increase in T1-weighted signal intensity, corresponding to an increase in marrow fat content. While this can certainly be accelerated by factors such as radiation treatment, the process in and of itself falls within the confines of normal aging.

Additionally, venous anatomy must not be mistaken for a pathological process. Embryologically, the vertebral body is composed of a fusion of a rostral and caudal sclerotome, and a midvertebral structure can persist. There is, for example, a midvertebral body vein that, when large, can be mistaken for a vascular abnormality or even a fracture (Fig. 1).

Congenital Malformations

Congenital malformations of the spine are commonly encountered in clinical practice. These are generally benign, but on occasion can be associated with severe problems such as spinal cord injury, in the case of os odontoideum. It is convenient to think of congenital vertebral body variants in terms of their corresponding embryological dysfunction, such as failure of ossification or abnormal segmentation. Although this approach may not suffice to encompass the myriad of complex congenital malformations, it applies to more common, straightforward incidental malformations.

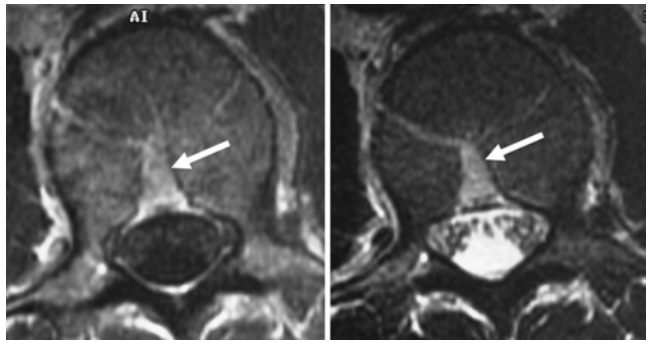

Fig. 1. Axial T1- **(left)** and T2-weighted **(right)** MR images demonstrating prominent midvertebral body vein *(arrow)*.

Abnormal Segmentation

Block Vertebra. Two or more vertebra can fail to segment, resulting in an immobile segment of the spine (Fig. 2). This tends to occur at upper cervical levels.[36] The clinical significance of this malformation remains uncertain. This condition is commonly observed in Klippel-Feil syndrome, in which there is a congenital fusion of 2 or more cervical vertebrae.[33] It is possible that an increase in either intradiscal pressure or movement adjacent to a block vertebra might contribute to accelerated degeneration of adjacent intervertebral discs. However, the effect may not be large or clinically significant, and the natural history is not well defined. Figure 3 illustrates a case of mild central canal stenosis caudal to an unsegmented upper cervical spine. In a radiographic study of 25 patients with a block vertebra, there was a significant decrease in the height caudal to the block vertebra, but not to the disc height rostrally. A kinetic analysis of the adjacent levels demonstrated no hypermobility in rotation or translation.[36] The effects of a congenitally fused vertebra on the adjacent spine may differ from those of a surgical fusion. In surgical fusion, the adjacent levels may already be degenerated, and surgery itself may have an effect on adjacent levels. Thus, it appears reasonable to inform patients with congenital fusion about the possibility of premature degeneration of adjacent levels, but the effect is largely unknown and is likely minor. Persons with Klippel-Feil syndrome and cervical stenosis may be at increased risk for spinal cord injury after minor trauma as a result of hypermobility of the various cervical segments.[2,48,55] Activity modification should be considered in patients Klippel-Feil syndrome who are at high risk for neurological compromise, such as those with severe central canal

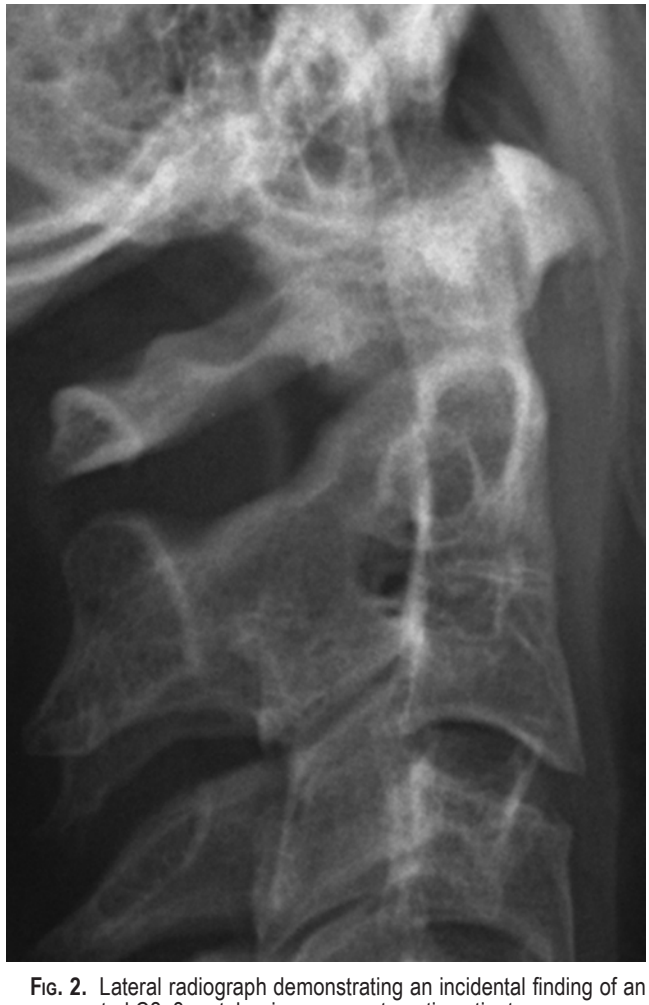

Fig. 2. Lateral radiograph demonstrating an incidental finding of an unsegmented C2–3 vertebra in an asymptomatic patient.

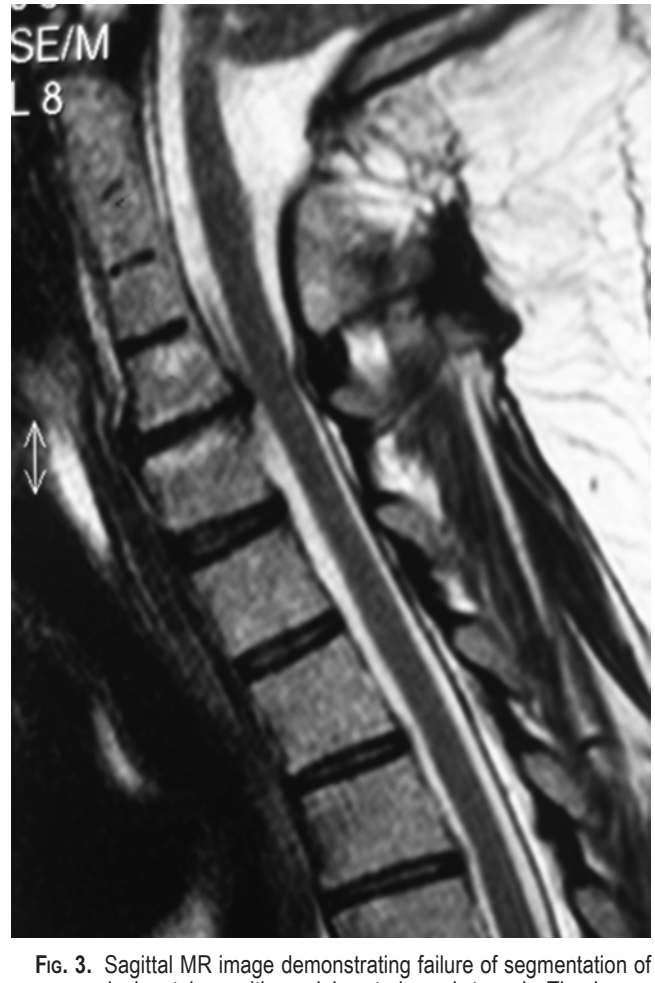

Fig. 3. Sagittal MR image demonstrating failure of segmentation of upper cervical vertebrae with caudal central canal stenosis. The degree to which unsegmented vertebrae predispose to adjacent disc degeneration or stenosis is unknown.

stenosis or myelopathy. Discovery of congenitally fused segments should prompt a systemic investigation because persons with Klippel-Feil Syndrome often have cardiac and/or genitourinary congenital anomalies as well.[39]

Aberrant Number of Vertebra. Approximately 20% of the population has an aberrant number of lumbar vertebral bodies.[28] This has a significant implication in clinical practice, with the most obvious being the accuracy of using numbered vertebral levels for surgical localization. When the number of vertebral segments is variant or even indeterminate, surgical localization has the potential to be misleading and not consistent between practitioners. In a large series of patients undergoing whole spine MR imaging, the number of lumbar vertebral bodies varied between 3 and 6.[28] While these findings are incidental, they can have profound consequences if care is not taken to accurately and consistently localize the correct surgical level.

Failure of Chondrification or Ossification

Early in embryonic development, mesodermal cells form somites lateral to the notochord. The paired somites divide into a medial part (the sclerotome) and a lateral part (the dermomyotome). Mesenchymal cells from each sclerotome pair migrate to the location of the presumptive vertebral body, giving rise to 3 chondrification centers per side. Once vertebral chondrification is complete, primary ossification centers appear: 1 ventrally and 2 at the level of the pedicles.[3,45] Failure of formation of 1 of the chondrification centers or subsequent failure of ossification results in the absence of part of a vertebra. The more severe malformations are not incidental findings and present with a deformity at birth or during infancy. Absence of an anterior chondrification center, for example, gives rise to a hemivertebral body and results in congenital scoliosis or kyphosis (Fig. 4). More mild developmental anomalies can present as incidental findings as discussed below.

Synchondrosis Mimicking Fracture. Knowledge of normal embryological development is essential to avoid misinterpretation of normal epiphyses or synchondroses as pathological conditions. Ossification of the vertebra continues after birth, and the synchondroses visible on imaging in young children can be mistaken for fractures.[5,26] The diagnosis of a fracture in the immature spine can be problematic because the synchondrosis can resemble a fracture or can itself be fractured. A common clinical scenario involves axial imaging through the immature spine following trauma. In general, synchondroses should be recognized by their characteristic locations and smooth margins with cortication. In contrast, fractures can occur at any location and have irregular, nonsclerotic margins.[37] A typical location for syncondroses include the 3 primary ossification centers of the atlas: 1 for the anterior arch and 1 for each of the lamina.[41] The lamina fuse posteriorly around 3 years of age and the anterior arch by 7 years of age. Another typical location of synchondroses is the axis. The second cervical vertebra has 4 ossification centers at birth: 1 for the odontoid process, 1 for the body, and 1 at each of the lamina. The odontoid process fuses with the body of the axis normally by 3–6 years of life, although the subdental synchondrosis may be visualized up until 11 years of age and should not be confused with a fracture.[37,42] As is the case for other conditions in which instability is suspected, controlled dynamic imaging can be helpful, as can delayed repeat imaging.[26]

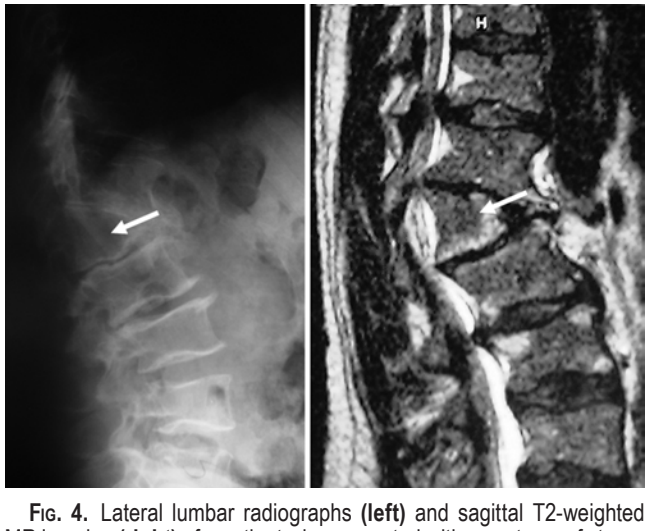

Fig. 4. Lateral lumbar radiographs **(left)** and sagittal T2-weighted MR imaging **(right)** of a patient who presented with symptoms of stenosis and a hemivertebral body *(arrow)*. He was unaware of his vertebral abnormality and associated focal kyphosis.

Absent Pedicle. Congenital absence of a pedicle or part of a facet can occur when a lateral chondrification center fails to form or subsequently ossify.[19] Congenital absence of the pedicle is rare. The C-5 and C-6 levels are most commonly affected. Because the chondrification center also forms part of the facet and lamina, these structures are usually dysplastic. An absent pedicle can present as an incidental finding or in association with neck pain. Failure to recognize this entity can lead to unnecessary halo fixation or instrumented fusion for presumed traumatic instability.[56] Given the associated dysplasia of the articulating pillar, it is recommended that the integrity of the articulating pillar be studied with CT scanning and that the stability of the column be assessed with dynamic radiographs. Unlike os odontoideum, this malformation is often associated with a stable spine and has been described in a football player.[19]

Butterfly Vertebra. Another rare failure of ossification is a butterfly vertebra.[44] This congenital anomaly is typically encountered incidentally but has been associated with pain. It probably represents a ventral ossification failure. Two chondrification centers that form the vertebral body fail to fuse and ossify across the midline. This results in an area of relative bone deficit in the midline. Because it is not associated with a significant deformity, it is typically incidental and can present later in life. Clinically, the scenario is encountered when a patient presents after an injury, and a compression fracture is suspected on plain radiographs. Computed tomography scanning often confirms the diagnosis. The presence of sclerotic bone along the suspected cleft is diagnostic.[50]

Os Odontoideum. An os odontoideum consists of an

ossicle-like odontoid process unconnected to the body of the axis. It remains uncertain whether this entity is developmental or posttraumatic. The odontoid synchondrosis closes at 5–6 years of age, and os odontoideum may represent a fracture through the synchondrosis.[59] Although it is commonly encountered as an incidental finding, it can be associated with cervical instability and spinal cord injury.[59] A cord signal change at the level of the odontoid suggests the sequelae of repetitive trauma. It is important to note that cord thinning or traumatic myelomalacia can occur in the absence of a history of frank traumatic spinal cord injury. Flexion-extension radiographs may disclose occult instability. The role of surgery is still being defined, and factors such as patient age, cervical instability, and lifestyle weigh into the decision. At present there are only Class III data, and the opinion of experts varies regarding whether or not to perform surgery.[32] At a minimum, when os odontoideum is encountered, the patient should be evaluated for signs of instability and myelopathy. Figure 5 illustrates the case of an incidentally discovered os odontoideum on lateral radiography obtained in the emergency department after a fall. The surgical risks including the biomechanical consequences of a C1–2 fusion and the possibility of pseudarthrosis should be weighed against the possibility of spinal cord injury with a minor trauma.[4] As with cervical stenosis, patients should also be warned about the risk of chronic progressive myelopathy.

Spinal Bifida Occulta. When the neural arch ossification centers fail to fuse, a posterior bone defect occurs, resulting in spina bifida. Spinal bifida occulta is common, with estimates of incidence in a general population of approximately 22%.[8,18] There is some evidence that links spina bifida occulta with other spinal anomalies and clinical syndromes, such as intraspinal lipoma, tethered cord syndrome, genitourinary dysfunction, increased incidence of disc pathology, lumbar spondylolysis, foot deformities, and syringomyelia.[25,30,34,47] However, some studies have shown that spina bifida occulta is not a reliable indicator of spinal cord structural abnormalities.[40,49] Spinal bifida occulta can take on subtle forms, such as incomplete formation of the ventral or dorsal arch of C-1 (Fig. 6) and can involve a large section of the sacrum. Spinal bifida occulta is important to recognize, not because it is pathologic per se, but because surgical exposure of the spine requires careful attention to the exposed neural structures (Fig. 7). The authors have treated a patient referred for a cauda equina injury and associated pseudomeningocele related to exposing the L5–S1 junction in a patient with no dorsal sacral bone. When exposing the cervical spine, especially the third, fourth, and fifth vertebrae, the surgeon can encounter a fully bifid spinous process. Failure to recognize this can cause one to enter the spinal canal while dissecting along the medial surface of a bifid process.

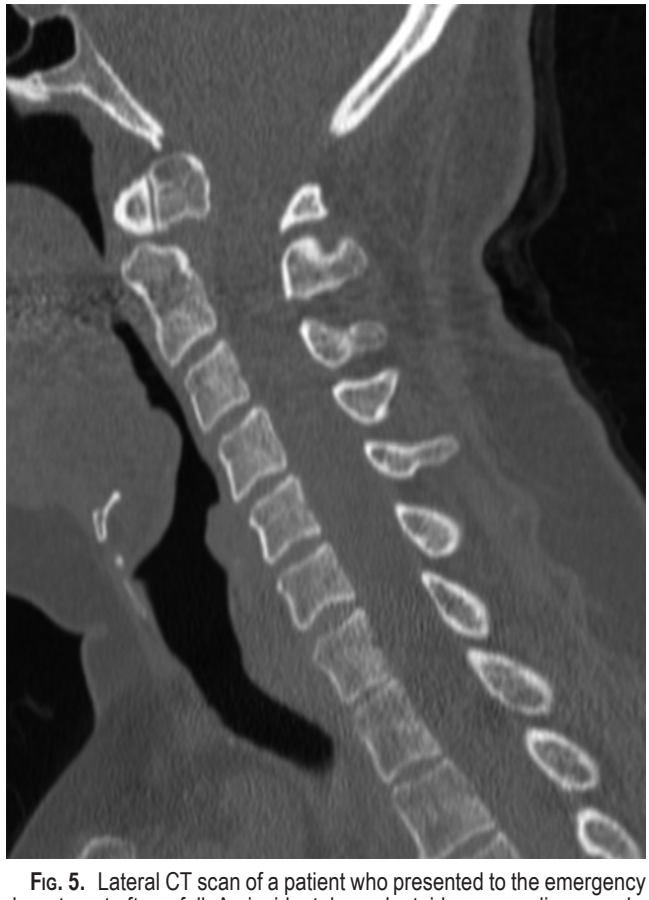

Fig. 5. Lateral CT scan of a patient who presented to the emergency department after a fall. An incidental os odontoideum was discovered.

Degenerative and Other Changes

Diffuse Vertebral Changes

Some systemic conditions can produce incidental imaging changes in the vertebral body. Because these abnormalities are related to an underlying metabolic process, they affect the spine diffusely. As such, they may be less obvious than focal lesions and are more likely to be missed.

Osteoporosis. One of the most common conditions affecting the spine is osteoporosis, affecting more than 10 million people in the US. It is responsible for more than 388,000 vertebral compression-type fractures annually.[12] The greatest risk for developing osteoporosis occurs in postmenopausal women and is related to maximum peak bone mass and bone mineral density development in young

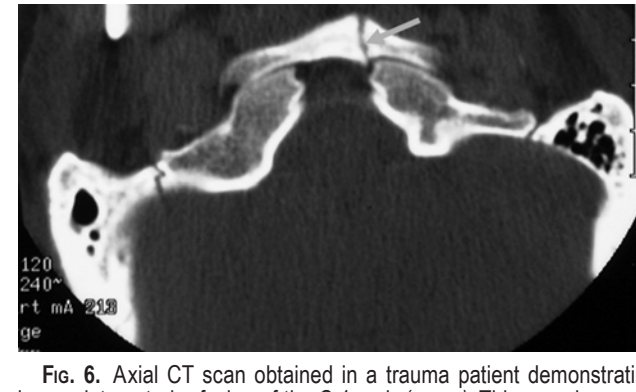

Fig. 6. Axial CT scan obtained in a trauma patient demonstrating incomplete anterior fusion of the C-1 arch *(arrow)*. This can also occur posteriorly and is typically not associated with mechanical instability.

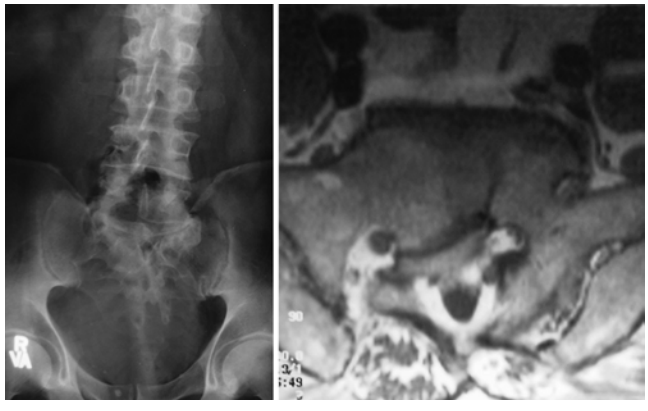

Fig. 7. Anteroposterior radiograph **(left)** and axial T1-weighted MR image **(right)** of a patient with spina bifida occulta. Surgical approach to the lumbosacral junction, if it were needed, could risk inadvertent entry into the spinal canal.

adult life.[9,51] Weight-bearing exercise, nutrition, and cigarette smoking are key factors in this disease process.[22] Diagnosis can be assessed by dual-energy x-ray absorptiometry, with the given T-score being a value that can also be used to track response to therapy.[27] With MR imaging, the appearance of the normal bone marrow normally varies. For example, with the normal aging process, bone marrow undergoes a gradual replacement from red marrow to yellow marrow, reflecting a loss of hematopoiesis.[46] The increased fat content is visible on imaging as an increase on T1-weighted images. These changes can be uniform, but on occasion focal areas of increased yellow marrow can be observed. In severe osteoporosis, there is greater than expected fatty replacement of bone marrow.[52]

Marrow Reconversion. At the opposite end of the spectrum, bone marrow reconversion refers to the return of hematopoiesis or to bone marrow hyperplasia. This can produce an incidental imaging finding opposite of the expected aging process, with decreased T1 signal intensity. When this is encountered, pathological conditions such as anemia should be suspected. Neoplastic marrow infiltration can also produce similar signal changes, but the pattern of involvement tends to be more diffuse with anemia. Another diffuse incidental finding is related to hemosiderin deposition, which causes decreased signal intensity in the bone marrow on both T1- and T2-weighted images. Increased marrow hemosiderin can be seen in cases of hemolytic anemia, sickle cell anemia, thalassemia, and in cases of chronic transfusions. Complete blood counts and serum iron studies can be useful in further investigation.

Focal Changes

Vertebral Hemangioma. Hemangiomas are benign lesions of bone (Fig. 8). They are common and may be more prevalent in adults than in children, suggesting that they are not congenital.[43] In a recent study of over 1200 lumbar MR imaging scans, incidental hemangiomas were encountered in 1.5% of patients.[43] Histologically, they consist of endothelium-lined sinuses interspersed between bone trabeculae. The bony trabeculations produce a characteristic speculated appearance on axial CT scans. They contain fat and have a characteristic T1 MR imaging appearance.[58] Some, however, demonstrate a low fat content and have an atypical MR imaging scan appearance. When examined with out of phase imaging, however, they demonstrate a greater degree of signal loss than malignant lesions and this can be used to distinguish them from metastatic processes.[58] In rare instances, the hemangioma can be so large that it becomes painful, perhaps related to a compromise of the stability of the vertebral body[16] or even fracture (Fig. 9). Symptomatic vertebral hemangiomas can be treated by a variety of modalities and strategies. A combination of transarterial emoblization with or without the use of surgical decompression can be used to treat the majority of lesions and is effective at treating cord compression and pain syndromes.[1] Vertebroplasty is another technique that can be useful for improving pain symptoms, especially when no neurological deficit is present.[1] Other treatments include radiotherapy[21] and alcohol embolization.[54]

Lipoma. Intraosseous lipomas of the vertebral bodies are rare lesions and are typically asymptomatic.[13,57] When discovered incidentally, careful interpretation of the MR image can obviate further investigation. Since these le-

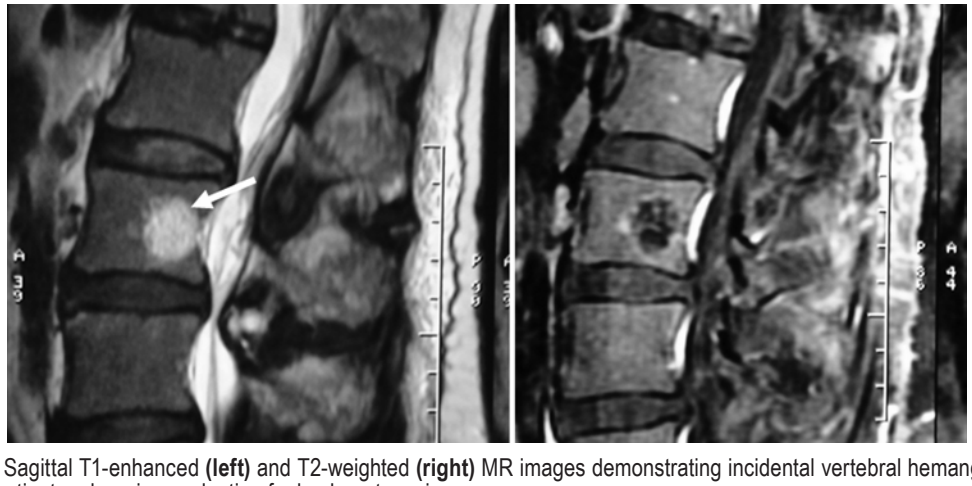

Fig. 8. Sagittal T1-enhanced **(left)** and T2-weighted **(right)** MR images demonstrating incidental vertebral hemangioma *(arrow)* in a patient undergoing evaluation for lumbar stenosis.

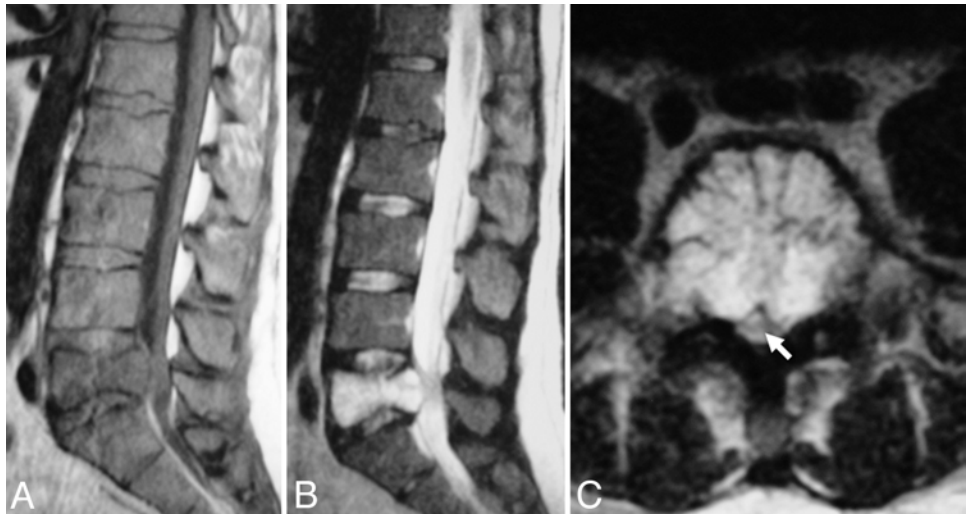

Fig. 9. Sagittal T1- **(A)** and T2-weighted **(B)** MR images in a patient with a very large hemangioma that fractured, causing compression of the cauda equina as noted on axial T2-weighted imaging (*arrow,* **C**).

sions have the potential to be confused with aneurysmal bone cysts, chondroid tumors, simple bone cysts, and fibrous dysplasia, detailed understanding of the MR imaging characteristics is necessary. For lipomas, the T1- and T2-weighted sequences are uniformly hyperintense and there is an absence of cortical destruction and soft tissue abnormality.

Degenerative Endplate Changes. Modic changes affecting the endplates are well-characterized.[38] Occasionally, however, the signal abnormality is so extensive that a more serious lesion is suspected. There are 2 main types and a less common type of endplate lesion. The first type represents endplate edema and is well-characterized on MR imaging; relative to marrow, Type I endplate changes demonstrate T1 signal hypointensity and T2 hyperintensity. Type II changes are more chronic and believed to represent fatty infiltration; relative to marrow, they are characterized by both T1 and T2 signal hyperintensity (Fig. 10). The third type represents endplate sclerosis and is characterized by signal hypointensity to normal marrow on both T1- and T2-weighted images.

There are certain characteristics of endplate changes that merit follow-up, because Modic changes do not always account for all signal changes on MR imaging. Whereas the MR imaging characteristics of fulminant osteomyelitis are easy to recognize, the signal characteristics of very early osteomyelitis are subtle and easy to overlook.[17] An example of this difference is when an MR image is obtained that demonstrates signal abnormality bridging 2 vertebral bodies, thereby raising the suspicion of osteomyelitis. Both degenerative changes and early osteomyelitis affect the endplate region.[17] Classically, an MR imaging signal change that spans 2 vertebra, or is associated with inflammatory changes in the disc, is a sign of potential osteomyelitis/discitis. Dunbar et al.[17] reviewed patients with confirmed vertebral osteomyelitis and identified 4 instances in which an initial early MR image was not diagnostic. These patients had demonstrated Modic Type I changes. Even though all 4 patients were receiving antibiotics, they later developed the full changes noted with infection. In the proper clinical context, repeat MR imaging should be performed a few days later because the infection can progress over days, even in the setting of antibiotic treatment. Additional suspicion for early osteomyelitis over degenerative endplate changes should be raised when the patient has an elevated serum C-reactive protein level, an elevated serum white blood cell count, pain out of proportion to the radiographic findings, or bacteremia.

In patients with a history of cancer, one must consider the possibility of metastasis if the endplate change is extensive. One technique that may help distinguish benign disease from metastasis involves examining the ratio of signal intensity between abnormal and normal bone mar-

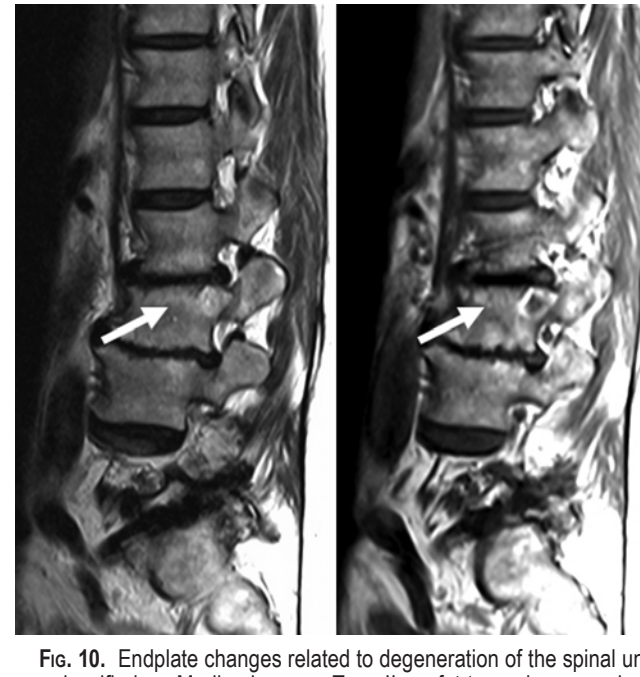

Fig. 10. Endplate changes related to degeneration of the spinal unit are classified as Modic changes. Type II, or fat-type changes, show both T1 **(left)** and T2 **(right)** signal hyperintensity (*arrow*) on MR imaging.

row for in-phase and out-of-phase images;[15,58] the following formula is useful: signal intensity ratio = (out-of-phase abnormal vertebra / in-phase abnormal vertebra) / (out-of-phase normal vertebra / in-phase normal vertebra). Benign lesions, including vertebral endplate changes, benign hemangiomas, and bone edema around Schmorl nodes, demonstrate greater loss of signal intensity between out-of-phase imaging and in-phase imaging compared with malignant lesions, where little loss of signal intensity is noted.[58]

Bone Stress. In areas of mechanical stress, a signal change can be observed prior to the occurrence of a fracture. This change can occur in the pedicle or in the pars interarticularis. It is uncertain whether these changes are strongly associated with a subsequent fracture or whether they even cause symptoms. Information on the management of these lesions is sparse. It is reasonable to assume that the risk of fracture is increased and that physical activity should be modified to avoid loading the spine, particularly in extension, and to strengthen the supporting core muscles.

Paget Disease. Paget disease, a disorder of disorganized bone formation, can be associated with pain. It can also be encountered in asymptomatic individuals. When symptomatic, it can cause considerable morbidity, causing bone pain, fractures, and hypercalcemia. In incidentally discovered lesions, systemic treatment with bisphosphonates is controversial.[53] The prospective randomized PRISM trial suggests that intensive medical management of Paget disease aimed at maintaining normal serum alkaline phosphatase levels conferred no advantage over symptomatic treatment.[35] Referral to a rheumatologist is appropriate. Figure 11 illustrates the case of a 58-year-old woman who presented for evaluation of sciatic pain and was found to have Paget disease of the L-1 vertebra without associated symptoms, despite loss of vertebral height. No additional treatment was undertaken.

Enostosis. Enostosis or "bone island" refers to an area of cortical bone within cancellous bone. It is more common in long bones, but can be found in the spine.[24] In a study of over 1200 patients who underwent CT scanning of the cervical spine for evaluation of trauma, only a single case was encountered.[6] Histologically these lesions are benign, and it remains unclear if they represent developmentally aberrant ossification or hamartomatous lesions. Enostosis has the imaging characteristics of cortical bone on MR imaging and can usually be diagnosed on imaging. However, CT scanning can help confirm the diagnosis. On plain radiographs the dense lesion has a peripheral brush-like spiculated appearance.[23] Because these lesions are usually metabolically hypoactive relative to bone marrow, bone scanning can also help confirm the diagnosis.

Conclusions

Incidental findings in the vertebral column are common and typically benign. While most have a characteristic imaging appearance, others must be differentiated from potentially concerning pathology and may require complementary or repeat imaging.

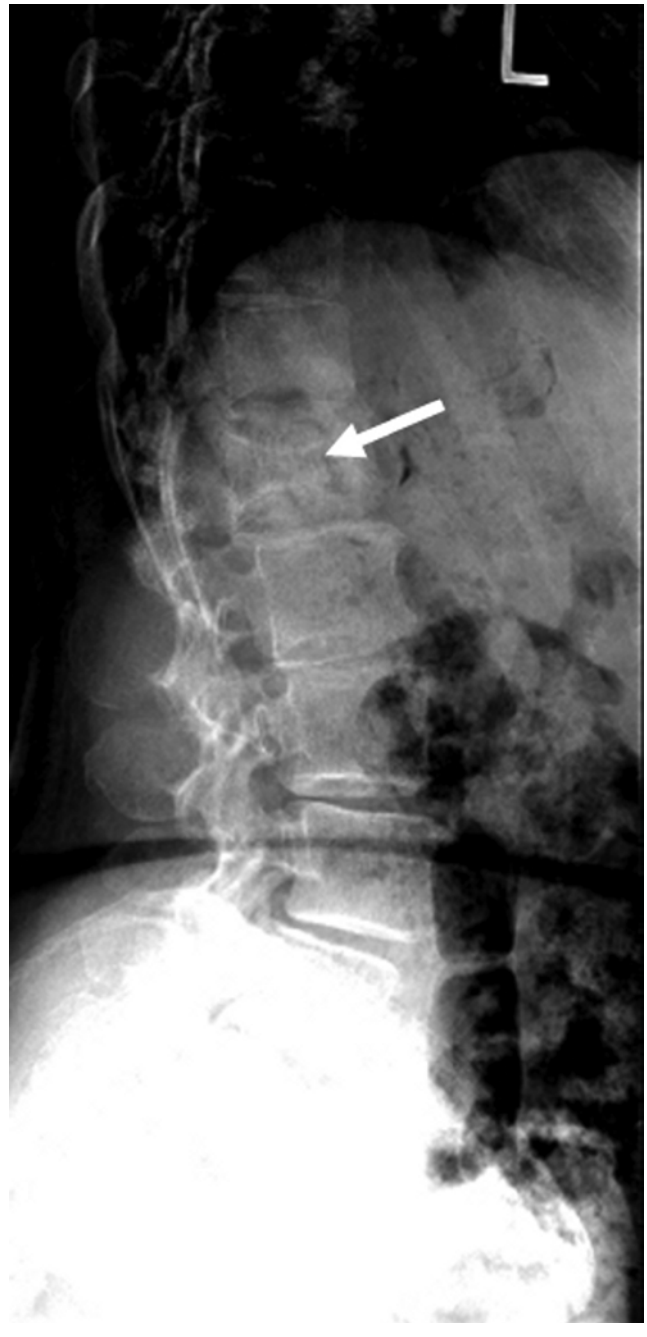

Fig. 11. Lateral radiograph of a patient who presented for evaluation of lumbar radiculopathy, in whom a loss of vertebral height was encountered incidentally *(arrow)*. A CT scan revealed changes consistent with Paget disease.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Acquisition of data: Coumans. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of all authors: Walcott. Study supervision: Coumans.

References

1. Acosta FL Jr, Dowd CF, Chin C, Tihan T, Ames CP, Weinstein PR: Current treatment strategies and outcomes in the management of symptomatic vertebral hemangiomas. **Neurosurgery 58:**287–295, discussion 287–295, 2006
2. Agrawal A, Badve AM, Swarnkar N, Sarda K: Disc prolapse and cord contusion in a case of Klippel-Feil syndrome following minor trauma. **Indian J Orthop 43:**210–212, 2009
3. Angevine JB Jr: Chapter 7. Clinically relevant embryology of the vertebral column and spinal cord. **Clin Neurosurg 20:**95–113, 1973
4. Arvin B, Fournier-Gosselin MP, Fehlings MG: Os odontoideum: etiology and surgical management. **Neurosurgery 66 (3 Suppl):**22–31, 2010
5. AuYong N, Piatt J Jr: Jefferson fractures of the immature spine. Report of 3 cases. **J Neurosurg Pediatr 3:**15–19, 2009
6. Barboza R, Fox JH, Shaffer LET, Opalek JM, Farooki S: Incidental findings in the cervical spine at CT for trauma evaluation. **AJR Am J Roentgenol 192:**725–729, 2009
7. Berne JD, Velmahos GC, El-Tawil Q, Demetriades D, Asensio JA, Murray JA, et al: Value of complete cervical helical computed tomographic scanning in identifying cervical spine injury in the unevaluable blunt trauma patient with multiple injuries: a prospective study. **J Trauma 47:**896–903, 1999
8. Boone D, Parsons D, Lachmann SM, Sherwood T: Spina bifida occulta: lesion or anomaly? **Clin Radiol 36:**159–161, 1985
9. Boot AM, de Ridder MAJ, van der Sluis IM, van Slobbe I, Krenning EP, Keizer-Schrama SM: Peak bone mineral density, lean body mass and fractures. **Bone 46:**336–341, 2010
10. Bressler HB, Keyes WJ, Rochon PA, Badley E: The prevalence of low back pain in the elderly. A systematic review of the literature. **Spine (Phila Pa 1976) 24:**1813–1819, 1999
11. Brown CVR, Antevil JL, Sise MJ, Sack DI: Spiral computed tomography for the diagnosis of cervical, thoracic, and lumbar spine fractures: its time has come. **J Trauma 58:**890–896, 2005
12. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A: Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. **J Bone Miner Res 22:**465–475, 2007
13. Chang H, Park JB: Intraosseous lipoma of lamina of the first thoracic vertebra: a case report. **Spine (Phila Pa 1976) 28:** E250–E251, 2003
14. Cheung KMC, Karppinen J, Chan D, Ho DWH, Song YQ, Sham P, et al: Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. **Spine (Phila Pa 1976) 34:**934–940, 2009
15. Disler DG, McCauley TR, Ratner LM, Kesack CD, Cooper JA: In-phase and out-of-phase MR imaging of bone marrow: prediction of neoplasia based on the detection of coexistent fat and water. **AJR Am J Roentgenol 169:**1439–1447, 1997
16. Doppman JL, Oldfield EH, Heiss JD: Symptomatic vertebral hemangiomas: treatment by means of direct intralesional injection of ethanol. **Radiology 214:**341–348, 2000
17. Dunbar JAT, Sandoe JAT, Rao AS, Crimmins DW, Baig W, Rankine JJ: The MRI appearances of early vertebral osteomyelitis and discitis. **Clin Radiol 65:**974–981, 2010
18. Fidas A, MacDonald HL, Elton RA, Wild SR, Chisholm GD, Scott R: Prevalence and patterns of spina bifida occulta in 2707 normal adults. **Clin Radiol 38:**537–542, 1987
19. Fowler JR, Moyer RA: Case report: absent C6 cervical pedicle in a collegiate football player. **Clin Orthop Relat Res 468:**1693–1696, 2010
20. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, et al: The rising prevalence of chronic low back pain. **Arch Intern Med 169:**251–258, 2009
21. Gerszten PC, Ozhasoglu C, Burton SA, Vogel WJ, Atkins BA, Kalnicki S, et al: CyberKnife frameless single-fraction stereotactic radiosurgery for benign tumors of the spine. **Neurosurg Focus 14(5):**e16, 2003
22. Giampietro PF, McCarty C, Mukesh B, McKiernan F, Wilson D, Shuldiner A, et al: The role of cigarette smoking and statins in the development of postmenopausal osteoporosis: a pilot study utilizing the Marshfield Clinic Personalized Medicine Cohort. **Osteoporos Int 21:**467–477, 2010
23. Gould CF, Ly JQ, Lattin GE Jr, Beall DP, Sutcliffe JB III: Bone tumor mimics: avoiding misdiagnosis. **Curr Probl Diagn Radiol 36:**124–141, 2007
24. Greenspan A: Bone island (enostosis): current concept—a review. **Skeletal Radiol 24:**111–115, 1995
25. Gregerson DM: Clinical consequences of spina bifida occulta. **J Manipulative Physiol Ther 20:**546–550, 1997
26. Grisoni NE, Ballock RT, Thompson GH: Second cervical vertebrae pedicle fractures versus synchondrosis in a child. **Clin Orthop Relat Res (413):**238–242, 2003
27. Hans D, Downs DW Jr, Duboeuf F, Greenspan S, Jankowski LG, Kiebzak GM, et al: Skeletal sites for osteoporosis diagnosis: the 2005 ISCD Official Positions. **J Clin Densitom 9:** 15–21, 2006
28. Hanson EH, Mishra RK, Chang DS, Perkins TG, Bonifield DR, Tandy RD, et al: Sagittal whole-spine magnetic resonance imaging in 750 consecutive outpatients: accurate determination of the number of lumbar vertebral bodies. Clinical article. **J Neurosurg Spine 12:**47–55, 2010
29. Huber-Wagner S, Lefering R, Qvick LM, Körner M, Kay MV, Pfeifer KJ, et al: Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multicentre study. **Lancet 373:**1455–1461, 2009
30. Iskandar BJ, Oakes WJ, McLaughlin C, Osumi AK, Tien RD: Terminal syringohydromyelia and occult spinal dysraphism. **J Neurosurg 81:**513–519, 1994
31. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS: Magnetic resonance imaging of the lumbar spine in people without back pain. **N Engl J Med 331:** 69–73, 1994
32. Klimo P Jr, Kan P, Rao G, Apfelbaum R, Brockmeyer D: Os odontoideum: presentation, diagnosis, and treatment in a series of 78 patients. Clinical article. **J Neurosurg Spine 9:** 332–342, 2008
33. Klimo P Jr, Rao G, Brockmeyer D: Congenital anomalies of the cervical spine. **Neurosurg Clin N Am 18:**463–478, 2007
34. Koyanagi I, Iwasaki Y, Hida K, Abe H, Isu T, Akino M: Surgical treatment of syringomyelia associated with spinal dysraphism. **Childs Nerv Syst 13:**194–200, 1997
35. Langston AL, Campbell MK, Fraser WD, MacLennan GS, Selby PL, Ralston SH: Randomized trial of intensive bisphosphonate treatment versus symptomatic management in Paget's disease of bone. **J Bone Miner Res 25:**20–31, 2010
36. Leivseth G, Frobin W, Brinckmann P: Congenital cervical block vertebrae are associated with caudally adjacent discs. **Clin Biomech (Bristol, Avon) 20:**669–674, 2005
37. Lustrin ES, Karakas SP, Ortiz AO, Cinnamon J, Castillo M, Vaheesan K, et al: Pediatric cervical spine: normal anatomy, variants, and trauma. **Radiographics 23:**539–560, 2003
38. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR: Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. **Radiology 166:**193–199, 1988
39. Naguib M, Farag H: Anaesthetic considerations in Klippel-Feil syndrome. **Can Anaesth Soc J 33:**66–70, 1986
40. Nejat F, Radmanesh F, Ansari S, Tajik P, Kajbafzadeh A, El Khashab M: Spina bifida occulta: is it a predictor of underlying spinal cord abnormality in patients with lower urinary tract dysfunction? **J Neurosurg Pediatr 1:**114–117, 2008
41. Ogden JA: Radiology of postnatal skeletal development. XI. The first cervical vertebra. **Skeletal Radiol 12:**12–20, 1984

42. Ogden JA: Radiology of postnatal skeletal development. XII. The second cervical vertebra. **Skeletal Radiol 12:**169–177, 1984
43. Park HJ, Jeon YH, Rho MH, Lee EJ, Park NH, Park SI, et al: Incidental findings of the lumbar spine at MRI during herniated intervertebral disk disease evaluation. **AJR Am J Roentgenol 196:**1151–1155, 2011
44. Patinharayil G, Han CW, Marthya A, Meethall KC, Surendran S, Rudrappa GH: Butterfly vertebra: an uncommon congenital spinal anomaly. **Spine (Phila Pa 1976) 33:**E926–E928, 2008
45. Pourquié O: Vertebrate segmentation: from cyclic gene networks to scoliosis. **Cell 145:**650–663, 2011
46. Ricci C, Cova M, Kang YS, Yang A, Rahmouni A, Scott WW Jr, et al: Normal age-related patterns of cellular and fatty bone marrow distribution in the axial skeleton: MR imaging study. **Radiology 177:**83–88, 1990
47. Sade B, Beni-Adani L, Ben-Sira L, Constantini S: Progression of terminal syrinx in occult spina bifida after untethering. **Childs Nerv Syst 19:**106–108, 2003
48. Samartzis D, Lubicky JP, Herman J, Kalluri P, Shen FH: Symptomatic cervical disc herniation in a pediatric Klippel-Feil patient: the risk of neural injury associated with extensive congenitally fused vertebrae and a hypermobile segment. **Spine (Phila Pa 1976) 31:**E335–E338, 2006
49. Samuel M, Boddy SA: Is spina bifida occulta associated with lower urinary tract dysfunction in children? **J Urol 171:**2664–2666, 2004
50. Satpathy A, Sloan R, Bhoora IG: Compression fracture or butterfly vertebra: diagnostic importance in a trauma setting. **Ann R Coll Surg Engl 86:**W41-W43, 2004
51. Schmiege SJ, Aiken LS, Sander JL, Gerend MA: Osteoporosis prevention among young women: psychosocial models of calcium consumption and weight-bearing exercise. **Health Psychol 26:**577–587, 2007
52. Shen W, Chen J, Punyanitya M, Shapses S, Heshka S, Heymsfield SB: MRI-measured bone marrow adipose tissue is inversely related to DXA-measured bone mineral in Caucasian women. **Osteoporos Int 18:**641–647, 2007
53. Singer FR: Paget disease: when to treat and when not to treat. **Nat Rev Rheumatol 5:**483–489, 2009
54. Singh P, Mishra NK, Dash HH, Thyalling RK, Sharma BS, Sarkar C, et al: Treatment of vertebral hemangiomas with absolute alcohol (ethanol) embolization, cord decompression, and single level instrumentation: a pilot study. **Neurosurgery 68:**78–84, 2011
55. Vaidyanathan S, Hughes PL, Soni BM, Singh G, Sett P: Klippel-Feil syndrome - the risk of cervical spinal cord injury: a case report. **BMC Fam Pract 3:**6, 2002
56. Wiener MD, Martinez S, Forsberg DA: Congenital absence of a cervical spine pedicle: clinical and radiologic findings. **AJR Am J Roentgenol 155:**1037–1041, 1990
57. Williams CE, Close PJ, Meaney J, Ritchie D, Cogley D, Carty AT: Intraosseous lipomas. **Clin Radiol 47:**348–350, 1993
58. Zajick DC Jr, Morrison WB, Schweitzer ME, Parellada JA, Carrino JA: Benign and malignant processes: normal values and differentiation with chemical shift MR imaging in vertebral marrow. **Radiology 237:**590–596, 2005
59. Zhang Z, Zhou Y, Wang J, Chu T, Li C, Ren X, et al: Acute traumatic cervical cord injury in patients with os odontoideum. **J Clin Neurosci 17:**1289–1293, 2010

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Address correspondence to: Brian P. Walcott, M.D., Massachusetts General Hospital, 55 Fruit Street, White Building, Room 502, Boston, Massachusetts 02114. email: walcott.brian@mgh.harvard.edu.

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Incidental pituitary adenomas

Walavan Sivakumar, M.D.,[1] Roukoz Chamoun, M.D.,[1] Vinh Nguyen, M.D.,[2] and William T. Couldwell, M.D., Ph.D.[1]

Departments of [1]Neurosurgery and [2]Radiology, University of Utah, Salt Lake City, Utah

Object. Pituitary incidentalomas are a common finding with a poorly understood natural history. Over the last few decades, numerous studies have sought to decipher the optimal evaluation and treatment of these lesions. This paper aims to elucidate the current evidence regarding their prevalence, natural history, evaluation, and management.

Methods. A search of articles on PubMed (National Library of Medicine) and reference lists of all relevant articles was conducted to identify all studies pertaining to the incidence, natural history, workup, treatment, and follow-up of incidental pituitary and sellar lesions, nonfunctioning pituitary adenomas, and incidentalomas.

Results. The reported prevalence of pituitary incidentalomas has increased significantly in recent years. A complete history, physical, and endocrinological workup with formal visual field testing in the event of optic apparatus involvement constitutes the basics of the initial evaluation. Although data regarding the natural history of pituitary incidentalomas remain sparse, they seem to suggest that progression to pituitary apoplexy (0.6/100 patient-years), visual field deficits (0.6/100 patient-years), and endocrine dysfunction (0.8/100 patient-years) remains low. In larger lesions, apoplexy risk may be higher.

Conclusions. While the majority of pituitary incidentalomas can be managed conservatively, involvement of the optic apparatus, endocrine dysfunction, ophthalmological symptoms, and progressive increase in size represent the main indications for surgery. *(DOI: 10.3171/2011.9.FOCUS11217)*

Key Words • adenoma • incidental pituitary lesion • incidentaloma • endocrine dysfunction • transsphenoidal surgery

In clinical series, pituitary tumors are the third most common primary brain tumor, behind gliomas and meningiomas, accounting for 10%–15% of all primary brain tumors.[43] At autopsy, these lesions are even more common, with an average frequency of approximately 14.4% in the general population.[20]

With the increase in the use of radiographic imaging, there has been a concurrent increase in the number of incidental pituitary lesions diagnosed. Generally defined as previously unsuspected pituitary lesions found on imaging performed for another reason, PIs are nevertheless not precisely delineated. While some studies include all lesions of the sella, others exclude lesions not fitting the criteria for pituitary adenoma, including Rathke cleft cysts, craniopharyngiomas, arachnoid cysts, colloid cysts, and epidermoid cysts.[42,47] For the purposes of this review, we will focus on lesions most likely representing adenomas of the pituitary. Long-standing convention has classified macroincidentalomas as being 1 cm or larger and microincidentalomas as being smaller than 1 cm.

In this report, we review the existing literature regarding the incidence, natural history, workup, treatment, and follow-up of incidental pituitary lesions with a particular focus on pituitary adenomas.

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; IGF-1 = insulin-like growth factor–1; PI = pituitary incidentaloma.

Methods

A search of articles on PubMed (National Library of Medicine) and reference lists of all relevant articles was conducted to identify all studies pertaining to the incidence, natural history, workup, treatment, and follow-up of incidental pituitary and sellar lesions, nonfunctioning pituitary adenomas, and incidentalomas. In total, 34 studies, 8 reviews, and 4 consensus reports were included. Studies including patients with pituitary lesions that were symptomatic at the time of diagnosis were excluded.

Results

Radiological and autopsy study estimates of the prevalence of PIs have varied between 1% and 30%.[11,32] The increased use of diagnostic imaging has yielded a dramatic increase in the number of incidentalomas diagnosed.[40,44] A recent report by Raappana et al.[36] highlighted that in the second half of an 18-year study, there was a 3-fold increase in incidentally found lesions. This accounted for the perceived increased trend in the prevalence rates of pituitary adenomas.

Despite the increased prevalence, it is believed that these data generally do not fully encompass the true frequency of these lesions. Some autopsy studies have revealed that up to 20%–25% of the general population may have a pituitary adenoma.[9] These lesions were clinically silent and were only found incidentally postmortem through microscopic dissection of carefully sectioned samples of pituitary gland. They included mostly null cell tumors but some stained positive for prolactin, growth hormone, ACTH, thyroid-stimulating hormone, and gonadotropic hormones.[29] It is thought that in these cases the hormone is not effectively secreted or the amount of hormone secreted is not elevated enough to be clinically significant.

Differential Diagnosis

While the majority of incidentally found pituitary lesions are adenomas, it is important to consider the large collection of other abnormalities of the sella *(Appendix 1)*. The differential diagnosis for sellar lesions includes cystic lesions, pituitary hyperplasia, germ cell tumors, glioma, lymphoma, meningioma, metastatic tumors, and other inflammatory or vascular lesions.

Endocrinological Evaluation

The first step is to evaluate all patients who present with PI for hormone hypersecretion or hypopituitarism through a complete history, physical examination, and a basic endocrinological workup.[31] The senior author (W.T.C.) performs an endocrinological evaluation even in asymptomatic patients. It is unknown whether downstream effects of silent somatotroph and corticotroph adenomas on cardiovascular complications, malignancy risk, and cerebrovascular disease are similar to the risk in the general population. Baldeweg et al.[5] reported a series of 22 patients who underwent transsphenoidal resection for silent corticotroph adenomas that stained positive for ACTH. Four (18.1%) of the patients began to show signs of hypercortisolemia during follow-up, providing evidence that even silent adenomas can become secretory and that the transformation to a more aggressive tumor type should be considered in all silent adenomas. Bradley et al.[8] reported a similar series of 28 patients who underwent transsphenoidal resection for silent corticotroph adenomas that stained positive for ACTH and compared them with patients whose nonfunctional adenomas were immunonegative for ACTH. A significant recurrence rate of 7.1% was observed in the immunopositive group compared with no recurrence in the immunonegative group.

While it is generally agreed that screening for hormone hypersecretion should be undertaken, there is currently no formal consensus on the extent of hormone screening needed. Most data on the prevalence of hormone hypersecretion come from small, retrospective studies and autopsy studies. The prevalence of clinically evident pituitary adenomas has been reported to be between 0.04 in 1000 and 1 in 1000 of the population.[15,16,23,36] This broad variation likely suggests an underdiagnosis within certain communities.[13]

Many studies have advocated obtaining a baseline serum prolactin level upon discovery of a PI. Positive staining for prolactin secretion has been seen in 11.9%–15.2% of microincidentalomas,[21,22] and 12.5% of macroincidentalomas in a small series of 16 patients stained positive for prolactin.[19] While large autopsy studies have reported that 39.5% of PIs stain positive for prolactin, the clinical relevance of these findings is unclear.[9,19,21,22] When assessing prolactin levels, mild elevations need to be taken in the right clinical context because of the possibility of stalk effect. Compression by lesions that block the outflow of the hypothalamus can impede hypothalamic inhibitory control on the anterior pituitary, resulting in moderate hyperprolactinemia (usually < 150 ng/ml). Typically, prolactin levels 200 ng/ml or greater indicate a primary prolactin-secreting tumor. Additionally, when assessing prolactin levels in the presence of very large PIs, having the laboratory do serial dilutions of the serum sample will decrease the potential for a false-negative result due to the hook effect. Excessive levels of prolactin can prevent the formation of the necessary antibody-prolactin-signal complexes required to provide the correct reading.[6]

Autopsy studies have shown that up to 1.8% of PIs stain positive for growth hormone.[9] If the decision is made to evaluate for the possibility for a somatotroph adenoma, assessment of IGF-1 is typically sufficient. In the event that this is not possible, an oral glucose tolerance test can be used. Failure to suppress growth hormone levels less than 2 ng/ml after a 75-g oral glucose load indicates dysfunction along the hypothalamic-pituitary axis.

In a series of 3048 autopsies, 334 pituitary adenomas were found and 13.8% stained positive for ACTH.[9] Whereas this was previously thought to be a benign finding, reports have shown that even nonobese, normoglycemic patients with adrenal incidentalomas have glucose intolerance, insulin insensitivity, and elevated blood pressure compared with age-matched controls.[1] Subclinical Cushing disease can be presumed to also result in the sequelae of hypertension, diabetes, and osteoporosis.[31] Subclinical hypercortisolemia in a patient with PI should prompt a further evaluation for Cushing disease. The most commonly used screening tests for hypercortisolemia due to Cushing syndrome are the dexamethasone suppression test and 24-hour urinary free cortisol, and more recently, midnight salivary cortisol.[4] Whether a baseline ACTH level should be measured in a patient with PI as part of the screening laboratory studies is currently a point of contention, as no systematic screening of incidentalomas for subclinical glucocorticoid excess has been reported. It is interesting to note that there have been reports of recurrence and florid hypercortisolemia in the presence of a previously resected presumed silent corticotroph adenoma.[28]

Gonadotroph adenomas comprise approximately 10% of all pituitary adenomas, but because they overwhelmingly present as a nonfunctioning sellar mass without any

associated symptoms, screening for these entities without clinical suspicion for hypogonadism is seldom performed.[45]

In patients with an initially normal endocrinological evaluation, the senior author (W.T.C.) typically repeats endocrinological laboratory studies at 1 year *(Appendix 2)* and then follows with additional laboratory studies thereafter only if the patient's clinical symptoms change. Abnormal laboratory values are followed up on an individualized basis depending on the patient's presentation.

In all patients with PIs, some consideration should be made toward the familial disorder multiple endocrine neoplasia type 1 (MEN-1). Patients who present with plurihormonal discrepancies have an increased risk of MEN-1, and further attention should be paid to obtaining a careful family history and evaluating parathyroid/pancreas function.[34,41] Although there are no recent consensus guidelines regarding how to screen for MEN-1, such patients at our institution undergo a molecular genetic analysis for *MEN1* gene mutations, as well as clinical, biochemical, and radiographic evaluations for MEN-1–associated tumors.

Evidence for the importance of screening for hypopituitarism has also come from small observational studies. Recent reports have shown rates of hypopituitarism in patients with PIs to be between 10.6% and 41.3%.[3,21] Macroincidentalomas are much more likely than microincidentalomas to induce hypopituitarism. Reports describing the natural history of PIs smaller than 1 cm show an overwhelmingly benign course with the maintenance of normal pituitary function. Reincke et al.[39] and Donovan and Corenblum[19] showed that all of the patients in their combined series of 22 microincidentalomas retained normal pituitary function. Macroadenomas likely prompt altered pituitary function by direct compression on the hypothalamus, pituitary stalk, or pituitary itself. Rates of hypopituitarism in macroincidentalomas have been reported to be as high as 41.3%.[22,27,44,46] Because of this high rate of decreased pituitary function in clinically asymptomatic patients, it is generally accepted to screen for hypopituitarism upon the discovery of macroincidentalomas. Of the endocrinopathies seen, hypogonadism, hypocortisolism, hypothyroidism, and decreased growth hormone were seen in up to 30%, 18%, 28%, and 8% of patients, respectively.[21,22,39]

Radiographic Evaluation

The advent and widespread use of MR imaging has revolutionized the visualization of the sellar region. This has also led to the increase in diagnosis of PIs, namely microincidentalomas. The use of Gd contrast allows for better differentiation of the pituitary-PI interface, evaluation of abutment of the optic chiasm, and invasion into the cavernous sinus, which are all important considerations when surgery is being discussed.[12] Coronal dynamic contrast-enhanced images are used to evaluate for nodules of decreased or delayed enhancement characteristic of microadenomas. Thin-section or volumetrically acquired T2-weighted sequences are particularly helpful in delineation of whether the mass is intrasellar or suprasellar and whether the pituitary gland is normal. These images also demonstrate the lesional anatomy and morphology and regional mass effects on adjacent structures such as the infundibulum, optic chiasm, or internal carotid arteries. A combination of T1-weighted, T2-weighted, and contrast-enhanced sequences, usually obtained coronally, can help distinguish between a cystic lesion (for example, Rathke cleft cyst, pars intermedia, and arachnoid cyst) and the presence of hemosiderin as can be seen in hemorrhagic adenomas. Delayed postcontrast sequences can show areas of enhancement in craniopharyngioma, macroadenoma, pilocytic astrocytoma, germ cell tumor, and Langerhans cell histiocytosis. Furthermore, granulomatous processes such as sarcoidosis or tuberculosis can have additional nodular basal cistern and leptomeningeal enhancement. Meningiomas, which are common suprasellar lesions, typically demonstrate marginal peripheral dural thickening and enhancement ("dural tail"). Computed tomography scanning plays an important role in determining the presence of calcifications, which are characteristic of craniopharyngiomas, or hyperostotic changes/osseous remodeling from a meningioma. Additionally, helically acquired CT scans can provide detailed nasal cavity anatomy and can be used for stereotactic guidance.

Routine pituitary imaging performed at our institution includes sagittal T1-weighted precontrast and postcontrast images with fat saturation. In the coronal plane, precontrast T1- and T2-weighted, dynamic T1-weighted postcontrast, and delayed T1-weighted postcontrast images with fat saturation sequences are acquired. Additional whole-brain images to evaluate for extrasellar disease include axial FLAIR, T2-weighted/refocused gradient echo and diffusion-weighted imaging.

Visual Field Testing

Visual loss is one of the devastating complications associated with larger lesions with suprasellar extent. Reincke et al.[39] monitored 11 patients with macroincidentalomas prospectively and found that 9.1% had visual field deficits and 18% had compression of the optic chiasm. In another prospective analysis of 25 patients with macroincidentalomas, initial ophthalmological evaluation yielded visual field deficits in 4.5% of patients.[22] Dekkers et al.[17] monitored 28 patients with newly diagnosed macroadenomas that were initially not surgically treated. Surgical treatment was eventually required in 6 (21.4%) of 28 patients who were initially asymptomatic but developed visual field deficits. Most authors propose formal visual field testing for all patients with PIs that demonstrate compression of or are adjacent to the optic chiasm on imaging.

Cost of Evaluation

Because of the frequency of incidental pituitary lesions in the general population, substantial expenses are incurred by the medical system for evaluation and monitoring even if they remain stable and no treatment is needed. A review of the experience of the University of Utah between 2002 and 2009 shows that the evaluation of a single patient with PI costs approximately $6000; this includes physicians' fees (neurosurgeon, endocrinologist, and radiologist fees), imaging, and laboratory tests.[38] Accounting for the average incidence of these lesions in the general population, the total cost for the US health system would be approximately $7 million in 1 year.[38]

Natural History

Although several studies have aimed to elucidate the natural history of PIs, the resultant data have been scarce and generally of poor quality. In 2011, Fernández-Balsells et al.[24] performed a meta-analysis of the available literature in an attempt to garner the prognostic factors involved in PI progression. Eleven primarily single-center studies were chosen. The mean follow-up time ranged from 2.3 to 8 years. Headache was the most common baseline complaint warranting obtaining MR images.[33,35] The overall frequency of PIs was higher in female patients. The average event rate for all PIs was 5.8 per 100 patient-years. The incidence was significantly higher in macroincidentalomas than in microincidentalomas (12.53 vs 3.32). The incidence of pituitary apoplexy (0.6/100 patient-years), worsening of visual field deficits (0.6/100 patient-years), and onset of endocrine dysfunction (0.8/100 patient-years) were found to be low. The authors concluded that despite the thorough literature search, the available literature was scarce and not particularly helpful in predicting the natural history of PIs. Additionally, the lack of separation of nonfunctional pituitary adenomas and PIs in a few of the studies made it difficult to predict distinct incidence rates. Future studies would need to contain larger sample sizes, be prospective in design, contain clear inclusion and exclusion criteria, and have uniform follow-up.[24]

An important paper[3] has documented that among 42 patients with asymptomatic macroadenomas monitored for 5 years, nearly 10% developed pituitary apoplexy. This risk is important to note when counseling patients with larger tumors that are found incidentally.[3] In addition, apoplexy may occur in microadenomas (Fig. 1).[38] It is likely that this occurs more frequently than is recognized, but the incidence is unknown. The senior author (W.T.C.) also counsels patients about this small risk when monitoring incidental microadenomas.

Treatment of PIs

The majority of PIs do not require surgery. The data evaluating various treatments and follow-up strategies for lesions that require intervention are not substantiated by high-quality evidence;[18] however, a few tenets appear to be generally accepted. Medical and surgical therapy is indicated when there is biochemical evidence of pituitary hypersecretion. This is well established in the literature and fortified by clinical guidelines for prolactinomas, somatotroph adenomas, and corticotroph adenomas. Untreated hyperprolactinemia can produce early and profound osteopenia in young women, in addition to infertility in both sexes. While medical therapy with prolactinomas in the form of dopamine agonists is attempted initially, early surgical intervention has emerged as the treatment of choice for hypersecreting somatotroph and corticotroph adenomas.[4,10,26]

Macroincidentalomas have an established tendency to grow and cause clinically evident symptoms via compression and mass effect, with rates as high as 40% over 5 years in one study.[3] As previously illustrated, they are almost 4 times more likely to grow as tumors smaller than 1 cm.[24] Macroincidentalomas should be monitored closely for radiographic evidence of optic nerve and chiasm involvement, biochemical evidence of pituitary hypersecretion and hypopituitarism, and ophthalmological signs of visual field deficits, which are all indications for surgical intervention.[2,14,18,30] While microincidentalomas are less likely than macroincidentalomas to grow significantly, close follow-up with history, clinical examination, biochemical testing, and radiological imaging are essential. Microincidentalomas are estimated to have a 10.6% incidence of tumor growth seen on MR imaging with follow-up periods of 8 years.[31] Surgery is usually reserved for patients who present with rapidly enlarging tumor masses, compression of the optic apparatus, pituitary apoplexy, and evidence of hypopituitarism.[14,30]

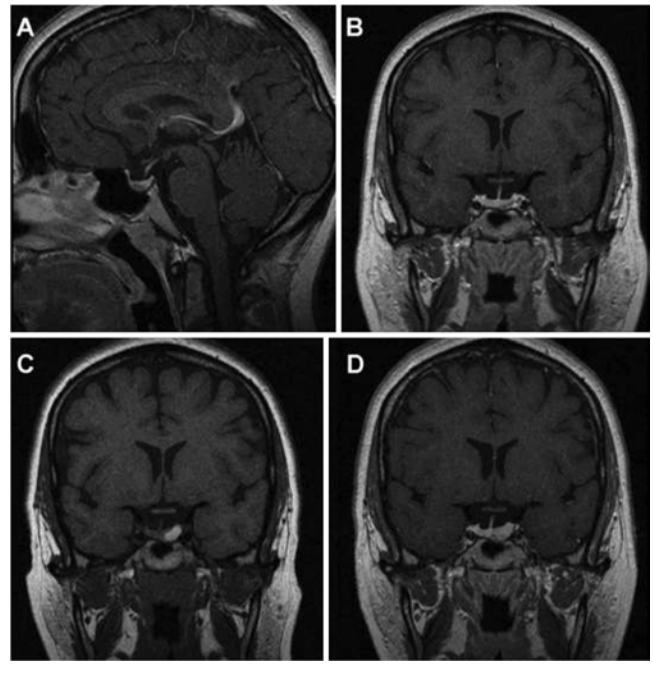

Fig. 1. Magnetic resonance images obtained in a 27-year-old woman who was being monitored by the senior author for a pituitary microadenoma who went on to develop pituitary apoplexy. **A and B:** Sagittal and coronal T1-weighted MR images with contrast enhancement obtained at initial presentation, showing a small adenoma in the left part of the pituitary gland. **C and D:** Coronal T1-weighted MR imaging studies without and with contrast enhancement, showing hemorrhage into the area of the previously diagnosed tumor. Reproduced from Randall BR, Couldwell WT: **Acta Neurochir (Wien) 152:**1737–1740, 2010, with permission from Springer-Verlag.

When surgery is indicated, the transsphenoidal approach has emerged as the preferred method. When performed by skilled, experienced neurosurgeons at high-volume centers, superior short-term outcomes with low morbidity and mortality have come to be expected.[7]

The senior author chooses to follow all incidental nonfunctional microadenomas that have normal documented endocrine function[37] with a study in 1 year. If there is no demonstrable growth of the tumor, the patient is not monitored further unless symptoms develop. In larger, nonfunctional tumors, those that are 15 mm or larger, treatment is considered in younger patients, given the higher incidence of growth known to occur in these patients and the relatively higher risk of apoplexy. If the patient chooses conser-

vative monitoring, yearly studies are done and the lesion is removed if growth is noted.

Practice Guidelines

In April 2011, the Endocrine Society attempted to critically analyze the data regarding the treatment of PIs and make practice guidelines regarding the evaluation, follow-up, and indications for surgery for these lesions.[25] Each recommendation was given a strength of recommendation ("1" referred to recommendations and "2" referred to suggestions), and an assessment score on a 4-point scale regarding the quality of the evidence was used to make the specific recommendation. A 4-star assessment indicated high-quality evidence, a 3-star assessment indicated moderate quality, a 2-star assessment indicated low quality, and a 1-star assessment indicated very low quality evidence. The members of the task force reached a significant consensus, adding to the strength of these guidelines. Table 1 shows the individual recommendations, recommendation strength, and assessment score for various lesion characteristics.[25] Strength and assessment scores for the recommendations regarding initial evaluation were strong, whereas those for nonsurgical follow-up were generally weaker. Indications for surgery were generally viewed as falling into 1 of 2 extremes, with some indications judged as recommendations with high-quality evidence but others as only suggestions with low-quality evidence. The lack of well-designed prospective studies directly comparing different treatment modalities accounts for this dichotomy.

Conclusions

Pituitary incidentaloma is a fairly common occurrence in the general population. With the increasing use of modern imaging technology, physicians are increasingly encountering these incidentally diagnosed pituitary lesions. The first step is to rule out a hypersecreting adenoma through a complete history, physical examination,

TABLE 1: Endocrine Society Clinical Practice Guidelines on PI*

Section No.	Recommendation	Strength	Assessment Score
1.0	initial evaluation		
1.1	complete history & physical examination for all patients		
1.1.1	clinical/laboratory evaluation for hormone hypersecretion (all patients)	1	***
1.1.2	clinical/laboratory evaluation for hypopituitarism (all patients)	1	***
1.1.3	formal VF testing (if lesion abutting optic nerve/chiasm on MRI)	1	****
1.1.4	MRI recommended if PI discovered on CT (if no contraindication)	1	****
2.0	follow-up testing for PI w/ no indications for surgery		
2.1	patients should have clinical & radiological follow-up as follow:	2	**
2.1.1	macroincidentaloma: repeat MRI in 6 mos; if unchanged then	1	**
	repeat MRI every yr for 3 yrs, & less frequently thereafter	2	**
2.1.1	microincidentaloma: repeat MRI in 1 yr; if unchanged then	1	**
	repeat MRI every 1–2 yrs for 3 yrs, & less frequently thereafter	2	**
2.1.2	formal VF testing for enlarging PI abutting/compressing chiasm	1	****
2.1.2	no VF testing recommended if PI has no contact w/ chiasm on MRI	2	*
2.1.3	macroincidentaloma: repeat biochemical testing for hypopituitarism at 6 mos then yearly if unchanged	1	**
2.1.3	microincidentaloma: repeat biochemical testing for hypopituitarism not recommended if clinical picture, history, & MRI unchanged	2	**
2.2	in case of new signs/symptoms or increase in size on MRI: more frequent/detailed evaluation	1	**
3.0	indications for surgery		
3.1	visual field deficit due to lesion	1	****
3.1	other visual abnormality or neurological deficit due to compression	1	****
3.1	PI abutting or compressing optic nerve or chiasm on MRI	1	****
3.1	pituitary apoplexy w/ visual disturbance	1	****
3.1	hypersecreting (except prolactinoma)	1	****
3.2	significant growth	2	**
3.2	loss of endocrine function	2	**
3.2	PI close to optic chiasm and patient planning to become pregnant	2	**
3.2	PI w/ unremitting headache	2	**

* The recommendations were obtained from Freda PU, et al: **J Clin Endocrinol Metab 96:**894–904, 2011. Abbreviation: VF = visual field. See *Practice Guidelines* for definition of assessment scores.

and hormonal profile. The other crucial element is to ensure that the lesion is not causing significant mass effect by checking for hypopituitarism and for visual defect if the mass is abutting the optic apparatus. Although the natural history of these lesions is not fully understood, most PIs can be treated conservatively. A close clinical and radiological follow-up is of paramount importance since these lesions (mostly macroincidentalomas) can potentially grow and are predisposed to apoplexy. In accordance with the published practice guidelines, it is our practice to reserve surgery for hypersecreting adenomas (except for prolactinomas), those causing visual defect, large masses abutting the chiasm, macroadenomas with secondary hypopituitarism, and lesions with a documented increase in size.

Appendix 1: Differential Diagnosis for Sellar Masses

- pituitary tumor
  - adenoma
  - carcinoma
- cystic lesion
  - Rathke cleft cyst
  - craniopharyngioma
  - arachnoid cyst
  - colloid cyst
  - epidermoid cyst
  - xanthogranuloma
  - dermoid cyst
- pituitary hyperplasia
- germ cell tumor
  - germinoma
  - teratoma
  - dermoid
- glioma
- lymphoma
- meningioma
- metastatic tumor
- inflammatory lesion
  - pyogenic infection
  - granulomatous infection
  - sarcoidosis
- vascular lesion
  - aneurysm
  - cavernous angioma

Appendix 2: Endocrinological Evaluation for Pituitary Incidentalomas

- initial evaluation
  - prolactin
  - IGF-1
  - growth hormone
  - fasting cortisol, serum
  - ACTH
  - thyroid-stimulating hormone
  - thyroxine
  - luteinizing hormone
  - follicle-stimulating hormone, serum
- if initial laboratory studies are normal, at 1 year
  - prolactin
  - IGF-1
  - growth hormone
  - fasting cortisol, serum
  - ACTH
  - thyroid-stimulating hormone
  - thyroxine
  - luteinizing hormone
  - follicle-stimulating hormone, serum

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Couldwell. Acquisition of data: Sivakumar. Analysis and interpretation of data: Sivakumar. Drafting the article: Sivakumar. Critically revising the article: Couldwell, Chamoun, Nguyen. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Couldwell. Study supervision: Couldwell.

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References

1. Angeli A, Terzolo M: Adrenal incidentaloma—a modern disease with old complications. **J Clin Endocrinol Metab 87:** 4869–4871, 2002
2. Arafah BM: Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. **J Clin Endocrinol Metab 62:**1173–1179, 1986
3. Arita K, Tominaga A, Sugiyama K, Eguchi K, Iida K, Sumida M, et al: Natural course of incidentally found nonfunctioning pituitary adenoma, with special reference to pituitary apoplexy during follow-up examination. **J Neurosurg 104:**884–891, 2006
4. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, et al: Diagnosis and complications of Cushing's syndrome: a consensus statement. **J Clin Endocrinol Metab 88:**5593–5602, 2003
5. Baldeweg SE, Pollock JR, Powell M, Ahlquist J: A spectrum of behaviour in silent corticotroph pituitary adenomas. **Br J Neurosurg 19:**38–42, 2005
6. Barkan AL, Chandler WF: Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the "high-dose hook effect": case report. **Neurosurgery 42:**913–916, 1998
7. Barker FG II, Klibanski A, Swearingen B: Transsphenoidal surgery for pituitary tumors in the United States, 1996-2000: mortality, morbidity, and the effects of hospital and surgeon volume. **J Clin Endocrinol Metab 88:**4709–4719, 2003
8. Bradley KJ, Wass JA, Turner HE: Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours but do not recur more frequently. **Clin Endocrinol (Oxf) 58:**59–64, 2003
9. Buurman H, Saeger W: Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. **Eur J Endocrinol 154:**753–758, 2006
10. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, et al: Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. **Clin Endocrinol (Oxf) 65:**265–273, 2006
11. Chambers EF, Turski PA, LaMasters D, Newton TH: Regions of low density in the contrast-enhanced pituitary gland: normal and pathologic processes. **Radiology 144:**109–113, 1982
12. Chong BW, Kucharczyk W, Singer W, George S: Pituitary gland MR: a comparative study of healthy volunteers and patients with microadenomas. **AJNR Am J Neuroradiol 15:**675–679, 1994
13. Couldwell WT, Cannon-Albright L: A heritable predisposition to pituitary tumors. **Pituitary 13:**130–137, 2010
14. Daly AF, Burlacu MC, Livadariu E, Beckers A: The epidemiology and management of pituitary incidentalomas. **Horm Res 68 (Suppl 5):**195–198, 2007
15. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa

MA, Beckers A: High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. **J Clin Endocrinol Metab 91:**4769–4775, 2006
16. Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T: Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. **Neuro Oncol 3:**152–158, 2001
17. Dekkers OM, Hammer S, de Keizer RJ, Roelfsema F, Schutte PJ, Smit JW, et al: The natural course of non-functioning pituitary macroadenomas. **Eur J Endocrinol 156:**217–224, 2007
18. Dekkers OM, Pereira AM, Romijn JA: Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. **J Clin Endocrinol Metab 93:**3717–3726, 2008
19. Donovan LE, Corenblum B: The natural history of the pituitary incidentaloma. **Arch Intern Med 155:**181–183, 1995
20. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al: The prevalence of pituitary adenomas: a systematic review. **Cancer 101:**613–619, 2004
21. Fainstein Day P, Guitelman M, Artese R, Fiszledjer L, Chervin A, Vitale NM, et al: Retrospective multicentric study of pituitary incidentalomas. **Pituitary 7:**145–148, 2004 (Erratum in **Pituitary 14:**198, 2011)
22. Feldkamp J, Santen R, Harms E, Aulich A, Mödder U, Scherbaum WA: Incidentally discovered pituitary lesions: high frequency of macroadenomas and hormone-secreting adenomas—results of a prospective study. **Clin Endocrinol (Oxf) 51:**109–113, 1999
23. Fernandez A, Karavitaki N, Wass JA: Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). **Clin Endocrinol (Oxf) 72:**377–382, 2010
24. Fernández-Balsells MM, Murad MH, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, et al: Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. **J Clin Endocrinol Metab 96:** 905–912, 2011
25. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al: Pituitary incidentaloma: an endocrine society clinical practice guideline. **J Clin Endocrinol Metab 96:** 894–904, 2011
26. Growth Hormone Research Society, Pituitary Society: Biochemical assessment and long-term monitoring in patients with acromegaly: statement from a joint consensus conference of the Growth Hormone Research Society and the Pituitary Society. **J Clin Endocrinol Metab 89:**3099–3102, 2004
27. Igarashi T, Saeki N, Yamaura A: Long-term magnetic resonance imaging follow-up of asymptomatic sellar tumors—their natural history and surgical indications. **Neurol Med Chir (Tokyo) 39:**592–599, 1999
28. Karavitaki N, Ansorge O, Wass JA: Silent corticotroph adenomas. **Arq Bras Endocrinol Metabol 51:**1314–1318, 2007
29. McComb DJ, Ryan N, Horvath E, Kovacs K: Subclinical adenomas of the human pituitary. New light on old problems. **Arch Pathol Lab Med 107:**488–491, 1983
30. Molitch ME: Nonfunctioning pituitary tumors and pituitary incidentalomas. **Endocrinol Metab Clin North Am 37:**151–171, xi, 2008
31. Molitch ME: Pituitary tumours: pituitary incidentalomas. **Best Pract Res Clin Endocrinol Metab 23:**667–675, 2009
32. Nammour GM, Ybarra J, Naheedy MH, Romeo JH, Aron DC: Incidental pituitary macroadenoma: a population-based study. **Am J Med Sci 314:**287–291, 1997
33. Nishizawa S, Ohta S, Yokoyama T, Uemura K: Therapeutic strategy for incidentally found pituitary tumors ("pituitary incidentalomas"). **Neurosurgery 43:**1344–1350, 1998
34. O'Brien T, O'Riordan DS, Gharib H, Scheithauer BW, Ebersold MJ, van Heerden JA: Results of treatment of pituitary disease in multiple endocrine neoplasia, type I. **Neurosurgery 39:**273–279, 1996
35. Oyama K, Sanno N, Tahara S, Teramoto A: Management of pituitary incidentalomas: according to a survey of pituitary incidentalomas in Japan. **Semin Ultrasound CT MR 26:**47–50, 2005
36. Raappana A, Koivukangas J, Ebeling T, Pirilä T: Incidence of pituitary adenomas in Northern Finland in 1992-2007. **J Clin Endocrinol Metab 95:**4268–4275, 2010
37. Randall BR, Couldwell WT: Apoplexy in pituitary microadenomas. **Acta Neurochir (Wien) 152:**1737–1740, 2010
38. Randall BR, Kraus KL, Simard MF, Couldwell WT: Cost of evaluation of patients with pituitary incidentaloma. **Pituitary 13:**383–384, 2010
39. Reincke M, Allolio B, Saeger W, Menzel J, Winkelmann W: The 'incidentaloma' of the pituitary gland. Is neurosurgery required? **JAMA 263:**2772–2776, 1990
40. Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y: A survey of pituitary incidentaloma in Japan. **Eur J Endocrinol 149:**123–127, 2003
41. Scheithauer BW, Laws ER Jr, Kovacs K, Horvath E, Randall RV, Carney JA: Pituitary adenomas of the multiple endocrine neoplasia type I syndrome. **Semin Diagn Pathol 4:**205–211, 1987
42. Sivakumar W, Cole CD, Couldwell WT: Rathke cleft cyst presenting with hyponatremia: an unusual presentation. **Neurosurg Focus 31(1):**E4, 2011
43. Terada T, Kovacs K, Stefaneanu L, Horvath E: Incidence, pathology, and recurrence of pituitary adenomas: study of 647 unselected surgical cases. **Endocr Pathol 6:**301–310, 1995
44. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al: Incidental findings on brain MRI in the general population. **N Engl J Med 357:**1821–1828, 2007
45. Young WF Jr, Scheithauer BW, Kovacs KT, Horvath E, Davis DH, Randall RV: Gonadotroph adenoma of the pituitary gland: a clinicopathologic analysis of 100 cases. **Mayo Clin Proc 71:**649–656, 1996
46. Yue NC, Longstreth WT Jr, Elster AD, Jungreis CA, O'Leary DH, Poirier VC: Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. **Radiology 202:**41–46, 1997
47. Zada G, Lin N, Ojerholm E, Ramkissoon S, Laws ER: Craniopharyngioma and other cystic epithelial lesions of the sellar region: a review of clinical, imaging, and histopathological relationships. **Neurosurg Focus 28(4):**E4, 2010

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Address correspondence to: William T. Couldwell, M.D., Ph.D., Department of Neurosurgery, University of Utah, 175 North Medical Drive East, 5th Floor, Salt Lake City, Utah 84132. email: neuropub@hsc.utah.edu.

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Incidental meningiomas

Roukoz Chamoun, M.D., Khaled M. Krisht, M.D., and William T. Couldwell, M.D., Ph.D.

Department of Neurosurgery, University of Utah, Salt Lake City, Utah

With the increasing availability and use of modern brain diagnostic imaging modalities, discovery of incidental meningiomas has become fairly common. This creates a dilemma among neurosurgeons as to whether these lesions should be treated. Numerous natural history studies have been published in an effort to shed light on the potential for growth of incidental meningiomas. The available data appear to suggest that these tumors can fall into 1 of 3 main growth patterns: no growth, linear growth, or exponential growth. The therapeutic strategy selected should also consider several other factors, mainly the risk of complications from an eventual surgery, the possibility of malignancies and other pathological conditions that mimic meningiomas, and the age and medical condition of the patient. The authors believe that most asymptomatic incidental meningiomas can be observed using serial imaging and clinical follow-up evaluations. Surgical interventions are typically reserved for large, symptomatic lesions and those with documented potential for significant growth. *(DOI: 10.3171/2011.9.FOCUS11220)*

Key Words • **incidental** • **meningioma** • **natural history** • **management**

In recent years, there has been a progressive increase in the use of brain imaging modalities. In practice, clinicians try to maintain a high index of suspicion in an effort to diagnose intracranial lesions at an early stage based on subtle signs and symptoms. In the research field, there is an ongoing effort to understand normal brain functions, as well as diseases affecting the central nervous system. The aforementioned inquiries—whether research- or clinically based—resulted in a large number of published studies based on structural and functional brain imaging in healthy volunteers and/or patients with neurological disorders. In addition, the concern of missing a diagnosis has led physicians to order more laboratory tests and imaging. All of these factors have resulted in a substantial increase in the number of brain imaging scans performed and consequently of incidentally found abnormalities.

Incidental findings on brain imaging have been defined as "previously undetected abnormalities of potential clinical relevance that are unexpectedly discovered and unrelated to the purpose of the examination."[13] Katzman et al.[15] reported the incidental findings on brain MR imaging from 1000 asymptomatic volunteers who participated as control subjects for research protocols at the NIH (age range 3–83 years; 54.6% male). Their participation resulted in the detection of incidental findings in several patients, some of them requiring medical referral, including 3 cases of suspected brain tumors. In another report involving 3672 people aged 65 years and older who were enrolled in a population-based study of cardiovascular and cerebrovascular disease, 64 (1.74%) clinically relevant abnormalities were found, and 19 of them were meningiomas (prevalence 0.52%).[35] In a more recent prospective population-based study in the Netherlands involving 2000 people who were 45 years of age or older, the prevalence of benign brain tumors was 1.6%, with meningiomas as the most common (0.9%).[31] These meningiomas ranged from 5 to 60 mm in diameter, and their prevalence was 1.1% in women and 0.7% in men. The study also detected an increase in prevalence from 0.5% in patients 45–59 years old to 1.6% in those 75 years old or older.

With the discovery of these incidental findings, physicians are faced with several important questions. What is the clinical significance of the lesion? What is the natural history, and what are the indications for a therapeutic intervention? In this article, we will focus specifically on incidental meningiomas. Our purpose is to review the relevant medical literature related to this topic and discuss the decision-making strategy involved in their management given the available data on their natural history and potential for complications.

Epidemiological Data

An epidemiological study conducted in Germany between 1961 and 1986 found an annual incidence of meningioma of 1.85 per 100,000 population.[28] The rates were 2.1 times higher in women (2.44) than in men (1.16),

and the incidence increased continuously with age. Interestingly, approximately 50% of the meningiomas in the study were discovered at autopsy. This high rate of meningiomas first found on postmortem examination can be explained by the fact that these are typically slow-growing benign tumors and that they can remain asymptomatic throughout the life of the individual. In the US, the prevalence of meningiomas is estimated to be 97.5 per 100,000 people.[7] Data from the Central Brain Tumor Registry of the US also showed a more than 2-fold higher incidence among females and a steady increase in incidence with age:[4] the incidence rates in 2002 for the age groups 20–34, 45–54, 65–74, and above 85 years were 0.74, 4.89, 12.79, and 18.86 per 100,000 individuals per year, respectively. Atypical and malignant meningiomas comprise a relatively small fraction of the total (estimated to be approximately 5%).[32]

Natural History of Incidental Meningiomas

Understanding the natural history of incidentally found meningiomas is a crucial step in formulating an approach to address them and deciding whether they should be treated. Several studies have been conducted to better understand the behavior of these lesions if left untreated. Nakamura et al.[19] reported their results in 47 asymptomatic patients monitored with serial imaging. The absolute annual growth rate ranged from 0.03 to 2.62 cm^3/year (mean 0.796 cm^3/year), and the majority of tumors (66%) grew less than 1 cm^3/year. The relative annual growth rates ranged from 0.48% to 2.8% (mean 14.6%). The tumor doubling time ranged from 1.27 to 143.5 years (mean 21.6 years). The authors also found a moderate correlation between age and annual growth rates, with younger patients showing a higher growth rate and shorter doubling time. Other important predictive factors included the presence of calcifications and hypointense or isointense tumor signal on T2-weighted MR imaging, which were associated with statistically significantly lower growth rates. Although annual growth rates appear to be higher in men than in women, the difference did not reach statistical significance.

In several studies that investigated the growth pattern of incidental meningiomas, annual growth rates were calculated by determining the initial and final volumes during the follow-up period based on the assumption that these tumors grow exponentially.[8,19] Hashiba et al.[11] performed serial monitoring of tumor volumes in 70 patients and used regression analysis to analyze tumor growth. In each case, the tumor volume was calculated at follow-up and plotted on time-to-volume coordinates. Patients were then divided into 2 groups: a growth group and a no-growth group. Growth curves in the first group were examined to determine whether they followed a linear or an exponential model. Twenty-six patients (37%) showed essentially no growth of their tumor. Among 44 patients with tumor growth, 16 followed an exponential growth pattern, 15 followed a linear pattern, and 13 did not fit either pattern. The presence of calcification was the only radiological characteristic predicting a no-growth pattern. Of note, there was no significant difference between growth/no-growth or between different growth patterns with regard to tumor location; however, the authors of the study admitted that tumor cell kinetics are complex and their relationship to tumor volume is still poorly understood. Fitting the growth curves to either linear or exponential patterns may be too simplistic, and meningiomas may actually exhibit various patterns of growth over multiple phases.

In the largest and most recent study on the topic published to date, Oya et al.[22] reported their results in 244 patients who harbored 273 incidental meningiomas. A 2-mm or greater increase in maximum diameter was observed in 120 tumors (44% of the cases), with a mean follow-up period of 3.8 years. Predictive factors of tumor growth in this study were younger age, absence of calcifications, T2 signal hyperintensity, and peritumoral edema. Tumor location was not found to be a significant predictive factor (Table 1). Nakasu et al.[20] suggested that atypical meningiomas grow exponentially, while benign meningiomas exhibit exponential, linear, or no growth. Exponential growth essentially means that the tumor grows with a constant growth fraction. Linear growth entails a gradual decrease in the tumor growth speed (decrease of the cell proliferation rate and/or increase of the cell death rate). Meningiomas may initially grow exponentially but then slow their growth, possibly in relationship to the availability of blood supply and progression of calcifications; the opposite may also happen, possibly through acquisition of new mutations resulting in an increase in growth rate.

Lesions Mimicking Meningiomas

Incidental meningiomas are, by definition, diagnosed on brain imaging, typically an MR image of the brain, with no histopathological confirmation. Although radiological findings are usually fairly characteristic, many lesions can mimic the appearance of meningiomas on imaging (Figs. 1 and 2). This possibility underscores the importance of an initial close follow-up evaluation if a conservative approach is chosen. The two classical differential diagnoses for meningioma are hemangiopericytoma and meningeal metastasis. Hemangiopericytoma is a rare intracranial malignancy believed to represent 2%–3% of all primary meningeal tumors.[24] Hemangiopericytomas were initially considered a subgroup of meningioma (angioblastic variant),[1] but since 1993 the WHO has classified them as a distinct entity.[27] Hemangiopericytomas are known for their aggressive behavior, high recurrence rate, and potential for metastasis. The median survival from the time of diagnosis is approximately 13 years.[24]

Dural metastasis can also look like meningiomas, with a similar enhancing pattern and dural tail. It is estimated that dural metastases are found in 8%–9% of patients with advanced systemic cancer at autopsy.[18] The clinical incidence is lower because many of these lesions are asymptomatic. The most commonly reported primary tumors that undergo meningeal metastases are prostate, lung, and breast cancer.[16,18] Numerous other diseases can also mimic meningiomas, including lymphoma,[9,23] ependymoma,[25] sarcoma,[3] periosteal osteoblastoma,[30] inflammatory pseudotumor,[14] and Rosai-Dorfman disease.[10]

TABLE 1: Summary of studies on natural history of incidental meningiomas published from 2000 through 2011*

Authors & Year	No. of Patients	Mean FU (mos)	No. (%) Showing Growth	Average Growth Rate Per Year	Factors Favoring Growth	Factors Favoring No Growth
Kuratsu et al., 2000	63	27.8	20 (31.7)	not available	T2 hyperintensity	calcification
Niiro et al., 2000	40	41.8	14 (35)	not available	larger size, T2 hyperintensity, male sex	calcification
Yoneoka et al., 2000	37	50.4	9 (24.3)	>1 cm^3	younger age	smaller tumors
Nakamura et al., 2003	41	43	(33% grew >1 cm^3/yr)	0.796 cm^3	younger age, T2 hyperintensity	calcification
Herscovici et al., 2004	43	67	16 (37.2)	>0.2 cm^3	younger age, sphenoid ridge	calcification, smaller tumors
Yano & Kuratsu, 2006	67	>60	25 (37.3)	1.9 mm	T2 hyperintensity	calcification
Hashiba et al., 2009	70	39.3	40 (57.1)	exponential growth in 16, linear in 15	none	calcification
Oya et al., 2011	244	45.6	120 (49.2)	0.54 cm^3 (patients <60 yrs), 0.83 cm^3 (patients >60 yrs)	younger age, T2 hyperintensity, peritumoral edema	calcification

* FU = follow-up.

Regular radiological and clinical monitoring can help ascertain the behavior of the lesion and can potentially raise uncertainties regarding the presumed diagnosis of a benign meningioma. Table 2 provides a summary of the main lesions that are usually considered in the differential diagnosis, although it is not an exhaustive list of all of the possibilities. In addition, depending on the anatomical location, other diagnoses should be considered. For instance, schwannomas may be included in the differential diagnosis for a cerebellopontine angle tumor and pituitary adenomas and craniopharyngiomas should be added for a sellar tumor.

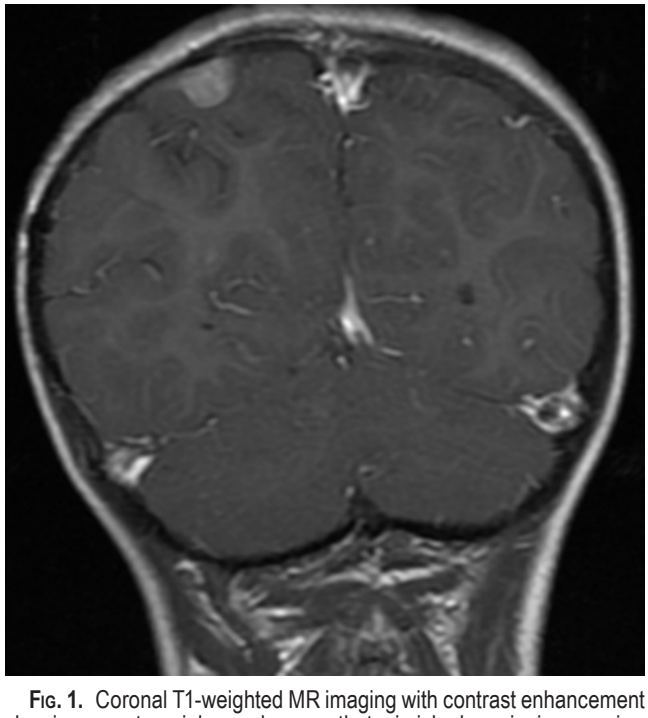

Fig. 1. Coronal T1-weighted MR imaging with contrast enhancement showing an extraaxial ependymoma that mimicked meningioma on imaging.

Complications of Surgery

Despite major advances in modern therapies, including state-of-the-art medical care and up-to-date surgical technologies, the risk of complications from a surgical intervention cannot be overlooked. Meningioma surgery as a

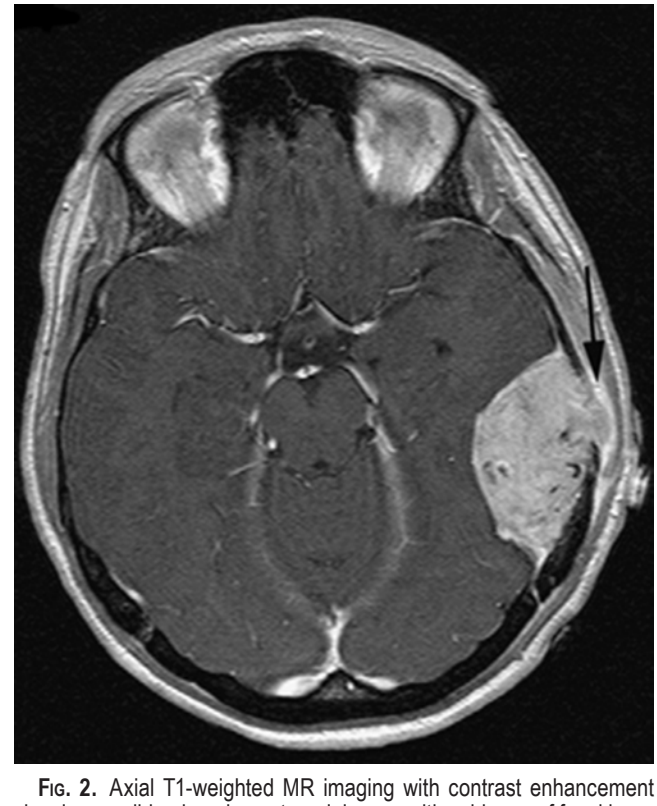

Fig. 2. Axial T1-weighted MR imaging with contrast enhancement showing a solid enhancing extraaxial mass with evidence of focal bone involvement of the temporal bone *(arrow)*. This lesion was an osteoblastoma that mimicked meningioma on imaging. Reprinted from **Pathol Res Pract 204:** Tawil A, Comair Y, Nasser H, et al. Periosteal osteoblastoma of the calvaria mimicking a meningioma, 413–422, Copyright (2008), with permission from Elsevier.

TABLE 2: Differential diagnosis for meningiomas

glial & mesenchymal neoplasms
hemangiopericytoma
solitary fibrous tumor
sarcoma (leiomyosarcoma, gliosarcoma)
ependymoma
osteoblastoma
dural metastatic tumors
prostate cancer, lung cancer, breast cancer, & others
hematopoietic neoplasms
Hodgkin disease
Non-Hodgkin lymphoma
plasmacytoma
inflammatory/infectious lesions
Rosai-Dorfman disease
sarcoidosis
granuloma
tuberculoma

whole constitutes a very heterogeneous group, and the risk of complications varies greatly within this group. The resection of a meningioma can vary from a technically simple procedure to a formidably challenging endeavor associated with a high risk of injury to critical structures. When recommending surgery, the clinician should be mindful of the risks involved and should balance them against the potential benefits of surgical intervention. Sanai et al.[26] reported a series of 141 consecutive patients who underwent resection for a supratentorial convexity meningioma. Their objective was to report the outcome of this kind of surgery in the modern neurosurgical era. They found an overall complication rate of 10%, including hematoma, infection, CSF leak, and pulmonary embolus. Unsurprisingly, the complication rate is significantly higher when more complex types of meningiomas are considered. In a series of 81 patients with tentorial meningiomas treated microsurgically, the permanent surgical morbidity rate was 19.8%, while the mortality rate was 2.5%.[2] Such a high rate of complications has also been reported with many skull base tumors such as petroclival meningiomas. In a surgical series of 109 consecutive patients, for instance, Couldwell et al.[6] reported a perioperative mortality rate of 3.7%; in addition, 56 significant complications occurred in 35 other patients.

Complications of meningioma surgery, however, are not solely related to tumor location and the technical aspects of surgery. Many patients that present are elderly individuals with comorbidities that put them at risk for serious medical complications that may be unrelated to their disease. In a review of 834 patients who underwent surgery for meningiomas in a large tertiary care center, 33% of the patients were older than 60 years of age.[29] Overall, 57 patients (6.8%) experienced serious medical complications, and 4 patients died. The most common complication was pneumonia, followed by renal dysfunction, arrhythmia, and deep venous thrombosis and/or pulmonary embolus. The risk factors for serious medical complications included a new or worsened neurological deficit, age greater than 65 years, hypertension, and currently taking more than 2 cardiac medications.

Indications for Surgery

The treatment strategy for an incidentally diagnosed meningioma should be formulated after a careful and thorough evaluation. Unfortunately, no Class I or Class II evidence is available to support the standard of care or practice guidelines. All recommendations are based on Class III evidence related to expert opinions and retrospective case series. Pertinent questions that should be addressed include the following. Is the lesion symptomatic? What is the size of the lesion? Does the patient have previous imaging? How old is the patient? What is the patient's medical condition? A number of arguments can be made in favor of resection of incidental meningiomas: 1) a certain percentage of these tumors can be atypical or malignant; 2) numerous more aggressive lesions can mimic meningiomas on imaging; 3) an untreated tumor can be the source of anxiety to the patient; and 4) resection would reduce the need for careful initial follow-up. Although these arguments support resection for some incidental meningiomas, we believe that the vast majority of asymptomatic incidental meningiomas should be treated conservatively. In our practice, surgery is recommended if 1) the tumor is large with obvious mass effect accompanied by neurological symptoms; 2) there is a documented increase in size on serial imaging; 3) there is a reasonable suspicion for malignancy based on tumor appearance or behavior; and 4) if the patient is medically fit for surgery.

The decision to use conservative management is supported by several factors. Although the differential diagnosis is vast and although some meningiomas may prove to be malignant, benign meningiomas remain by far the most common lesion when the MR imaging is characteristic for this tumor. Furthermore, a close initial radiographic and clinical monitoring can detect rapid growth, change in imaging characteristics, or unexpected worsening in the neurological examination, leading to an adjustment in the management plan. A reasonable approach would be to start with a first follow-up in 3–4 months from the time of diagnosis to rule out growth of an aggressive lesion. The time frame can then be further increased to 6–9 months and thereafter to 1 year. Furthermore, the vast majority of asymptomatic meningiomas either remain stable or grow slowly. In a large clinical series of 603 asymptomatic meningiomas,[33] 63% did not increase in size, and only 6% of patients eventually experienced symptoms (mean follow-up of 3.9 years). In light of these data, and because the risk of serious complications can clearly outweigh any potential benefit in the elderly and patients with significant comorbidities, a conservative approach is often sufficient. Finally, patient education on the nature of these lesions and their natural history would alleviate anxiety in most cases. The senior author (W.T.C.) specifically removes incidental tumors that are of significant size in young individuals, those tumors that are associated with significant edema, or those found in younger individuals in locations in which further growth might limit the ability to remove the lesion with

TABLE 3: General criteria for treatment selection in patients with intracranial meningioma*

Patient Age (yrs)	Type of Intracranial Meningioma	Treatment
≤65	asymptomatic	observation: serial imaging and clinical FU; surgery recommended for growing lesions or stereotactic radiosurgery can be considered for some tumor locations associated w/ high surgical morbidity (such as cavernous sinus)
	symptomatic	primary treatment is surgery; stereotactic radiosurgery considered adjunctively when complete resection is not possible; adjuvant radiotherapy considered for atypical & anaplastic tumors
>65 (or poor surgical candidate)	asymptomatic	observation: serial imaging & clinical FU; stereotactic radiosurgery considered for growing lesions; surgery considered for further progression & neurological deterioration
	symptomatic (tumor <3 cm)	stereotactic radiosurgery is considered; surgery considered for further progression & neurological deterioration
	symptomatic (tumor ≥3 cm)	close monitoring if minimally symptomatic; surgery considered for further progression &/or significant impact on quality of life

* From Couldwell 2011.[5]

the lowest possible Simpson grade. Stereotactic radiosurgery is usually considered for lesions showing documented growth on serial imaging in older patients, those with comorbidities, and for lesions in locations associated with a high surgical morbidity. Table 3 illustrates the general criteria that we use when deciding which treatment option is best for the individual patient.[5]

Case Illustrations

Case 1

This patient was a 79-year-old woman who complained of swelling of the throat. On physical examination, she was found to have bruit over the left internal carotid artery. As part of her evaluation, she underwent MR angiography of the neck that showed the presence of asymptomatic stenosis of the internal carotid artery. Magnetic resonance imaging of the brain showed the presence of an incidental tuberculum sella meningioma (Fig. 3). The patient did not have visual symptoms and was neurologically intact on examination. Her endocrinological workup was normal as well. In view of her age and the size of the lesion, the decision was made to proceed with serial imaging for follow-up. She has since been followed-up for more than 5 years without tumor growth or visual symptoms.

Case 2

This patient was a 27-year-old woman with longstanding nonspecific headaches and a normal neurological examination. Magnetic resonance imaging of the brain showed the presence of a large lateral sphenoid wing meningioma (Fig. 4). The mass had a maximum diameter of 4.5 cm and was associated with significant brain edema and mass effect. The decision to operate was made because of the large size of the tumor, the peritumoral edema, and the young age of the patient.

Conclusions

In recent years, physicians have increasingly been faced with an aging population in a technologically advanced world of preventative medicine that affords more screening modalities performed over a longer time period. This ultimately results in the identification of a number of patients with asymptomatic meningiomas. While these lesions can be the source of anxiety for the patient, a thorough discussion with the physician and an education on the nature of incidental meningioma can help the patient to better understand the condition and participate in the decision-making. The available data on the natural history of incidental meningioma suggest that most of these lesions either remain stable in size or grow very slowly over time. In light of this, physicians should try to be conservative in their approach for treating incidentally found meningiomas, keeping in mind, however, that some of these lesions can grow significantly and become symptomatic. The possibility of a malignant meningioma or other kinds of malignancies mimicking meningiomas should also be kept in mind. A prudent approach would be a close initial radiographic and clinical follow-up to detect unexpected tumor behavior. The follow-up period

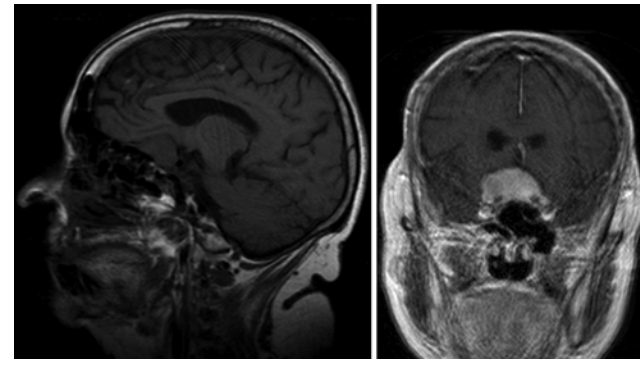

Fig. 3. Case 1. Sagittal T1-weighted MR imaging without contrast enhancement **(left)** and coronal T1-weighted MR imaging with contrast enhancement **(right)** showing a tuberculum sella extraaxial lesion consistent with meningioma. The lesion measured 2.5 × 1.7 cm. No treatment was offered, and the tumor has been monitored for more than 5 years with no changes in size or symptoms.

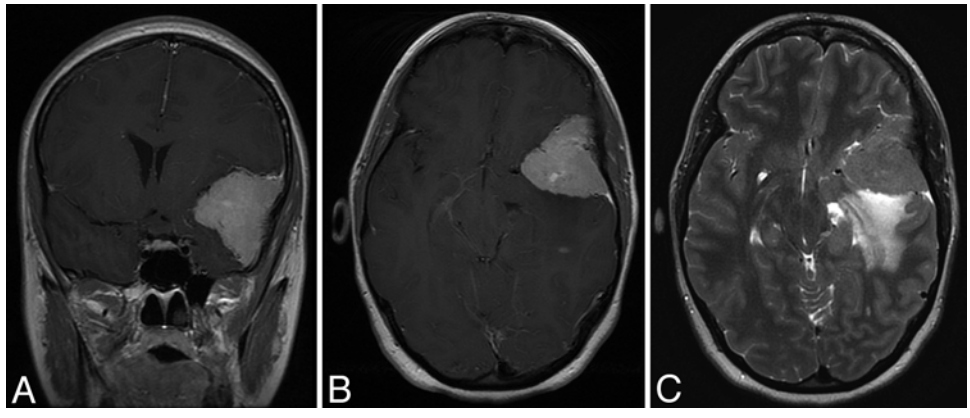

Fig. 4. Case 2. Coronal **(A)** and axial **(B)** T1-weighted MR imaging with contrast enhancement and axial T2-weighted MR imaging **(C)** showing the presence of a large, left, lateral sphenoid wing meningioma. The lesion was 4.5 × 3.0 cm. The T2-weighted image demonstrates significant peritumoral edema. The large lesion (WHO Grade I meningioma) was surgically resected; 2 smaller contralateral lesions are being monitored with serial imaging.

can then be increased gradually once the tumor is found to be stable. In addition, the possibility of complications in a population of older patients who may harbor comorbidities that puts them at higher risk for serious complications from surgery argues for a conservative management approach. We prefer to reserve surgical interventions for large symptomatic lesions and those with a documented potential for growth. A high index of suspicion for malignancy based on imaging characteristics and/or patient's medical history would also favor resection.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Couldwell. Acquisition of data: Chamoun, Krisht. Analysis and interpretation of data: Chamoun. Drafting the article: Chamoun, Krisht. Critically revising the article: Couldwell, Chamoun. Reviewed submitted version of manuscript: Couldwell, Chamoun. Approved the final version of the manuscript on behalf of all authors: Couldwell. Study supervision: Couldwell.

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References

1. Bailey P, Cushing H, Eisenhardt L: Angioblastic meningiomas. **Arch Path 6:**953–990, 1928
2. Bassiouni H, Hunold A, Asgari S, Stolke D: Tentorial meningiomas: clinical results in 81 patients treated microsurgically. **Neurosurgery 55:**108–118, 2004
3. Cho WH, Choi YJ, Choi BK, Cha SH: Isolated recurrence of intracranial granulocytic sarcoma mimicking a falx meningioma in acute myeloblastic leukemia. **J Korean Neurosurg Soc 47:**385–388, 2010
4. Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, Black PM: Epidemiology of intracranial meningioma. **Neurosurgery 57:**1088–1095, 2005
5. Couldwell WT: Meningiomas. **Epocrates Online** (https://online.epocrates.com/noFrame/showPage.do?method=diseases&MonographId=730&ActiveSectionId=11) [Accessed September 27, 2011]
6. Couldwell WT, Fukushima T, Giannotta SL, Weiss MH: Petroclival meningiomas: surgical experience in 109 cases. **J Neurosurg 84:**20–28, 1996
7. Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T: Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. **Neuro Oncol 3:**152–158, 2001
8. Firsching RP, Fischer A, Peters R, Thun F, Klug N: Growth rate of incidental meningiomas. **J Neurosurg 73:**545–547, 1990
9. Grau S, Schueller U, Weiss C, Tonn JC: Primary meningeal T-cell lymphoma at the clivus mimicking a meningioma. **World Neurosurg 74:**513–516, 2010
10. Gupta K, Bagdi N, Sunitha P, Ghosal N: Isolated intracranial Rosai-Dorfman disease mimicking meningioma in a child: a case report and review of the literature. **Br J Radiol 84:**e138–e141, 2011
11. Hashiba T, Hashimoto N, Izumoto S, Suzuki T, Kagawa N, Maruno M, et al: Serial volumetric assessment of the natural history and growth pattern of incidentally discovered meningiomas. Clinical article. **J Neurosurg 110:**675–684, 2009
12. Herscovici Z, Rappaport Z, Sulkes J, Danaila L, Rubin G: Natural history of conservatively treated meningiomas. **Neurology 63:**1133–1134, 2004
13. Illes J, Kirschen MP, Edwards E, Stanford LR, Bandettini P, Cho MK, et al: Ethics. Incidental findings in brain imaging research. **Science 311:**783–784, 2006
14. Kasliwal MK, Suri A, Gupta DK, Suri V, Rishi A, Sharma BS: Sphenoid wing inflammatory pseudotumor mimicking a clinoidal meningioma: case report and review of the literature. **Surg Neurol 70:**509–513, 2008
15. Katzman GL, Dagher AP, Patronas NJ: Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. **JAMA 282:**36–39, 1999
16. Kheradmand A, Smith T: Dural metastatic adenocarcinoma mimicking meningioma. **Neurology 74:**1396, 2010
17. Kuratsu J, Kochi M, Ushio Y: Incidence and clinical features of asymptomatic meningiomas. **J Neurosurg 92:**766–770, 2000
18. Laigle-Donadey F, Taillibert S, Mokhtari K, Hildebrand J, Delattre JY: Dural metastases. **J Neurooncol 75:**57–61, 2005
19. Nakamura M, Roser F, Michel J, Jacobs C, Samii M: The natural history of incidental meningiomas. **Neurosurgery 53:** 62–71, 2003
20. Nakasu S, Fukami T, Nakajima M, Watanabe K, Ichikawa M,

Matsuda M: Growth pattern changes of meningiomas: long-term analysis. **Neurosurgery 56:**946–955, 2005
21. Niiro M, Yatsushiro K, Nakamura K, Kawahara Y, Kuratsu J: Natural history of elderly patients with asymptomatic meningiomas. **J Neurol Neurosurg Psychiatry 68:**25–28, 2000
22. Oya S, Kim SH, Sade B, Lee JH: The natural history of intracranial meningiomas. Clinical article. **J Neurosurg 114:**1250–1256, 2011
23. Paiva J, King J, Chandra R: Extra-axial Hodgkin's lymphoma with bony hyperostosis mimicking meningioma. **J Clin Neurosci 18:**725–727, 2011
24. Rutkowski MJ, Sughrue ME, Kane AJ, Aranda D, Mills SA, Barani IJ, et al: Predictors of mortality following treatment of intracranial hemangiopericytoma. Clinical article. **J Neurosurg 113:**333–339, 2010
25. Salunke P, Kovai P, Sura S, Gupta K: Extra-axial ependymoma mimicking a parasagittal meningioma. **J Clin Neurosci 18:**418–420, 2011
26. Sanai N, Sughrue ME, Shangari G, Chung K, Berger MS, McDermott MW: Risk profile associated with convexity meningioma resection in the modern neurosurgical era. Clinical article. **J Neurosurg 112:**913–919, 2010
27. Spatola C, Privitera G: Recurrent intracranial hemangiopericytoma with extracranial and unusual multiple metastases: case report and review of the literature. **Tumori 90:**265–268, 2004
28. Staneczek W, Jänisch W: Epidemiologic data on meningiomas in East Germany 1961–1986: incidence, localization, age and sex distribution. **Clin Neuropathol 11:**135–141, 1992
29. Sughrue ME, Rutkowski MJ, Shangari G, Chang HQ, Parsa AT, Berger MS, et al: Risk factors for the development of serious medical complications after resection of meningiomas. Clinical article. **J Neurosurg 114:**697–704, 2011
30. Tawil A, Comair Y, Nasser H, Hourani R, Rebeiz J, Chamoun R: Periosteal osteoblastoma of the calvaria mimicking a meningioma. **Pathol Res Pract 204:**413–422, 2008
31. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al: Incidental findings on brain MRI in the general population. **N Engl J Med 357:**1821–1828, 2007
32. Wiemels J, Wrensch M, Claus EB: Epidemiology and etiology of meningioma. **J Neurooncol 99:**307–314, 2010
33. Yano S, Kuratsu J: Indications for surgery in patients with asymptomatic meningiomas based on an extensive experience. **J Neurosurg 105:**538–543, 2006
34. Yoneoka Y, Fujii Y, Tanaka R: Growth of incidental meningiomas. **Acta Neurochir (Wien) 142:**507–511, 2000
35. Yue NC, Longstreth WT Jr, Elster AD, Jungreis CA, O'Leary DH, Poirier VC: Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. **Radiology 202:**41–46, 1997

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Address correspondence to: William T. Couldwell, M.D., Ph.D., Department of Neurosurgery, University of Utah, 175 North Medical Drive East, Salt Lake City, Utah 84132. email: neuropub@hsc.utah.edu.

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Incidental findings of mass lesions on neuroimages in children

Corinne Perret,[1] Eugen Boltshauser, M.D.,[2] Ianina Scheer, M.D.,[3] Christian J. Kellenberger, M.D.,[3] and Michael A. Grotzer, M.D.[1]

Departments of [1]Oncology, [2]Neurology, and [3]Diagnostic Imaging, University Children's Hospital of Zurich, Switzerland

Increasing use of neuroimaging in children has led to more incidental findings of CNS mass lesions, the management of which is uncertain. The authors' aims in this study are to describe these mass lesions and their evolution, as well as to discuss the management options and determine the prevalence of incidental CNS mass lesions at their pediatric clinic. A retrospective study was undertaken in children with primary CNS tumors who were younger than 18 years old and were admitted to the University Children's Hospital of Zurich, Switzerland, between January 1995 and December 2010. In 19 (5.7%) of 335 patients with newly diagnosed CNS tumors, the diagnosis of a CNS mass lesion was an incidental finding. Reasons for obtaining neuroimages in these 19 patients were head trauma (in 6 patients); research protocols (in 3); nasal/orbital malformations (in 2); endocrinological and psychiatric evaluations (in 2); and vertebral bone anomaly without neurological signs, absence seizures, congenital ataxia, recurrent vomiting, developmental delay, and "check-up" at the explicit request of the parents (in 1 patient each). Seven patients underwent immediate surgery for low-grade glioma (4 patients) and craniopharyngioma, ependymoma, and choroid plexus papilloma (1 patient each); and 12 were treated conservatively or were observed. Ten of 12 conservatively treated patients remained stable (median follow-up time 1.8 years) and the other 2 underwent delayed surgery because of tumor progression (medulloblastoma in one patient and fibrillary astrocytoma in the other).

Clinicians are increasingly challenged by the discovery of incidental CNS mass lesions. A subgroup of such lesions (with typical imaging patterns such as tectal glioma and dysembryoplastic neuroepithelial tumor) can be monitored conservatively, clinically, and radiographically. Future prospective studies are needed to define optimal management strategies based on larger collections of natural histories, as well as to assess the true prevalence of incidental CNS mass lesions. *(DOI: 10.3171/2011.9.FOCUS11121)*

Key Words • **incidental finding** • **magnetic resonance imaging** • **brain imaging** • **children** • **brain tumor**

In recent decades, the increasing use of CT and MR imaging of the CNS has led to the more frequent discovery of unexpected results. Incidental findings (also called "incidentalomas") are defined as previously undetected abnormalities that are unrelated to the purpose of the examination. This phenomenon, as well as the prevalence and the nature of the lesions, have been reported in several publications, mainly those involving adults.[1,4,9,12,20,21] In their meta-analysis, Morris et al.[15] found an overall prevalence of 2.0% (range 1.1%–3.1%) of nonneoplastic incidental brain findings and an overall prevalence of 0.7% (95% CI 0.47%–0.98%) of neoplastic incidental brain findings.

Only recently, studies have been published on CNS incidentalomas in children. These studies have reported variable rates of incidental findings, which are most often benign and do not need referral. Most lesions described are extracerebral lesions (for example, fluid-filled paranasal sinuses), cerebral malformations (for example, Chiari I malformation), or cysts (for example, a pineal or arachnoid cyst). A minority consist of vascular malformations (for example, cavernoma or developmental venous anomaly), tissue changes, or tumoral lesions, accounting for less than 1% of all the incidental brain findings.[6,8,11,14,18] The nature and the spontaneous evolution of these neoplastic lesions, as well as their appropriate management, remain under debate in view of limited literature reports and personal experience.

The aims of this study are to describe incidental CNS mass lesions and their evolution, to discuss management options, and to determine the prevalence of incidental CNS mass lesions in our pediatric clinic.

Abbreviations used in this paper: DNT = dysembryoplastic neuroepithelial tumor; LGG = low-grade glioma; NF1 = neurofibromatosis Type 1.

Methods

A retrospective study was undertaken in children 18 years old and younger with primary CNS tumors, who were admitted consecutively to the University Children's Hospital of Zurich, Switzerland, between January 1995 and December 2010. Medical case notes, referral letters, neurosurgical records, histopathology reports, follow-up data, and survival outcomes were reviewed. An incidental finding is generally defined as being unexpected and without any correlation with the patient's history and clinical examination. In this specific context, we use the following inclusion criteria for an "incidental mass lesion:" 1) imaging evidence of a clearly space-occupying lesion, without or with a characteristic neuroimaging pattern in favor of a specific tumor type (that is, craniopharyngioma, dysembryoplastic neuroepithelial tumor, or tectal glioma); or 2) imaging evidence of a permanent lesion that does not correspond to the usual appearance of an inflammatory (as seen in multiple sclerosis or acute disseminated encephalomyelitis), residual (such as postischemic or posttraumatic), hamartomatous, or migrational (as heterotopia) lesion. Excluded from this study were children with neurocutaneous disorders (NF1, NF Type 2, or tuberous sclerosis).

Results

Patient and Tumor Characteristics

Between January 1995 and December 2010, a total of 24,047 neuroimaging studies (12,725 brain MR images, 9161 brain CT scans, and 2161 spinal MR images) were obtained at the University Children's Hospital of Zurich, Switzerland. Since some children underwent more than 1 neuroimaging examination (for example, postoperative and/or oncological follow-up investigations), the number of patients is smaller (estimated to be approximately 15,000).

In the same period, 335 patients with a primary CNS tumor were admitted. The tumor characteristics of these patients are summarized in Table 1. The median age at diagnosis for all patients was 7.6 years (range 0.0–18.4 years). Two hundred three patients (61%) were boys and 132 (39%) were girls. Diagnoses were established by histological assessment of a tumor specimen obtained at surgery in 297 patients (89%) and by typical imaging findings in 20 patients (6%) (for example, diffuse intrinsic pontine glioma). In 4 patients (1%) with large tumors and poor general condition, no biopsy was undertaken and the histology remains unknown. In 16 patients (5%) in good general condition, no biopsy was undertaken, and the patients were monitored using a wait-and-see policy.

In 19 (5.7%) of 335 patients with newly diagnosed CNS tumors, the diagnosis of a CNS mass lesion was an incidental finding (Table 2). The median age at diagnosis for patients with incidentalomas was 7.5 years (range 1.0–14.9 years). Reasons for obtaining neuroimages in these 19 patients were head trauma (in 6 patients); research protocols (in 3); nasal/orbital malformations (in 2); endocrinological and psychiatric evaluations (in 2); and vertebral bone anomaly without neurological signs, absence seizures, congenital ataxia, recurrent vomiting, developmental delay, and "check-up" at the explicit request of the parents (in 1 patient each). Therefore, no patient had an imaging finding related to and/or explaining an underlying neurological disorder. In retrospect, the indication for neuroimaging in the patients in Cases 2 (anxiety disorder), 3 ("check-up" at the request of the parents), and 4 (absence seizures) is debatable.

Seven patients underwent immediate surgery for LGG (4 patients) and craniopharyngioma, ependymoma, and choroid plexus papilloma (1 patient each); and 12 were treated conservatively or with observation. Ten of these 12 conservatively treated patients remained stable (median follow-up time 1.8 years, range 0.3–16.3 years) and the remaining 2 patients underwent delayed surgery because of tumor progression (medulloblastoma in one patient and fibrillary astrocytoma in the other).

The following comments are intended to illustrate the rationale behind the treatment decisions.

TABLE 1: Location und histology of 335 consecutively diagnosed CNS tumors*

Location & Tumor Histology	No. of Tumors (%)
infratentorial	145 (43)
medulloblastoma	50 (15)
cerebellar LGG	29 (9)
brainstem glioma	36 (10)
ependymoma	12 (3)
other	11 (3)
tumors of unknown histology	7 (2)
supratentorial hemispheric	121 (36)
LGG	35 (10)
HGG	19 (5)
choroid plexus tumor	2 (0.6)
ependymoma	8 (2)
PNET	7 (2)
neuronal/mixed neuronal-glial tumor	19 (5)
meningioma	11 (3)
other	15 (4)
tumors of unknown histology	5 (1)
supratentorial midline	56 (17)
craniopharyngioma	16 (5)
germ cell tumor	8 (2)
LGG	16 (5)
PNET	3 (0.9)
other	13 (4)
tumors of unknown histology	0 (0)
spinal cord	13 (4)
LGG	6 (2)
ganglioglioma	2 (1)
other	4 (1)
tumors of unknown histology	1 (0.3)

* HGG = high-grade glioma; PNET = primitive neuroectodermal tumor.

TABLE 2: Incidental findings of CNS mass lesions and patient characteristics*

Case No.	Age at Diagnosis (yrs), Sex	Reason for Neuroimaging	Location	Size (mm)	Histology	Initial Management	Clinical Course	FU Time Since Diagnosis (yrs)
1	7.5, M	head trauma	cerebellum/brainstem	ax 20 × 20	medulloblastoma	observation (1.5 yrs)	delayed subtotal resection, radio-chemotherapy; SD	3.8
2	14.9, M	anxiety disorder	cerebellum	cor 23 × 18	LGG	observation	SD	1.7
3	5.2, M	"check-up" due to parental request	cerebellum	ax 11 × 10	LGG†	observation	SD	1.3
4	8.1, F	absence seizures	cerebellum	ax 29 × 22	pilocytic astrocytoma	primary subtotal resection	SD	2.1
5	1.0, M	developmental delay	4th ventricle/cerebellum	cor 35 × 60	choroid plexus papilloma	primary total resection	CR	5.4
6	2.1, M	head trauma	4th ventricle	ax 25 × 25	anaplastic ependymoma	primary total resection, radio-chemotherapy	CR	9.3
7	14.6, F	research protocol: cardiac malformations	tectum mesencephali	ax 11 × 10	LGG†	observation	SD	1.5
8	14.3, M	orbital trauma	tectum mesencephali	cor 32 × 30	pilocytic astrocytoma	primary subtotal resection	SD	5.2
9	5.4, F	evaluation for tall stature	pons	ax 26 × 15	LGG†	observation	spontaneous regression	4.1
10	1.0, M	research protocol: HIE	occipital	ax 24 × 21	fibrillary astrocytoma	biopsy	delayed total resection due to tumor progression; CR	11.7
11	10.8, M	head trauma	occipital	cor 30 × 21	DNT†	observation	SD	9.7
12	1.5, M	head trauma	temporoparietooccipital	ax 90 × 70	desmoplastic ganglioglioma	primary total resection	CR	9.6
13	13.1, M	research protocol: cardiac malformations	lat ventricle	cor 15 × 12	neurocytoma†	observation	SD	1.6
14	2.1, M	nasal fistula	thalamus	cor 7 × 5	LGG†	observation	SD	1.8
15	11.8, M	recurrent vomiting	thalamus	ax 4 × 3	LGG†	observation	SD	0.3
16	9.1, F	congenital cerebellar ataxia	thalamus	ax 6 × 3	LGG†	observation	slow progression, 2nd lesion subthalamic	5.8
17	1.2, M	orbital lymphangioma	sellar/suprasellar	ax 37 × 23	mature teratoma	observation (3.8 yrs)	delayed subtotal resection; SD	5.6
18	10.8, M	orbital trauma	suprasellar	sag 20 × 20	craniopharyngioma	primary total resection	CR	8.1
19	12, M	vertebral malformation	intramedullar	sag 25 × 10	LGG†	observation	slow progression	16.3

* ax = axial; cor = coronal; CR = complete remission; FU = follow=up; HIE = hypoxic/ischemic encephalopathy; sag = sagittal; SD = stable disease.

† Assumed diagnosis based on neuroimaging findings.

Incidental Lesions With Subsequent (Immediate) Surgical Intervention (7 patients)

Case 4. This patient underwent examination elsewhere for absence seizures. The cerebellar hemispheric tumor found on MR imaging was not considered responsible for the seizures. Although there was no CSF obstruction and the neurological examination findings were normal, the parents opted for surgical exploration. As expected, the histological examination confirmed pilocytic astrocytoma.

Case 5. The MR imaging findings in this patient, who underwent investigation for general developmental delay, were suggestive of a choroid plexus tumor, which was surgically treated in view of its considerable size. As expected, the developmental delay did not improve.

Case 6. This patient underwent MR imaging after a fall from a considerable height. The fourth ventricle was occluded and, thus, in our view, surgical removal was indicated.

Case 8. This patient was hit by a snowball in the orbital region. Papilledema was confirmed by an ophthalmologist. A large tectal tumor and early signs of supratentorial ventricular dilation prompted surgery before clinical signs of increased intracranial pressure were evident.

Case 10. This patient underwent follow-up in the context of a research protocol for perinatal hypoxic/ischemic encephalopathy. A subcortical lesion was first detected at 1 year of age and was assumed to be an LGG. The lesion increased in size over the next few months. The parents finally agreed to biopsy and surgical removal.

Case 12. This patient was seen after a fall in a play group. Neurological examination findings were normal, but the patient was markedly macrocephalic. Magnetic resonance imaging revealed a large space-occupying lesion with midline shift. An operative procedure was performed with excellent results.

Case 18. This patient was found to have a craniopharyngioma on MR images obtained for orbital trauma. Findings on neurological, ophthalmological, and endocrine evaluations were normal. An interdisciplinary discussion concluded that surgical intervention was indicated.

Incidental Lesions Managed Conservatively (10 patients)

Cases 2 and 3. In these patients, a cerebellar tumor was found incidentally on neuroimages obtained for anxiety (Case 2) and for a "check-up" at the explicit wish of the parents in view of an "extreme sport" adventure (Case 3). Given that the MR imaging patterns in both patients were typical of LGGs with no evidence of CSF obstruction (Fig. 1) and that the neurological examination findings were normal, we observed these patients by conducting regular clinical and neuroimaging investigations.

Cases 7 and 13. These patients underwent neuroimaging in the context of a comprehensive outcome study of congenital cardiac malformations. The lesion in the patient in Case 7 was compatible with a tectal LGG not leading to aqueductal obstruction; therefore, we only ob-

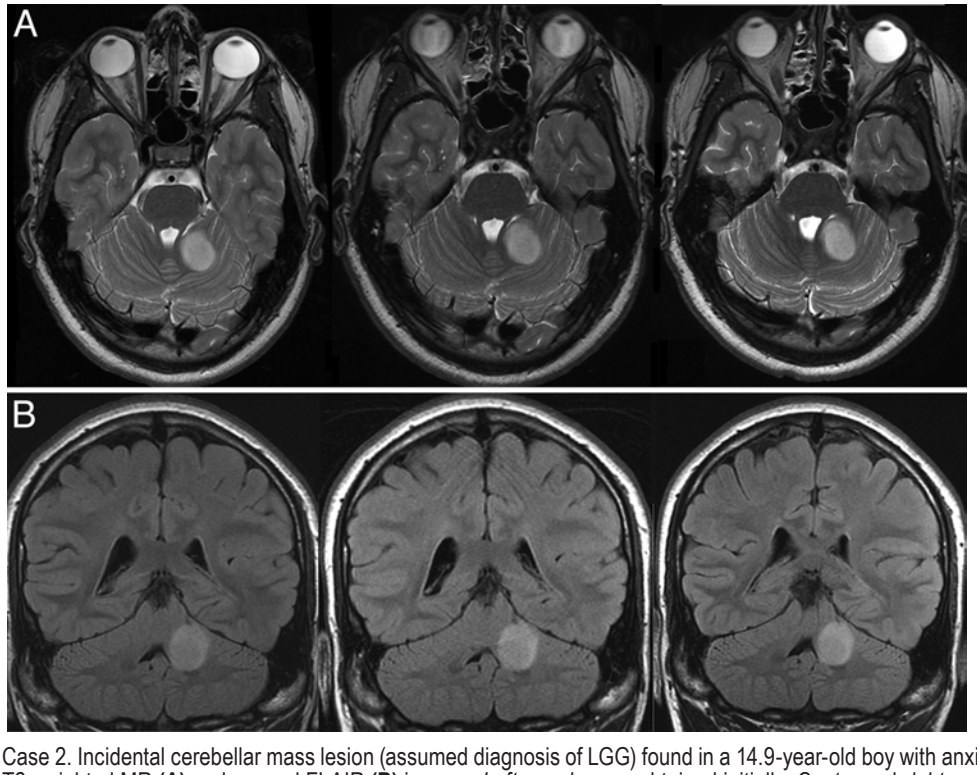

Fig. 1. Case 2. Incidental cerebellar mass lesion (assumed diagnosis of LGG) found in a 14.9-year-old boy with anxiety disorder. Axial T2-weighted MR **(A)** and coronal FLAIR **(B)** images. *Left panels* were obtained initially. *Center* and *right panels* show the lesion after a period of 5 and 13 months, respectively, of wait-and-see.

served this patient. The lesion in the patient in Case 13 (Fig. 2) was suggestive of a neurocytoma. A diagnostic (stereotactic or open) biopsy was considered to carry a substantial risk of surgical morbidity. Observation with repeat (every 6 months) clinical and MR imaging investigations proved justified.

Case 9. In this patient, neuroimaging was requested by an endocrinologist in view of the patient's tall stature. The brainstem appeared mildly enlarged with ill-defined, rather diffuse T2-weighted signal abnormalities reminiscent of "unidentified bright objects" as often seen in cases of NF1. However, there were no clinical signs of NF1, and findings from the neurological examination were normal. Two years later, MR imaging findings were unchanged, and on a third MR imaging study obtained 2 years later, the lesion was no longer evident. We have no explanation for this observation.

Case 11. The lesion found in this patient, who was evaluated after he fell off his bicycle, had the characteristic imaging pattern of a DNT (Fig. 3). As this was an incidental finding, conservative management was suggested. In the subsequent 9.7 years, the patient has remained well and never experienced a seizure.

Cases 14–16. These patients were found incidentally to harbor small thalamic lesions (Fig. 4), not explaining the clinical picture or corresponding to findings seen as residual findings (that is, postischemic), such as heterotopia or gliosis, but being compatible with an LGG. A diagnostic biopsy was not considered justified, balancing the diagnostic benefit against the potential morbidity of the diagnostic procedure. These children will continue to be managed conservatively.

Case 19. This patient had vertebral anomalies at the cervicothoracic junction. He underwent initial examination elsewhere for a vague suspicion of closed spinal dysraphism. Spinal MR imaging was suggestive of a cystic neoplastic lesion. Findings on neurological examination were normal. The patient was lost to follow-up but was again seen 16.3 years later. He was a healthy, active student. Additional MR imaging revealed an increase in the size of the lesion, which was considered to be an LGG (Fig. 5). In view of normal findings on the neurological examination, the patient opted for further observation.

Incidental Findings Initially Observed, With Delayed Intervention (2 patients)

Case 1. This patient underwent cranial CT scanning at 7.5 years of age after mild head trauma. The images revealed an ill-demarcated vermian lesion with small focal calcifications. Magnetic resonance imaging confirmed a lesion with extension in the brainstem; there was no CSF obstruction and no contrast enhancement. Computed tomography scanning had already been performed 1 year previously, after a fall on the playground. Findings on this CT scan, which were considered normal at that time, were in retrospect identical to the findings on the recent CT scan. In view of this apparently prolonged stable situation in a boy with normal findings on neurological examinations, a conservative attitude was adopted, with imaging follow-up investigations performed every 6 months. A year and a half later, slow motor deterioration was noted, accompanied by tumor progression. Surgical exploration revealed a medulloblastoma. In view of extension into the brainstem, only partial removal was achievable.[22]

Case 17. This patient was initially investigated at the age of 1.2 years for an orbital process with fluctuating

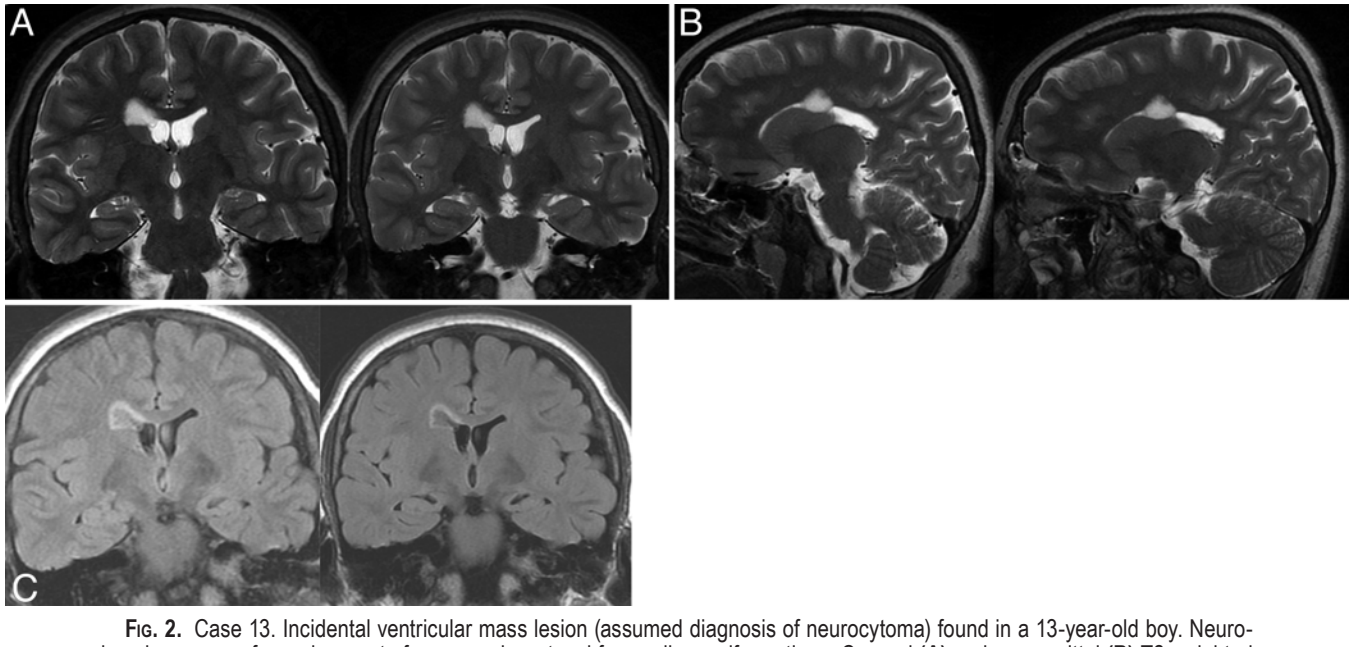

Fig. 2. Case 13. Incidental ventricular mass lesion (assumed diagnosis of neurocytoma) found in a 13-year-old boy. Neuroimaging was performed as part of a research protocol for cardiac malformations. Coronal **(A)** and parasagittal **(B)** T2-weighted MR and coronal FLAIR **(C)** images. *Left panels* were obtained initially. *Right panels* show the lesion after a period of 6 months of wait-and-see.

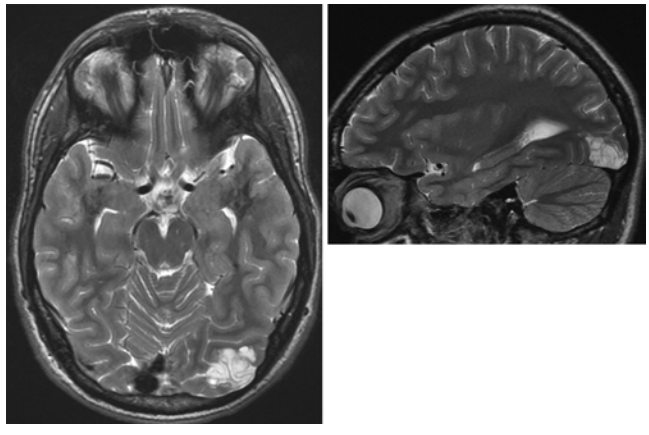

Fig. 3. Case 11. Axial **(left)** and sagittal **(right)** T2-weighted MR images showing an incidental occipital mass lesion (assumed diagnosis of DNT) that was found in a 10.8-year-old boy after a traffic accident.

proptosis. Magnetic resonance imaging revealed a cystic orbital lesion that was later confirmed as lymphangioma, and a partially calcified multicystic sellar/parasellar lesion most likely corresponding to a mature teratoma. In view of normal neurological, ophthalmological, and endocrine assessments, the patient underwent regular clinical and neuroimaging investigations. The lesion remained unchanged on imaging. At the age of 5 years, the lesion was subtotally removed, at the explicit request of the parents, by a transsphenoidal approach. Histology confirmed a mature teratoma.

Discussion

Advancements in diagnostic imaging have revolutionized the practice of modern medicine.[6] Neuroimaging, in particular, facilitates more accurate diagnosis of CNS disorders and neuroanatomical variants. Recommendations for the use of neuroimaging are based on the principles of evidence-based medicine. Observation of current practice patterns, however, indicate that neuroimaging overuse is common in the clinical evaluation of certain symptoms such as headache in children.[5]

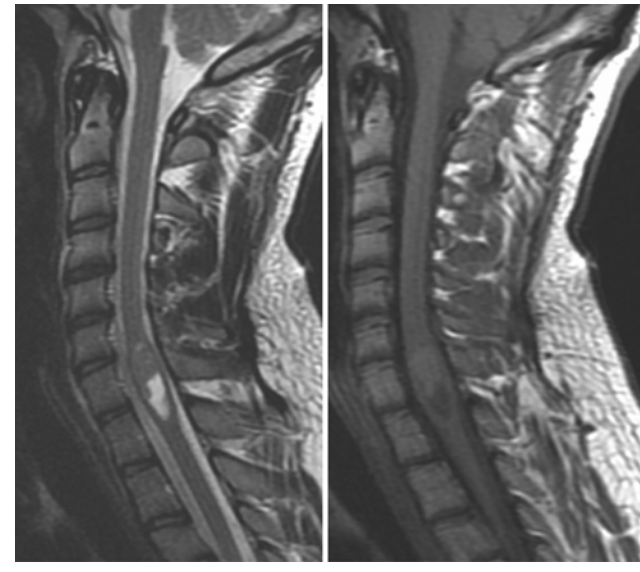

Fig. 5. Case 19. Sagittal T2-weighted **(left)** and T1-weighted **(right)** MR images showing an incidental intramedullar mass lesion (assumed diagnosis of LGG) in a 12-year-old boy who was found to have a vertebral fusion anomaly.

There is a current lack of neuroimaging data that can provide baseline images of "normal" brains at various ages and upon which the possible clinical significance of incidental findings can be evaluated.[10] Projects are under way to address this need.[4]

There is only sparse literature on incidental CNS mass lesions in children (Table 3). Analyzing the brain

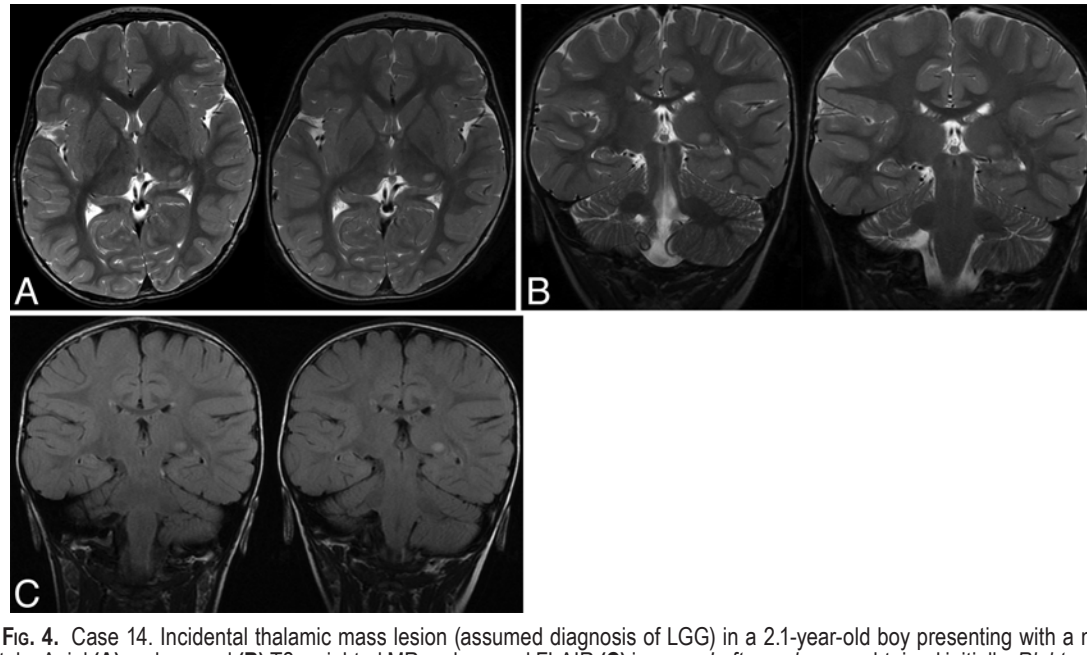

Fig. 4. Case 14. Incidental thalamic mass lesion (assumed diagnosis of LGG) in a 2.1-year-old boy presenting with a nasal fistula. Axial **(A)** and coronal **(B)** T2-weighted MR and coronal FLAIR **(C)** images. *Left panels* were obtained initially. *Right panels* show the lesion after a period of 16 months of wait-and-see.

TABLE 3: Pediatric incidental CNS mass lesions reported in the literature*

Authors & Year	Population	Study Period	Indications for Imaging	No. of Incidental CNS Mass Lesions
De Braganca et al., 2010	312 children w/ posterior fossa masses reviewed by the pediatric neuro-oncology team at Memorial Sloan-Kettering Cancer Center	1993–2010	head trauma (2), seizures (2), headache (1), NF-1 surveillance (1), endocrinopathy (1),	7
Keating et al., 2010	unspecified no. of brain tumor patients (0.3–21 yrs old) treated at Children's National Medical Center (Washington, DC) & Dana Children's Hospital (Tel Aviv)	2005–2010	head trauma (9), seizures (2), headache (2), genetic workup (1), developmental disorder (1), endocrinological evaluation (1), Lyme disease (1), unknown (7)	24
Seki et al., 2010	110 neurologically healthy children, 5–8 yrs old, seen at the Research Institute of Science & Technology for Society, Tokyo	2006–2008		0
Jordan et al., 2010	953 patients, 5–14 yrs old, w/ sickle cell anemia or sickle β-null thalassemia, screened with MRI of the brain for the Silent Infarct Transfusional Trial at the School of Medicine of The Johns Hopkins University, Baltimore	2005–2008	research protocol	4
Gupta et al., 2010	771 patients, aged 0–18 yrs old, w/ developmental delay (363), autistic spectrum disorder (55), & healthy controls (353) seen at Temple University Children's Medical Center, Philadelphia	2003–2007		0
Pirotte et al., 2010	442 patients, 4–15 yrs, w/ newly diagnosed brain lesions reviewed at Erasme Hospital, Brussels	1995–2007	seizures (21), headache (13), sinusitis (8), head trauma (7), viral meningitis (4), suspicion of Chiari malformation (2)	55*
Gupta & Belay, 2008	666 patients, 0–21 yrs old, seen by neurology & general pediatrics teams at the Temple University Children's Medical Center, Philadelphia	2003–2005		0
Graf et al., 2008	185 otherwise healthy children w/ headache, seen by the neurology & radiology teams at the Children's Mercy Hospitals & Clinics, Kansas City	2000–2004		0
Kim et al., 2002	225 healthy children, 0.1–18 yrs old, reviewed at Stanford, CA	1997–2000		0

* This total includes 20 nontumoral lesions (dysplasia, vasculitis, gliosis, cavernoma, and sarcoidosis).

MR imaging of school-aged children with sickle cell disease, Jordan et al.[11] found a total prevalence of incidental findings of 6.6%. The majority of these incidental findings are without clinical impact (for example, cavum septum pellucidum, pineal cyst, arachnoid cyst, and other variants). Potentially urgent or serious abnormalities were present in 0.6%. In children with posterior fossa brain tumors, 7 (2.2%) of 312 were found to be incidentalomas.[3]

In the present study, analyzing 335 tumors of the CNS, we found 19 (5.7%) incidental mass lesions. In the entire cohort of children undergoing neuroimaging at our institution, the prevalence of incidental CNS mass lesions is estimated to be approximately 0.1%.

Clearly, the incidental finding of a mass lesion requires further evaluation. However, the optimal management strategies are largely unknown and are certainly debatable in view of limited published and personal experience. When the diagnostic benefit is balanced against the potential morbidity of the diagnostic procedure in an asymptomatic child, neurosurgery is not necessarily justified for all incidental CNS mass lesions. We favor an individual management strategy following an interdisciplinary discussion, with full comprehension by the parents being essential. It must be acknowledged that a wait-and-see approach may be accompanied by uncertainties that may have significant psychological repercussions on the parents and child.

We have opted for surgical intervention for large space-occupying lesions, impending CSF obstruction, documented tumor growth, and at the request of the parents. However, we have found conservative management (including regular clinical and neuroimaging follow-up, usually every 6 months) justified in children with either a typical neuroimaging pattern of the incidentaloma (for example, DNT, cerebellar LGG, or teratoma) or with small thalamic or periventricular lesions. This management algorithm is summarized in Fig. 6. Clearly, this is work in progress and needs revisions/emendations based on further experience. So far, we have not encountered any psychological or compliance problems with this approach.

This management option has also been chosen by other authors in individual patients; when a DNT was an incidental imaging diagnosis in the absence of epilepsy, surveillance with serial imaging was used.[16] Similar management was adopted for a tectal glioma that was diagnosed incidentally on imaging. This tumor was smaller than 2 cm in diameter and did not exhibit tumor extension or contrast enhancement.[2] Meanwhile, conservative management of tectal gliomas is a well-accepted treatment strategy by many neurosurgeons.[19]

In patients with medulloblastoma the median interval from onset of symptoms to histologically confirmed diagnosis ranges from several days to months. As most posterior fossa tumors are removed upon detection, very little is known about their natural growth rate. To our knowledge, such a long observation period of the growth of a primary medulloblastoma as described in the patient in Case 1 has not been described before.

Limitations of the Study

Limitations of this study include the fact that not all neuroimaging studies were performed after contrast injection and that many neuroimaging studies were performed using CT scanning only. Further limitations are the retrospective nature of the study, the relatively long study period, possible selection and referral bias, and a relatively short follow-up for some of the patients.

Conclusions

Incidental CNS mass lesions should be anticipated in the use of neuroimaging in clinical practice and in the design of research protocols. Information on the natural course and prognosis of these lesions is needed to define

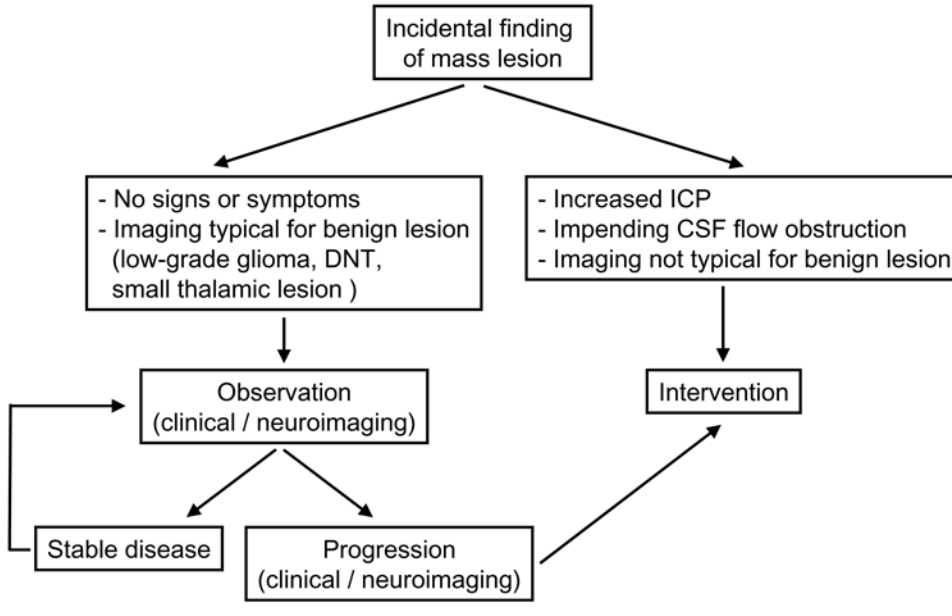

Fig. 6. Flow chart showing the suggested preliminary management algorithm for incidental findings of mass lesions. ICP = intracranial pressure.

clinical management. Future prospective studies are required to determine the true prevalence of this problem and to develop optimal management strategies based on larger collections of natural histories of incidental CNS mass lesions.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Grotzer, Boltshauser. Acquisition of data: all authors. Analysis and interpretation of data: Grotzer, Perret, Boltshauser, Scheer. Drafting the article: Grotzer, Perret, Boltshauser. Critically revising the article: Grotzer, Boltshauser, Kellenberger, Scheer. Reviewed submitted version of manuscript: Perret, Boltshauser. Approved the final version of the manuscript on behalf of all authors: Grotzer. Study supervision: Grotzer.

References

1. Alphs HH, Schwartz BS, Stewart WF, Yousem DM: Findings on brain MRI from research studies of occupational exposure to known neurotoxicants. **AJR Am J Roentgenol 187:**1043–1047, 2006
2. Dağlioğlu E, Cataltepe O, Akalan N: Tectal gliomas in children: the implications for natural history and management strategy. **Pediatr Neurosurg 38:**223–231, 2003
3. De Braganca KC, Dunkel IJ, Souweidane MM, Greenfield JP, Khakoo Y: Outcome of patients with incidentally discovered asymptomatic posterior fossa (PF) masses. **Neuro Oncol 12:** ii130, 2010 (Abstract)
4. Evans AC: The NIH MRI study of normal brain development. **Neuroimage 30:**184–202, 2006
5. Graf WD, Kayyali HR, Abdelmoity AT, Womelduff GL, Williams AR, Morriss MC: Incidental neuroimaging findings in nonacute headache. **J Child Neurol 25:**1182–1187, 2010
6. Graf WD, Kayyali HR, Alexander JJ, Simon SD, Morriss MC: Neuroimaging-use trends in nonacute pediatric headache before and after clinical practice parameters. **Pediatrics 122:**e1001–e1005, 2008
7. Gupta S, Kanamalla U, Gupta V: Are incidental findings on brain magnetic resonance images in children merely incidental? **J Child Neurol 25:**1511–1516, 2010
8. Gupta SN, Belay B: Intracranial incidental findings on brain MR images in a pediatric neurology practice: a retrospective study. **J Neurol Sci 264:**34–37, 2008
9. Hartwigsen G, Siebner HR, Deuschl G, Jansen O, Ulmer S: Incidental findings are frequent in young healthy individuals undergoing magnetic resonance imaging in brain research imaging studies: a prospective single-center study. **J Comput Assist Tomogr 34:**596–600, 2010
10. Illes J, Kirschen MP, Edwards E, Bandettini P, Cho MK, Ford PJ, et al: Practical approaches to incidental findings in brain imaging research. **Neurology 70:**384–390, 2008
11. Jordan LC, McKinstry RC III, Kraut MA, Ball WS, Vendt BA, Casella JF, et al: Incidental findings on brain magnetic resonance imaging of children with sickle cell disease. **Pediatrics 126:**53–61, 2010
12. Katzman GL, Dagher AP, Patronas NJ: Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. **JAMA 282:**36–39, 1999
13. Keating RF, Myseros JS, Yaun AL, Magge SN, Roth J, Constantini S: Incidentalomas: significance of a growing problem and therapeutic options. **Neuro Oncol 12:**ii46, 2010 (Abstract)
14. Kim BS, Illes J, Kaplan RT, Reiss A, Atlas SW: Incidental findings on pediatric MR images of the brain. **AJNR Am J Neuroradiol 23:**1674–1677, 2002
15. Morris Z, Whiteley WN, Longstreth WT Jr, Weber F, Lee YC, Tsushima Y, et al: Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. **BMJ 339:**b3016, 2009
16. O'Brien DF, Farrell M, Delanty N, Traunecker H, Perrin R, Smyth MD, et al: The Children's Cancer and Leukaemia Group guidelines for the diagnosis and management of dysembryoplastic neuroepithelial tumours. **Br J Neurosurg 21:** 539–549, 2007
17. Pirotte BJ, Lubansu A, Massager N, Wikler D, Van Bogaert P, Levivier M, et al: Clinical interest of integrating positron emission tomography imaging in the workup of 55 children with incidentally diagnosed brain lesions. Clinical article. **J Neurosurg Pediatr 5:**479–485, 2010
18. Seki A, Uchiyama H, Fukushi T, Sakura O, Tatsuya K: Incidental findings of brain magnetic resonance imaging study in a pediatric cohort in Japan and recommendation for a model management protocol. **J Epidemiol 20 (Suppl 2):**S498–S504, 2010
19. Sievert AJ, Fisher MJ: Pediatric low-grade gliomas. **J Child Neurol 24:**1397–1408, 2009
20. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et al: Incidental findings on brain MRI in the general population. **N Engl J Med 357:**1821–1828, 2007
21. Weber F, Knopf H: Incidental findings in magnetic resonance imaging of the brains of healthy young men. **J Neurol Sci 240:**81–84, 2006
22. Zeilhofer UB, Gerber NU, Scheer I, Warmuth-Metz M, Bison B, Bertalanffy H, et al: A 10 year-old boy with an incidentaloma diagnosed as a medulloblastoma 2 1/2 years later. **Neuro Oncol 12:**ii130, 2010 (Abstract)

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Address correspondence to: Michael A. Grotzer, M.D., University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland. email: Michael.Grotzer@kispi.uzh.ch.