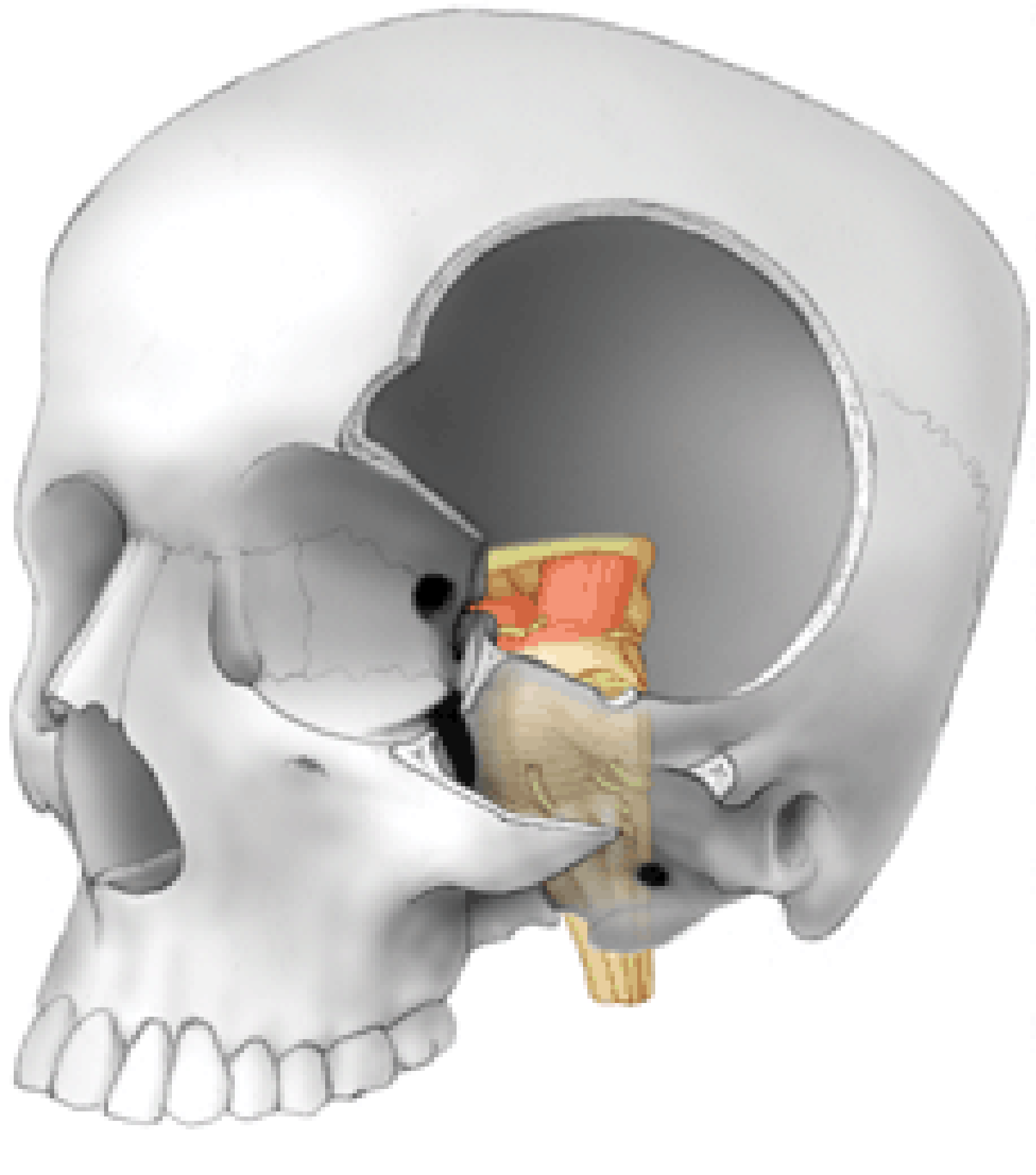

Introduction

Cavernous malformations

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Cavernous malformations are relatively rare vascular anomalies that occur in approximately 0.1%–4% of the population and account for 8%–15% of all vascular malformations of the CNS. These hamartomatous hemorrhagic lesions consist of cavernous spaces lined by epithelial cells and collagen. Our knowledge of the etiology, natural history, and indications for therapy were relatively primitive prior to the development of MR imaging. Unless associated with a recent hemorrhage or calcification, these lesions are difficult to diagnose on CT, and the minute feeding and draining vessels without arteriovenous shunting within the lesion make them angiographically invisible. Prior to the advent of MR imaging, even the nomenclature for cavernous malformations was confusing, including such vague terms as angiographically occult vascular malformations, cryptic malformations, cavernous hemangiomas, and cavernous angiomas. With the routine use of MR imaging, and the characteristic, if not nearly pathognomonic appearance, these lesions were readily identified in asymptomatic and minimally symptomatic patients. Furthermore, patients in whom doctors made misdiagnoses, such as demyelinating disease or neoplastic disorders, were able to be appropriately diagnosed with cavernous malformations. In the relatively short period of time since the advent and routine use of MR imaging, our knowledge of cavernous malformations has virtually exploded. The ability to accurately image cavernous malformations has led to a better understanding of the natural history of these lesions, the clinical manifestations, additional imaging characteristics, the role of microsurgical resection, the role of radiosurgical treatment, and even the genetics of cavernous malformations.

With such a rapid expansion of our database on this topic, it is incumbent on our scientific journals to periodically reassess that knowledge base and present it to our colleagues in a peer-reviewed and well-organized manner. This monograph attempts to accomplish that goal. We were fortunate to receive outstanding manuscripts from many of the world's authorities and experts in the biology, genetics, natural history, imaging, and therapeutic management of these interesting and complex lesions. Manuscripts by the Zhu, Couldwell, and Burkhardt groups update us on laboratory investigations into the pathogenetics of cerebral cavernous malformations with the Awad group proposing a novel theory relating pathogenesis to vascular permeability. Articles on the newest techniques for imaging and natural history observations lead into a virtual Who's Who of technical expertise discussing the surgical and radiosurgical management of eloquently positioned lesions. *(DOI: 10.3171/2010.9.FOCUS.Intro)*

Neurosurg Focus 29 (3):E1, 2010

Differential angiogenesis function of *CCM2* and *CCM3* in cerebral cavernous malformations

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Object. Loss-of-function mutations in *CCM* genes are frequently detected in familial cerebral cavernous malformations (CCMs). However, the current functional studies of the *CCM* genes in vitro have been performed mostly in commercially purchased normal cell lines and the results appeared discrepant. The fact that the cerebral vascular defects are rarely observed in *CCM* gene-deficient animals suggests the requirement of additional pathological background for the formation of vascular lesions. Consistent with these data, the authors assumed that silencing *CCM* genes in the endothelium derived from CCMs (CCM-ECs) serves as a unique and valuable model for investigating the function of the *CCM* genes in the pathogenesis of CCMs. To this end, the authors investigated the role and signaling of *CCM2* and *CCM3* in the key steps of angiogenesis using CCM-ECs.

Methods. Endothelial cells (ECs) derived from CCMs were isolated, purified, and cultured from the fresh operative specimens of sporadic CCMs (31 cases). The *CCM2* and *CCM3* genes were silenced by the specific short interfering RNAs in CCM-ECs and in control cultures (human brain microvascular ECs and human umbilical vein ECs). The efficiency of gene silencing was proven by real-time reverse transcriptase polymerase chain reaction. Cell proliferation and apoptosis, migration, tube formation, and the expression of phosphor-p38, phosphor-Akt, and phosphor-extracellular signal-regulated kinase–1 and 2 (ERK1/2) were analyzed under *CCM2* and *CCM3* silenced conditions in CCM-ECs.

Results. The *CCM3* silencing significantly promoted proliferation and reduced apoptosis in all 3 types of endothelium, but accelerated cell migration exclusively in CCM-ECs. Interestingly, *CCM2* siRNA influenced neither cell proliferation nor migration. Silencing of *CCM3*, and to a lesser extent *CCM2*, stimulated the growth and extension of sprouts selectively in CCM-ECs. Loss of *CCM2* or *CCM3* did not significantly influence the formation of the tubelike structure. However, the maintenance of tube stability was largely impaired by *CCM2*, but not *CCM3*, silencing. Western blot analysis revealed that *CCM2* and *CCM3* silencing commonly activated p38, Akt, and ERK1/2 in CCM-ECs.

Conclusions. The unique response of CCM-ECs to *CCM2* or *CCM3* siRNA indicates that silencing *CCM* genes in CCM-ECs is valuable for further studies on the pathogenesis of CCMs. Using this model system, the authors demonstrate a distinct role of *CCM2* and *CCM3* in modulating the different processes of angiogenesis. The stimulation of endothelial proliferation, migration, and massively growing and branching angiogenic sprouts after *CCM3* silencing may potentially contribute to the formation of enriched capillary-like immature vessels in CCM lesions. The severe impairment of the tube integrity by *CCM2*, but not *CCM3*, silencing is associated with the different intracranial hemorrhage rate observed from *CCM2* and *CCM3* mutation carriers. The activation of p38, ERK1/2, and Akt signal proteins in *CCM2*- or *CCM3*-silenced CCM-ECs suggests a possible involvement of these common pathways in the pathogenesis of CCMs. However, the specific signaling mediating the distinct function of *CCM* genes in the pathogenesis of CCMs needs to be further elucidated. *(DOI: 10.3171/2010.5.FOCUS1090)*

Key Words • cerebral cavernous malformation • *CCM2* • *CCM3* • short interfering RNA • angiogenesis

Cerebral cavernous malformations are major vascular anomalies in the CNS that occur sporadically or as a familial form with an incidence of approximately 10%–20% in European cases. Familial CCM, an autosomal dominant disorder attributable to loss-of-function mutations in any of the 3 *CCM* genes (*CCM1*, *CCM2*, and *CCM3*), commonly show multiple lesions and an increased risk of recurrent intracerebral hemorrhages that may cause headaches, seizures, focal neurological deficits, or even death.[7,21]

All 3 *CCM* genes/proteins are expressed in a variety of cell types including neurons and astrocytes and in endothelium.[18,23] Recent studies indicated that endothelia-specific ablation of *CCM2* led to midgestation embryonic death due to failed angiogenesis, and these

Abbreviations used in this paper: CCM = cerebral cavernous malformation; EC = endothelial cell; ECGM = EC growth medium; ERK1/2 = extracellular signal-regulated kinase–1 and 2; GAPDH = glyceraldehyde-3-phosphate-dehydrogenase; HBMEC = human brain microvascular EC; HUVEC = human umbilical vein EC; RT-PCR = reverse transcriptase polymerase chain reaction; siRNA = short interfering RNA

* Drs. Zhu and Wu contributed equally to this work.

vascular defects are endothelially autonomous,[4,13,25] suggesting that any of the genes causing CCMs are needed in the endothelium. Supporting these findings, a complete inactivation of CCM proteins[16] or somatic mutations of *CCM* genes are found in the affected ECs of all forms of familial CCMs.[1] These data indicate the crucial role of endothelial *CCM* genes both in the vascular development and in the pathogenesis of CCMs.

Among these 3 genes, the functions of *CCM1*[9,12,28] and *CCM2*[4,13,25] have been most extensively studied. However, the role of *CCM2* in angiogenesis and the signaling affected by *CCM2* deficiency appeared discrepant. Fewer studies have focused on the role of *CCM3* in angiogenesis.[14] Furthermore, the vascular defects in *CCM2*-deficient zebrafish[13] or mice[25] occurred exclusively extracerebrally. It is most likely that additional genetic, epigenetic, or local microenvironmental factors determine whether *CCM* gene mutations predispose the individuals to CCMs.[1,17] Recent findings that frequent epigenetic alteration in phosphatase and tensin homolog promoter led to deficiency of this protein expression in the ECs of familial CCMs may support this notion.[30,31] Furthermore, we (unpublished data, 2010) and others[2,29] have found that ECs derived from CCMs (CCM-ECs) exhibit unique angiogenesis properties, indicating a pathological background of CCM-ECs. Clinically, a different intracranial hemorrhage rate has been observed in CCMs carrying individual *CCM* gene mutations.[8] Consistent with these data, we assumed that silencing of individual *CCM* genes in CCM-ECs serves as a valuable model simulating the pathogenesis of familial CCMs and that these disease genes play a distinct role in angiogenesis of CCMs. To this end, the present study investigated the function of *CCM2* and *CCM3* in regulating the key steps of angiogenesis in CCM-ECs. Furthermore, the signaling pathways affected by *CCM2* and *CCM3* gene silencing were also studied.

Methods

Cell Culture

Endothelial Cells Derived From CCMs. The patients enrolled in the present study were all diagnosed with sporadic CCMs based on the specific characteristics of MR imaging and histopathological and familial criteria. Patients provided informed consent and the experimental protocol was approved by the local ethics committee. Participants with a possible family history of CCM or with mutations in *CCM* genes were excluded in the present study. Endothelial cells derived from resected specimens were obtained in 31 patients (mean age 42 years; 18 females and 13 males), who presented with intracerebral hemorrhage or seizure. The cells were cumulatively prepared according to the protocol by Baev and Awad,[2] with modifications. Briefly, the fresh surgical specimens were incubated with collagenase IV at 37°C for 30 minutes. After the tissue suspension was filtered, cell pellets were collected by centrifugation and suspended in ECGM-MV (PromoCell). The ECs were obtained by purifying the cell suspension using CD31 antibody-labeled Dynabeads (Dynal Biotech ASA) according to the manufacturer's protocol. The purified ECs were cultured in ECGM-MV at 37°C in a humidified environment supplemented with 5% CO_2 and 95% air. The CCM-ECs from 31 single donors were cultured until passage 3 and then frozen in liquid nitrogen for further experiments after controlling the purity (> 90%) by immunostaining of von Willebrand factor or fluorescence-activated cell sorting (unpublished data, 2010). The CCM-ECs from 3 to 5 donors were pooled in the same proportion for individual experiments. All experiments were reproduced in at least 3 independent pooled CCM-ECs.

Human Umbilical ECs and Human Brain Microvascular ECs. Human umbilical ECs (PromoCell) and human brain microvascular ECs (Provitro GmbH) were cultured in ECGM and ECGM-MV, respectively, in a humidified incubator containing 95% air and 5% CO_2 at 37°C. Cells were used between passages 3 to 5 for experiments.

Silencing of CCM2 *or* CCM3 *by siRNA*

Cells were seeded at a density of $1.0 \times 10^4/cm^2$ in culture dishes or 24-well plates. After 24 hours of culturing, the cells were transfected with 70 nM of *CCM2*- or *CCM3*-specific siRNA or negative control siRNA (Neg. C, Ambion) using GeneSilencer (Gene Therapy System). The cells were incubated for different time periods after the transfection as indicated in the individual experiments. The efficiency of silencing was controlled by real-time RT-PCR in all experiments when siRNA transfections were concerned.

Total RNA/Protein Extraction and cDNA Synthesis

Total RNA/protein was extracted using a Nucleospin RNA/protein purification kit (Macherey-Nagel), and cDNA was synthesized using the First Strand cDNA Synthesis Kit (Fermentas) following the manufacturer's instructions.

Real-Time RT-PCR

The reaction mixture was prepared to a final volume of 25 μl containing 10 μl of the cDNA solution (4 ng/μl), 15 μl of Absolute QPCR SYBR Green Mixes (ABgene), 0.5 μl of forward and reverse primers (10 μM), and RNase-free H_2O. The following primers were used: *CCM2* forward 5′-CCCTGTCGGAGAGTGCAG-3′ and reverse 5′-AGCAG ACAGCAAAGCTCCTC-3′; *CCM3* forward 5′-TGGCAG CTGATG ATGTAGAAG-3′ and reverse 5′-TCGTGCCT TTTCGTTTAGGT-3′; and *GAPDH* forward 5′-AGCCAC ATCGCTCAGACA-3′ and reverse 5′-GCCCAATACGAC CAAATCC-3′. Real-time RT-PCR was performed using the following settings: initial denaturation at 95°C for 15 minutes; 35 cycles of amplification at 95°C for 30 seconds, 59°C for 20 seconds, and 72°C for 50 seconds; and for the melting curve, 72°C for 30 seconds, 95°C for 1 minute, and 55–95°C with a heating rate of 0.5°C every 10 seconds. Relative mRNA expression (fold of change) for each sample was quantified using the cycle threshold approach, normalized to the reference gene *GAPDH*. The specificity of amplification was monitored at the end of each reaction by melting curve analysis.

Proliferation Assay

Cell proliferation assay was performed 72 hours after the transfection using WST-1 reagent (Roche Diagnostics)

according to the manufacturer's instructions. The absorbance was measured at 450 nm by a plate reader.

Migration Assay

After 72 hours of the transfection, cells were trypsinized and resuspended in supplement-free ECGM basal medium and then loaded to the upper part of the transwell insert at identical cell numbers per well. The ECGM basal media containing 10% fetal calf serum were added to the lower well. After 6 hours of incubation, the nonmigrated cells on the upper side of the inserts were removed by a swab. The migrated cells were stained using Hoechst 33258, and photographed and counted (in a blinded fashion) in 6 random fields per transwell under a microscope at a magnification of 100.

Tube Formation Assay

Cells were seeded in Matrigel-coated 96-well plates 72 hours after siRNA transfection and incubated for 6 hours, 24 hours, or 48 hours. Six random fields were blindly photographed from each well and the number of tubes was counted under the microscope at a magnification of 40.

Induction and Detection of Apoptosis

To minimize the influence of the proliferation effect of *CCM3* siRNA on the apoptosis study, cells were reseeded at the identical density 48 hours after the transfection followed by another 24 hours of incubation. Cells received 100 nM of staurosporine treatment for 5 hours and were then stained with Hoechst 33258. The total number of cells and the number of apoptotic cells were counted (in a blinded fashion) in 6 random fields from each dish. The cells showing condensed nuclei or apoptotic bodies were considered apoptotic cells.

Western Blot Analysis

The total protein was extracted from CCM-ECs in parallel with the RNA extraction using a Nucleospin RNA/protein purification kit as described above. Samples containing an equal amount of total protein were loaded on 12.5% sodium dodecyl sulfate-polyacrylamide gels. Following electrophoresis, protein was transferred onto a nitrocellulose membrane. Unspecific binding was blocked by a buffer containing 0.1% Tween-20, 2% bovine serum albumin, and 5% nonfat dry milk in tris-buffered saline. The blots were then incubated overnight at 4°C with the following phosphor-antibodies (1:1000) from Cell Signaling Technology: rabbit antiphosphor-p38 (P-P38), rabbit antiphospho-Akt (P-Akt, Ser473), mouse antiphospho-ERK1/2 (P-ERK1/2), or mouse antiactin (1:1000, Sigma). After the secondary antibody reaction, the signal was produced by incubating the blots with enhanced chemiluminescence detection solutions.

Statistical Analysis

All data are expressed as means ± SDs. The statistical analysis was performed using the WinSTAT program. The differences between the 2 groups were analyzed using ANOVA followed by the Scheffé test. A probability value < 0.05 was considered statistically significant.

Results

Time Course of CCM2 *and* CCM3 *Gene Silencing*

Real-time RT-PCR demonstrated a consistent expression of *CCM2* and *CCM3* genes in individual CCM-EC cultures as evidenced by the comparable cycle threshold values normalized to the housekeeping gene *GAPDH* (data not shown), suggesting a homogeneous *CCM* gene background of the cultures. The time courses of gene silencing were then established in CCM-ECs as well as in HBMECs and HUVECs by siRNA transfection. As shown in Fig. 1A, the expression of the *CCM2* gene in CCM-ECs declined by more than 70% of the control value at 48 hours and 72 hours after the transfection. The level of *CCM2* slowly returned but was still 30% lower than the control at 96 hours after the transfection, whereas *CCM3* gene expression decreased by 70%, 90%, and 65% of the control at 48 hours, 72 hours, and 96 hours, respectively, after the transfection. Similar time courses of *CCM2* and *CCM3* gene silencing were observed in HBMECs (Fig. 1B) and HUVECs (Fig. 1C) after the transfection. Based on these time courses of gene silencing, the functional studies of *CCM2* and *CCM3* genes were all performed at 72 hours after siRNA transfection. The possible unspecific effect of the siRNAs was ruled out by the detection of *CCM2* and *CCM3* gene expression after *CCM3* and *CCM2* siRNA, respectively (data not shown).

Role of CCM2 *and* CCM3 *in Endothelial Proliferation and Migration*

As shown in Fig. 2A, silencing *CCM3* significantly promoted cell proliferation as evidenced by a 39%, 36%, and 24% increase in the absorbance generated by proliferating CCM-ECs, HBMECs, and HUVECs, respectively ($p < 0.001$ in CCM-ECs and HBMECs; $p < 0.05$ in HUVECs). However, the cell proliferation was not altered by *CCM2* silencing in all 3 types of ECs.

Subsequently we checked cell mobility after *CCM2* and *CCM3* silencing by the transwell migration assays. Surprisingly, a significantly higher number of migrated cells were detected after *CCM3* silencing only in CCM-ECs ($p < 0.05$; Fig. 2B and C), but not in HBMECs and HUVECs. Furthermore, the change of cell mobility was not observed in CCM-ECs nor in HBMECs and HUVECs after *CCM2* siRNA transfection (Fig. 2B).

Influence of CCM2 *and* CCM3 *Silencing on Sprout Growth and Tube Formation*

To examine the role of *CCM2* and *CCM3* genes in the process of tube formation, HUVECs and CCM-ECs were seeded on Matrigel 72 hours after the siRNA transfection. Interestingly, dramatic growth and extension of sprouts were observed exclusively in CCM-ECs after *CCM3* silencing and to a lesser extent after *CCM2* silencing (Fig. 3), which even made the quantification of the number of tubes difficult. Therefore, the quantification of tube formation was performed in HUVECs (Fig. 4). The tubelike structure was similarly observed in HUVECs transfected with negative control siRNA, *CCM2* siRNA, or *CCM3* siRNA at 6 hours after seeding cells on Ma-

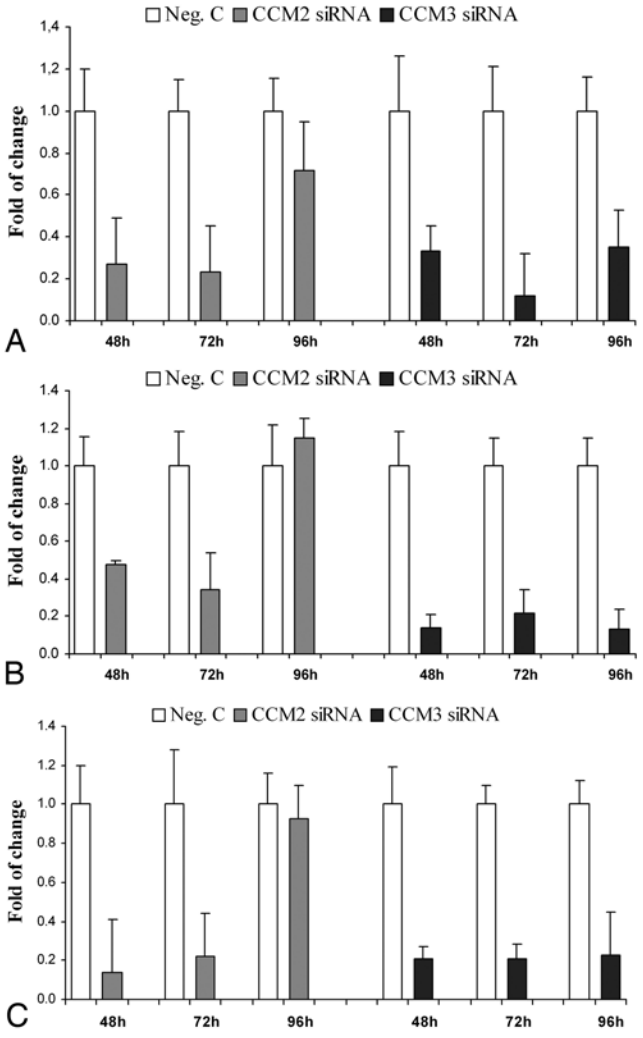

Fig. 1. Time courses of *CCM2* and *CCM3* gene expression after siRNA transfection in ECs. CCM-ECs (**A**), HBMECs (**B**), and HUVECs (**C**) were transfected with 70 nM of specific siRNA or of negative control siRNA (Neg. C). Cells were harvested for total RNA extraction at 48 hours, 72 hours, and 96 hours after the transfection. The expression of *CCM2* and *CCM3* genes was detected by real-time RT-PCR and presented as fold of change. The *CCM2* gene was efficiently downregulated 48 hours and 72 hours after the transfection in all 3 types of cells, whereas the level of *CCM3* remained consistently downregulated from 48 hours to 96 hours after the transfection.

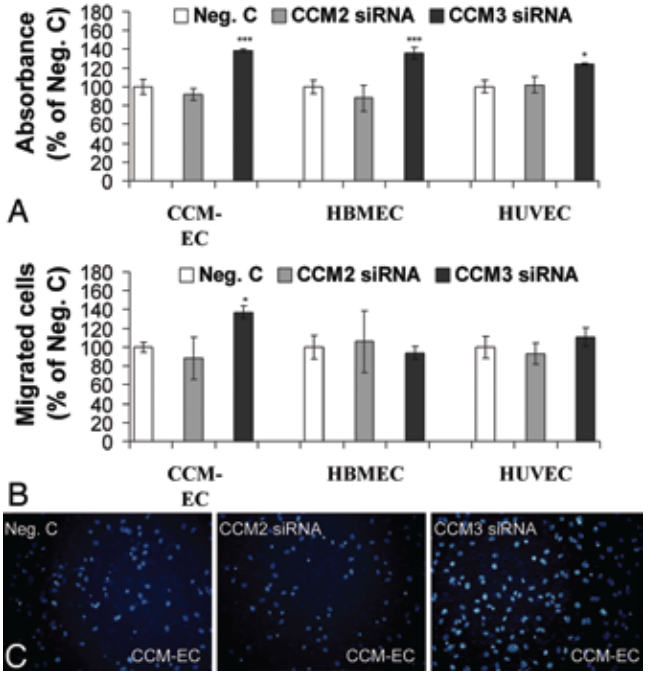

Fig. 2. Silencing of *CCM3*, but not *CCM2*, promoted endothelial proliferation and migration after siRNA. The CCM-ECs, HBMECs, and HUVECs were transfected with 70 nM of specific siRNA or of negative control siRNA for 72 hours. **A:** The *CCM3* siRNA increased cell proliferation in all 3 types of endothelium. The proliferation assay was performed by adding proliferation reagent WST-1 to the culture and the absorbance was detected at 450 nm in a plate reader. *$p < 0.05$ and ***$p < 0.001$, compared with negative control. **B:** Silencing of *CCM3* accelerated migration of CCM-ECs, but not of HBMECs and HUVECs. To rule out the influence of a proliferation effect of *CCM2* and *CCM3* siRNA, the cells were reseeded at identical cell numbers in each transwell 72 hours after the transfection. After 6 hours of reseeding, the migrated cells were stained with Hoechst 33258 and blindly photographed in 6 random fields per transwell under a microscope at a magnification of 100. The number of the migrated cells was blindly counted. *$p < 0.05$ compared with negative control. **C:** Photomicrographs of the migrated CCM-ECs after staining with Hoechst 33258. Original magnification × 100.

trigel. However, the tubelike structures collapsed at 24 hours and were completely lost at 48 hours after *CCM2* siRNA transfection, whereas the tubes remained intact at 24 hours and were slightly injured at 48 hours in cells transfected with negative control and *CCM3* siRNA (Fig. 4 upper). Quantitative analysis confirmed a significant reduction of the tube numbers at 24 hours after *CCM2*, but not *CCM3,* siRNA transfection ($p < 0.001$; Fig. 4 lower).

Influence of CCM3 *on Endothelial Apoptosis*

The *CCM3* gene, alternatively referred to as the programmed cell death gene, codes for a protein related to apoptosis. It is thus highly interesting to investigate the role of the *CCM3* gene in endothelial apoptosis. Staurosporine, a broad spectrum kinase inhibitor and a widely used apoptosis inducer, induced a pronounced apoptosis in CCM-ECs, HBMECs, and HUVECs ($p < 0.001$). Of note, the percentage of apoptosis was significantly reduced by approximately 15% after *CCM3* gene silencing in all 3 cell types ($p < 0.001$ in CCM-ECs; $p < 0.01$ in HBMECs and HUVECs; Fig. 5).

Effect of CCM2 *and* CCM3 *Silencing on p38, Akt, and ERK1/2 Activation in CCM-ECs*

To identify the signaling pathway possibly affected by *CCM2* or *CCM3* silencing, the protein and RNA were extracted in parallel for detection of protein levels of P-p38, P-Akt, and P-ERK1/2 and for detection of the expression of the *CCM2* and *CCM3* genes, respectively, at 72 hours after the transfection. Western blot analysis revealed a clear upregulation of P-p38, P-Akt, and P-ERK1/2 after *CCM2* and *CCM3* siRNA transfection (Fig. 6 upper). Real-time RT-PCR confirmed a more than 90% downregulation of *CCM2* and *CCM3* gene expression in the

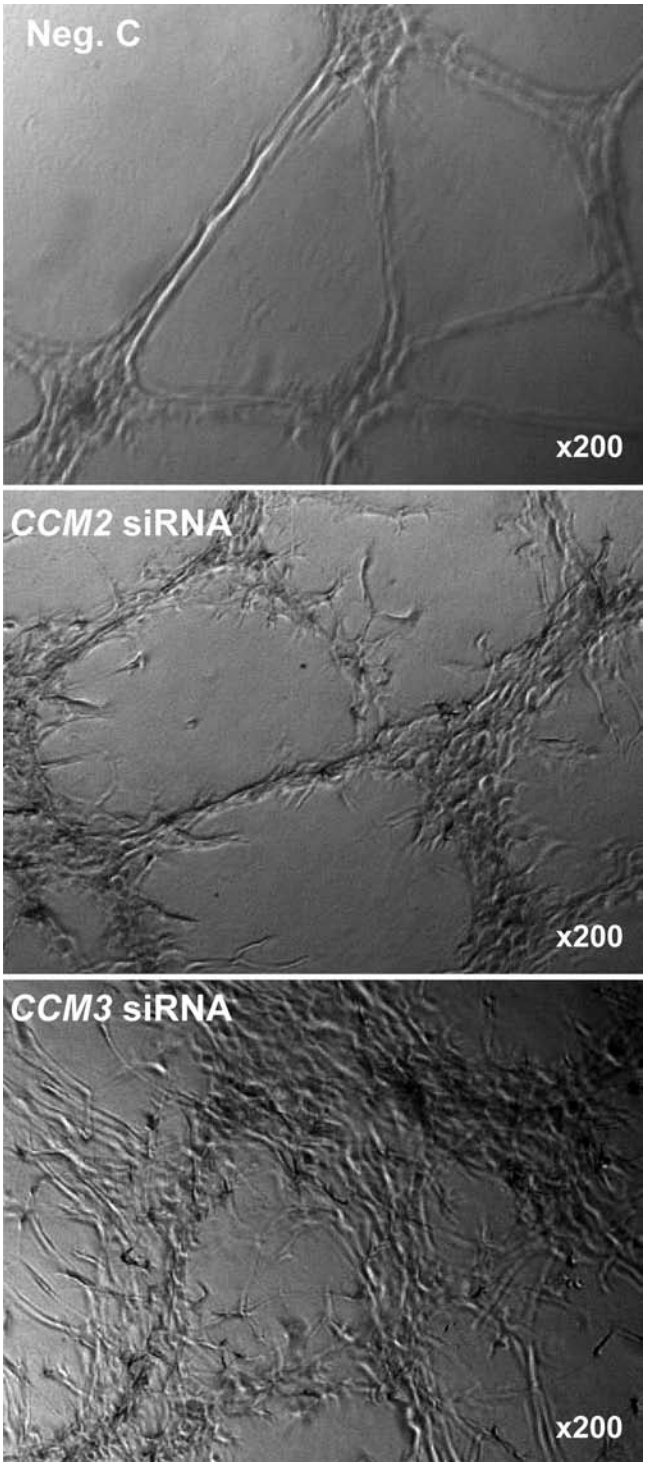

Fig. 3. Photomicrographs showing that *CCM2* and *CCM3* silencing stimulated the sprout growth in CCM-ECs. The CCM-ECs were transfected with 70 nM of specific *CCM2* or *CCM3* siRNA or negative control siRNA for 72 hours, and thereafter cells were reseeded on the Matrigel-coated 96-well plate followed by 24 hours of incubation. The *CCM3,* and to a lesser extent *CCM2* siRNA, stimulated the sprout growth. Original magnification × 200.

same sourced cells (Fig. 6 lower), indicating an association of the increased activation of these signaling proteins and an efficient *CCM2* and *CCM3* silencing.

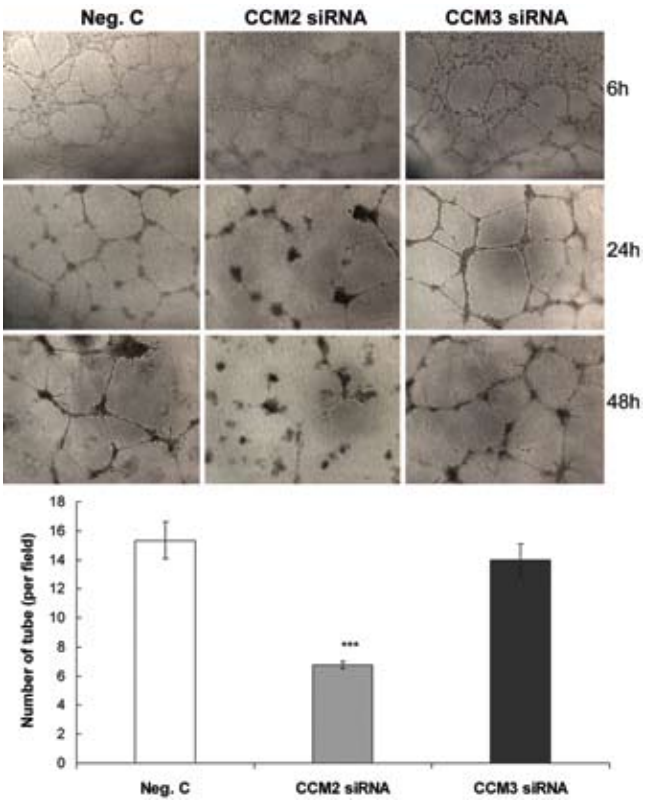

Fig. 4. Silencing of *CCM2,* but not *CCM3*, affected the stability of tubelike structures in HUVECs. Human umbilical vein ECs were transfected with 70 nM of specific *CCM2* or *CCM3* siRNA or a negative control siRNA for 72 hours, and thereafter cells were reseeded on the Matrigel-coated 96-well plate followed by 6 hours, 24 hours, and 48 hours of incubation. **Upper:** Microscope view of the tube formation at different time points after the incubation. Silencing of *CCM2* and *CCM3* did not influence the formation of the tubelike structure at 6 hours, but knockdown of *CCM2* largely impaired the integrity of the tube structure at 24 hours and 48 hours after pooling cells on the Matrigel. Original magnification x 40. **Lower**: Quantification of the number of tubes at 24 hours of incubation. Quantitative data indicated a significant disruption of the integrity of tubes after transfection with *CCM2,* but not *CCM3,* siRNA. ***$p < 0.001$ compared with negative control.

Discussion

Recently, several studies have revealed a pivotal role of endothelial *CCM* genes in vascular development and in disease states.[4,13,14,25,26] It is noteworthy, however, that the vascular defects occurred exclusively extracerebrally in *Ccm2* deficient animals[13,25] and that the typical CCM-like vascular lesions were rarely observed in heterozygote *Ccm1*$^{+/-}$[19] or *Ccm2*$^{+/-}$ mice.[20] These findings raised the assumption that additional factors may determine whether CCMs occur in *CCM* gene mutation carriers.[17] Although this proposal remains speculative, one could imagine that the endothelium in CCM lesions harbors certain unique properties because the lesions have been exposed to this abnormal, yet undefined, microenvironment. Within this context and considering that the functional study of *CCM* genes in culture has been performed exclusively in cell lines[3,5,6,14] or in commercially purchased normal ECs (HUVECs and HBMECs),[6,25] silencing *CCM* genes in CCM-ECs established in the present work may simulate

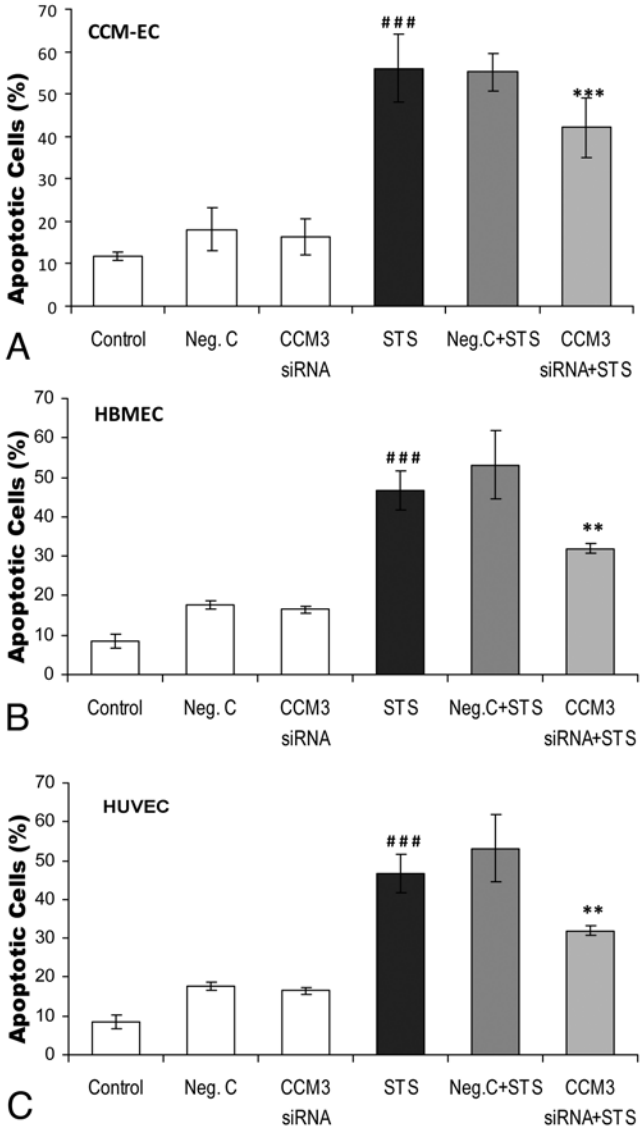

Fig. 5. Bar graphs showing that *CCM3* silencing caused a significant resistance of ECs to apoptotic stimuli. CCM-ECs **(A)**, HBMECs **(B),** and HUVECs **(C)** received 70 nM of *CCM3* siRNA or a negative control siRNA for 48 hours. To minimize the influence of the cell proliferation mediated by the gene silencing on the apoptosis study, the transfected cells were then trypsinized and reseeded at the identical density in a 24-well plate. After 24 hours of incubation, cells were treated with staurosporine (STS) at 100 nM for 5 hours. Apoptotic cells were detected by the nuclear staining with Hoechst 33258. Cells exhibiting condensed nuclei or apoptotic bodies were counted as apoptotic cells. $^{**}p < 0.01$ and $^{***}p < 0.001$ compared with negative control and STS. $^{###}p < 0.001$ compared with controls.

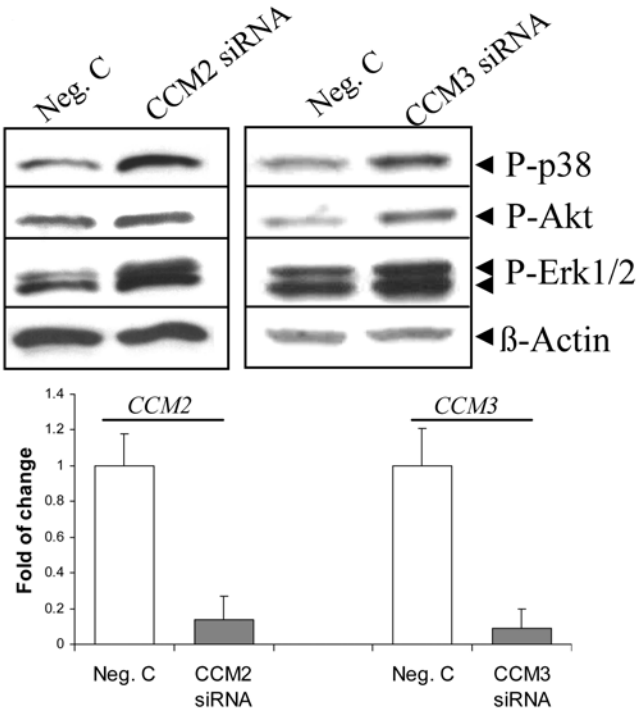

Fig. 6. Silencing *CCM2* and *CCM3* activated p38, Akt, and ERK1/2 in CCM-ECs. The CCM-ECs were transfected with 70 nM of specific *CCM2* or *CCM3* siRNA or a negative control siRNA. After 72 hours of incubation, cells were harvested for extraction of total RNA and protein in parallel. The protein extracts were used for the Western blot of the signaling proteins, whereas RNA extracts were applied for the confirmation of the efficiency of the gene silencing by real-time RT-PCR. **Upper:** Western blot revealed an increase in expression of P-p38, P-Akt, and P-ERK1/2 after *CCM2* and *CCM3* silencing. **Lower:** Real time RT-PCR demonstrated an efficient silencing of *CCM2* and *CCM3* at 72 hours after the transfection of *CCM2* siRNA and *CCM3* siRNA, respectively.

some aspects of the diseased endothelium in the CCM lesions, and thus may serve as a unique and valuable model for investigating the function of *CCM* genes in the pathogenesis of CCMs.

Cerebral cavernous malformations occur either sporadically (in approximately 80% of cases) or in a familial pattern. The former usually appears as a single lesion, whereas the latter occurs as multiple lesions along with a family history of CCMs and/or an autosomal dominant mode of inheritance. In the present study, we prepared CCM-ECs from sporadic CCMs. Because sporadic CCMs account for the majority of cases, there are more specimens available than from familial CCMs. More importantly, sporadic CCMs do not harbor *CCM* gene mutations and express comparable levels of *CCM* genes in individual cases (unpublished data, 2010), which allows us to manipulate individual *CCM* gene expression in CCM-ECs under a more homogeneous genetic background. Technically, the CCM-ECs from our laboratory exhibited the following advantages in comparison with the previous protocol:[2,29] 1) a purification step using EC marker (CD31) antibody-labeled Dynabeads was performed during the preparation, thereby ensuring the purity (90–95%) of ECs and minimizing the responses/effects derived from nonECs; and 2) the CCM-ECs used in all experiments were pooled at the same proportions from multiple donors in the present study. The pooled CCM-ECs displayed very similar properties as the single donor (unpublished data, 2010), but provided more efficient work with more representative participants.

Angiogenesis is the primary mode of vascularization for the brain, requiring the precise coordination of multiple different steps.[22] Based on the aberrant angiogenetic features of CCMs, we focused on the role of *CCM2* and *CCM3* genes in angiogenesis of CCM-ECs, and in addition, these functional studies were also performed in HBMECs

and in HUVECs as a parallel comparison. Furthermore, all individual functional studies were performed only when the real-time RT-PCR confirmed efficient gene silencing in the sister culture. We demonstrated a significantly increased cell proliferation in CCM-ECs as well as in HBMECs after *CCM3* silencing, whereas this effect was only slightly observed in HUVECs, suggesting the physiological variability between the ECs derived from cerebral microvessels (CCM-ECs and HBMECs) and from veins (HUVECs; Fig. 2A). Interestingly, *CCM3* silencing accelerated cell migration exclusively in CCM-ECs, but not in HBMECs and HUVECs (Fig. 2B), indicating a unique property of CCM-ECs. The migration effect of *CCM3* siRNA observed exclusively in CCM-ECs does not appear to be a simple consequence of the enhanced cell proliferation because *CCM3* silencing promoted proliferation in all 3 types of tested cells (Fig. 2A). Furthermore, the migration assay was performed after reseeding cells at identical cell numbers per transwell 72 hours after the transfection, followed by only 6 hours of incubation. Interestingly, knockdown of *CCM2* influenced neither cell proliferation nor migration in all 3 types of ECs. These results indicate a distinct role of *CCM2* and *CCM3* in regulating endothelial proliferation and migration.

Tube formation is another key step involved in angiogenesis. In the present study, we studied tube formation after *CCM2* and *CCM3* silencing in both CCM-ECs and HUVECs. The *CCM2* or *CCM3* silencing did not significantly affect the formation of tubelike structures as evidenced by the similar formation of tubelike structures in negative control-, *CCM2* siRNA-, and *CCM3* siRNA-treated HUVECs at 6 hours after pooling cells on Matrigel (Fig. 4 upper). Interestingly, silencing *CCM2,* but not *CCM3,* largely impaired the tubelike structure at 24 hours and 48 hours after cell growth on Matrigel (Fig. 4 upper and lower), indicating an essential role of *CCM2* for maintenance of tube integrity. Our findings are partially in agreement with the recent report that knockdown of *CCM1–3* inhibited tube formation in the EC line derived from mouse brain.[3] The variant results from the tube formation study may be a result of using different types of ECs and due to a broader time course of the tube formation assay in the present study.

More interestingly, we observed a massive growth of sprouts after *CCM3* and, to a lesser extent, *CCM2* siRNA in CCM-ECs, again indicating the unique angiogenetic property of CCM-ECs. These sprouts appear to undergo the formation of a microtube-like structure (Fig. 3). Whether this phenomenon is associated with the increased cell proliferation and migration remains questionable, because *CCM3* silencing promoted proliferation in all 3 types of cells tested (Fig. 2A), but the formation of these sprouts was exclusively observed in CCM-ECs. Furthermore, *CCM2* siRNA influenced neither cell proliferation (Fig. 2A) nor migration (Fig. 2B). Activation of notch signaling has been previously shown in sprouting ECs.[15] Nevertheless, the mechanism for the sprout growth after *CCM2* and *CCM3* silencing in CCM-ECs needs to be further elucidated.

Intracerebral hemorrhage is a consistent pathological feature of CCMs. The severe impairment of the tube structure integrity after endothelial *CCM2* silencing is closely associated with the clinical observation that *CCM2* mutation-related familial CCMs presented with a higher incidence of hemorrhages in comparison with *CCM1* and *CCM3* forms of familial CCMs.[8,24] The role of *CCM2* in maintenance of vascular integrity has been proposed through regulating the activity of Ras homolog gene family member A. The mechanism of this regulation has been recently addressed by Crose et al.[6]

The *CCM3* gene is suggested to be involved in apoptosis[5,14] and tumor signaling.[14] We found that loss of *CCM3* led to a significant resistance of all 3 tested types of ECs to apoptotic stimuli (Fig. 5), suggesting a dominant apoptotic function of *CCM3* in ECs. Considering apoptosis and proliferation as two conflicting cellular events, *CCM3* silencing-mediated promotion of endothelial proliferation (Fig. 2A) could be at least partially a consequence of the increased antiapoptotic potency of endothelium. If this is true, targeting endothelial apoptosis could be a possible therapeutic strategy for CCMs, particularly for *CCM3* mutation carriers.

The signaling proteins p38, Akt, and ERK1/2 are all importantly involved in the pathways necessary for regulating cell growth, proliferation, and apoptosis, as well as cell migration. The *CCM2* gene has been defined as a scaffold for p38 activation in response to hyperosmotic stress induced by sorbitol in mouse *Ccm2*$^{+/-}$ cell line.[27] However, *CCM2* silencing in HMBECs did not affect the activation of p38 and ERK1/2.[25] The different studies also showed various regulations of p38 activation in response to *CCM3* silencing.[5,14] These data suggest that *CCM* genes trigger cellular signaling pathways in a cell type-specific manner. We demonstrated that *CCM2* or *CCM3* silencing commonly activated p38, ERK1/2, and Akt in CCM-ECs, consistent with the current opinion that these 3 *CCM* genes interact as an intracellular complex and share some common signaling pathways.[11] However, the individual CCM proteins may have a specific function,[3] and thus it cannot be ruled out that the diverse cellular functions of individual *CCM* genes signal independently besides sharing some common pathways.[10] Our finding that silencing *CCM2* or *CCM3* differently regulates the key steps of angiogenesis in CCM-ECs supports this notion. The specific signaling that accounts for the different function of *CCM* genes needs to be further studied.

Conclusions

Performing a functional study of *CCM* genes in CCM-ECs derived from familial CCMs would be an ideal strategy. However, this strategy is limited practically by the rarity of cases and by the availability of the genetic diagnosis. The present study, silencing *CCM* genes in CCM-ECs derived from sporadic CCMs, established an in vitro model simulating certain aspects of familial CCMs. The unique response of CCM-ECs to *CCM2* or *CCM3* silencing indicates that this model could be valuable for further studies on the pathogenesis of CCMs. The distinct role of *CCM2* and *CCM3* in modulating the different processes of angiogenesis may be associated with the different clinical penetrance rates observed in *CCM2* and *CCM3* mutation carriers. The identification of the activation of p38, ERK1/2, and Akt signal proteins in *CCM2*- or *CCM3*-silenced CCM-ECs suggests a possible involvement of these signal-

ing pathways in the pathogenesis of CCMs that harbor the individual *CCM* gene mutations.

Disclosure

This study was financially supported by University Hospital of Essen.

Author contributions to the study and manuscript preparation include the following. Conception and design: Zhu. Acquisition of data: Wu, Xu. Analysis and interpretation of data: Zhu, Miller, Sandalcioglu. Drafting the article: Zhu. Critically revising the article: Zhang, Sure. Reviewed final version of the manuscript and approved it for submission: Zhu, Zhang, Sure. Statistical analysis: Miller. Study supervision: Zhu, Sure.

Acknowledgment

The authors thank Ms. Rita Haase for technical assistance.

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Manuscript submitted March 22, 2010.
Accepted May 18, 2010.

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Neurosurg Focus 29 (3):E2, 2010

The pathogenetic features of cerebral cavernous malformations: a comprehensive review with therapeutic implications

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Cerebral cavernous malformations (CCMs) are common vascular lesions of the CNS that may lead to seizures, focal neurological deficits, and fatal hemorrhagic stroke. Human genetic studies have identified 3 genes associated with CCM, and biochemical and molecular studies in mice have elucidated signaling pathways with important therapeutic implications. In this review, the authors shed light on the 3 discovered *CCM* genes as well as their protein products, with particular emphasis on their signal transduction pathways and their interaction with one another. Close focus is directed at mice model studies involving the Ccm2 gene product signaling pathway, revealing an important role for the use of simvastatin or other RhoA inhibitors as a therapeutic modality in the treatment of CCM. The remaining challenges to creating a more faithful CCM animal model as well as future clinical and research implications are reviewed. *(DOI: 10.3171/2010.6.FOCUS10135)*

Key Words • cerebral cavernous malformation • *CCM* gene • signal transduction pathway • simvastatin

Cerebral cavernous malformations are vascular lesions of the CNS that consist of a group of dilated, thin-walled, leaky capillaries with no intervening pia mater. This cluster of vessels or "caverns" is surrounded by a connective tissue matrix distinct from the surrounding pia mater. They are usually leaky, leaving a hemosiderin-laden rim circumferentially around the lesion that is easily detectable on T2-weighted echo-gradient MR imaging. Should the CM hemorrhage, the patient may experience seizures or may sustain focal neurological deficits from either a stroke or focal irritation.[19] Apart from the usual intracerebral location, CMs have also been observed in the spinal cord and retina, and as hyperkeratotic cutaneous capillary–venous malformations on the skin. The prevalence of CCMs in the general population is approximately 0.5%, based on MR imaging and necropsy studies of large cohorts of patients.[9,15] The clinical prevalence, however, is much lower, because only 25% of individuals are symptomatic. Symptoms usually develop between the 3rd and 5th decades of life.[15] The incidence of CCM is estimated at 0.2 to 0.4 lesions per patient-year.[6,16] The diameter of the lesions ranges from a few millimeters to several centimeters. Histologically, CCMs have poorly formed tight junctions between adjacent endothelial cells, with gaps often noted between individual cells. Pericytes, the precursors to smooth muscle cells, are scant. In addition, no astrocytic foot processes and no normal nervous tissues are present within the lesion.[4,19]

Abbreviations used in this paper: CCM = cerebral cavernous malformation; GTP = guanosine triphosphate; HMVEC = human microvascular endothelial cell; HUVEC = human umbilical vein endothelial cell; ICAP1-α = integrin cytoplasmic domain–associated protein 1α; JNK = c-jun N-terminal kinase; KRIT1 = Krev interaction trapped 1; LOH = loss of heterozygosity; MAPK = mitogen-activated protein kinase; MEKK3 = mitogen-activated protein kinase kinase kinase 3; MKK3 = mitogen-activated protein kinase kinase 3; PDCD10 = programmed cell death 10; PTB = phosphotyrosine binding; siRNA = small interfering RNA; VEGF = vascular endothelial growth factor.

Both sporadic and familial forms of CCM have been identified. The familial form of CCM follows an autosomal dominant form of inheritance, with incomplete penetrance and variable expression. The proportion of familial cases is estimated at 50% among Hispanic-American patients of Mexican descent, and seems to be less in other populations.[12,13] With familial forms, multiple cerebral lesions are often noted (Fig. 1), whereas the majority of sporadic cases comprise a single CCM. By linkage and LOH analysis, 3 genetic loci have been implicated on chromosomal arms 7q (*CCM1*), 7p (*CCM2*), and 3q (*CCM3*).[8,13] In this review, we describe the 3 aforementioned genes that have been implicated in CCM. We then focus our attention on *CCM2*, with particular consideration of its molecular and pathophysiological implications and its clinical application in the treatment of CCM.

The Ccm1 *Gene*

The *Ccm1* gene, *KRIT1*, was the first gene involved in CCM to be identified. It encodes a protein containing known protein–protein interaction domains. Using linkage analysis, a mutation in *Ccm1* was found in approximately 40% of familial cases.[12] Despite the vascular nature of CCMs, KRIT1 mRNA and protein have been detected in astrocytes, neurons, and various epithelial cells during embryogenesis; however, only protein and not mRNA was detected in vascular endothelial cells during early angiogenesis. Murine embryos lacking the *Ccm1* gene suggested an important role for KRIT1 in arterial morphogenesis and identity. The homozygous mutant embryos died in midgestation with vascular defects, including narrowed branchial arch arteries and decreased expression of artery-specific markers.[6,19]

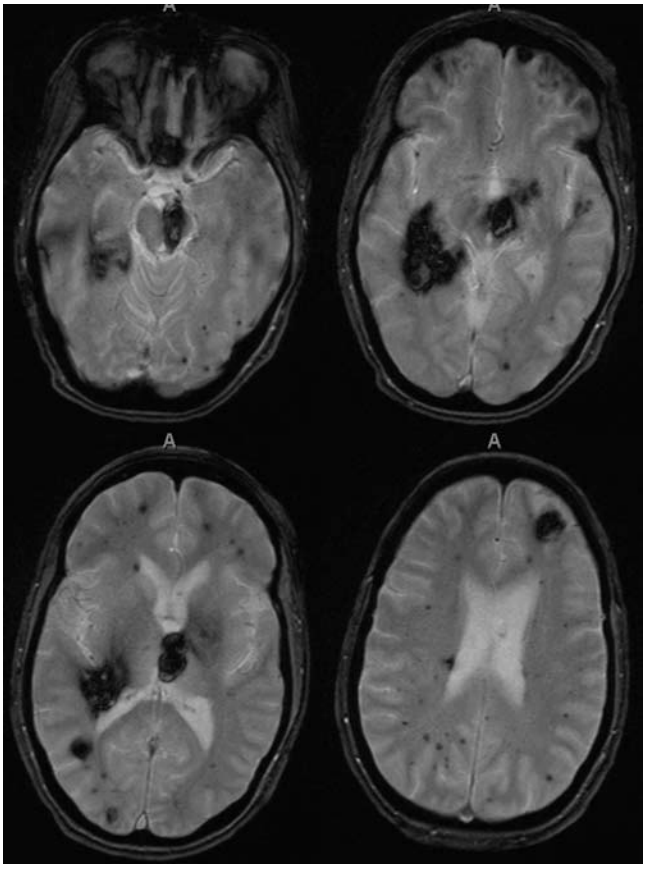

Fig. 1. Axial gradient-recalled echo MR images obtained in a 52-year-old woman with familial CMs. This patient had multiple foci of gradient blooming artifact.

KRIT1 interacts with ICAP1-α.[4] The latter is known to participate in integrin β1–mediated cell adhesion and migration. The interaction of integrin β1 and KRIT1 with ICAP1-α occurs through an NPxY motif/PTB domain. ICAP1-α and KRIT1 have a functional nuclear localization sequence with the capacity to shuttle back and forth from cytoplasm to nucleus. Moreover, ICAP1-α is able to sequester KRIT1 in the nucleus. It seems, therefore, that KRIT1 acts as an intracellular signaling molecule through extracellular adhesion signals that are important for the activation of cellular differentiation and that help determine arterial identity.[4,6,12,13,19]

The Ccm2 *Gene*

The *malcavernin (MGC4607) Ccm2* gene was discovered through LOH mapping and sequencing of positional candidate genes. As in Ccm1, in situ hybridization studies have shown Ccm2 mRNA expression in neurons and astrocytes as well as transient expression in meningeal and parenchymal cerebral vessels.[7,11,16] In further molecular studies, it was noted that malcavernin contains a PTB domain similar to that of ICAP1-α, suggesting an interaction between KRIT1 and malcavernin and, therefore, a common functional pathway. The similar phenotypic perturbation (failure of angiogenesis and vascular arrest during the embryonic stage) evident with Ccm1 and Ccm2 knockout mice further supports a common pathway involving the protein products of the respective genes.[13] A working molecular model (Fig. 2) based on molecular genetic studies of CCM1 and CCM2 protein interaction and signaling proposes that CCM2 acts as a scaffold for Rac/MEKK3/MKK3 for downstream p38 MAPK signaling. An RNA interference knockdown study has shown that malcavernin and MEKK3 were both required for activation of p38 in response to sorbitol-induced hyperosmotic stress.[13] This points to a possible interaction between CCM2 and MEKK3. In addition, CCM2 heterozygous mice were shown to have significantly decreased levels of phosphorylated p38. Zawistowski et al.[19] were also able to demonstrate that CCM1 can be detected with MEKK3 as a multiprotein complex involving CCM1 and CCM2 proteins. Therefore, a function of the CCM1/2 complex may be to organize and regulate p38 MAPK signaling. In their model, Zawistowski et al. proposed that ICAP1-α may tether CCM1 in the nucleus until a stimulus (osmotic stress/inflammation) is present, at which time CCM2 functions as a cytoplasmic anchor and recruits CCM1 to a signaling complex for integrin- and p38 MAPK–associated functions. The dynamics of the CCM1 cytoplasmic and nuclear localization suggests that this function is highly coordinated through compartmentalization.

The Ccm3 *Gene*

Bergametti and coworkers[2] used LOH mapping to identify the *Ccm3* gene. The *Ccm3* gene, PDCD10, was

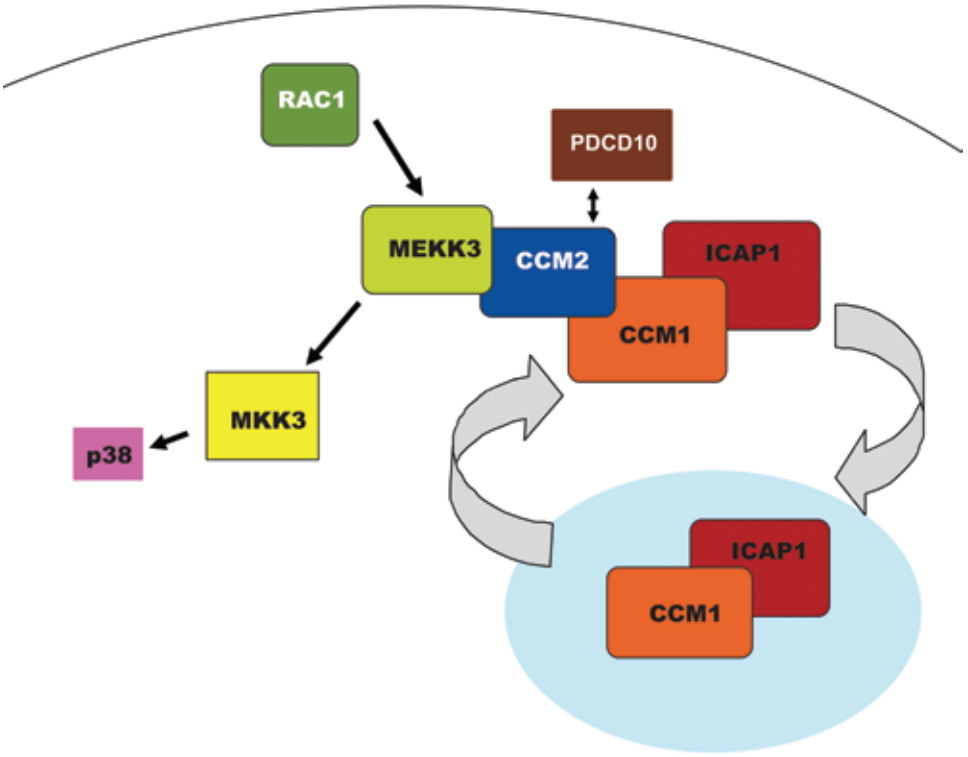

Fig. 2. Schematic presentation of molecular pathways involving the CCM proteins.

found to be ubiquitously expressed on the basis of Northern blot analysis. As with Ccm1 and Ccm2, in situ hybridization showed Ccm3 mRNA expression in neuronal cells at both adult and embryonic stages. In addition, its expression overlapped with that of Ccm2 in meningeal and parenchymal cerebral vessels.[10,13] Interestingly, its expression was found to be upregulated in the human myeloid cell line TF-1 on induction of apoptosis. Because the expression of CCM3 seems to be very similar to that of CCM1 and CCM2, with overlapping mRNA patterns, and because PDCD10 has been shown to bind Krit1 and malcavernin, it most likely has a closely linked function. The endothelial and/or smooth muscle cell nature of vascular cells expressing Ccm3 mRNA as well as the venous and/or arterial nature of the cerebral vessels expressing Ccm3 mRNA remain to be identified with antibodies specific for PDCD10.[10] Currently, several ongoing studies are examining expression patterns of CCM3. For further information, there are several recently published articles highlighting the cellular context of the various CCM protein actions, including a working model for CCM3.[4,5,14]

From Bench to Bedside

In an attempt to bridge the gap between bench work and the bedside, a number of studies have used animal models to begin to address the role of abnormal biochemical signaling pathways in states of CCM protein deficiencies. Whitehead et al.[18] focused on the *Ccm2* gene by studying mice with a gene trap mutation of *Ccm2*, and developing mice with tissue-specific, conditional mutations of *Ccm2*. Mice with a complete loss of *Ccm2* share a common phenotype with mice lacking *Krit1*. In both instances, the homozygous knockout mice die in midgestation, having failed to connect the beating heart to the aorta through the branchial arch arteries. Although endothelium is present in the expected location, these cells fail to form a proper lumen, and circulation is not established. Using the Cre-Lox system to direct the mutation of *Ccm2* to specific tissues, it was shown that *Ccm2* is required in the endothelium for normal vascular development.

Having established a rationale for studying the role of CCM2 in endothelial cells, the authors used siRNA to deplete HUVECs or HMVECs for cell biology and biochemical studies.[18] The CCM2-depleted HUVECs formed fewer lumina with a smaller cross-sectional area when compared with control cells. These observations point to the essential role of Ccm2 in endothelial cells for directing vacuole formation and coalescence to help form the vascular lumen.[18] According to the studies by Bayless and Davis[1] on microtubule depolymerization, lumen formation is dependent on the cellular cytoskeleton. Furthermore, CCM2-deficient HMVECs had an increase in actin stress fibers, with less cortical actin at the cell periphery, which was correlated with decreased barrier function and increased permeability. Because GTPases in the Rho family are important regulators of the cellular cytoskeleton, these observations suggested increased activity of the GTPase RhoA. Whitehead et al.[18] also observed increased active (GTP-bound) RHOA in CCM2-depleted HMVECs compared with control cells and found that inhibition of RHOA signaling was able to rescue the stress fiber and permeability defects in CCM2-depleted cells (Fig. 3).

The CCM proteins have also been found to interact with MAPK pathways. Although CCM2 had previously

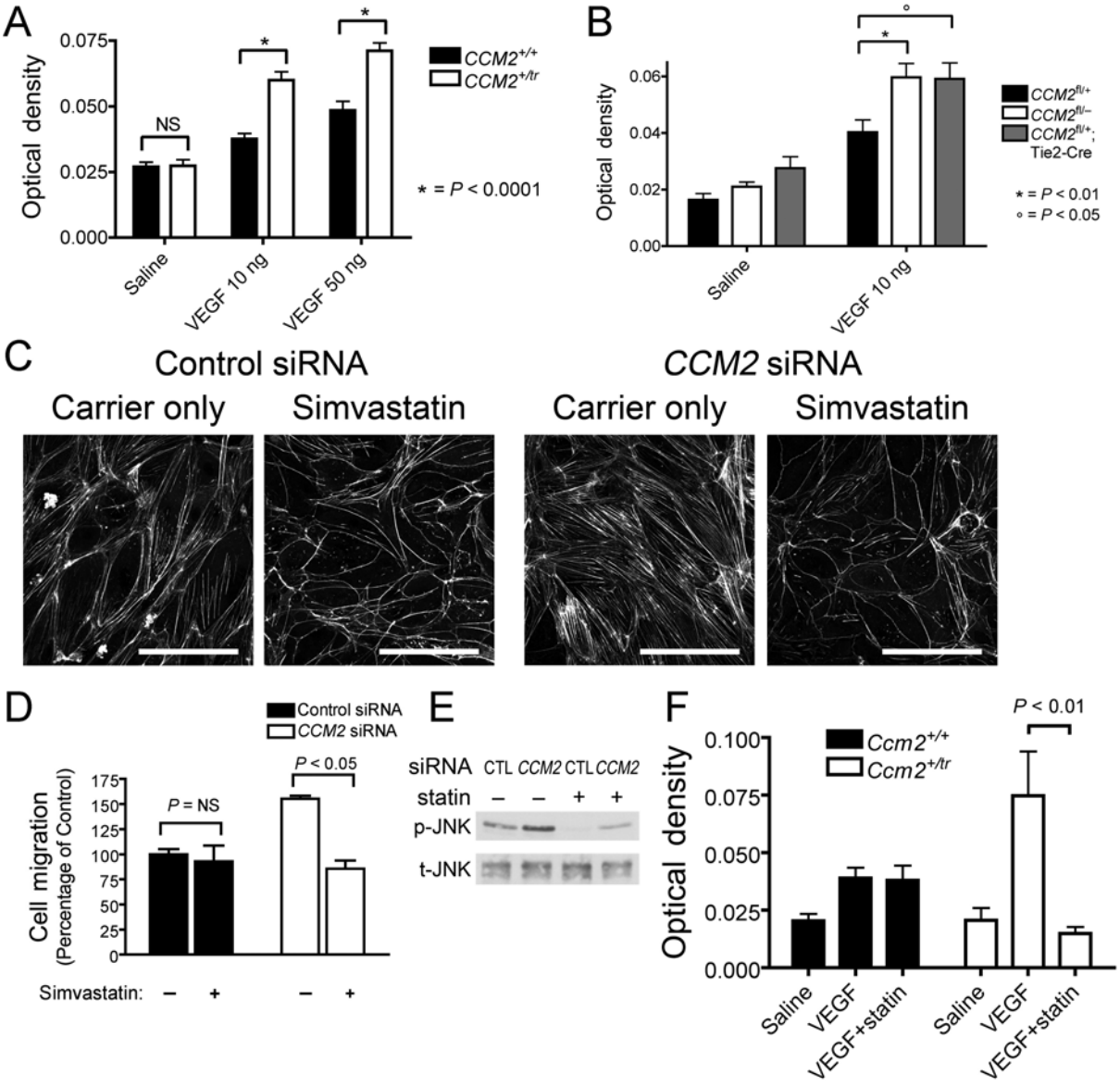

Fig. 3. Heterozygous Ccm2$^{+/tr}$ mice have permeability defects that can be rescued by treatment with simvastatin. **A:** Bar graph showing spectrophotometric quantification of Evans blue extravasation in the Miles assay of dermal permeability in *Ccm2*$^{+/tr}$ versus *Ccm2*$^{+/+}$ mice across a range of doses of VEGF compared with saline control. Five mice were studied for each genotype. **B:** Bar graph showing quantification of dermal permeability in mice with endothelial-specific heterozygosity for *Ccm2* (*Ccm2*$^{fl/+}$;Tie2-Cre) compared with mice with both *Ccm2* alleles intact (*Ccm2*$^{fl/+}$) and mice with complete *Ccm2* heterozygosity (*Ccm2*$^{fl/–}$). The authors studied 5 *Ccm2*$^{fl/+}$ mice, 9 *Ccm2*$^{fl/-}$ mice, and 10 *Ccm2*$^{fl/+}$;Tie2-Cre mice. **C:** Phalloidin staining for cellular actin fibers after treatment with carrier or simvastatin. Results are representative of 3 independent experiments. Bar = 100 μm. **D:** Bar graph showing haptotactic migration of HMVECs to fibronectin after treatment with *CCM2* or random control siRNA and treatment with either simvastatin or ethanol carrier. A minimum of 3 independent experiments were performed. **E:** Immunoblot for phosphorylated and total JNK in HMVECs treated with *CCM2* or random control siRNA and treated with either simvastatin or ethanol carrier. Results are representative of 3 independent experiments. **F:** Bar graph showing quantification of Evans blue extravasation in the Miles assay in response to saline or VEGF after pretreatment with simvastatin or ethanol carrier. For both genotypes, 3 mice were used with control treatment and 4 mice with simvastatin treatment. Values are presented as the mean ± SEM. Reprinted with permission from Macmillan Publishers Ltd: Nature Medicine (Whitehead KJ, Chan AC, Navankasattusas S, Koh W, London NR, Ling J, et al: The cerebral cavernous malformation signaling pathway promotes vascular integrity via Rho GTPases. **Nat Med 15:**177–184), copyright 2009. CTL = control; NS = not significant.

been shown to be important for p38 MAPK signaling in the cellular response to osmotic shock, Whitehead et al.[18] found that a reduction of CCM2 increased the phosphorylation of JNK and its upstream kinases MKK4 and MKK7. Interestingly, Rho-kinase inhibitor decreased the phosphorylation level of JNK, pointing to a link between the GTPase and MAPK signaling. Therefore, a working molecular hypothesis is that loss of CCM2 leads to constitutive activation of RHOA and downstream activation of JNK that is also associated with cytoskeletal changes

that result in impaired lumen formation and vascular permeability.[18]

To test this hypothesis in vivo, we studied mice with heterozygous mutations in *Ccm2* (the genotype equivalent of human disease). Although these mice appear normal and do not develop vascular lesions, increased vascular permeability was observed in the heterozygous mutants. Taking advantage of the ability of the cholesterol-lowering statin drugs to inhibit posttranslational lipid modifications of the Rho GTPases that are required for activity, Whitehead et al.[18] showed that Rho inhibition by simvastatin was sufficient to stabilize the Ccm2-deficient endothelium in vivo (Fig. 3).

Subsequently, Stockton et al.[17] showed that RhoA activation is also present in endothelial cells depleted of KRIT1, and that mice with heterozygous mutations of Krit1 also have increased permeability. These authors demonstrated that an alternate strategy of Rho inhibition with the Rho-kinase inhibitor fasudil was also able to reverse the vascular stability defects of both Ccm2 and Krit1 deficiency in vivo. Together these studies suggest a central role for RhoA activation in the pathogenesis of CCM lesions in familial CCM associated with mutations in KRIT1 or CCM2.

Although a role for increased RhoA activation in vivo has not been shown for PDCD10, Borikova et al.[3] recently demonstrated that, in addition to KRIT1 or CCM2, the loss of PDCD10 in endothelial cells also results in an increase in RhoA protein levels and activity. Taken together, these studies suggest the possibility that RhoA activation in endothelial cells of the CNS may represent a final common pathway for development of CCM lesions. Therapies directed at disrupting RhoA activity or downstream signaling such as the cholesterol-lowering statin family of drugs or the investigational agent fasudil are exciting candidates for medical therapy to stabilize CCM lesions and are worthy of further study.

Future Prospects

The working hypothesis of CCM onset is a "two-hit" hypothesis in which one germline mutant allele is inherited and the remaining somatic allele undergoes a spontaneous mutation, experiences an environmental insult such as osmotic stress, or has an inflammatory response that alters the stability of the endothelial cells that do not have the full CCM2 protector role as demonstrated with the in vivo VEGF studies. In a study by Zawistowski et al.,[19] Ccm2 heterozygous p53 mutant mice showed an increased incidence as well as number of CCMs compared with control mice as a result of increased incidence of second-hit somatic mutations. The environmental as well as genetic second-hit model paves the way for future studies to unravel therapeutic means of reversing environmental insults as well as targeted gene therapy to add allelic stability. Taking advantage of the high rate of spontaneous mutations in mice lacking the tumor suppressor p53, Krit1 heterozygous knockouts have been mated onto a p53 knockout background in hopes of producing an adult viable mouse model of CCM, because the viable adult heterozygous mice develop no CCM lesions.[6] Indeed, cerebral vascular lesions were observed in a large number of animals on this background, but the potential second-hit mutation was not localized. In addition, the mice had a shortened lifespan because of a high frequency of spontaneous tumors, making it difficult to study the natural history of CCM and its response to therapy.[4,19] Alternate means of inducing a second hit in an adult mouse without the confounding effects of the p53 mutation have yet to be reported, but it is hoped that such a strategy would create an animal model that closely resembles human CCM. Such a model could then be used to study the development of CCM lesions in vivo as well as the effect of therapeutic modalities.

Preliminary cellular and animal data suggest that statins may alter CCM biology. It is likely, given the widespread use of statins, that a considerable number of patients with CCMs have already been under observation while on this therapy. Further insight into the effect of statins on patients with known CCMs may be gained through retrospectively studying the clinical and radiological progression in those patients who are taking simvastatin for other medical indications. Between further preclinical studies of Rho inhibition in animal models and observational studies in humans, the goal is to establish a rationale for a double-blinded randomized controlled clinical trial to study the efficacy of statins on the course of CCM.

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: Krisht. Analysis and interpretation of data: Krisht, Niazi. Drafting the article: Krisht. Critically revising the article: Couldwell, Whitehead, Niazi. Reviewed final version of the manuscript and approved it for submission: Couldwell. Administrative/technical/material support: Couldwell.

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Manuscript submitted May 14, 2010.
Accepted June 10, 2010.
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Upregulation of transmembrane endothelial junction proteins in human cerebral cavernous malformations

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Object. Cerebral cavernous malformations (CCMs) are among the most prevalent cerebrovascular malformations, and endothelial cells seem to play a major role in the disease. However, the underlying mechanisms, including endothelial intercellular communication, have not yet been fully elucidated. In this article, the authors focus on the endothelial junction proteins CD31, VE-cadherin, and occludin as important factors for functional cell-cell contacts known as vascular adhesion molecules and adherence and tight junctions.

Methods. Thirteen human CCM specimens and 6 control tissue specimens were cryopreserved and examined for the presence of VE-cadherin, occludin, and CD31 by immunofluorescence staining. Protein quantification was performed by triplicate measurements using western blot analysis.

Results. Immunofluorescent analyses of the CCM sections revealed a discontinuous pattern of dilated microvessels and capillaries as well as increased expression of occludin, VE-cadherin, and CD31 in the intima and in the enclosed parenchymal tissue compared with controls. Protein quantification confirmed these findings by showing upregulation of the levels of these proteins up to 2–6 times.

Conclusions. A protocol enabling the molecular and morphological examination of the intercellular contact proteins in human CCM was validated. The abnormal and discontinuous pattern in these endothelial cell–contact proteins compared with control tissue explains the loose intercellular junctions that are considered to be one of the causes of CCM-associated bleeding or transendothelial oozing of erythrocytes. Despite the small number of specimens, this study demonstrates for the first time a quantitative analysis of endothelial junction proteins in human CCM.
(DOI: 10.3171/2010.6.FOCUS10125)

Key Words • cerebral cavernous malformation • cell contacts • adherence junction • tight junction • occludin • VE-cadherin

Cerebral cavernous malformations constitute 5%–10% of all cerebrovascular malformations with a prevalence of approximately 0.5%. The condition affects cerebral blood vessels, resulting in dilation as well as thinning of the vessel wall.[1,17] Depending on the location of the affected vessel, this often leads to bleeding, causing seizures, the main clinical sign of CCMs, or other neurological deteriorations.[4,18] Currently, 2 types of CCMs can be distinguished: a familial form, which follows an autosomal dominant pattern of inheritance, and a sporadic form.[16] The familial form is caused by loss-of-function mutations in 3 known genes:[6,7,13,20] *KRIT1* (also known as *CCM1*), *CCM2* (also known as *malcalvernin* or *osm*[14]), and *PDCD10* (also known as *CCM3*). However, in many CCM patients such gene mutations are absent, which indicates additional pathogenic mechanisms. The recent findings of PTEN promotor methylation[28] or disease-modulating factors such as the HEG transmembrane receptor[12] and the RhoA GTPase[25] support this hypothesis.

In vitro cell studies have suggested that endothelial cells play a significant role in CCM[13,25] and that contacts to neighbor cells, such as neuroglia or neurons, and interendothelial cell contacts may be altered.[9,15] Zhao et al.[27] showed an impairment of intercellular barrier function of endothelial cells, while Clatterbuck et al.[5] detected gaps in endothelial tight junction formation in CCM. These authors and others conclude that the absence of intercellular barrier components renders vessels more susceptible to hemorrhage.[11,19,23,26] Looking at the intercellular junctions in more detail, occludin, as an integral plasma-membrane

Abbreviations used in this paper: CCM = cerebral cavernous malformation; DAPI = 4,6′-diamino-2-phenylindole-dihydrochloride; DVA = developmental venous anomaly; PBS = phosphate-buffered saline; SDS = sodium dodecyl sulfate.

* Drs. Bertalanffy and Hoerstrup contributed equally to this work.

protein, is found specifically at tight junctions. This protein, as well VE-cadherin, is specifically expressed in endothelial adherence junctions and plays a critical role in endothelial cell contacts.[22] Intercellular cohesion and organization as well as lining and sealing are important features of these protein complexes.[22,24] Their alterations lead to leaky cell contacts followed by permeability and paracellular outflow with oozing of erythrocytes. To analyze expression of these intracellular proteins within the pathological CCM tissue, we focused on the protein expression of occludin, VE-cadherin, and CD31 and the quantification of possible alteration of these proteins in human CCM tissue compared with control tissue.

Methods

Patients and Tissue Specimens

Surgery was performed for indications unrelated to this research project, and there was no sex, age, or race bias in the selection of patients. After ethics review board approval (No E-69/2008) and patient informed consent were obtained, 13 specimens were obtained from 13 patients (Table 1) undergoing neurosurgical resection of CCMs in accordance with institutional guidelines at the University Hospital Zurich. (All specimens were obtained by the same surgeon [H.B.].) Specimens of nontumor tissue obtained from patients undergoing tumor resection and of tissue obtained from patients undergoing epilepsy surgery were used as controls. Control tissue was treated in the same manner as CCM tissue. The median age of the 6 female and 7 male patients was 32 years (range 16–51 years). After resection, the tissue specimens were transferred immediately to the laboratory (Fig. 1) and divided into sections for protein extraction by snap-freezing in liquid nitrogen and for cryosection by embedding in optimal cutting temperature medium and frozen over dry ice. In addition, parts of the tissue were used for routine clinical neuropathological examination to verify that the specimens met the criteria for the diagnosis of CCM.

Immunofluorescence Analysis

For immunofluorescence analyses, tissue cryosections (12-μm thick) were mounted on uncoated slides and stored at −80°C. For analysis, slides were blocked with 0.1 M glycine in PBS for 5 minutes and permeabilized in 0.2% Triton X-100/PBS for 10 minutes. After blocking with 5% goat serum in 1% BSA/PBS for 30 minutes, primary antibodies against CD31 (Clon JC70A, monoclonal mouse antihuman antibody, DakoCytomation), occludin (polyclonal rabbit anti–human antibody, Invitrogen Corp.), and VE-cadherin (polyclonal rabbit anti–human antibody, Cell Signaling Technology Inc.) were added and incubated overnight at 4°C. After 3 washing steps with PBS (each for 5 minutes), secondary antibodies (Cy3-conjugated goat anti–mouse IgG, bivalent fragment antigen binding ($F[ab']_2$) fragments, as well as Cy5-conjugated goat anti–rabbit antibodies, both from Jackson Immuno Research) were added for 45 minutes. Thereafter the specimens were washed again 3 times with PBS and mounted in Lisbeth medium (0.1 M Tris-HCl (pH 9.5)/glycerol (3:7) containing 50 mg/ml n-propyl gallate. Qualitative analysis was performed by means of conventional fluorescence microscopy (Leica DM 6000B). Image processing was performed on a PC workstation using

TABLE 1: Summary of patient and lesion characteristics*

Patient Characteristics							Lesion Characteristics						
Case No.	Age (yrs), Sex	Ethnicity	Clinical Presentation	mRS score (adm/30-day FU)	Radiol Findings	Family Hx	Location	Side	Diameter (mm)	MRI Type†	Multiple Lesions	MRI Type, Unoperated Lesions	DVA/ Associated‡
1	59, F	caucasian	SH	4/3	RH	non	temporal	left	33.1	I	N	—	Y/Y
2	16, M	caucasian	SH	3/1	RH	non	parietal	right	55.1	I	N	—	N
3	38, M	caucasian	NH-FND	2/1	NRH	non	frontal	left	12.1	II	N	—	N
4	35, M	caucasian	SH	3/2	RH	non	parietal	left	24.2	I	Y	III	Y/Y
5	25, F	caucasian	NH-FND	0/0	NRH	non	frontal	right	22.4	II	Y	III, IV	N
6	32, F	caucasian	NH-FND	1/0	NRH	non	thalamic	right	15.8	II	N	—	N
7	23, F	caucasian	SH	5/5	RH	1 SR	brachium pontis	right	36.7	I	Y	III, III	N
8	39, F	caucasian	SH	1/1	RH	non	brachium pontis	left	26.8	I	N	—	N
9	30, M	caucasian	SH	4/3	RH	non	cerebellar	right	34.1	I	Y	III	Y/Y
10	50, M	caucasian	NH-FND	3/3	NRH	1 SR	brachium pontis	right	19.9	II	Y	III, IV	N
11	51, F	caucasian	NH-FND	2/1	NRH	non	brachium pontis	left	15.1	II	Y	III	Y/Y
12	19, M	caucasian	NH-FND	1/1	NRH	non	brachium pontis	right	12.1	II	N	—	Y/Y
13	20, M	African	NH-FND	1/1	NRH	non	brachium pontis	left	11.6	III	N	—	N

* Adm = admission; FU = follow-up; N = no; NH-FND = nonhemorrhagic focal neurological deficit; mRS = modified Rankin Scale; NRH = no recent hemorrhage; Radiol = Radiological; RH = recent hemorrhage; SH = symptomatic hemorrhage; SR = symptomatic relative; Y = yes.

† The MRI type classification was used as previously described.[2,4]

‡ The letters before the virgule indicate whether or not a DVA was present; the letters after the virgule indicated whether a DVA was directly associated with the surgically treated CCM lesion.

PhotoShop (Adobe Systems) and Image J 1.42q, and images were processed uniformly.

Polyacrylamide Gel Electrophoresis and Immunoblotting

The CCM and control samples were homogenized by slam freezing, resuspended in SDS sample buffer (3.7 M urea, 134.6 mM Tris–HCl, pH 6.8, 5.4% SDS, 2.3% NP-40, 4.45% β-mercaptoethanol, 4% glycerol, and 6 mg/100 ml of bromophenol blue) followed by boiling for 1 minute. Samples were run on 8% polyacrylamide gels together with All Blue (Bio-Rad Laboratories, Inc.) molecular weight marker. Equal amounts of protein were loaded for the different tissue extracts as judged by Coomassie blue staining from the previous gel. Blotting was carried out overnight onto nitrocellulose Amersham Hybond-C Extra (GE Healthcare). The same primary antibodies as those used for immunofluorescence (against CD31, occludin, and VE-cadherin) and an antibody against all actin isoforms (polyclonal rabbit anti–human antibody [Sigma-Aldrich]) were used for protein loading control. These primary antibodies, as well as horseradish peroxidase-conjugated anti–rabbit Igs (Calbiochem), which were used as secondary antibodies, were diluted in low-salt buffer supplemented with 4% nonfat milk powder. Antibody incubation was set for 1 hour and was followed by repeated washing with low-salt buffer. Chemiluminescence reaction was performed with SuperSignal (Pierce) and visualized on Fuji Medical x-ray films (Fujifilm).

Statistical Analysis

Statistical data analysis was performed with Microsoft Excel and SPSS Statistics software. To assess whether 2 independent samples of observations came from the same distribution, a nonparametric test was used (Wilcoxon–Mann-Whitney test). Probability values less than 0.05 were considered significant.

Results

Occludin, VE-Cadherin, and CD31

Occludin, VE-cadherin, and CD31 were detected in all human cryosection specimens, with a preferred localization in the intima of the vascular structures. In the controls, these proteins were almost exclusively present in the small vessels and capillaries and were undetectable in the surrounding brain tissue (Figs. 2 and 3), whereas immunofluorescent analyses revealed expression of occludin, VE-cadherin, and CD31 beyond the vascular intima in the CCM specimens. The localization of these proteins was mainly detected in small vessels including the capillary beds in a dispersed pattern. In some parts of the CCM tissue samples, occludin and/or VE-cadherin were arranged in clusters with a high concentration, in other parts primarily CD31 was present. Furthermore, in addition to the intima of the vessels, the surrounding tissue layers next to these clusters also stained positive for these proteins.

Cell-Contact Protein Levels

Expression analysis of the proteins of interest was performed by means of Western blot, and all 3 proteins could be analyzed by triplicate measurements in all CCM and control samples (Fig. 4). Statistical analysis revealed a significantly higher expression of CD31 ($p = 0.001$), occludin ($p = 0.044$), and VE-cadherin ($p = 0.028$) in the CCM samples than in the control counterparts. The range of expression varied within the individual CCM samples (Fig. 4). Analyzing clinicopathological correlations, no significant results regarding the localization of the CCM lesion (supratentorial vs infratentorial, $p = 0.25$–0.56), associated DVA ($p = 0.086$–0.31) or number of CCM lesions (1 vs > 1, $p = 0.39$–0.56) could be obtained. Comparing the active lesions with inactive CCM lesions showed differences (although not statistically significant) in the measured protein levels (Fig. 4). Active state was defined according to Al-Shahi Salman et al.[2] as a CCM lesion with an associated acute hemorrhage before surgery, detected by MR imaging/CT scan and confirmed during surgery and by pathological examination. The analyses in active CCM lesions revealed enhanced levels of CD31 and occludin and decreased levels of VE-cadherin compared with the inactive counterparts.

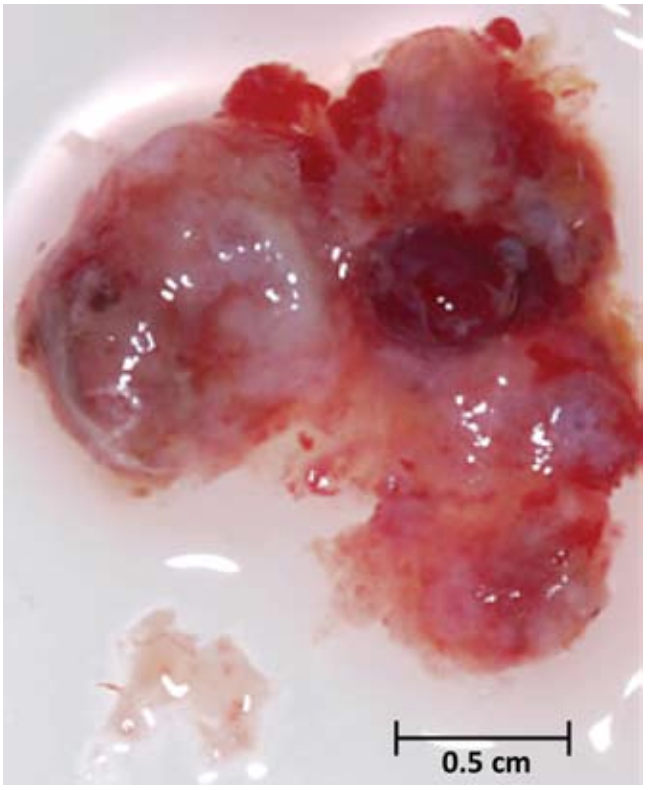


Fig. 1. Macroscopic view of a CCM lesion after resection.

Discussion

Endothelial cells are thought to be the governing cell type involved in CCM, but little is known about intra- and intercellular pathogenetic mechanisms, especially in humans.[25,27] Although CCM patients are more likely symptomatic in lesions associated with acute hemorrhagic complications, detailed large human clinicopathological as well as experimental studies regarding these underlying molecular mechanisms of the disease are currently

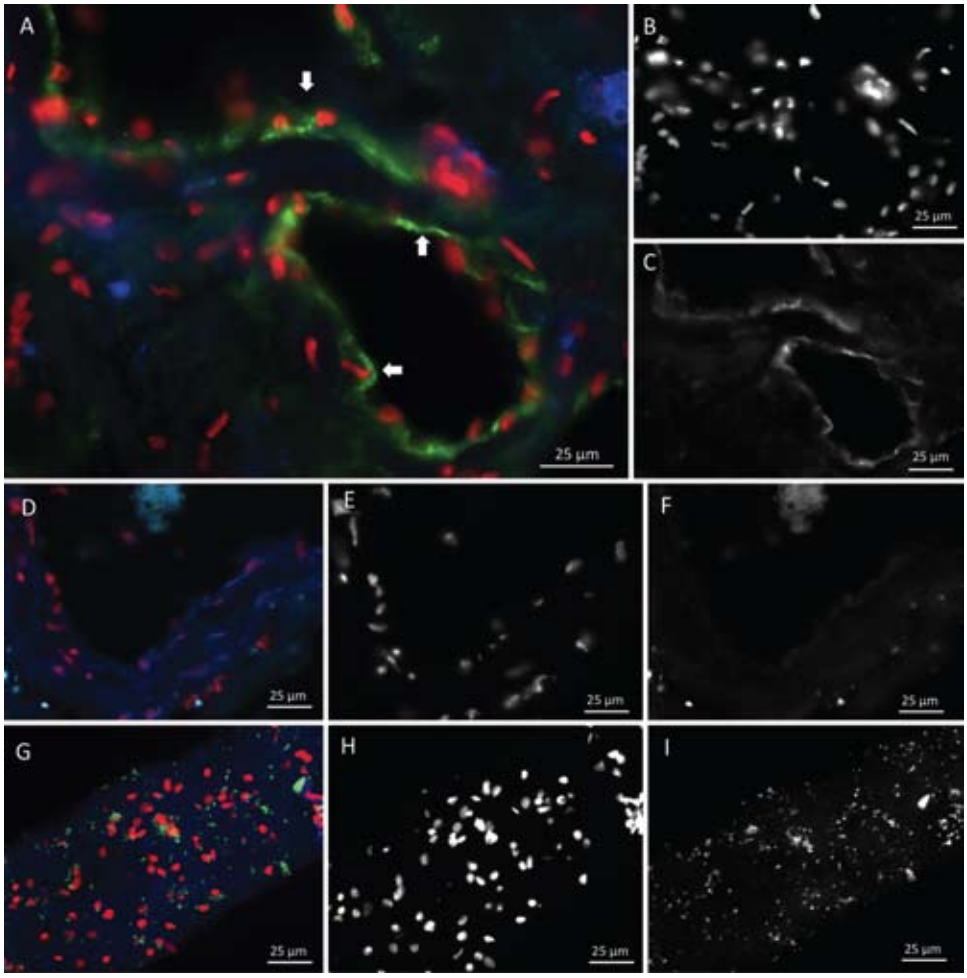


Fig. 2. Immunostaining of CCM **(A–F)** and control tissue **(G–I)** for occludin. **A:** Overlay of occludin *(green)*, DAPI *(red)*, and phalloidin *(blue)*. **B:** Single-channel image, DAPI. **C:** Single-channel image, occludin. **D:** Negative control without primary antibodies; overlay of occludin *(green)*, DAPI *(red)*, and phalloidin *(blue)*. **E:** Single-channel image, DAPI. **F:** Single-channel image, occludin. **G:** Control tissue, overlay of occludin *(green)*, DAPI *(red)*, and phalloidin *(blue)*. **H:** Single-channel image, DAPI. **I:** Single-channel image, occludin. *Arrows* indicate localization of occludin in the inner layer of the vessel.

missing. Interestingly, it seems that CCM-associated bleeding is a multifactorial event at the capillary level caused by alteration of endothelial cell or blood-brain barrier components leading to leakage of red blood cells through these lesions into the surrounding brain tissue.[13] In vitro studies of endothelial CCM cells showed that mutations of the known CCM genes induce dysfunction of endothelial cells by changes in the cascade of intracellular tubular proteins.[10,20] While the exact cascades of involved intracellular factors and proteins are not completely understood,[12,25] involvement of intercellular proteins, such as VE-cadherin, has been recently implicated in this process.[10,13] Indeed, a growing body of evidence supports the notion of the alteration of intercellular junctions between neurons, glia, pericytes, and endothelial cells.[5,11,19,23,27]

In this study, we quantified for the first time in human CCM tissue the transmembrane cell-contact proteins occludin and VE-cadherin (representing main proteins in tight and adherence junctions) and the vascular adhesion molecule CD31. We found a significant overexpression of these proteins in CCM tissue compared with control tissue, with slight variations within the patient samples (Fig. 4). These differences suggest that patient-specific or other unknown factors may influence the expression rate. The molecular CCM protein complex model of Hilder et al.,[10] which interacts closely with cytoskeletal proteins and modulates interendothelial cell junctions, may explain these changes in protein regulation.

Based on these individual protein profiles, protein expression levels in the specimens obtained from CCM patients were associated to the corresponding clinical phenotype to provide further details within the different patient subgroups. Although patients with infratentorial CCMs are more likely to have neurological symptoms than those with supratentorial CCM, we did not find any correlation between differences in protein levels in CCM tissue and CCM location. The distinctive clinical symptoms found in association with infratentorial CCMs are rather related to the limitation of the infratentorial space and the presence of important and sensitive neuronal tracts and centers within the brainstem, representing a challenge for neurosurgical treatment of these lesions.[3,8,21]

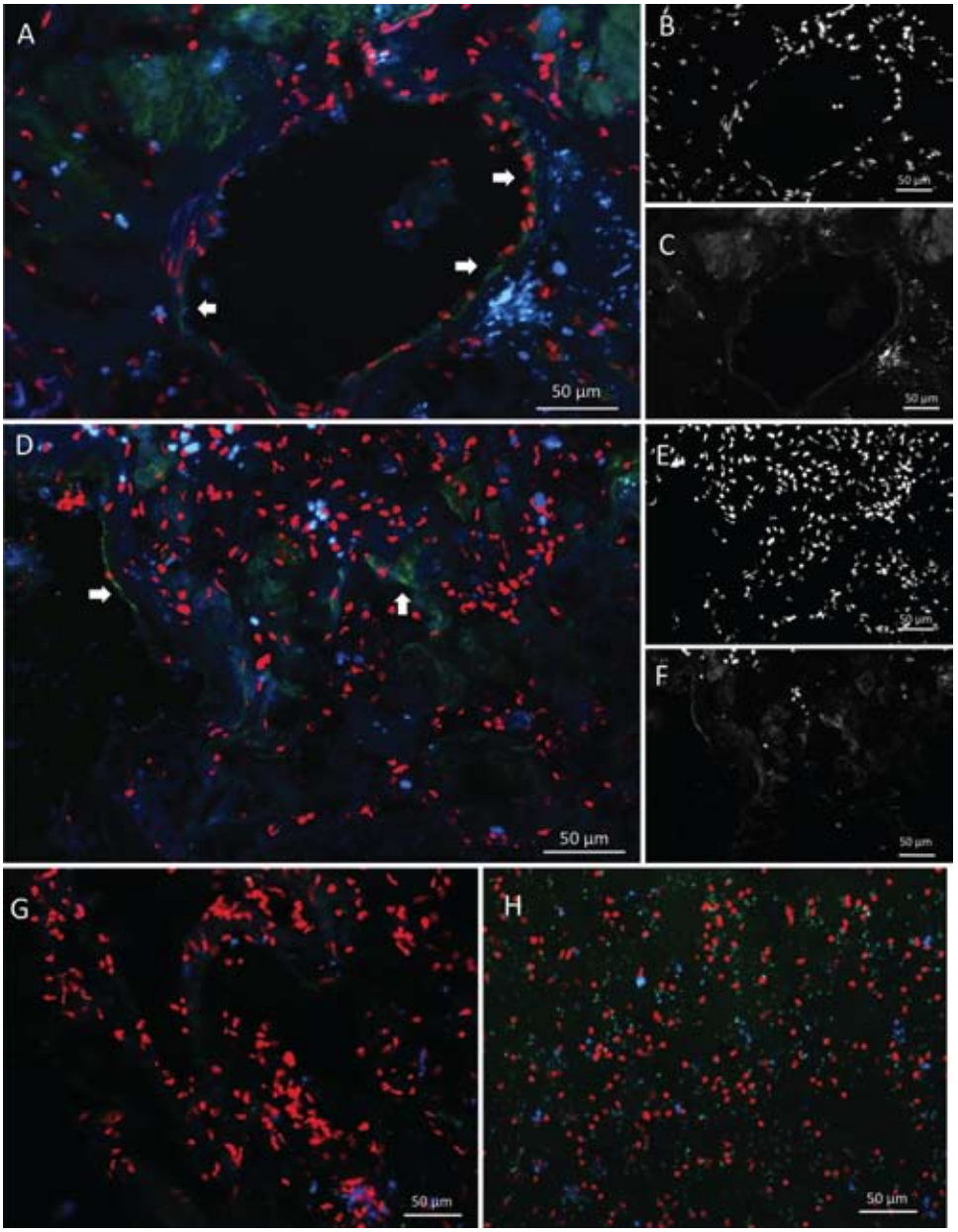
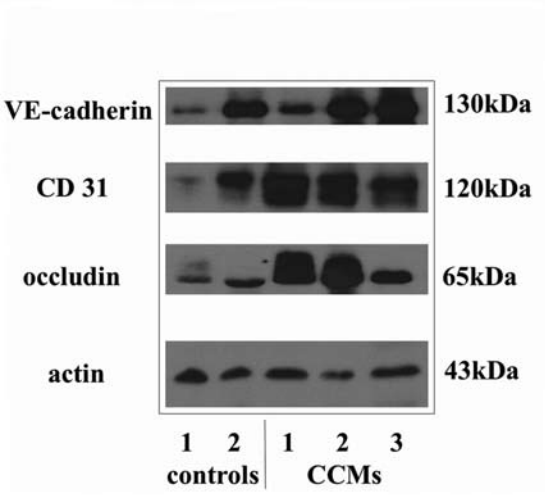


Fig. 3. Immunostaining of CCM **(A–G)** and control tissue **(H)** for CD31 and VE-cadherin. **A:** Overlay of CD31 *(green)*, DAPI *(red)*, and phalloidin *(blue)*. **B:** Single-channel image, DAPI. **C:** Single-channel image, CD31. **D:** VE-cadherin *(green)*, DAPI *(red)*, and phalloidin *(blue)*. **E:** Single-channel image, DAPI. **F:** Single-channel image, VE-cadherin. **G:** Negative control without primary antibodies, overlay of CD31 *(green)*, VE-cadherin *(blue)*, and DAPI *(red)*. **H:** Control tissue, overlay of CD31 *(green)*, VE-cadherin *(blue)*, and DAPI *(red)*. *Arrows* indicate localization of CD31 and VE-cadherin in the inner layer of the vessel.

The differences in the protein levels in CCM lesions found by Western blot analysis with respect to the presence of acute associated hemorrhages were highly interesting, although they did not reach statistical significance. However, a precise reason for the higher mean rates of CD31 and occludin and the lower mean rate of VE-cadherin in active CCM lesions remains unclear. These findings therefore need to be further explored in studies involving larger patient groups. This also applies to CCM-associated DVAs and the number of CCM lesions in single patients, since in this study no significant results were found regarding the relationship between the levels of the proteins of interest and DVAs (their presence or absence) or number of CCMs (multiple or single locations).

The immunofluorescence analyses of the CCM tissues showed staining for VE-cadherin, occludin, and CD31 in the intima and the surrounding brain tissue. In some specimens an arrangement in clusters was found; these clusters seem to originate in the intima and expand to the surrounding brain tissue. However, the vessels in the controls specimens were only slightly stained and did not show any cluster arrangements or spread to the sur-



I	CD 31	VE-cad.	occludin
MW control (n=6)	1	1	1
MW patients (n=13)	4.08	2.18	1.7
STABW	1.33	1.26	1.4
p-value	0.001	0.028	0.044
II			
MW active (n=6)	4.63	2.13	2
STABW	1.36	0.63	1.81
MW inactive (n=7)	3.6	2.22	1.44
STABW	1.3	1.77	1.14
p-value	0.11	0.27	0.22

Fig. 4. Immunoblotting and analyses of control and CCM tissue samples. **Left:** Immunoblotting of 2 control and 3 CCM tissue samples (single measurements are shown). **Right:** Protein quantification by triplicate measurement of all CCM samples relative to controls and statistical analysis (Wilcoxon–Mann-Whitney test) with regard to their significance compared with controls (I) and the difference between CCM samples with (active) and without (inactive) recent hemorrhage (II). MW = mean value; STABW = standard deviation from the mean value; VE-cad. = VE-cadherin.

rounding brain tissue. These immunohistochemical findings confirm the results of the increased protein levels revealed by Western blot and are suggestive of compensatory production due to nonfunctional cell contacts.

The weakness of this study can be found in the sample size, which may lead to an underpowered value of the clinicopathological correlation. However, this study does quantitatively identify alterations in endothelial junction protein expression in human CCMs for the first time. Future studies will be designed to pursue functional assays in vitro using tissue samples from a larger number of patients.

Conclusions

Based on the presented results we conclude that 1) the abnormal and discontinuous pattern in the investigated endothelial cell-contact proteins compared with control tissue explains the CCM-associated bleeding or oozing of erythrocytes; 2) endothelial cells appear to compensate for the loose cell contacts in the pathological situation by production of new proteins to strengthen their contacts; 3) the alterations of VE-cadherin, occludin, and CD31 in these CCM patients are not locally based or associated with multiplicity of lesions or the presence of DVAs. A difference in the expression level of the proteins of interest in the CCM lesions associated with acute hemorrhage compared with lesions without recent hemorrhage might be possible, but needs to be validated by means of functional assays and studies involving a larger number of patients.

Disclosure

This work was financially supported partly by the Swiss National Science Foundation and the Swiss Center of Integrative Human Physiology.

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: Burkhardt, Schmidt, Bertalanffy, Hoerstrup. Acquisition of data: Burkhardt, Schoenauer, Agarkova. Analysis and interpretation of data: Burkhardt, Schmidt, Schoenauer, Brokopp, Agarkova, Bozinov, Hoerstrup. Drafting the article: Burkhardt, Schmidt, Schoenauer, Brokopp, Bozinov. Critically revising the article: Schmidt, Brokopp, Agarkova, Bozinov, Bertalanffy, Hoerstrup. Reviewed final version of the manuscript and approved it for submission: Burkhardt, Bertalanffy, Hoerstrup. Statistical analysis: Burkhardt, Schoenauer. Study supervision: Bertalanffy, Hoerstrup.

Acknowledgments

The authors thank Ines Lohse (Department of Radio-Oncology, University Hospital Zurich) for her support with respect to the control tissue and the Institute of Biostatistics at the University of Zurich for assistance with the statistic analyses.

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Manuscript submitted May 14, 2010.
Accepted June 23, 2010.

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Neurosurg Focus 29 (3):E4, 2010

Cerebral cavernous malformations as a disease of vascular permeability: from bench to bedside with caution

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Tremendous insight into the molecular and genetic pathogenesis of cerebral cavernous malformations (CCMs) has been gained over the past 2 decades. This includes the identification of 3 distinct genes involved in familial CCMs. Still, a number of unanswered questions regarding the process from gene mutation to vascular malformation remain. It is becoming more evident that the disruption of interendothelial junctions and ensuing vascular hyperpermeability play a principal role. The purpose of this review is to summarize the current understanding of CCM genes, associated proteins, and functional pathways. Promising molecular and genetic therapies targeted at identified molecular aberrations are discussed as well. *(DOI: 10.3171/2010.5.FOCUS10121)*

Key Words • cerebral cavernous malformation • genetics • angiogenesis • endothelial cell junction • CCM1 • CCM2 • CCM3

Cerebral cavernous malformations are vascular malformations consisting of a cluster of enlarged capillary-like channels with a single layer of endothelium and without intervening brain parenchyma.[63] They are among the most common vascular malformations of the brain and are detected in the population at a rate of approximately 0.6 per 100,000.[4,39] Patients with CCMs may present with seizures, hemorrhage, focal deficits, or nonspecific headaches.[2,6,21,50] Magnetic resonance imaging, particularly with gradient reversal acquisition techniques, reveals reticulated lesions surrounded by low-intensity signals from hemosiderin-laden macrophages, giving a classic "popcorn" or "mulberry" appearance.[62]

Cerebral cavernous malformations are characterized by separate familial and sporadic forms of the disease that have been described in multiple reports over the past 4 decades.[8,13,22,27,33,34,46] The familial form of the disease is inherited in an autosomal dominant pattern. It is involved in up to 30% of all cases and is present in a greater proportion of Hispanic Americans of Mexican descent than other ethnic groups.[17,36,40] Familial CCMs are more likely to hemorrhage, grow, and form new lesions than sporadic CCMs.[45,57] Sporadic CCMs are more likely to have a benign course and to be associated with developmental venous anomalies.[10,56,57] Cerebral cavernous malformations have also been reported after brain irradiation.[38,51]

Treatment for CCMs is tailored to the symptoms, location, and hemorrhagic activity of a particular lesion. Authors of several case series have reported good outcomes with surgery for medically intractable seizures due to a CCM and for superficial lesions in patients who present with recurrent symptomatic hemorrhages.[6,15,24,52,53,80] Surgery for deep-seated or brainstem lesions is less successful and is associated with an early morbidity rate of roughly 30%–70% and a mortality rate of 2%.[30] Stereotactic radiosurgery for these lesions remains controversial and its associated morbidity is significant.[59] The timing and choice of treatment is further complicated by the difficulty in predicting the natural history of specific lesions.[6]

There has been great progress in the understanding of vasculogenesis and the pathogenesis of CCMs over the past 2 decades.[6,39] Three separate genes have been identified in association with familial CCMs: *CCM1*/*KRIT1*, *CCM2*/*MGC4607*, and *CCM3*/*PDCD10*.[7,19,23,41] Each exhibits a Mendelian autosomal dominant inheritance due to a heterozygous loss-of-function mutation at 1 of 3 distinct loci. The respective encoded proteins appear to interact with cytoskeletal and interendothelial cell junction proteins.[39]

Abbreviations used in this paper: CCM = cerebral cavernous malformation; ICAP-1 = integrin cytoplasmic domain–associated protein-1a; KRIT1 = Krev interaction trapped 1; PCDP10 = programmed cell death protein 10.

There has been a concurrent progression in the identification of genetic targets and biotherapeutics for other human diseases, targeted at molecular defects or signaling pathways affected by disease mutations.[1,47–49,64] Furthermore, it is anticipated that the identification of molecular disease pathways in familial cases will unlock pathobiological mysteries and reveal therapeutic opportunities for the sporadic form of the disease. The purpose of this review is to summarize current concepts of CCM pathogenesis including its genetic and molecular basis. The concept of vascular hyperpermeability as it relates to CCM pathobiology and potential therapeutic targets are discussed as well.

Throughout this review we have employed the conventional and distinct rules of nomenclature for disease, lesion, human gene, mouse gene, and protein. The human inherited disease cerebral cavernous malformation, or the vascular lesion that characterizes the phenotype, is abbreviated CCM. Human CCM genes are fully capitalized and italicized, *CCM1*, *CCM2*, and so forth. Similarly, murine genes are italicized and use both upper and lower case letters, as *Ccm1*, *Ccm2*, and so forth. To avoid confusion, we refer to the respective protein products in capitalized nonitalicized letters (CCM1, 2, or 3), or by their protein database names—KRIT1, malcavernin (or OSM), and PDCD10, respectively. With these clarifications, it should be evident whether the term in question refers to the disease, a vascular lesion, a gene (mouse or human), or a protein.

The CCM Genes

CCM1 (KRIT1)

CCM1 is located at chromosome locus 7q11–q22 and was the first gene identified in association with the familial form of CCMs.[23] Linkage studies have shown that a *CCM1* mutation is involved in 40% of familial CCMs and nearly half of those patients will have neurological symptoms before 25 years of age.[6,21,61] The product of *CCM1*, named Krev interaction trapped 1 or KRIT1, is an ankyrin repeat–containing protein that interacts with RAP-1A (Krev-1), which is a member of the RAS family of GTPases.[37,66] It has also been revealed that KRIT1 interacts with integrin cytoplasmic domain–associated protein-1a (ICAP-1), a protein involved in β1-integrin–mediated signal transduction.[81]

Germline mutations in *CCM1* cause CCMs, and roughly 100 distinct mutations in this gene have been identified to date with familial CCM disease.[11,31,35,37,44,61] Homozygous *Ccm1* knockout mice die in midgestation with gross dilations of the major arteries and heart chambers and narrowing of other arteries.[77] CCM lesions are not documented in mice with heterozygous *Ccm1* knockout alone but when coupled with *Trp53* mutation, vascular anomalies similar to CCMs can develop.[60,67]

KRIT1 binds CCM2 and SNX17, a protein involved in endocytosis and the sorting machinery of transmembrane proteins.[16] KRIT1 mRNA and protein have been found in vascular endothelium as well as in astrocytes, pyramidal cells, and epithelial cells.[18,32] KRIT1 is predominantly localized in the cytoplasm but it can shuttle between the cytoplasm and nucleus.[26,76] ICAP-1 also shuttles between the nucleus and the cytoplasm but is mainly found in the nucleus.[81,82] KRIT1 and ICAP-1 have a synergistic role in β1-integrin–mediated cell proliferation. KRIT1 also appears to modulate ICAP-1 regulation of β1-integrin–mediated signal transduction.[81] In addition, KRIT1 binds to RAP-1A, a GTPase involved in interendothelial junction intergrity.[29] RNA-mediated depletion of KRIT1 impairs the ability of RAP-1A to stabilize endothelial junctions, and this may most directly explain the role of KRIT1 in the molecular pathogenesis of CCMs.[29]

CCM2 (MGC4607)

CCM2 is localized at 7p15–13 and was initially identified by 2 independent teams using different approaches, gene sequencing and loss of heterozygosity mapping.[19,41,61] *CCM2* mutations are involved in up to 40% of familial CCMs.[19,42] Patients with *CCM2*-associated disease have a lower number of gradient-echo sequence lesions than those with *CCM1* or *CCM3* disease, and the number of lesions increases less rapidly with age than in patients with *CCM1* disease.[20] Homozygous deletion of *Ccm2* from mouse endothelial cells leads to morphogenic defects in major arteries and veins and ultimately midgestational death.[9] Heterozygous mice with *Ccm2*$^{\pm}$ mutations do not form CCM lesions, unless sensitized by a second hit such as the loss of *P53* tumor suppression gene function.[67]

The CCM2 protein, also referred to as malcavernin, shows similar temporal expression patterns as KRIT1, although KRIT1 is expressed in a greater variety of tissues.[65] Zawistowski and colleagues demonstrated that CCM2 binds to KRIT1 via a phosphotyrosine-binding domain, in a manner similar to ICAP-1, and is able to sequester KRIT-1 in the cytoplasm.[61,79] This suggests a common functional pathway and loss of the KRIT1-CCM2 interaction may result in CCM development. The KRIT1-CCM2 interaction also stabilizes endothelial cell junctions by suppressing a protein called RhoA and its effector protein ROCK that are involved in actin stress fiber formation and endothelial monolayer permeability.[70]

CCM3 (PDCD10)

CCM3, localized at 3q25.2–q27, encodes programmed cell death protein 10 (PDCD10) and is the most recently discovered gene involved in familial CCMs.[7] *CCM3* mutation carriers are less common than *CCM1* or *CCM2* carriers, but they are more likely to present with hemorrhage and to have symptom onset before 15 years of age.[20] The temporal expression of *CCM3* mRNA correlates with that of *CCM2* in meningeal and parenchymal cerebral vessels.[58] Both CCM2 and CCM3 proteins have been identified in developing placental endothelium, corroborating their role in vasculogenesis.[72]

The exact function of CCM3 has not been fully clarified. Chen et al.[12] found that overexpression of wild-type CCM3 induces endothelial cell apoptosis. Induction of apoptosis by serum starvation of endothelial cells leads conversely to increased expression of CCM3, and siRNA-mediated inhibition of CCM3 is responsible for decreased

cell death.[12] These findings led the authors to suggest that aberrant apoptosis, in the endothelium or neural cells, may play a role in the pathogenesis of CCMs.[12] More recently, Fidalgo et al.[25] found that CCM3 is located on the Golgi apparatus in a complex with proteins of the germinal center kinase III family (GCKIII). Depletion of CCM3 leads to Golgi apparatus disassembly and impaired cellular migration.[25]

Importantly, CCM3 protein precipitates and colocalizes with CCM2.[75] Thus, all 3 CCM proteins interact to form a complex that then interacts with other proteins such as β1-integrin and ICAP-1.[6,61] Patients with *CCM1*, *CCM2*, or *CCM3* disease exhibit histologically indistinguishable CCM lesions and their respective mRNA expression patterns suggest closely linked functions and a common disease pathway.[6,61] Interestingly, discrepancies in linkage data and the frequency of identified mutations have suggested the presence of an additional CCM gene that has yet to be identified.[43] This gene may account for some kindreds with clear familial inheritance that has not been linked to any of the 3 known loci.

Vascular Permeability and CCMs

More than a decade ago, one of the authors (I.A.A.) reported defective interendothelial cell junctions in human CCM lesions examined by electron microscopy.[78] That finding has since been corroborated by other investigators.[14,74,78] The understanding of the cellular functions of the CCM proteins is slowly unfolding, and there is growing evidence that the ultimate cellular pathology in this disease lies in dysregulation of vascular development and endothelial permeability (Fig. 1).

It has been demonstrated that KRIT1 is localized, in part, to interendothelial cell junctions and that its loss results in disruption of junctional stability that leads to increased permeability in vitro and in vivo.[29,70] Moreover, loss of malcavernin has similar effects on endothelial cell junction stability.[70,76] Importantly, although patients with familial CCM may be heterozygous for *CCM1*, *CCM2*, or *CCM3* mutations, the endothelial cells within CCM lesions appear to lack the relevant protein.[54] One of the authors (I.A.A.) and others have shown that this is often due to a somatic mutation of the remaining wild-type allele at the relevant locus.[3,28] Loss of endothelial cell junctions readily explains the leakage of blood in CCMs and their associated hemosiderosis and can account for the observed inflammatory response in CCM lesions.[68,69] (This concept of CCM protein impact on the interendothelial cell junction was recently illustrated in a compelling editorial by Patterson.[55])

Ccm2 knockout mice show a failure of angiogenesis and die in midgestation. Mice that lack CCM2 in the endothelium alone develop vascular defects and impaired vessel formation. Whitehead et al.[76] found that CCM2-deficient mice also develop impaired endothelial barrier function and increased actin stress fibers through RhoA GTPase activation. These investigators found that simvastatin, which is a known inhibitor of RhoA GTPase, was able to reverse CCM2-mediated barrier dysfunction.

The relationship of CCM proteins and RhoA has been investigated by the current authors' (I.A.A. and R.S.) team. Working with Stockton and colleagues, we have recently demonstrated that the loss of either KRIT1 or CCM2 disinhibits RhoA and ROCK activity leading to interendothelial barrier instability and vascular leaking.[70]

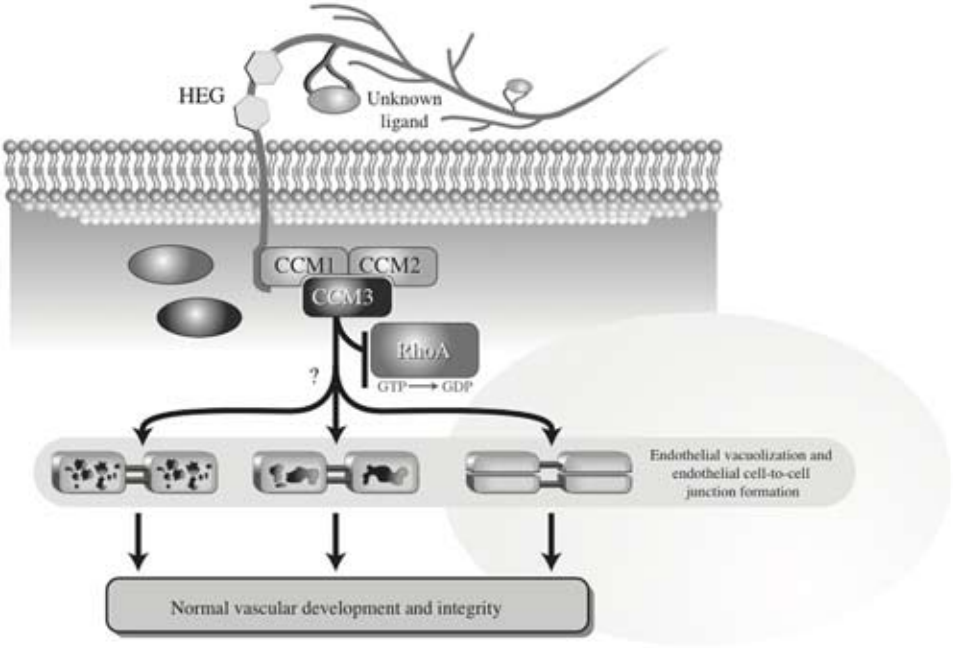

Fig. 1. Depiction of the current understanding of the CCM pathway. An unidentified ligand binds to a transmembrane receptor named heart of glass (HEG) that interacts with an intracellular protein complex comprised of the CCM proteins. This interaction leads to a number of processes, including the inhibition of a RhoA GTPase, that ultimately result in normal interendothelial cell junctions and vascular integrity.

We also discovered that administration of fasudil, a potent inhibitor of ROCK, reverses the vascular leak in vivo offering a potential therapy for CCM disease.

In this same work, we demonstrated markers of increased ROCK activity in endothelial cells lining sporadic and familial human CCM lesions that were excised surgically.[70] This suggests that a final common signaling aberration involving ROCK activation takes place in both sporadic and inherited lesions. Background hyperpermeability in familial cases may be one factor in lesion genesis. A second hit (that is, a focal somatic mutation) might lead to full-blown lesion genesis, likely through complete loss of CCM protein. This is then accompanied by more profound failure of the vascular barrier, hemorrhage, and reactive inflammation—all characteristic of the mature CCM lesion phenotype. The background hyperpermeability and the final CCM lesion both exhibit increasing activation of ROCK. It is possible that developmental venous anomalies and brain irradiation may also cause vascular hyperpermeability in the respective brain regions and predispose to CCM lesion genesis via a similar mechanism involving ROCK activation.[70]

Development of CCM Therapies

The ultimate goal of cellular and genetic investigations of CCMs is the development of molecular or genetic therapies to alter the clinical phenotype.[5] Identification of therapies that prevent lesion genesis or make lesions less likely to hemorrhage or more likely to regress will have a profound impact on the morbidity associated with CCMs. Other therapies might make the lesions more sensitive to apoptosis in reaction to ablative therapies or irradiation. One hurdle that has been cleared is the selectivity of gene therapy vectors for endothelial cells. Tan et al.[71] developed a method of coupling antibodies to liposome-DNA complexes that are internalized by cells. They were also able to show that this vector can deliver a selected gene to activated endothelial cells.[71] In addition, Trepel et al.[73] have described a method of selective gene therapy delivery to specific vascular targets using an adenovirus vector.

Other therapies for CCM may not require selective vector delivery to endothelial cells. Early results with statin and fasudil, as discussed above, suggest that the background predisposition to CCM disease can be rescued by ROCK inhibition, a well-tolerated therapy in humans. Whether such treatment will in fact prevent lesion genesis remains to be demonstrated, and the advent of animal models with transgenic mice has offered new opportunities to test this hypothesis.[60,67] It is unclear if such therapy can reverse markers of ROCK activation in actual, full-blown CCM lesions and what overall effect it might have on such lesions.

Conclusions, Implications, and Cautions to Patients

A number of discoveries regarding the cellular and molecular pathogenesis of CCMs have been unveiled over the past 2 decades. It is becoming more evident that the protein products of the CCM genes are associated within the cell and likely share a common final pathway, one that ultimately impairs endothelial cell-cell junctions and vasculogenesis. The development of molecular and genetic therapies for CCMs is still in its infancy; however, there is great hope that effective treatments will be found.

With these exciting research discoveries, there is now the genuine hope of vascular permeability therapy in this disease. Still, we do not know if such treatment will prevent lesions from forming or prevent existing lesions from growing or what other effects it might have. It is still unclear if one particular drug or class of drugs, such as the commonly available statins, is the best permeability therapy or if as-yet-undiscovered drugs might do better. We have no idea about the potential magnitude of any treatment effect (that is, how many lesions or bleeds are prevented per year, if any, per hundred patients treated) or if side effects, both known and unforeseen, will wipe out any potential benefit. The good news is that all these questions are answerable with careful research. Animal studies will attempt to define therapeutic effect on actual lesions so we can know better what effect to expect and pursue in humans. Better animal models are being developed that will allow such testing.

In the end, the only results that count are those recorded in human patients. It is certainly appropriate to attempt to define an effect on lesions in a carefully selected group of patients in an exploratory (Phase I) clinical trial in man or even a Phase I or II study that looks for the best dose, safety, and estimates of treatment effect. In a disease where there is no proven therapy to date, it is perfectly reasonable to pursue such exploratory trials with apparently safe drugs, such as statins. Controversies will arise over whom to include and exclude from these exploratory trials, what effects to look for (lesion number, lesion size, and/or bleeds), and how long to follow the treated and untreated cases to glean a potential benefit. If a convincing effect is shown in these exploratory trials, a more definitive prospective double-blinded randomized trial (Phase III) will be needed to prove effectiveness and alter the standard of clinical practice. A negative exploratory trial may not mean complete futility. The same drug might work with a different group of patients or in combination with other interventions or with different outcome measures.

Additional research might suggest further therapeutic approaches, including other CCM signal–modulating, antiinflammatory, or blood vessel–modifying (antiangiogenesis) drugs. Enthusiasm or concern about each will need to be assessed based on potential risks and benefits of the individual therapy. Exploratory clinical trials will obviously be easier to justify if they involve safe drugs already in widespread clinical use. More powerful and potentially more risky therapies will require convincing proof of effect and safety in animals before trials can proceed in humans.

We are quite excited about the scientific promise of these advances, but proofs of benefit and safety on any aspect relevant to clinical CCM disease are not yet in hand. There will be disappointments, and good and bad surprises. Concerns about ethics and safety will deliberately slow the process down. Yet nothing will chill this

research colder than a bad side effect in a human study participant or a false promise that causes unintentional harm through ill-advised exuberance for an ineffective treatment. False starts might threaten the enthusiasm toward more promising future research. Furthermore, no trial will include all CCM cases nor be automatically applicable to every patient. Ultimately, some treatments might work best at preventing lesion formation while others succeed at shrinking lesions or preventing growth and hemorrhage. Some treatments might work better in older or younger patients, in cohorts with more aggressive disease, in one genotype but not others, in combination with another therapy, or in genetic but not sporadic lesions or vice versa. Much research is still needed, but there are glimmers of hope on the horizon, none of which could have been imagined a short decade ago.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. They acknowledge past and ongoing collaborations with the laboratories of Douglas Marchuk at Duke University, and Mark Ginsberg at the University of California San Diego, cited in this paper. Dr. Awad, Dr. Shenkar, and Dr. Shi have received grant support from the NIH/NINDS for research related to CCM disease pathobiology (R21-NS052285 and R01-NS060748). Dr. Awad is the chairman of the scientific advisory board of the Angioma Alliance (www.angioma.org).

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Jabbour, Awad. Analysis and interpretation of data: Campbell, Awad. Drafting the article: all authors. Critically revising the article: Jabbour, Yadla, Shi, Campbell, Awad. Reviewed final version of the manuscript and approved it for submission: Yadla, Shenkar, Shi, Campbell, Awad.

Acknowledgment

The authors would like to thank Paul Schiffmacher for his assistance with the illustration.

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Manuscript submitted May 10, 2010.
Accepted May 27, 2010.
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Neurosurg Focus 29 (3):E5, 2010

Susceptibility weighted magnetic resonance imaging of cerebral cavernous malformations: prospects, drawbacks, and first experience at ultra–high field strength (7-Tesla) magnetic resonance imaging

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High-resolution susceptibility weighted MR imaging at high field strength provides excellent depiction of venous structures, blood products, and iron deposits, making it a promising complementary imaging modality for cerebral cavernous malformations (CCMs). Although already introduced in 1997 and being constantly improved, susceptibility weighted imaging is not yet routine in clinical neuroimaging protocols for CCMs. In this article, the authors review the recent literature dealing with clinical and scientific susceptibility weighted imaging of CCMs to summarize its prospects and drawbacks and provide their first experience with its use in ultra–high field (7-T) MR imaging. *(DOI: 10.3171/2010.6.FOCUS10130)*

Key Words • cavernous malformation • venous anomaly • susceptibility weighted imaging • high-field magnetic resonance imaging

Susceptibility weighted imaging is a high-resolution 3D–gradient echo MR imaging sequence that uses both magnitude and filtered phase information, separately or combined, to create an image based on T2*-contrast and phase changes due to magnetic susceptibility. The latter is defined as the magnetic response of a substance when placed in an external magnetic field.[9] As most biological tissues are diamagnetic, for example, brain parenchyma,[36] phase image contrast is dominated by paramagnetic substances that have a large impact on its surrounding magnetic field, such as deoxygenated blood, hemosiderin, methemoglobin, or ferritin. They produce a strong hypointense signal in the processed susceptibility weighted images and therefore allow high-resolution depiction of venous structures, blood products, and iron deposits (Fig. 1). These principles of susceptibility weighted imaging do not depend on high intravascular flow such as in T2-weighted imaging, time-of-flight angiography, and phase-contrast MR angiography when depicting small vessel structures.[38] Among several potential clinical applications in neurosurgery, as already proposed by Mittal et al.,[21] susceptibility weighted imaging may therefore be most helpful in imaging CCMs. Occurring as sporadic or hereditary forms,[44] these low-flow vascular lesions affect 0.4%–0.9% of the population[28] and represent 8%–15% of all cerebrovascular malformations.[4] Pathologically, CCMs are characterized by closely packed, thin-walled, enlarged vessels without intervening brain parenchyma[43] and are filled with blood at different stages of thrombosis.[41] The lesions are accompanied by associated venous malformations in many of the reported cases.[24] Recurrent intralesional microhemorrhages and secondary iron deposit mainly determine the symptoms in patients[16] and form the typical appearance of these lesions on conventional MR imaging.[17,32]

Although the first article on susceptibility weighted imaging was already published in 1997[31] and sequence software has constantly been improved and is available from all major developers, it has not yet been routinely incorporated into clinical "neuroimaging protocols" for CCM.[9] This may be due to the fact that at lower field strength (1.5-T) MR imaging, the full application of sus-

Abbreviations used in this paper: CCM = cerebral cavernous malformation; DVA = developemental venous anomaly; MIP = minimum intensity projection.

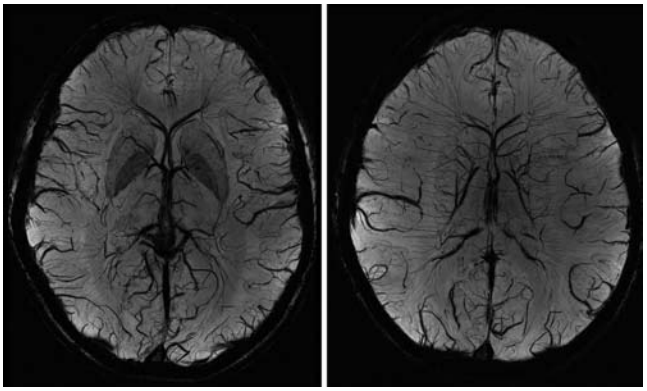

Fig. 1. Axial slices of susceptibility weighted MR images of the brain at 7-T field strength of the basal ganglia **(left)** and the cerebrum **(right)**. Minimum intensity projection over 5 slices was used to further enhance vessel/brain contrast leading to discreet overemphasized vessel dimensions. Note the clear depiction of the venous vessel structures (up to venule size) and the sharp delineation of putamen and globus pallidus **(left)** due to their iron content.

ceptibility weighted imaging is limited because of the demanding echo time and spatial resolution, which leads to extensively long acquisition times. With the development of higher field strength (≥ 3 T) MR imaging systems, however, these limitations can be overcome.[2,30] As signal-to-noise ratio and susceptibility contrast increase with magnetic field strength (B_0),[18] higher field strength MR imaging provides significantly improved conditions for susceptibility weighted imaging.

In this article, we review the recent literature dealing with clinical and scientific susceptibility weighted imaging of CCMs to summarize prospects and drawbacks of this complementary imaging modality, and we present our first experience with its application at 7 T.

Susceptibility Weighted Imaging in Detection of CCMs

Gradient echo T2*-weighted imaging is currently considered a clinical gold standard in detection of CCM.[7,20] The typical signal loss caused by hemosiderin deposits within and around the lesion together with susceptibility changes between deoxygenated blood and the surrounding brain tissue can reveal CCMs that are missed on conventional T1- and T2-weighted images. However, several authors suggested relatively early[29,38] that susceptibility weighted imaging should be theoretically superior to conventional T2*-weighted gradient echo imaging in this regard, especially at higher magnetic field strengths. In 1999, Lee et al.[19] demonstrated that susceptibility weighted imaging at 1.5-T field strength revealed additional lesions in 2 of 10 patients with CCMs compared with standard T2*-weighted gradient echo imaging. In 2007, Pinker et al.[25] reported an improvement in lesion detection using 3-T high-resolution susceptibility weighted imaging compared with T2*-gradient echo imaging at 1.5 T in a series of 17 patients with CCMs. They were able to detect an additional 7 lesions in 6 patients. All of these lesions were very small, on average smaller than 0.33 cm. A study of 15 patients with familial CCMs conducted by de Souza et al.[6] compared the sensitivity of lesion detection of susceptibility weighted imaging, T2*-gradient echo imaging, and T2-weighted turbo spin echo sequences at 1.5-T field strength. They found that especially in these patients presenting with multiple lesions, susceptibility weighted imaging has a significantly higher sensitivity than conventional imaging. Recently, Schlamann et al.[37] presented a series of 10 patients with CCMs. The authors focused on the comparison of T2*-weighted gradient echo imaging at 1.5-T and 7-T field strength. They detected an additional lesion in 1 patient and numerous new lesions in a patient with a familial CCM using 7-T MR imaging. An additional sensitivity of susceptibility weighted imaging at 7-T field-strength imaging compared with T2* gradient echo imaging could not be observed; however, imaging protocols were designed to be comparable to routine 1.5-T MR imaging protocols and not to maximize the detectability of CCM lesions.

In summary, these small series show an improved sensitivity of susceptibility weighted imaging in identifying the number of lesions in patients with CCM compared with conventional T2*-weighted gradient echo imaging. Naturally, the effect is suggested to be higher in patients with multiple lesions. Even very small lesions could be detected. These effects might be beneficial for preoperative imaging, screening, and follow-up imaging in patients with familial CCM or multiple CCM after radiation therapy (Fig. 2). In patients with "cryptogenic" epilepsy or atypical intracerebral hemorrhage, susceptibility weighted imaging may also help to confirm the diagnosis of a CCM in cases in which the lesion could not be detected on conventional MR imaging.

Susceptibility Weighted Imaging in Detection of Associated Venous Malformations

The association of CCMs with venous malformations is still controversial. Initially regarded as unusual coincidences,[33] several authors reported series with higher numbers of CCMs presenting with associated venous malformations.[14,24,28,39,45] Up to now, no consensus has been found regarding whether associated venous malformations are involved in the CCM's pathogenesis and natural history or how they should be treated.[14,24,49] One problem in clarifying this ambiguity is the challenging imaging of associated venous malformations, which are often occult on preoperative MR imaging or digital subtraction angiography.[14,28] Recently, Hong et al.[11] reported a series of 21 patients who presented with a CCM in the territory of a DVA. They investigated the presence of a curved medullary or draining vein in the distal portion of the CCM, the narrowing of the distal draining vein, and the presence of severe medullary venous tortuosity using contrast-enhanced gradient echo imaging at 3-T field strength. They observed a significantly higher amount of these angioarchitectural findings than in a control group and thus suggested these findings to be key factors in causing concurrent sporadic CCMs. Susceptibility weighted imaging might be a powerful complementary imaging tool in this regard. Although no large clinical series focusing the detection of associated venous malformations in CCMs exist, evidence from single cases is promising (Fig. 3C). Several authors have already reported an excellent depiction of DVAs, demonstrating the supe-

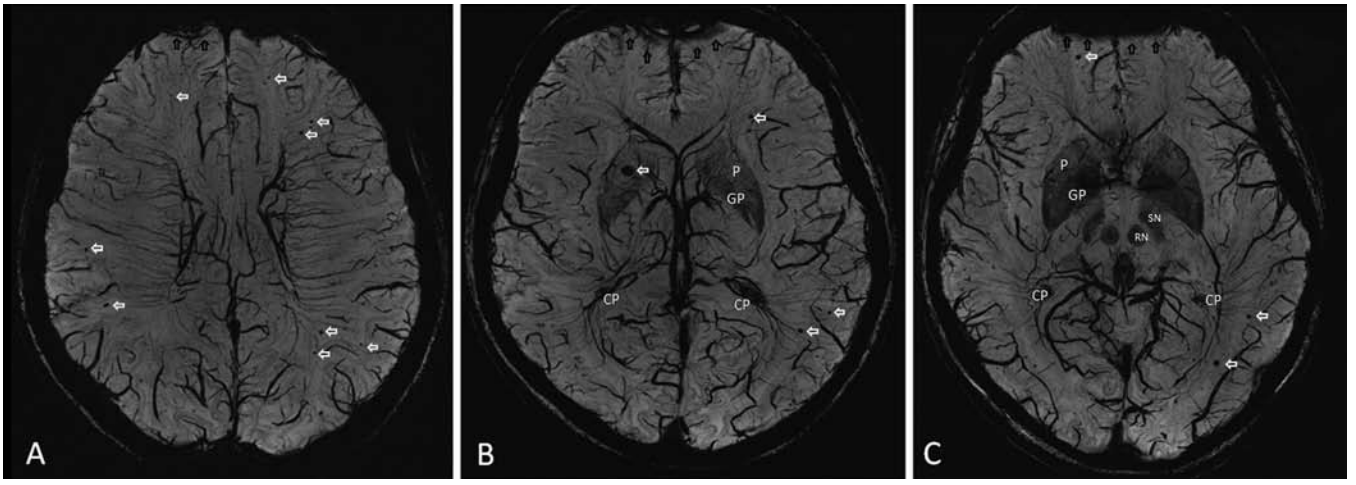

Fig. 2. Axial slices of susceptibility weighted MR images with MIP in a 34-year-old man with confirmed familial CCM revealing multiple hypointense lesions (several labeled with *small white arrows*) suggestive of CCM. CP = choroid plexus; GP = globus pallidus; P = putamen; RN = red nucleus; SN = substantia nigra. The *small black arrows* denote the signal cancellations caused by the adjacent frontal sinus.

rior visualization of both medullary and collector veins in non–contrast enhanced susceptibility weighted imaging over conventional MR imaging.[1,8,19,21,46] However, in the series by Pinker et al.,[25] among 17 patients with CCMs, no associated DVAs could be detected using 3-T susceptibility weighted imaging. A correlation with intraoperative findings of associated venous malformations was not possible because most of the patients in this series underwent Gamma Knife surgery rather than surgical removal of the CCM. Hence, the sensitivity of susceptibility weighted imaging in this task has to be investigated in larger series of CCMs undergoing surgical removal.

Susceptibility Weighted Imaging in Preoperative and Postoperative Imaging

Once a neurosurgical treatment decision is made, preoperative MR imaging of the lesion and its surrounding anatomical structures is crucial, especially to identify the optimal surgical approach,[4,22,28,34,35] estimate the amount of hemosiderin deposit in the adjacent brain tissue,[3,5,15,42] and reveal associated venous malformations.[14,24,28] Besides the improved depiction of venous malformations, as mentioned above, susceptibility weighted imaging may foremost be helpful in preoperatively delineating even very small amounts of hemosiderin deposits[9] or residuals of these deposits on postoperative images. Most authors recommend complete removal of the deposits in the adjacent brain to achieve optimal seizure control,[3,10,42,50] and residual hemosiderin deposits have been found to be associated with impaired seizure control,[3] although its complete role in this regard has yet to be discovered.[50] Clearly, susceptibility weighted imaging will be superior in the detection of even the smallest residual CCM postoperatively and has the potential to monitor increase or decrease in lesion vascularity after, for example, Gamma Knife surgery[48] as already mentioned by Pinker et al.[25]

Scientific Applications of Susceptibility Weighted Imaging in CCM Research

There are only a few studies that have addressed the application of MR imaging in fundamental CCM research. Shenkar et al.[40] reported the visualization of CCMs in

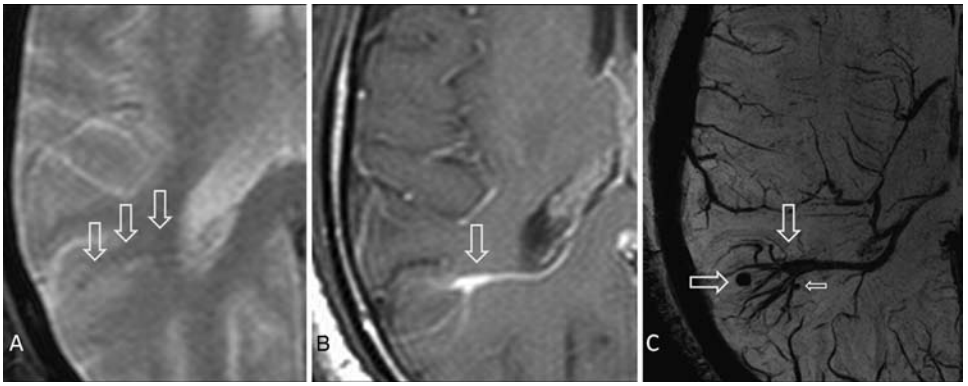

Fig. 3. Case 1. Neuroimaging was performed routinely in this 39-year-old man after a car accident. **A:** On 1.5-T MR imaging, T2*-weighted gradient echo imaging reveals very discreet signal changes in the right parietal white matter *(arrows)* suggestive of a DVA. **B:** An additional contrast-enhanced T1-weighted turbo spin echo image **(B)** confirms that suspicion *(arrow)*. **C:** Susceptibility weighted imaging at 7 T, using MIP, precisely delineates the DVA *(vertical arrow)* and reveals 2 hypointense lesions *(horizontal arrows)* most likely to be associated CCMs.

various states of their development in *CCM1* and *CCM2* knockout mice using T2*-weighted gradient echo imaging at ultra–high field strength MR imaging. Furthermore, they reported the delineation of intralesional angioarchitecture in ex vivo MR imaging of excised human CCM lesions and compared their results with histopathological findings.[41]

A variety of animal models of CCM have been recently described to help translate the cellular and biochemical insights into a better understanding of disease mechanism. However, neither *CCM1* nor *CCM2* heterozygous knockout mice sufficiently develop CNS vascular lesions.[26,27] The combination of homozygous loss of the tumor suppressor $p53^{(-/-)}$ with heterozygous knockout *CCM1* sensitizes mice to develop cerebral vascular lesions,[26] but still with an unsatisfactory incidence. These data indicate the requirement of the manipulation of the current animal models to more closely mimic human disease. On the other hand, CCMs in humans can grow for years, whereas the shorter lifespan of mice is likely to limit the size of the lesions that cannot be easily detected using routine histological methods. Applying advanced detection technologies such as susceptibility weighted imaging may largely improve the sensitivity of the visibility of lesions. More importantly, susceptibility weighted imaging is a noninvasive, non–contrast enhanced imaging tool and allows long-term tracking of lesion development. Therefore, susceptibility weighted imaging could be a powerful tool not only in clinical applications but also especially in repetitively monitoring the changes in the venous vascular system of animal models.

Drawbacks and Pitfalls of Susceptibility Weighted Imaging in Imaging of CCMs

As mentioned above, susceptibility weighted imaging requires long echo times and high spatial resolution, and therefore leads to an unreasonably long measurement time at lower field strength for covering the whole brain volume. However, this can be compensated by the increased signal-to-noise ratio available at higher field strength MR imaging ($B_0 \geq 3$ T). The main drawbacks of susceptibility weighted imaging are signal dropouts and phase artifacts especially at the air-tissue boundaries, such as the rostral skull base and the temporal lobe adjacent to the petrosal bone (Fig. 2). In these areas, detection of CCMs might be compromised. Another problem, especially at higher field strengths, could be the increasing "blooming" of susceptibility in the susceptibility weighted imaging data. These circular hypointense artifacts, caused by the strongly paramagnetic blood products within the lesion, can mask venous malformations associated with the CCM or other small CCMs nearby (Figs. 4 and 5). One simple approach to these problems may be the adaptation of the echo time, in-plane resolution and readout bandwidth of the sequence to reduce these artifacts, but also a separate analysis of magnitude, phase, and susceptibility weighted imaging information can be helpful. Further methods to reduce artifacts in susceptibility weighted imaging have been proposed already.[12,13] Generally, we always have to consider other reasons for hypointense lesions in T2*-weighted gradient echo imaging or susceptibility weight-

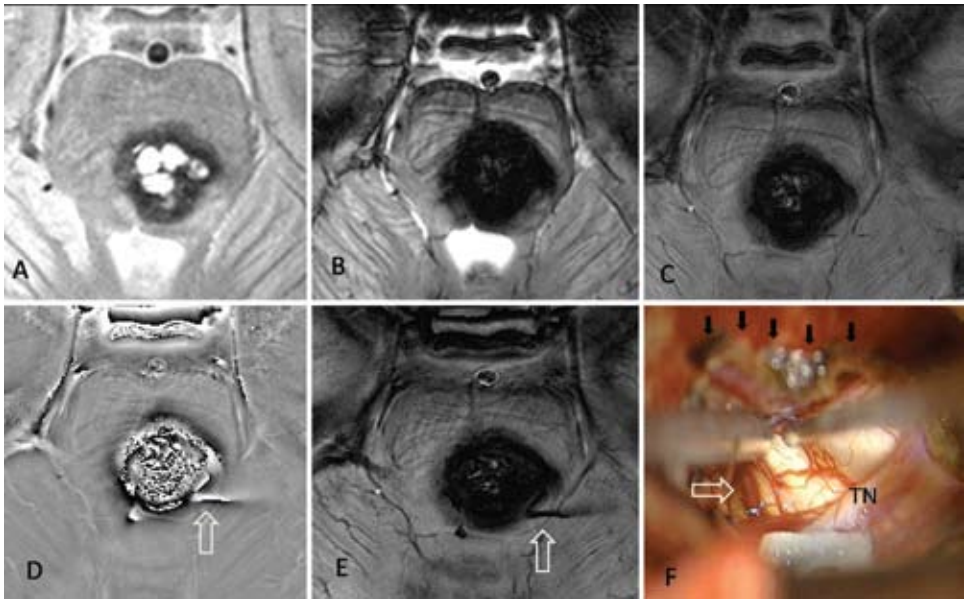

Fig. 4. Case 2. Preoperative 7-T MR images of a pontine CCM in a 29-year-old woman. The patient presented with a hemihypesthesia of the left half of the face and the right half of the body, and a mild motor weakness. The CCM was fully removed using a left subtemporal transtentorial approach. Comparison of T2-weighted turbo spin echo **(A)**, T2*-weighted gradient echo **(B)**, and susceptibility weighted **(C–E)** imaging at the same brain level. In the phase image **(D)** and in the processed susceptibility weighted image **(E)**, a curved draining vein can be seen *(white arrows)*, which was identified intraoperatively **(F)**. In the T2*-weighted gradient echo **(B)** and in the magnitude **(C)** images, as well as in the routine preoperative contrast-enhanced T1-weighted turbo spin echo, this vessel structure could not be delineated. The T2-weighted turbo spin echo **(A)** is showing the typical popcorn-like aspect of the CCM, representing different stages of microhemorrhage. The rather acute hemorrhages lead to stronger intralesional signal cancellations in the T2*-weighted gradient echo and susceptibility weighted images. TN = trochlear nerve. *Small black arrows* denote the incised tentorium.

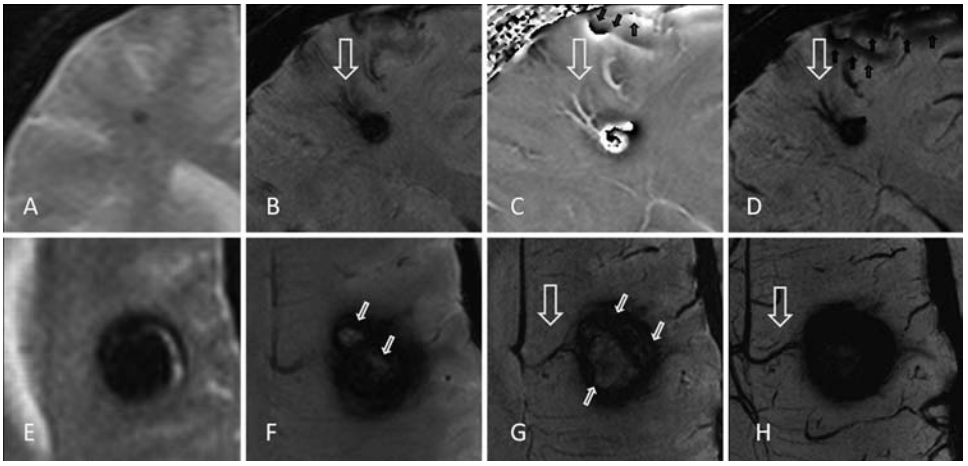

Fig. 5. Susceptibility weighted imaging of 2 CCMs in patients with seizures refractory to anticonvulsive medication at 7 T **(B–D and F–H)** compared with T2*-gradient echo imaging at 1.5 T **(A and E)**. Preoperative axial images of a right frontal and a left frontal CCM provide a detailed depiction of associated venous structures *(large arrows)* in susceptibility weighted imaging at 7 T in the phase **(C)**, processed susceptibility weighted **(D and G)**, and MIP **(H)** images. Furthermore, magnitude **(F)** and processed susceptibility weighted **(G)** images provide excellent visualization of intralesional structures *(small white arrows)*. Note that with MIP, intralesional signal cancellation occurs due to cumulative susceptibility effects **(H)**. In signal cancellations in **C and D**, respective phase artifacts caused by the adjacent frontal sinus can be seen *(small black arrows)*.

ed imaging, even in patients with multiple CCMs. In this regard, especially calcifications of a different origin or microangiopathic lesions have to be taken into account. Schlamann et al.[37] also observed differences in lesion size between 1.5-T and 7-T MR imaging in T2*-weighted gradient echo imaging up to 11%, which might also account for susceptibility weighted imaging. It will be difficult to investigate whether this increase in lesion size is caused by higher sensitivity to adjacent hemosiderin deposits or an artifact of the increased susceptibility at higher magnetic field strength MR imaging.

First Experience With Susceptibility Weighted Imaging of CCM at 7-T Field Strength

The local ethics committee authorized the patient examinations as part of fundamental research on high-field MR imaging. Written consent was obtained from all patients before imaging.

Susceptibility weighted imaging was performed using a 7-T MR imaging system (Magnetom 7T, Siemens Healthcare) equipped with a gradient coil (coil length 125 cm) capable of 45 mT/m maximum amplitude and a slew rate of 220 mT/m/msec. We used a custom-built 8-channel transmit/receive (Tx/Rx) head coil, which was previously characterized in simulations and benchmark measurements,[23] and a commercially available 1-channel Tx and 32-channel Rx (Nova Medical) head coil. The standard susceptibility weighted imaging sequence parameters are as follows: TE 15 msec, TR 27 msec, flip angle 14°, in-plane resolution 250 × 250 μm^2, slice thickness 2 mm, bandwidth 140 Hz/pixel. Note that the flip angle was chosen to maximize the vessel/brain contrast leading to a decreased CSF signal. Recommended sequence parameters for different magnetic field strength can be found elsewhere.[9] After image acquisition magnitude, phase, susceptibility weighted imaging, and MIP, susceptibility weighted imaging data were analyzed separately. Minimum intensity projection is a postprocessing tool to accumulate image information from multiple slices into a single plane of projection, thereby creating a 3D impression.[47] Patients undergoing 7-T MR imaging were rather admitted to the department of neurosurgery for treatment of a CCM or included in follow-up or screening MR imaging examinations at the department of radiology. Figures 3–5 display the different findings in a group of selected patients.

Conclusions

Susceptibility weighted imaging is a very helpful complementary MR imaging sequence for CCMs. It has proven to be superior to conventional MR imaging in the detection of these lesions, and the data available from single case reports suggest that the modality has further applications, especially in imaging of the associated venous structures. Now that higher field strength (≥ 3-T) MR imaging becomes more and more available, the technical limitations of susceptibility weighted imaging can be overcome and its integration into standard neuroimaging protocols for CCM may expand.

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: Dammann. Acquisition of data: Dammann. Analysis and interpretation of data: Dammann. Drafting the article: Dammann, Sure. Critically revising the article: Barth, Zhu, Maderwald, Schlamann, Ladd, Sure. Reviewed final version of the manuscript and approved it for submission: Ladd, Sure. Administrative/technical/material support: Barth, Zhu, Maderwald, Schlamann.

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Manuscript submitted May 14, 2010.
Accepted June 10, 2010.
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Neurosurg Focus 29 (3):E6, 2010

Emerging clinical imaging techniques for cerebral cavernous malformations: a systematic review

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Cerebral cavernous malformations (CCMs) are divided into sporadic and familial forms. For clinical imaging, T2-weighted gradient-echo sequences have been shown to be more sensitive than conventional sequences. Recently more advanced imaging techniques such as high-field and susceptibility-weighted MR imaging have been employed for the evaluation of CCMs. Furthermore, diffusion tensor imaging and functional MR imaging have been applied to the preoperative and intraoperative management of these lesions. In this paper, the authors attempt to provide a concise review of the emerging imaging methods used in the clinical diagnosis and treatment of CCMs.
(DOI: 10.3171/2010.5.FOCUS10120)

Key Words • **magnetic resonance imaging** • **cavernoma** • **cavernous malformations** • **susceptibility-weighted imaging** • **gradient echo** • **functional magnetic resonance imaging**

Cerebral cavernous malformations are present in approximately 0.5% of the population.[17,44] These lesions are made up of clusters of deformed vessels, lined by endothelium and filled with blood at various stages of thrombosis.[12,20] The annual risk of hemorrhage ranges from 0.7% to 1.1% per lesion per year.[44] Typically, patients with single lesions have a sporadic form of the disease, while those with multiple lesions (10%–31% of all cases) often have an autosomal dominant form localizable to the *CCM1*, *CCM2*, or *CCM3* gene loci.[7,18,28,32,45] The hallmark of familial CCM is the presence of multifocal lesions throughout the brain with the appearance of new lesions over time.[26] The sporadic form of CCM is often characterized by a solitary lesion (or a cluster of lesions) in association with a DVA.[3]

Prior to the widespread use of MR imaging, CCMs were thought to be rare entities. Modern MR imaging sequences are highly sensitive for detecting CCMs as well as associated hemorrhage at various stages of thrombosis and reorganization.[30] Typically, T2-weighted sequences portray these lesions as areas of mixed signal intensity, with a central complicated core and a peripheral rim of decreased signal intensity.[9,16] T2-weighted gradient-echo (T2*GRE) imaging has been promoted as the gold standard MR imaging sequence for both sporadic and familial CCMs.[30,54] In the current study, we review the current literature and describe the use of emerging imaging techniques being used for the diagnosis and treatment of this entity.

Abbreviations used in this paper: CCM = cerebral cavernous malformation; DT = diffusion tensor; DVA = developmental venous anomaly; GRE = gradient echo; fMR = functional MR; SW = susceptibility-weighted; T2*GRE = T2-weighted GRE.

Methods

The PubMed and MEDLINE databases were searched for publications from 1966 through May 2010 using the MeSH terms "cavernoma," "cavernous malformation," "imaging," "diffusion tensor imaging," "susceptibility weighted," "gradient echo," "functional MR imaging," "Tesla," and "high field MR imaging." The search was limited to articles in the English language and relating to human subjects. Reference sections of recent articles and reviews were reviewed and pertinent articles identified. Initially, relevant articles were retrieved in abstract format. Full-text manuscripts were subsequently obtained for all original articles applicable to the current review. The review was supplemented by work currently in progress at the authors' institutions.

Results and Discussion

Conventional MR Imaging Features of CCM

Conventional MR imaging sequences (T1- and T2-weighted imaging) have been associated with the ability to identify clinically symptomatic CCM lesions with a specificity and sensitivity nearing 100%.[42] Many CCMs have a characteristic MR imaging appearance that includes a peripheral ring of hypointensity due to hemosiderin deposition in the surrounding parenchyma from repeated microhemorrhages.[43] Some authors describe this manifestation as an imaging appearance associated with a limited differential diagnosis.[19] A classification system based on imaging and pathological features has been reported to stratify these heterogeneous lesions.[54] Type I lesions are characterized by hyperintensity on both T1- and T2-weighted images (depending on the state of methemoglobin), which is consistent with subacute hemorrhage.[16] In Type II malformations, loculated regions of hemorrhage are surrounded by gliosis and hemosiderin-stained brain parenchyma. These CCMs exhibit a mixed–signal intensity core on both T1- and T2-weighted images, with a well-circumscribed hypointense rim on T2-weighted images; these lesions are the classic CCMs, with a "popcorn" appearance and a predilection to produce recurrent symptoms.[11] Type III lesions demonstrate a core that is iso- or hypointense on T1-weighted sequences and hypointense on T2-weighted sequences as well as a rim that is hypointense on T2-weighted sequences, compatible with chronic resolved hemorrhage or hemosiderin within and surrounding the lesion. Type IV malformations are minute lesions often seen as punctate hypointense foci on GRE MR images. Pathologically, Type 4 lesions may represent capillary telangiectasias or early-stage CCMs seen frequently in the familial form.[33,43,54] The appearance of CCMs may vary by MR imaging sequence as a result of differential magnetic susceptibility of blood products at different ages within the lesion and the surrounding hemosiderin ring (Fig. 1).

Contrast-enhanced imaging is particularly useful in the diagnostic evaluation of CCM, and in clarifying differential diagnosis. The presence of an associated DVA is more likely to define the nongenetic nonfamilial form of the disease.[3,20] Also, the presence of an associated DVA may influence surgical decisions, especially with regard to surgical maneuvers aimed at avoiding injury to the DVA and consequences of venous ischemia. The concept of lesion cure with resection must be tempered when resecting a solitary CCM but leaving behind an overt DVA (which could later contribute to CCM recurrence). Contrast administration may delineate patterns of overt enhancement consistent with pathological conditions other than CCM, particularly tumors (homogeneous enhancement) or arteriovenous malformations (serpiginous enhancement). Finally, punctate enhancement in association with CCMs on contrast-enhanced T1-weighted images, without hemosiderin "blossoming" on T2*GRE sequences, has been suggested to represent capillary telangiectasia, most commonly reported in the pons as well as in the bed of DVAs.[40]

Diagnosis of CCM: Gradient Echo

Areas of the brain containing hemosiderin-laden tissue demonstrate a more recognizable hypointensity on T2-weighted GRE MR images than either T2-weighted conventional spin echo (SE) or fast spin echo (FSE) MR sequences due to magnetic susceptibility effects.[4,8,21,23] As such, T2*-weighted GRE imaging has been recommended as the most sensitive technique to evaluate CCM lesions in both the sporadic and familial forms of the disease.[30,54] During an in-depth evaluation of 57 French families with a history of familial CCM, Labauge et al.[27] found an approximately 5% probability that conventional MR imaging, without a T2*GRE sequence, would fail to spot a CCM. Furthermore, these authors reported that the mean number of lesions per person was five on standard MR imaging, while on T2*GRE sequences, the mean number of lesions detected was 16 ($p < 0.001$).[27] Other authors have reported a higher sensitivity with T2*GRE when compared with other sequences as well.[10,39] In evaluating a 3-generation family with familial CCM, Lehnhardt et al.[30] compared standard T1-weighted and T2-weighted SE sequences to T2*GRE sequences and noted a dramatically improved sensitivity with regard to lesion number and disease extension. When evaluating CCMs in association with DVA, the T2*GRE sequences may exclude or better delineate associated CCMs (Fig. 2).

The advantages of T2*GRE must be tempered by the effect of hemosiderin "blossoming," which effectively increases the apparent size of the CCM lesion. Hence, lesions may appear to extend to a pial or ependymal surface on T2*GRE images, while in fact they are surrounded by several millimeters of normal or simply hemosiderin-stained brain tissue. This is extremely important to realize when planning surgical approaches to lesions in the brainstem or other eloquent or deep-seated locations. Also, T2*GRE sequences often reveal multifocal lesions in elderly patients with hypertension and a history of stroke, and the lesions often are distributed in the same territory as hypertensive angiopathy, and should be differentiated in the clinical context from CCM (Fig. 3). Currently, T2*GRE sequences are considered an essential adjunct to the MR imaging of CCM. They are the method of choice for the sensitivity of detection and diagnosis of CCM, but should be supplemented by other sequences for more precise lesion definition, and by careful differential diagnosis.

Emerging Concepts in CCM Imaging

High-Field MR Imaging. At present, low-flow vascular malformations, such as CCMs, are most frequently evaluated with standard 1.5-T MR imaging based upon hemosiderin-induced susceptibility effects, which cause signal cancellations visible on T2*GRE sequences.[29] With standard imaging techniques, approximately 30% of epilepsy patients are not found to have an underlying lesion; some authors have posited that an improved detection of CCMs could aid in the identification of CCMs (causing cryptogenic seizures) not visualized at 1.5 T.[22,46] Several authors have investigated the imaging effects of high-field MR imaging in both experimental and clinical settings.[36,38,46,48,49] Shenkar et al.[48,49] evaluated ex-vivo human CCMs and murine CCMs by high-resolution MR imaging at 9.4 or 14.1 T. The results obtained using high-field MR imaging results correlated with the histopathological

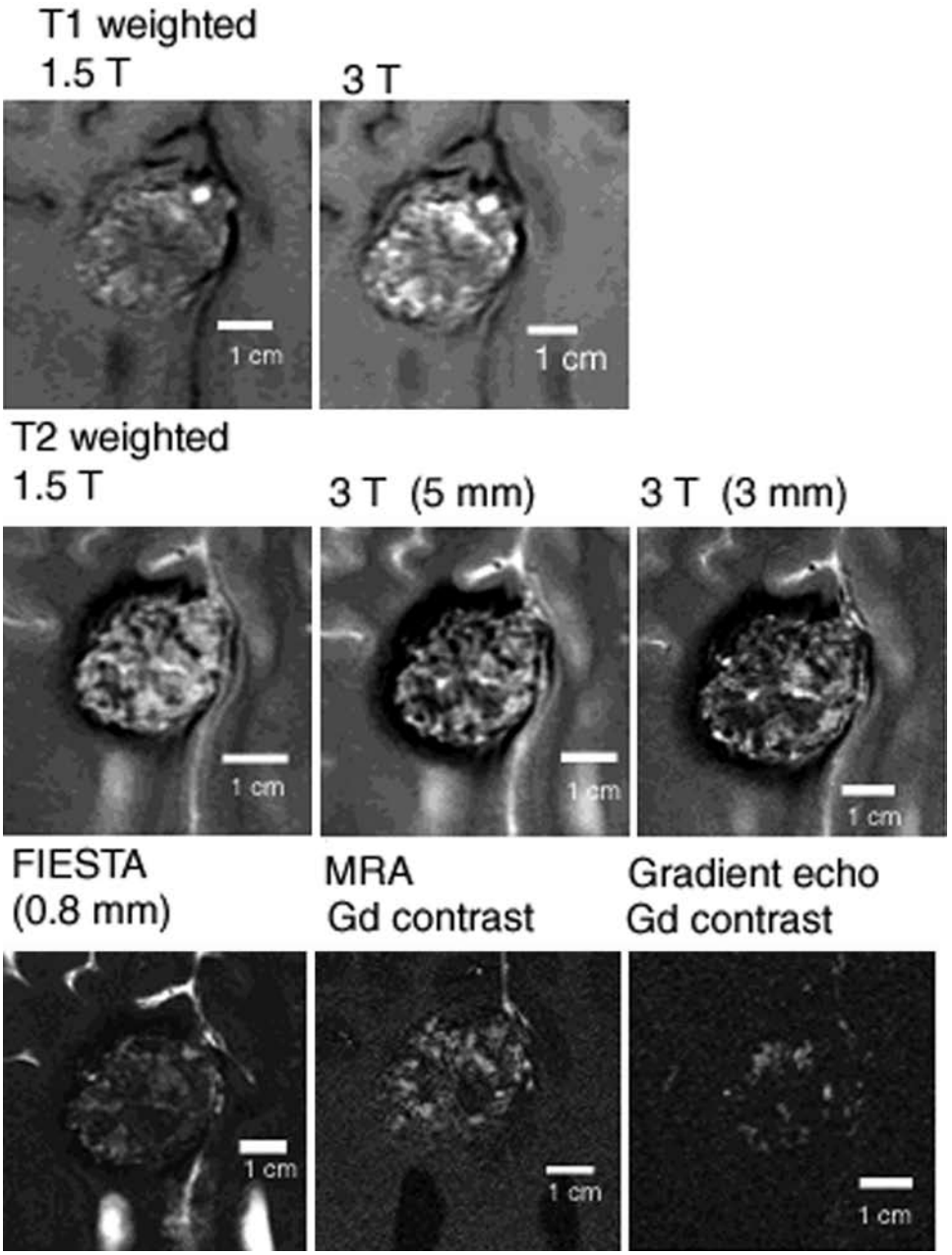

Fig. 1. Subtle changes in the appearance of a solitary CCM with different MR imaging sequences, reflecting differential sensitivity of blood breakdown products at different ages, and low flow in dilated cavernous channels. The MR imaging appearance of human CCM lesions, including high-field ex-vivo image correlations with confocal microscopy are presented in detail by Shenkar et al.[49]

findings obtained using confocal microscopy, confirming the angioarchitecture of CCMs at near histological resolution. Novak et al.[36] reported a case of a 55-year-old with a frontal hemorrhage, although at 1.5 Tesla the CCM was not apparent. When closely analyzed, the CCM appeared larger and signal loss was several times greater on 8 T MR images than on 1.5-T images.[36] Schlamann et al.[46] performed imaging in 10 consecutive CCM patients at 1.5 and 7 T. These authors found one additional hypointensity, which was not visible in the 1.5-T examination, and multiple new small hypointense lesions were detected at 7 T in a patient with familial CCM. However, because of increased susceptibility artifacts, these lesions appeared on average 11% larger in the 7-Tesla images.[46] Given that magnetic susceptibility artifact is known to increase with the field strength and is readily captured by T2*GRE, CCMs not readily apparent on 1.5-T MR imaging may become more decisively detectable with higher magnetic field strengths.[1,2] Furthermore, these authors assessed lesion prevalence at high field using SW imaging, and at lower field using GRE sequences.[46] As a result, it remains unknown if the increased sensitivity reported by those authors is attributable to high field strength per se, or to SW imaging sequences as discussed below.

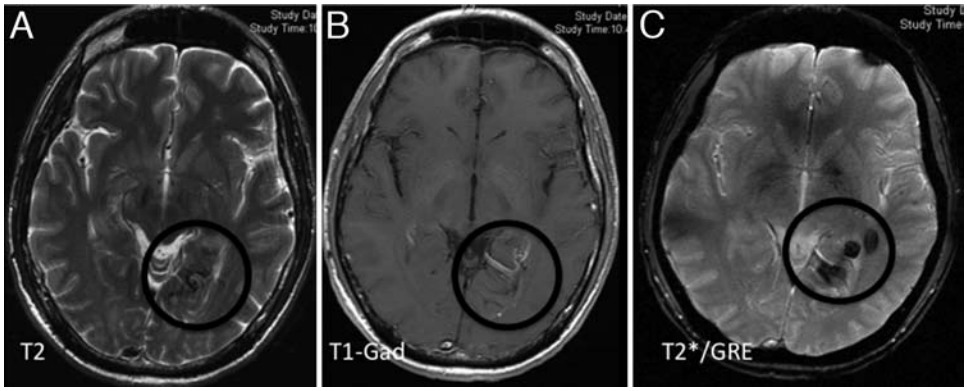

Fig. 2. Multiple MR imaging sequences obtained in a patient presenting with temporal lobe seizures. The T2-weighted sequence **(A)** illustrates subtle abnormality in the left posterior mesiotemporal region, consistent with nonspecific hemosiderin deposition. The Gd-enhanced T1-weighted image **(B)** delineates a prominent venous structure with "caput medusae" pattern, associated with the T2 signal, likely suggesting an associated DVA. The T2*GRE image **(C)** reveals much better delineation of multiple foci of the CCM.

Susceptibility-Weighted MR Imaging. The CCM lesions contain deoxyhemoglobin and hemosiderin, which causes susceptibility effects and a decrease in signal intensity on T2-weighted sequences. Susceptibility-weighted imaging provides a new mode that is particularly suited for imaging vascular malformations as it is very sensitive to deoxyhemoglobin and iron content.[6,53] This sequence is assembled from both magnitude and phase images from a high-resolution, 3D velocity-compensated GRE sequence.[41] Currently, this method is believed to be the only imaging method capable of appropriately detecting nonhemorrhagic cavernomas and telangiectasias.[38] Lee et al.[29] were the first to describe the use of SW imaging for imaging cavernomas. These authors presented a series of 10 patients who underwent both T2-weighted and SW MR imaging and found that not only were the margins of the CCMs better delineated, but SW imaging also revealed 2 additional lesions that were not seen on T2-weighted images.[29] Cooper et al.[15] reported a case of a 59-year-old familial CCM patient in which SW imaging detected nearly triple the number of lesions compared to the T2*GRE sequences. Pinker et al.[38] evaluated 17 patients harboring CCMs with standard 1.5-T MR imaging in comparison with 3-T MR imaging that included the SW imaging sequences. In this series, the 3-T SW MR imaging revealed an additional 7 lesions in 6 patients; however, it is unclear whether these patients had sporadic or familial CCMs. In a recent study, based on 15 patients with familial CCMs and a mean age of 34 years, de Souza et al.[16] found the following average number of lesions per patient: 5.7 on T2-weighted imaging; 26.3 on T2*GRE imaging; and 45.6 on SW imaging. Thus the number of lesions seen on SW imaging was 1.7 times higher than that seen on T2*GRE sequences ($p = 0.001$).[16] In the largest study to date, 23 cases were assessed by the senior author (I.A.A.) and colleagues in Montpellier, France, confirming that nearly twice as many lesions were detected by SW imaging as compared with T2*GRE sequences; however, this phenomenon was only observed in the 14 familial cases. In none of 9 patients with solitary CCM or clustered lesions in the bed of a DVA did the SW imaging reveal additional lesions other than those noted on T2*GRE images (Menjot et al., manuscript in preparation). Hence, SW imaging seems to increase the sensitivity of lesion detection in familial multifocal CCM lesions; it does not per se appear to reveal lesion multiplicity that had not been already demonstrated by T2*GRE (Figs. 4 and 5). The SW images are highly sensitive to delineation of associated venous anomalies, and possibly telangiectasias, without the need for contrast enhancement. This feature

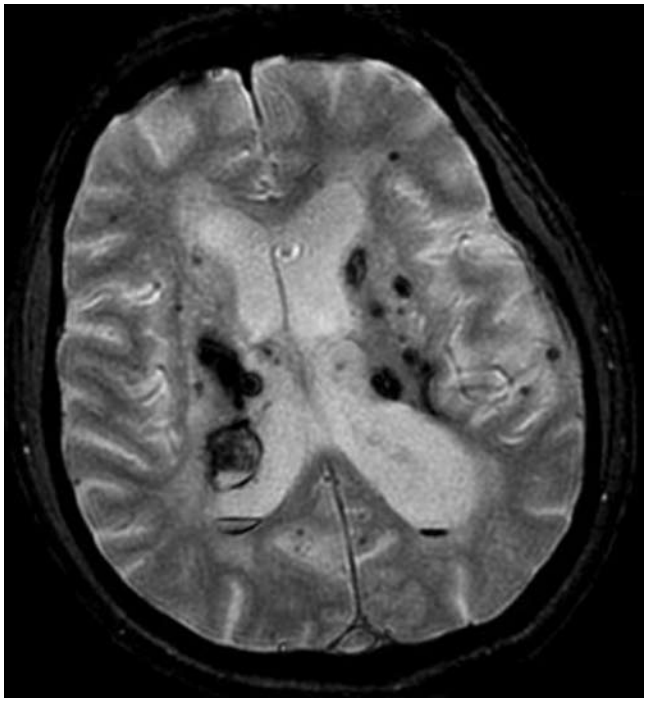

Fig. 3. A T2*GRE MR image showing multifocal hemorrhagic lesions in an elderly patient with previous strokes, including recent intracerebral hemorrhages associated with untreated hypertension. The T2*GRE MR imaging sequences revealed multifocal occult tiny hemorrhagic lesions, interpreted as hypertensive angiopathy. These are differentiated from familial CCM disease by the clinical setting and by the clustering of lesions in periventricular areas most vulnerable to hypertensive angiopathy. Conversely, CCM disease is associated with lesions in a volume distribution throughout the brain.

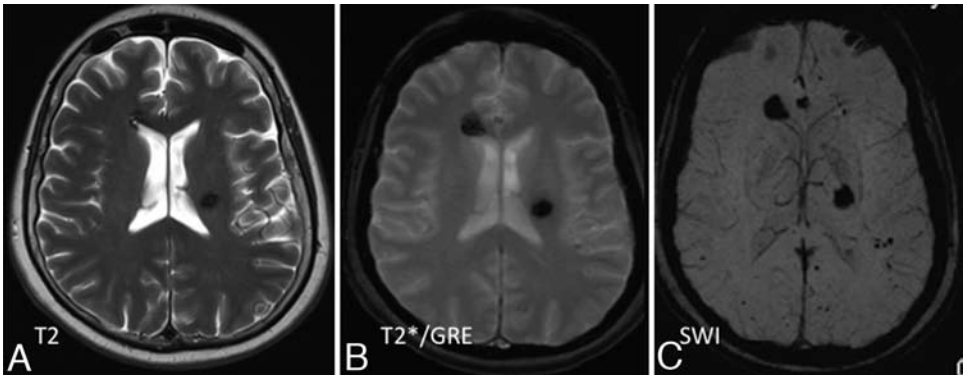

Fig. 4. Representative T2-weighted **(A)**, T2*GRE **(B)**, and SW **(C)** MR images obtained in a patient with a family history of familial CCM disease, who presented for routine MR imaging screening. The T2 sequences **(A)** revealed 2 suspected CCM lesions, which were better delineated on T2*GRE sequences. The T2*GRE sequences **(B)** also suggested perhaps 1 or 2 additional subtle lesions. The SW images **(C)** revealed many additional lesions throughout the brain.

may be a significant advantage in pregnant patients, those with renal impairment, and patients with allergic reactions to Gd-based contrast agents.

While SW imaging is not yet widely available, it is possible that, given the early clinical data suggesting its effectiveness, the technique may be added into the routine imaging assessment of vascular malformations as improvements in software technology allow acquisition and dissemination. These sequences might provide endophenotypic markers of disease burden in familial CCM that should be correlated with disease penetrance and aggressiveness in different individuals and kindreds, and with the response to potential therapeutic interventions.

The ultimate applicability of SW imaging is limited by several factors. First, as with T2*GRE, it is difficult to differentiate small venous structures from small areas of hemorrhage and thrombosis. However, sequential SW imaging before and after Gd administration, could ameliorate this deficiency.[31] As previously noted, the higher sensitivity of SW sequences may not apply to sporadic or solitary CCMs, or CCM clusters associated with DVA. While SW imaging has shown greater ability to identify lesions in familial CCM, the necessity to apply this imaging modality to sporadic CCMs has yet to be demonstrated. We are not aware of a case in which a solitary lesion was detected on T2*GRE imaging that was later found to be associated with occult lesion multiplicity on the more sensitive SW imaging (Fig. 5). As such, future studies should specifically address SW imaging sensitivity in cases of sporadic CCM, those associated with DVA, and radiation-induced CCMs.

Finally, the nature of those lesions that are delineated on SW images and remain occult on T2*GRE images remains unclear (Fig. 4). Some may be better resolved in the 3D sequence acquisition of SW imaging, while they may have been diminished by "volume averaging" in the typically 2D acquisition of T2*GRE images. The occult punctate lesions may also represent nonhemorrhagic capillary telangiectasias, often reported in conjunction with CCM, which could also represent precursors to more mature CCMs.[5]

Imaging in Intraoperative Management

The Use of DT Imaging. Diffusion tensor imaging is an MR imaging technique that may be effectively used to

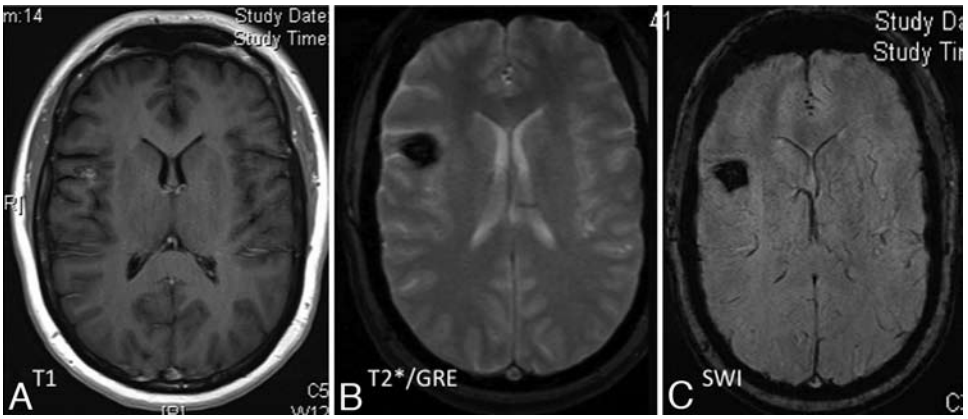

Fig. 5. Representative T1-weighted **(A)**, T2*GRE **(B)**, and SW **(C)** MR images obtained in a patient with a solitary sporadic CCM that was discovered incidentally in the workup of an unrelated neoplasm. The T1-weighted contrast-enhanced images **(A)** revealed a suspected CCM in the right frontal cortex and a subtle abnormal venous prominence superior and medial to the lesion (not shown). The T2*GRE images **(B)** better delineated the same lesion. The SW sequences **(C)** revealed no additional lesions, although they also demonstrated the suspected venous anomaly.

visualize the directionality and orientation of white matter tracts in the brain.[37] Diffusion tensor tractography has been effectively used to evaluate the characteristics of the hemosiderin rim surrounding CCMs as well as in surgical planning for the resection of CCM in eloquent areas.[11,13,14,35] Cauley et al.[11] performed DT tractography in 18 patients with solitary CCMs and found that white matter tracts deviated around the center of CCMs, often passing through the hemosiderin rim. Niizuma et al.[35] successfully used DT with fiber tracking to determine the location of the displaced corticospinal tract in the removal of a paraventricular CCM. Chen et al.[13,14] have reported the used of DT imaging for the removal of several brainstem lesions including a CCM. They reported that DT fiber tracking revealed the anatomical relationship between the local eloquent tracts and the CCM, thus altering their approach and preventing patient morbidity.[14] Several authors speculate that DT imaging may be a useful preoperative evaluation for patients with deep-seated lesions impinging upon white matter tracts.[14,35] Thus, the use of DT imaging may enhance the decision-making process in the selection of surgical approaches by providing an enhanced understanding of the relevant functional tracts.

The Use of fMR Imaging. Functional MR imaging has the ability to integrate anatomical and functional information. Preoperatively, this imaging technique has the capacity to provide a useful representation of task-related hemodynamic changes in the associated cortical area as well as the pathology through a single imaging modality.[25] An early case report described the successful use of fMR imaging in the preoperative assessment of a left central CCM.[34] Thickbroom et al.[52] evaluated blood-O_2-level–dependent contrast fMR imaging in 3 CCM patients and noted some difficulty in correctly isolating the critical regions of eloquent cortex due to the associated susceptibility effect. Schlosser et al.,[47] working with the senior author (I.A.A.), did not report any such difficulty. These authors continue to use fMR imaging in clinical practice, even in patients with recent bleeding (Fig. 6). The data from fMR imaging are often supplemented by intraoperative mapping of sensorimotor cortex by reversal of evoked potential amplitude or direct cortical stimulation.[55] Zotta et al.[56] used traditional MR imaging and fMR imaging fusion to aid in preoperative planning as well as intraoperative guidance. In this series, the authors achieved greater rates of seizure freedom in the group of patients with CCMs in eloquent areas who underwent surgery with fMR imaging than in the group in whom this modality was not used.[56] While fMR imaging has demonstrated a clear benefit over other modalities such as brain mapping or somatosensory evoked potentials for tumors located in primary motor cortex, more comprehensive studies to evaluate this technique in the setting of CCMs are needed.[50] Specifically, an improved outcome may be attributed to fMR imaging information, while in fact it was achieved because of a combination of information modalities. In CCM, functional data may affect the surgical route chosen to a lesion, and also the extent of resection of perilesional epileptogenic brain in patients with intractable epilepsy.[24,51,56]

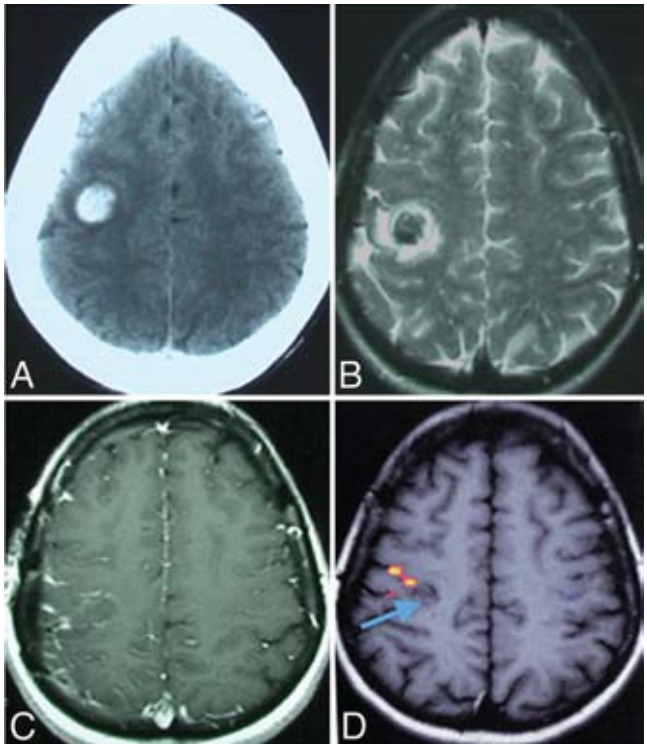

Fig. 6. Representative CT scan and T2-weighted (B), T1-weighted (C), and functional (D) MR images obtained in a patient who presented with acute onset of left arm and hand paresis. The CT examination **(A)** revealed focal hemorrhage in the rolandic region. The T2-weighted images **(B)** revealed a hemorrhagic lesion with surrounding edema, consistent with an acute hemorrhage. The T1-weighted images **(C)** did not clearly identify the location of sensorimotor structures in relation to the lesion. These were easily outlined by functional MR imaging **(D)**, with zones of activation in response to left hand movement shown in *red-orange*. The region of functional activation on fMR imaging corresponded to reversal of somatosensory median nerve evoked sensory potential recording on the cortical surface, confirming the location of the rolandic sulcus. A more posterior sulcus was chosen for image-guided transsulcal microsurgical resection of the lesion *(blue arrow)*, which proved to be a CCM, and the resection was accomplished without worsening of motor or sensory function.

Conclusions

Prior to the advent of MR imaging, evaluation of CCMs was limited to diagnostic angiography and CT. Currently, MR imaging is the best imaging method to evaluate CCMs, with T2*GRE sequences being described as the "gold standard."[10,30,54] As the use of more advanced imaging techniques continues to achieve widespread distribution, high-field MR imaging and SW MR imaging are likely to become commonplace for the diagnosis and follow-up of these lesions. Additionally, applications such as DT imaging and fMR imaging may achieve more relevance as intraoperative navigational modalities for the treatment of deep-seated lesions in eloquent areas.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. IAA is supported by grant from the NIH/NINDS for research on cerebral cavernous malformation, including advanced imaging techniques (R01-NS060748).

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Campbell, Awad. Analysis and interpretation of data: Yadla, Awad. Drafting the article: Jabbour, Campbell, Yadla. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: Jabbour, Awad. Administrative/technical/material support: Campbell.

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Manuscript submitted May 9, 2010.
Accepted May 27, 2010.

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Neurosurg Focus 29 (3):E7, 2010

Update on the natural history of cavernous malformations and factors predicting aggressive clinical presentation

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Cavernous malformations (CMs) are angiographically occult, low-pressure neurovascular lesions with distinct imaging and clinical characteristics. They present with seizure, neurological compromise due to lesion hemorrhage or expansion, or as incidental findings on neuroimaging studies. Treatment options include conservative therapy, medical management of seizures, surgical intervention for lesion resection, and in select cases stereotactic radiosurgery. Optimal management requires a thorough understanding of the natural history of CMs including consideration of issues such as mode of presentation, lesion location, and genetics that may impact the associated neurological risk. Over the past 2 decades, multiple studies have been published, shedding valuable light on the clinical characteristics and natural history of these malformations. The purpose of this review is to provide the reader with a concise consolidation of this published material such that they may better understand the risks associated with CMs and their implications on patient treatment. *(DOI: 10.3171/2010.5.FOCUS10149)*

Key Words • cavernous malformation • cavernoma • cavernous angioma • natural history • familial cavernous malformation

Cerebral CMs, also referred to as cavernous angiomas, cavernous hemangiomas, or cavernomas, are vascular malformations consisting of thin hyalinized vascular channels without interposed brain. These lesions are also referred to as angiographically occult vascular malformations due to the fact that they are low-pressure systems that do not shunt blood and are not generally apparent on diagnostic catheter angiography.[8,29] Prior to the development of MR imaging, diagnosis of CMs was uncommon; only 163 cases had been presented in the literature by 1976, the vast majority of which presented as symptomatic lesions.[54] However, with the ever-increasing availability and fidelity of MR imaging technology, the diagnosis of CMs has become exceedingly more common. Another byproduct of the MR imaging era has been a dramatic increase in the number of CMs being diagnosed prior to symptom onset, with at least 40% of CMs now being identified incidentally.[5] Our ability to make appropriate clinical judgments regarding the management of these lesions is predicated on our understanding of the hemorrhagic and neurological risk associated with CMs and what factors potentially impact this risk. The purpose of this paper is to consolidate the current body of knowledge of the natural history of CMs into a form that helps the cerebrovascular practitioner with patient treatment.

Abbreviation used in this paper: CM = cavernous malformation.

Methods

A literature search using the online database PubMed provided through the National Center for Biotechnology was performed. Search terms were "natural history," "cavernous malformation," "cavernoma," "cavernous angioma," and "cavernous hemangioma." The search was limited to studies in the English language and specific to humans. Articles were reviewed along with any pertinent citations provided by these articles. Studies of interest included those that provided information regarding modes of presentation, hemorrhage rates, and factors affecting prognosis (for example, age, sex, size, and genetic components to the disease).

Epidemiology

Cavernous malformations occur in sporadic and familial forms.[21,47] They are the second most common vascular lesion behind developmental venous anomalies and account for 10%–15% of all vascular malformations.[5] Based on autopsy and MR imaging studies, the incidence ranges from 0.4% to 0.8%,[5,34,42,48] with 25% of these oc-

curring in children.[34] The average age of adult presentation is in the 4th or 5th decade of life. Children present in a bimodal pattern with peaks at 0–2 years of age and 13–16 years of age.[34,41]

The familial form of CMs comprises approximately 6%–50% of all cases, and a higher prevalence has been noted in people with Mexican-American ethnicity. Based on current imaging studies, more than 50% of patients with familial CMs have multiple lesions compared with only 12%–20% in those with the sporadic form.[5,40,47,57] In regard to sex, the prevalence of CMs appears equal among men and women. However, some studies (see detailed discussion below) have raised the question of an increased incidence of symptomatic lesions in women.[2,27,40,44,49,53,54]

Presentation

Cavernous malformations have a wide range of presenting symptoms. These can vary from mild symptoms such as headache to more severe symptoms including seizure, focal neurological deficit, and even death. In addition, since the introduction of MR imaging, more and more CMs are being found incidentally. With supratentorial lesions, the most common presenting symptom is new onset seizure, representing 23%–79% of cases.[1,2,12,25–27,40,43–45,48,51,56,57] With infratentorial lesions, most patients present with either a focal neurological deficit (for example, cranial nerve palsy, hemiparesis, and hemisensory deficits) or gait ataxia.[20,30,44,52,55] Brainstem CMs have also been reported to cause symptoms such as cardiovascular instability, respiratory compromise, and hiccups.[55] Cavernous malformations located in the basal ganglia and/or thalamus most commonly present with sensorimotor deficits, but less common presentations of hemiballismus and hydrocephalus have also been reported.[17]

All of the above symptoms can be found with or without acute hemorrhage. The definition of hemorrhage varies greatly from study to study, thus creating difficulty in quantifying bleeding rates. Some consider a lesion as having hemorrhaged only when there is a new neurological event in association with positive imaging findings. Others consider only the imaging. Given this, there is a wide range in percentage of patients presenting with hemorrhage, from a low of 9% to a high of 88%.[1,2,12,14,15,26,27,30,38,40,43–45,50–52,55,56]

As noted above, there is also a growing group of patients with CMs that are being diagnosed incidentally or during workup for chronic headaches. Patients in the pre–MR imaging era, such as those presented by Voigt and Yaşargil,[54] were 100% symptomatic. Currently, the percentage of CM patients with incidental presentation is 2%–32%, and the percentage of patients with chronic headache presentation is 6%–65%.[1,12,25–27,30,37,40,43–45,48,52,56,57] Table 1 shows the breakdown of presenting symptoms and location of CMs.

Natural History

Overall Hemorrhage Risk

In the early 1990s (corresponding to the increase in MR imaging availability and usage), a rapid increase in

TABLE 1: Summary of presenting symptoms and locations of CMs in the literature*

Authors & Year	Type of Study	No. of Patients	Mean Age (yrs)	Presenting Symptom (%)						Location (%)	
				Hemorrhage	Seizure	FND	GND	HA	Incidental	Supratentorial	Infratentorial
Xia et al., 2009	retro	66	11.6	20.0	47.7	12.3	NA	46.2	NA	83.3	9.1
Kivelev et al., 2009	retro	33	44.0	46.0	43.0	18.0	NA	21.0	6.0	70.0	30.0
Hauck et al., 2009	retro	44	37.5	NA	NA	86.0	57.0	NA	NA	0.0	100.0
Acciarri et al., 2009	retro	42	<18.0	40.5	59.5	NA	14.3	26.2	NA	87.5	12.5
Tarnaris et al., 2008	retro	21	36.8	57.1	NA	23.8	NA	NA	19.0	0.0	100.0
Wang et al., 2003	retro	137	33.5	67.2	NA	51.1	NA	NA	NA	0.0	100.0
Kupersmith et al., 2001	retro	37	37.5	73.0	NA	NA	NA	43.0	5.0	0.0	100.0
Porter et al., 1999	retro	100	37.0	97.0	NA	69.0	39.0	37.0.	NA	0.0	100.0
Moriarity et al., 1999[40]	pro	68	34.6	13.0	49.0	46.0	NA	65.0	1.5	73.0	27.0
Moran et al., 1999	review/retro	690	NA	16.0	79.0	NA	NA	NA	NA	100.0	0.0
Porter et al., 1997	retro	173	37.5	25.0	36.0	20.0	NA	6.0	12.0	63.0	37.0
Kim et al., 1997	retro	62	32.2	NA	40.8	8.2	32.6	6.1	12.2	69.4	30.6
Pozzati et al., 1996	retro	145	30.0	18.0	46.9	NA	20.7	10.3	4.1	86.9	13.1
Aiba et al., 1995	retro	110	NA	56.4	22.7	NA	NA	NA	20.9	67.8	32.2
Kondziolka et al., 1995	retro/pro	122	37.3	50.0	23.0	NA	NA	18.0	NA	48.0	52.0
Zabramski et al., 1994	pro	31	25.0	NA	39.0	NA	26.0	52.0	39.0	91.0	9.0
Robinson et al., 1993	retro	66	34.6	NA	51.5	45.5	NA	30.3	13.6	84.2	15.8
Del Curling et al., 1991	retro	32	42.0	9.0	50.0	22.0	NA	34.0	19.0	86.0	14.0
Simard et al., 1986	review/retro	138	NA	28.7	35.5	NA	NA	NA	NA	NA	NA

* FND = focal neurological deficit; GND = global neurological deficit; HA = headache; NA = not available; pro = prospective; retro = retrospective.

the knowledge of the hemorrhage risk associated with CMs occurred. Del Curling et al.[12] were one of the first groups to report on this risk. In their study, MR images from 8000 patients were retrospectively reviewed. Symptoms in these patients included seizure (50%), headache (34%), and focal neurological symptoms (16%). Thirty-two patients with CMs were identified, for an MR imaging–based incidence of 0.39%. They reported symptomatic hemorrhage rates of 0.25% per patient-year and 0.10% per lesion-year. Robinson et al.[48] retrospectively reviewed MR images from over 14,000 patients. Symptoms in these patients included seizure (52%), focal neurological deficit (46%), headache (30%), and incidental (14%). Sixty-six patients with 76 CMs were identified, for an MR imaging–based incidence of 0.47%. They reported a symptomatic hemorrhage rate of 0.7% per lesion-year. Kim et al.[25] retrospectively reviewed 62 patients with 108 CMs. Most lesions were symptomatic, but 12% were incidental. They reported symptomatic hemorrhage rates of 2.3% per patient-year and 1.4% per lesion-year. Zabramski et al.[57] reported on 21 asymptomatic patients in whom familial CM was diagnosed who were prospectively observed (including serial MR imaging studies) for an average of 2.2 years. They reported symptomatic hemorrhage rates of 6.5% per patient-year and 1.1% per lesion-year. They also identified numerous asymptomatic hemorrhages by MR imaging and calculated asymptomatic hemorrhage rates of 13% per patient-year and 2% per lesion-year. Numerous other natural history studies have been reported over the years, most of which have documented hemorrhage rates ranging from 0.7% to 6% per patient-year (see Table 2 for a complete listing of reported hemorrhage rates).

Risk Factors That Increase Hemorrhage Risk

Hemorrhagic Presentation. Aiba et al.[2] were the first to provide evidence that hemorrhagic presentation negatively impacts the natural history of CMs. In their retrospective review of 110 patients with CMs, they found that patients presenting with hemorrhage were at higher risk for new hemorrhage than those presenting with incidental findings or with seizure (22.9% per patient-year vs 0.39% per patient-year, respectively). Other investigators have documented similar findings. Kondziolka et al.[27] performed a combined retrospective/prospective evaluation of 122 patients with conservatively managed CMs, documenting a symptomatic hemorrhage rate of 0.6% per patient-year in patients without hemorrhagic pre-

TABLE 2: Summary of initial hemorrhage and rehemorrhage rates found in the literature*

Authors & Year	Type of Study	No. of Patients	Mean Age (yrs)	Hemorrhage Rate/ Patient-Yr (%)	Rehemorrhage Rate/ Patient-Yr (%)	Hemorrhage Rate/Lesion-Yr (%)	Rehemorrhage Rate/Lesion-Yr (%)
Hauck et al., 2009	retro	44	37.5	NA	42.0	NA	NA
Tarnaris et al., 2008	retro	21	36.8	NA	0.05	NA	NA
Ghannane et al., 2007	retro	39		0.013	6.27	NA	NA
Wang et al., 2003	retro	137	33.5	6.0	60.0	NA	NA
Mathiesen et al., 2003	pro	34		2 incidental/7 symptomatic	NA	NA	NA
Sandalcioglu et al., 2002	retro	12	29.2	6.8	1.9	NA	NA
Labauge et al., 2001	pro	33	40.8	4.3	0.6	NA	NA
Kupersmith et al., 2001	retro	37	37.5	2.46	5.1	NA	NA
Labauge et al., 2000	retro	37		16.5	NA	2.5	NA
Porter et al., 1999	retro	100	37.0	5.0	30.0	NA	NA
Moriarity et al., 1999[40]	pro	68	34.6	3.1	NA	NA	NA
Moran et al., 1999	review/retro	690		0.7	NA	NA	NA
Porter et al., 1997	retro	173	37.5	1.6	0.4 infratentorial/ 3.8 supratentorial	NA	NA
Kim et al., 1997	retro	62	32.2	2.3	3.8	1.4	2.6
Aiba et al., 1995	retro	110		NA	NA	NA	0.39 no hemorrhage hx/ 22.9 hemorrhage hx
Kondziolka et al., 1995	retro/pro	122	37.3	1.3	0.6 no hemorrhage hx/ 4.5 hemorrhage hx	NA	NA
Zabramski et al., 1994	pro	31	25.0	6.5 symptomatic/ 13 MRI based	NA	1.1 symptomatic/ 2 MRI based	NA
Fritschi et al., 1994	retro	139	31.8	2.7	21.0	2.7	21.0
Robinson et al., 1993	retro	66	34.6	NA	NA	0.7	NA
Del Curling et al., 1991	retro	32	42.0	0.25	NA	0.1	NA

* hx = history.

sentation versus 4.5% per patient-year for patients with hemorrhagic presentation. Mathiesen et al.[37] performed a retrospective analysis of 34 patients, reporting a symptomatic hemorrhage rate of 2% per year for patients with incidental lesions versus 7% per year in patients with symptomatic presentation. Moriarity et al.[40] prospectively evaluated 68 patients with 228 CMs and reported an overall hemorrhage rate of 3.1% per patient-year. While they did not identify hemorrhagic presentation as a standalone risk factor, they did find that patients who presented with hemorrhagic or nonhemorrhagic focal neurological deficits had higher hemorrhage rates than those who presented without focal neurological deficits (8.9% vs 0.4% per patient-year, respectively).

It should be noted, however, that although patients with CMs who present with symptomatic hemorrhage are at an increased risk for new hemorrhage after diagnosis, this period of higher risk appears time limited. This phenomenon, known as "temporal clustering," was suspected by several early clinicians; however, in 2001 Barker et al.[4] provided compelling evidence for temporal clustering when they studied the hazard curve of rehemorrhage for 141 patients with CMs with a history of previous hemorrhage. They noted a spontaneous decline in the hazard risk of CM rehemorrhage approximately 2 years after a previous hemorrhage. Since this report, other investigators have also documented temporal clustering of hemorrhages in patients with CMs.[55]

Deep Anatomical Location. In the aforementioned study by Robinson et al.,[49] a higher incidence of neurological disability was noted in patients with infratentorial than in those with supratentorial CMs. Similar findings have been noted by other investigators. Porter et al.[43] retrospectively analyzed 173 patients with CM and categorized the CMs by location: 1) infratentorial versus supratentorial, and 2) deep versus superficial (brainstem, thalamus, and basal ganglia CMs were considered deep; the remaining CMs were considered superficial). They reported a higher rate of recurrent symptomatic hemorrhage in infratentorial than in supratentorial lesions (3.8% per patient-year vs 0.4% per patient-year) as well as in deep than in superficial lesions (4.1% per patient-year vs 0% per patient-year). Others provided evidence indicating that brainstem CMs have a particularly poor natural history. Fritschi et al.[14] presented their series of 139 patients with brainstem CMs along with a literature review. They calculated a relatively high symptomatic hemorrhage rate of 2.7% per patient-year and a very high rehemorrhage rate of 21% per patient-year. Porter et al.[44] retrospectively reviewed their experience with 100 patients with brainstem CMs, documenting a symptomatic hemorrhage rate of 5% per patient-year and a symptomatic rehemorrhage rate of 30% per patient-year. Kupersmith et al.[30] retrospectively evaluated 37 brainstem CMs, finding a symptomatic hemorrhage rate of 2.5% per patient-year and symptomatic rehemorrhage rate of 5.1% per patient-year. Kim et al.[25] retrospectively analyzed 62 patients with 108 CMs including 10 whose lesions were located within the brainstem. They found that brainstem CMs had a significantly higher frequency of presenting with a major neurological deficit compared with other lesion locations (80% of brainstem CMs presented with major neurological deficit vs 123% of cortical lesions). Although most studies suggested that brainstem CMs carry higher risk of symptomatic hemorrhage, at least one study by Tarnaris et al.[52] suggests otherwise, as their retrospective analysis of 21 patients with brainstem CMs documented surprisingly low rates of rebleeding and neurological deterioration (0.05% and 0.1% per patient-year, respectively).

Female Sex. Vaquero et al.[53] were one of the first groups to document a female predominance in symptomatic CMs (female/male ratio 2:1). Many studies since have found an increase in the frequency of symptomatic lesions in women. Robinson et al.[48] found a significant increase in hemorrhage rate in females. This was reiterated by studies presented by Aiba et al.[3] and Porter et al.[44] In fact, Porter and colleagues went further to question the effect of pregnancy on hemorrhage risk. Kupersmith et al.[30] found a higher risk of rehemorrhage in women (5.9%) than in men (3.3%). Not all studies, however, have documented a difference in hemorrhage rates between male and female patients.[14,27,43]

Other Factors Affecting Natural History

Seizure. The most common presenting symptom for patients with CMs is seizure (25%–79%).[38,39] These seizures are thought to be induced by recurrent microhemorrhages from the CM, resulting in perilesional gliosis and inflammation, both of which are epileptogenic.[3] In a retrospective review by Kondziolka et al.,[27] 4.3% of patients developed new seizures after initial CM diagnosis. In a retrospective review by Del Curling et al.,[12] 1.5% of patients developed new seizures after initial CM diagnosis. In the retrospective review by Moriarity et al.,[40] the risk of developing seizures following CM diagnosis was 2.4% per patient-year for patients not initially presenting with seizures. If the presenting symptom was seizure, the rate of having recurrent seizures was 5.5% per patient-year. While the presumed etiology of seizures in this patient population is recurrent microhemorrhages, there is no evidence to date suggesting that seizure (either at presentation or in follow-up) impacts the risk of CM hemorrhage.

De Novo Formation. Initially it was believed that CMs were developmental anomalies that were present since birth; however, there is now compelling evidence that CMs—in the sporadic and familiar forms—can develop de novo.[22,47] Several studies have quantified the incidence of de novo CM development, with results ranging from 0.1 to 0.6 new lesions per patient-year.[23,32,57] This phenomenon is much more common in the familial than the sporadic forms of the disease, as 27.5%–30% of patients with familial forms develop de novo CM formation while only 4.1% of patients with sporadic lesions develop de novo CM formation over time.[31,32,45]

Size Dynamics. De novo formation is not the only dynamic aspect of CMs. Lesion size can also vary substantially over time. Pozzati et al.[46] were the first to dem-

onstrate the dynamic nature of CMs when they presented 3 cases in which the CM grew substantially over time. They theorized the mechanism to be serial microhemorrhages followed by organization, fibrosis, and calcification. Others have shown that CMs can decrease in size over time. In the retrospective series by Kim et al.,[25] the average CM size was 14.2 mm at initial diagnosis and 9.1 mm on repeat imaging. Perhaps the best study demonstrating the dynamic nature of CMs over time is that by Clatterbuck et al.[10] who observed 68 patients with 114 CMs with serial imaging over a mean period of 3.7 years. Over this follow-up period, they found that 22% of lesions were stable in size, 43% of lesions increased in size, and 35% of lesions decreased in size. Many of these lesions had periods of both increase and decrease in size. To date, no study has correlated CM growth with risk of symptomatic hemorrhage.

Familial Inheritance and Genetics. It was long suspected that a genetic link to CMs existed;[7,9,24,28] however, definitive evidence remained elusive until 1982 when Hayman et al.[21] published their seminal paper on CM inheritance. They reported on a kindred of 122 individuals, of whom 5 had cerebral vascular malformations and 3 had CMs. They documented autosomal dominant inheritance with variable expressivity. This report was followed by the studies of Rigamonti et al.[47] and Mason et al.[36] who found that familial inheritance was especially high in Hispanic-American families.

This newly found information provided a patient population through which genetic mapping was used to elucidate the genetic cause of familial CMs. Dubovksy et al.[13] and Gil-Nagel et al.[16] were able to map the responsible gene to 7q. Guenl et al.[18] discovered through analysis of genetic markers a founder mutation among familial and sporadic cases in Hispanic-Americans of Mexican descent, suggesting a common ancestor among these patients. This mutation was later identified as truncating mutations in *CCM1*.[33] Further studies found that *CCM1* was likely not the only responsible gene.[11,19] Subsequently, Craig et al.[11] discovered 2 additional loci associated with familial CMs, *CCM2* on 7p and *CCM3* on 3q. They also found that Caucasian forms of familial CMs were 40% linked to *CCM1*, 20% linked to *CCM2*, and 40% linked to *CCM3*. Recent data suggest that a fourth gene may be present.[6,35]

The identification of familial inheritance and the genetic mutations that underlie it not only shed light on the underlying molecular mechanisms leading to CM formation, but also impacted clinical management. First, the number of cases of familial CMs appears higher than initially reported, with several studies showing that as many as 50% of patients with CMs have familial inheritance.[33,47,57] A detailed family history is therefore imperative when evaluating all patients with CMs, and genetic testing should be considered in those with evidence of familial inheritance. Second, the incidence of CM multiplicity is far higher in familial than in sporadic forms of the disease, with a reported incidence as high as 96% in patients with familial inheritance.[57] Third, the rate of de novo CM formation is much higher in familial than in sporadic forms of the disease.[31,32,45] This observation suggests that additional MR imaging studies over time may be appropriate for patients with familial CMs. Finally, familial inheritance appears to have some impact on the risk of hemorrhage. Although no study has thus far documented a higher than expected hemorrhage rate per lesion, the high incidence of CM multiplicity and the high rate of de novo CM formation strongly suggests that the greater overall CM burden in patients with familial forms leads to an increased risk of hemorrhage per patient. Consistent with this notion, annual hemorrhage rates of 4.3% per patient-year have been reported for patients with familial but asymptomatic CMs[31] compared with 0.6% per patient-year for patients with sporadic forms but asymptomatic CMs.[27] Vigilant counseling of familial patients with familial forms regarding the signs and symptoms of hemorrhage is therefore necessary.

Conclusions

Based on our review of the literature, CMs have symptomatic hemorrhage rates ranging from 0.1% to 2.7% per lesion-year and 0.013% to 16.5% per patient-year. Although the hemorrhage rates per patient-year at first appear broad, the majority of studies report rates of hemorrhage that fall within a narrower range of 0.7% to 6% per patient-year. In addition, many studies have identified risk factors that increase the risk of hemorrhage including presenting with a symptomatic hemorrhage, deep or infratentorial location, and perhaps female sex. Seizures are also a significant source of patient morbidity. The reported rates of new seizure following CM diagnosis range from 1.5% to 4.3% per patient-year, and history of a previous seizure increases this rate to 5.5% per patient-year. Finally, available evidence suggests that the greater overall CM burden found in familial versus sporadic forms of CMs leads to a higher annual risk of symptomatic hemorrhage for patients with familial inheritance.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Similarly, none of the authors have any personal or institutional financial interest related to this submission.

Author contributions to the study and manuscript preparation include the following. Conception and design: Zipfel, Washington. Acquisition of data: Washington, McCoy. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Zipfel, Washington. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Zipfel.

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Manuscript submitted May 19, 2010.
Accepted May 27, 2010.
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Neurosurg Focus 29 (3):E8, 2010

Surgical approaches to brainstem cavernous malformations

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Brainstem cavernous malformations (CMs) are low-flow vascular lesions in eloquent locations. Their presentation is often marked with symptomatic hemorrhages that appear to occur more frequently than hemorrhage from supratentorial cavernomas. Brainstem CMs can be removed using 1 of the 5 standard skull-base approaches: retrosigmoid, suboccipital (with or without telovelar approach), supracerebellar infratentorial, orbitozygomatic, and far lateral.

Patients being referred to a tertiary institution often have lesions that are aggressive with respect to bleeding rates. Nonetheless, the indications for surgery, in the authors' opinion, are the same for all lesions: those that are symptomatic, those that cause mass effect, or those that abut a pial surface. Patients often have relapsing and remitting courses of symptoms, with each hemorrhage causing a progressive and stepwise decline. Many patients experience new postoperative deficits, most of which are transient and resolve fully. Despite the risks associated with operating in this highly eloquent tissue, most patients have had favorable outcomes in the authors' experience. Surgical treatment of brainstem CMs protects patients from the potentially devastating effects of rehemorrhage, and the authors believe that the benefits of intervention outweigh the risks in patients with the appropriate indications.
(DOI: 10.3171/2010.6.FOCUS10128)

Key Words • hemorrhage • cavernous malformation • surgical approach

Cavernous malformations are low-flow vascular lesions thought to be related to capillary telangiectasias and developmental venous anomalies.[1] They are found throughout the CNS, with a minority of these lesions occurring in the brainstem. Cavernous malformations were once considered to be congenital lesions; however, it is now well established that these lesions also form de novo.[8,10,13,16,18] Cavernous malformations located in the brainstem are particularly difficult to treat, given their location in eloquent tissue. Brainstem CMs can be found anywhere within the brainstem, but most commonly occur in the pons.[5]

It has been reported that infratentorial CMs are more dangerous than their supratentorial counterparts. In terms of bleeding propensity, one series showed that the rates of hemorrhage in infratentorial lesions were 30 times greater in prospectively followed patients.[14] Resection of brainstem CMs is associated with a significant risk of morbidity due to their highly eloquent location. However, complete removal can cure the patient of the often devastating symptoms associated with recurrent hemorrhages and hemosiderin deposition in the brainstem. In 1928 Walter Dandy[4] reported the first case of a brainstem CM, which was surgically removed from the pontomedullary region in a 21-year-old patient. In the years since, our understanding of brainstem CMs has continued to evolve. Our knowledge is derived from a variety of publications that have reported on the pathophysiological characteristics of brainstem CMs, the natural history of the disease, and surgical approaches and outcomes.

We review the natural history of brainstem CMs, prior reports of surgically treated lesions, and the surgical technique and philosophy of the senior author (R.F.S.), and offer recommendations on surgical approach based on lesion location. We also include preliminary data on the clinical presentation, lesion location, and surgical approaches used, from the largest series ever reported in both children and adults.

Natural History and Annual Rates of Hemorrhage

It is difficult to have confidence in the various estimates of bleeding rates in patients with a brainstem CM due to 2 primary confounding factors. First, to determine accurate rates, the denominator of "time" must be well established. Although it was once assumed that all CMs

Abbreviations used in this paper: CM = cavernous malformation; CN = cranial nerve; MCP = middle cerebellar peduncle; OZ = orbitozygomatic; SCIT = supracerebellar infratentorial.

were congenital, it is now understood that these lesions can also form de novo (resulting from irradiation, for example). However, due to an inability to diagnose the onset of de novo lesions, most retrospective studies that have reported hemorrhage rates have assumed that all lesions have been present since birth. Without accounting for de novo lesions, these studies probably underestimate true bleeding rates.

Second, the various reports on the natural history of brainstem CMs have an inherent selection bias. Surgical series are primarily based on a selected cohort of patients who have presented as a result of a symptomatic hemorrhage, and who have been referred to tertiary care centers for consideration of surgical treatment. Patients who have experienced silent hemorrhages are not considered in these studies. It is also likely that patients with large, highly symptomatic, and/or recurrent hemorrhages are part of a higher-risk subpopulation. At our institution, for example, a retrospective hemorrhage rate from 260 adult patients (assuming brainstem CMs were present since birth) was calculated to be 4.6%, and the rate of rehemorrhage was greater than 30%. Most of our patients (97%) had a history of hemorrhage, and 146 patients (56%) had a history of repeat hemorrhages before surgery, a fact that probably reflects both our referral and selection biases. We suspect that the true hemorrhage rate for patients with a brainstem CM in the general population is likely to be significantly lower. We have previously reported a 5% annual rate of hemorrhage for all patients from the same institution.[15] In another large surgical series of 137 patients who were surgically treated, an approximately 6% hemorrhage rate per year was reported.[17] Our data show that a prior rupture increases the annual hemorrhage rates during the observational period carried forward from that time point, as compared with the hemorrhage rate for the initial event.

Conversely, observational studies probably represent less aggressive brainstem CMs and underestimate hemorrhage rates. Brainstem CMs that have resulted in devastating presentations and cannot be observed are excluded from the analysis. Several attempts have been made to evaluate prospectively the natural histories of untreated lesions. Kondziolka et al.[6] found an annual bleeding rate of 0.6% in patients without a prior rupture, and of 4.5% in those who had prior hemorrhages. Of 122 patients, 43 harbored cavernomas in the brainstem. The bleeding rates were similar to supratentorial lesions. In a prospective group of 68 patients with CMs (20% infratentorial), Moriarity et al.[11] found a rehemorrhage rate of 3.1% per patient-year. In female patients, the prospectively recorded rate was 4.2%. Prior ruptures did not correlate with a higher annual bleeding rate during observation. In a prospective study of patients with familial CMs, Zabramski et al.[19] found a 6.5% annual hemorrhage rate per patient-year.

Indications for Surgical Treatment of Brainstem CMs

Not every patient with a brainstem CM who is referred to us will be offered surgery. Significant morbidity is potentially associated with the treatment of these lesions, even at a high-volume center. In appropriately selected patients, however, surgery is warranted given that surgical outcomes can be favorable when balanced against observation, which often leads to further morbidity in patients with more aggressive lesions.

The risks of surgery need to be balanced against the natural history of the disease. As stated, the natural history of CMs is controversial. Although we presume that cavernomas are histologically the same in all locations, brainstem CMs manifest and behave differently from supratentorial lesions: hemorrhages are far less likely to be subclinical and are more likely to be accompanied by more severe symptoms.

Dates of initial presentation, dates of hemorrhage, and interval between hemorrhages were determined for all patients who presented to our institution. We defined a history of hemorrhage as follows: 1) intra- or extralesional blood products on MR imaging, and 2) an acute onset of focal neurological deficit. We did not include patients with progressive symptoms without hemosiderin staining on their radiographs (or vice versa) as having definitive hemorrhage. Surgery was offered to patients with either acute extralesional hemorrhage, an exophytic (that is, pial surface–abutting) lesion, repeat hemorrhages and clinical deterioration, or mass effect caused by hemorrhages. Those with mild symptoms and/or deep-seated CMs were observed until further bleeding episodes made the lesions more amenable to intervention (that is, the pial surface could be reached via the hemorrhagic cavity). Over the years, based on the large experience of the senior author, more lesions that did not abut a pial surface have been removed. Across time, morbidity has been minimized by improvements in surgical navigation, surgical instruments, and surgical technique, and by the reduced use of more invasive approaches, including transcochlear approaches or full OZ craniotomies. Lesions that do not place eloquent tissue at risk when traversing a pial surface are removed with the help of intraoperative navigation, which facilitates resection of lesions that do not leave hemosiderin staining on the cortical surface.

It is important to note that because the cumulative lifetime risk of bleeding is higher in patients with a longer life expectancy, it may be appropriate to have a lower threshold for surgical intervention in children. The prevention of rehemorrhage is likely to have a greater impact in the pediatric population than in adults, and this fact should be considered during treatment planning.

Note on Offering Patients Radiation Treatment for Lesions That are not Amenable to Surgery

There are reports of the use of radiation therapy, including proton beam therapy, to treat CMs that are unsuitable for surgery.[2,9,12] We believe that this treatment requires further validation. Our preference has not been to recommend radiation treatment for brainstem CMs. Although a cause and effect relationship has not been established, in a patient at our institution, a previously irradiated brainstem CM later degenerated into an arteriovenous malformation at the same location. The significance of this finding requires further study.

Common Presentations

Symptomatology tends to correspond with the deficits that would be predicted by lesions in various parts of the brainstem (Table 1). Cranial nerves are affected depending on the site of hemorrhage. Those in the midbrain are more likely to affect CNs III and IV as well as motor fibers of the cerebral peduncles. Pontine lesions are more likely to be associated with palsy of CNs V, VI, and VII. Medullary lesions often manifest with hiccoughs, swallowing difficulty, or vocal cord paralysis. In our experience, the combined presentation of a brainstem hemorrhage and the acute onset of any of those common deficits, which first gradually remit but later relapse, can predict the finding of a brainstem CM, even in the absence of MR imaging.

A Relapsing and Remitting Course

Most patients whom we evaluate have a history of rupture and have been referred from other institutions. Many neurological deficits caused by hemorrhage ultimately resolve over time. This clinical improvement is probably due to the resorption of blood products within the cavity, and supports the theory that the blood products displace rather than invade the surrounding tissue. Additional hemorrhages will create a new stepwise deterioration in baseline neurological status. When patients undergo surgery, the procedure often creates symptoms that were present during previous events. As many as half of patients have temporary deficits, but these deficits also tend to resolve in many of them. In patients with permanent "new" deficits, these are frequently similar to prior deficits that may have improved before treatment. We believe that this relapsing and remitting course can be halted by resection of the brainstem CM in most patients. Our preoperative consultation informs patients of the possibility of new deficits, and that surgery will often mimic an additional bleeding event, with the hope that no further events will occur. Patients who have had the best outcomes have had extended follow-up of 10 years or longer, with gradual improvement in new or prior deficits in the absence of recurrent hemorrhages in almost 90% of all those treated.

Surgical Techniques and Philosophy

We routinely monitor somatosensory evoked potentials and motor evoked potentials, but we do not routinely map the motor fibers or floor of the fourth ventricle, nor do we use diffusion tensor imaging modalities.

When a CM is resected, a small cortical opening is made, and the fibers of the brainstem are stretched. The lesion is removed piecemeal to limit the cortical opening. The use of a CO_2 laser can help break up, vaporize, or cut the cavernoma within the brainstem, and has been helpful in select cases. Even in the case of more deeply seated lesions, in our opinion, a minimal access approach renders these surgeries better tolerated.

We have found the use of intraoperative image guidance to be indispensable in these procedures. The image guidance aids in transtentorial approaches when the tentorium is sectioned for further access to thalamic lesions originating in the brainstem, as well as to deep-seated lesions that do not exhibit a telling hemosiderin stain at the cortical entry point. Without image guidance, we do not believe that the cortical opening can proceed safely when lesions are hidden from the surface of the brainstem.

We have found that a developmental venous anomaly is inherently associated with each brainstem CM. Such venous anomalies are benign but abnormal constellations of veins draining normal brain tissue. Our observations do not support removal of a developmental venous anomaly to prevent recurrence or regrowth. Because the anomaly may indeed be essential to the venous drainage of the surrounding brainstem, its removal is unnecessary and can pose an unnecessary risk of venous infarction.

Although the corridors involved in the surgical removal of brainstem CMs are often long, we do not advocate the use of retraction, to minimize potential retraction injuries. Our preference is to perform retraction with the use of the 2 instruments in hand, the dissection instrument or the suction instrument, which is moved as the lesion is removed or the surgical focus moves farther from the retractor. This process avoids placing further stretch on normal brain tissue. We have begun to find that using lighted instruments, a bipolar device, or a microsuction device can help with illumination when the microscope's focused area of view and the light source are sufficiently divergent, as tends to occur at high magnification. We do not attempt to resect hemosiderin-laden brain surrounding a brainstem CM, but we do attempt to remove as much of the CM as can be performed safely.

In the evolution of the surgical treatment of brainstem CMs, we have largely abandoned more invasive approaches, including anterior petrosectomy, transcochlear, and full OZ craniotomy in favor of the following most-used approaches in the removal of brainstem CM: the retrosigmoid, suboccipital with or without telovelar, and lateral SCIT craniotomies (Table 2). With these 3 "workhorse" approaches as well as with the far-lateral and a miniature/modified OZ approach,[7] a lesion in any part of the brainstem is accessible. The specific approach is selected on a case-by-case basis, according to the anatomical location of the lesion. The 2-point method was used as an objective means to choose the surgical approach.[3] One point is placed in the center of the lesion, and a second point is placed either where the lesion comes closest to a pial surface or at the safest entry point into the brainstem.

TABLE 1: Most common presenting deficits in 260 adult patients with brainstem CMs

Deficit	% of Patients w/ Deficit
CN	63
sensory	53
headache	39
motor deficit of extremity	37
diplopia	33
ataxia	29
vertigo	25

TABLE 2: Surgical approaches in 300 patients with brainstem CMs

Approach	No. (%)		
	Adults	Children	Total
suboccipital (w/ or w/o telovelar)	74 (28.5)	11 (27.5)	85 (28.3)
retrosigmoid	57 (21.9)	10 (25.0)	67 (22.3)
lat SCIT	53 (20.4)	8 (20.0)	61 (20.3)
far lat	33 (12.7)	4 (10.0)	37 (12.3)
OZ	18 (6.9)	4 (10.0)	22 (7.3)
retrolabyrinthine	6 (2.3)	1 (2.5)	7 (2.3)
subtemporal/anterior petrosectomy	6 (2.3)	0 (0.0)	6 (2.0)
other	13 (5.0)	2 (5.0)	15 (5.0)
total	260	40	300

TABLE 3: Location of lesion in 300 patients with brainstem CMs

Brainstem CM Location	No. (%)		
	Adults	Children	Total
medullary*	29 (11.2)	4 (10.0)	33 (11.0)
pontomedullary	40 (15.4)	3 (7.5)	43 (14.3)
pontine†	112 (43.1)	22 (55.0)	134 (44.7)
pontomesencephalic	31 (11.9)	3 (7.5)	34 (11.3)
mesencephalic‡	48 (18.5)	8 (20.0)	56 (18.7)
total	260	40	300

* Includes cervicomedullary lesions.
† Includes lesions involving the floor of the fourth ventricle and/or MCP.
‡ Includes mesencephalic lesions extending into the thalamus.

Connecting these 2 points, a line is drawn and extended to the skull; this method guides the selection of the most appropriate craniotomy.

When necessary, it is possible to combine the approaches; for example, a combined far-lateral/retrosigmoid approach for anterolateral lesions at the pontomedullary junction, or a combined supracerebellar/retrosigmoid approach when a lesion sits farther superiorly and lateral in the MCP than can reasonably be accessed with a telovelar approach. Recently, we have incorporated more uses for the SCIT approach than we previously had anticipated. Such cases include resection of pontomesencephalic lesions, laterally located lesions of the cerebral peduncle, and supratentorial lesions such as those located in the midbrain and thalamus, which can be resected by a SCIT approach with the added step of opening the tentorial edge to increase working room.

Correlating Lesion Location With Approach

Although we have moved away from more invasive approaches, we still believe that exposure and adequate visualization are the most important goals in these surgeries. We advocate increased bone removal, within reason, to limit brain retraction and to enhance visibility. Most lesions are located in the pons (Table 3), which requires several approaches to address adequately all lesions in this location (Table 2 and Fig. 1). In the case of a brainstem CM of the cerebellopontine angle, the 2-point method might suggest a lateral trajectory such as a transpetrosal approach, which would have been our approach early in the experience at our institution. However, a sufficiently lateral trajectory can be achieved with mild cerebellar retraction and a retrosigmoid approach. Anterolateral lesions in the pons and midbrain also may require modifications to the suggested approach when the 2-point method is used. We avoid entry into the cerebral peduncle to resect a CM by entering lateral to the peduncle from an OZ approach to reach a brainstem CM situated more anteriorly in the midbrain, unless it sits between the peduncles, at which point the 2-point method is valid in suggesting an interpeduncular OZ approach. If a lesion is situated in the posterolateral pons, we use either a retrosigmoid approach for more inferior lesions, ideally making a cortical entry between fibers of CNs V and VII (Fig. 2), or a lateral SCIT approach for more superior lesions in the posterolateral pontomesencephalic junction and midbrain/thalamus. The suboccipital approach is useful for cavernomas in the floor of the fourth ventricle or posterior medulla. We add the telovelar variation to the suboccipital approach for inferomedial MCP lesions (Fig. 1). Cavernomas laterally situated in the MCP can be accessed via retrosigmoid or lateral SCIT approaches. Lateral or anterolateral lesions of the medulla necessitate a far-lateral approach.

Postoperative Imaging

Magnetic resonance imaging is performed in all patients while they are hospitalized on postoperative Day 1. Patients undergo repeat imaging each year for the first 2 to 3 years, and then every 2 to 4 years thereafter. Patients who develop symptoms between MR imaging follow-up examinations undergo imaging sooner. In patients with MR imaging studies that suggest residual or recurrent growth of a residual lesion, images are obtained as often as annually. We routinely obtain imaging while the patients are hospitalized, although the immediate postoperative milieu of the surgical cavity can make it difficult to discern residual brainstem CM from hemostatic agents. We have considered obtaining MR imaging 2 weeks after surgery, but it becomes difficult to implement because many patients have already left the state or the country to return home by then. An enlarging surgical cavity or evidence of rehemorrhage probably represents an incompletely resected lesion that has grown and/or rebled. If we suspect residual lesion on the immediate postoperative MR imaging study, we return patients to surgery to remove additional cavernoma during the same hospitalization to maximize protection from future events. However, we do not advocate an overly aggressive resection or one that involves removal of hemosiderin-laden tissue. Rather, if postoperative surgical products in the resection cavity (such as hemostatic agents or blood) cannot be distinguished from CMs, we obtain subsequent imaging sooner than the first annual MR imaging session.

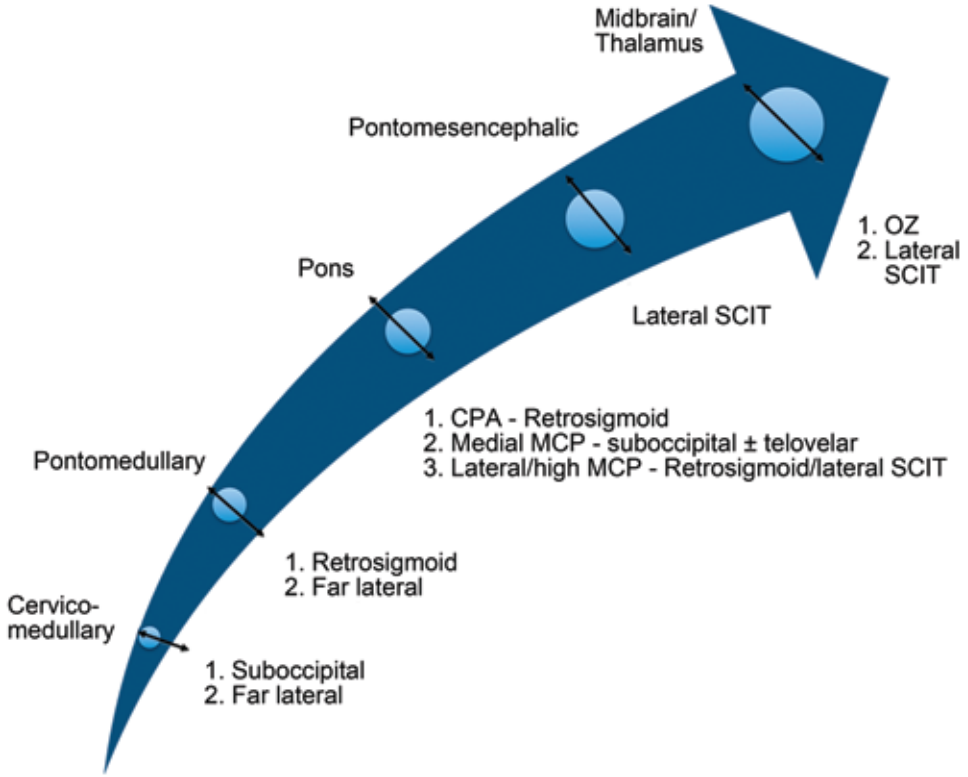

Fig. 1. Schematic of preferred surgical approaches based on locations of brainstem CMs. CPA = cerebellopontine angle; ± = with or without.

Forthcoming Reports

We are currently in the process of reporting our series of 300 surgically treated patients (260 adults and 40 children) with brainstem CMs with regard to preoperative hemorrhage rates, rates of postoperative hemorrhage and/or regrowth of cavernomas, rate of new postoperative deficits, and clinical outcomes.

Conclusions

Brainstem CMs warrant resection in patients with symptomatic lesions that are surgically accessible. Those that reach or are near a pial surface can be removed using standard skull base techniques (Table 3), and as suggested, by using the 2-point method.[3] Asymptomatic patients or those with considerable brainstem tissue that would need to be transgressed to resect a brainstem CM should be observed. Future hemorrhagic events in observed patients may provide a more accessible corridor to the cavernoma for resection.

In most patients, surgical treatment of brainstem CMs is associated with new neurological deficits, most of which resolve by the last follow-up. Given the high rates of rehemorrhage in patients who have not had surgery, and the improved quality of life due to a reduced relaps-

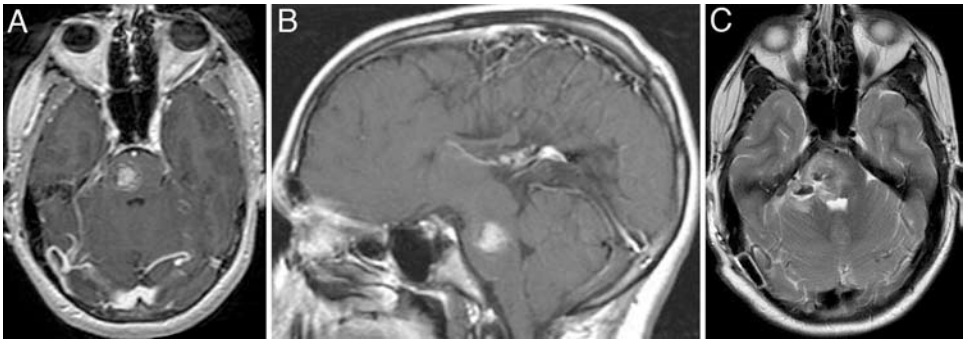

Fig. 2. This 12-year-old boy presented with the following symptoms: 2 months of headaches; an episode involving loss of consciousness; dysarthria; paresthesias on the left side of the body and face; and left lower-extremity weakness. Axial **(A)** and sagittal **(B)** MR images showed a 1.7-cm CM of the right pons. The patient underwent a right retrosigmoid craniotomy and was discharged 4 days after surgery (**C**, postoperative axial MR image) with no new deficits, although he did experience some mild left-sided dyscoordination during the first 6 months after surgery. All symptoms had resolved at his 1-year follow-up examination.

ing and remitting clinical course with repeat hemorrhages, a relatively low rate of rebleeding from recurrence/residual lesion, and excellent postoperative neurological outcomes, resection is indicated in symptomatic patients with accessible lesions. Patients with new deficits experience symptoms similar to those that appeared with prior hemorrhages, and often make a significant recovery over time while attaining increased protection from future bleeding events.

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: Abla, Spetzler. Acquisition of data: Abla, Turner, Mitha, Lekovic. Analysis and interpretation of data: Abla, Turner, Mitha, Lekovic. Drafting the article: Abla, Turner. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Abla, Turner. Administrative/technical/material support: Spetzler, Turner, Mitha, Lekovic. Study supervision: Spetzler, Mitha.

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Manuscript submitted May 13, 2010.
Accepted June 7, 2010.

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Neurosurg Focus 29 (3):E9, 2010

Brainstem cavernous malformations: anatomical, clinical, and surgical considerations

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Symptomatic brainstem cavernous malformations carry a high risk of permanent neurological deficit related to recurrent hemorrhage, which justifies aggressive management. Detailed knowledge of the microscopic and surface anatomy is important for understanding the clinical presentation, predicting possible surgical complications, and formulating an adequate surgical plan. In this article the authors review and illustrate the surgical and microscopic anatomy of the brainstem, provide anatomoclinical correlations, and illustrate a few clinical cases of cavernous malformations in the most common brainstem areas. *(DOI: 10.3171/2010.6.FOCUS10133)*

Key Words • cavernous malformation • brainstem • safe entry zone • developmental venous anomaly

With recent advances in imaging, surgical techniques and electrophysiological monitoring, CMs of the brainstem can be treated safely with resection. To maximize the chances of effective and safe removal, a thorough knowledge of the surface and intrinsic brainstem anatomy, as well as of the clinical and surgical correlates, is critical. In this article, we review and illustrate the anatomy of the brainstem and correlate it with clinical considerations in relation to the most common locations of CMs in this area. Moreover, we provide clinical examples and summarize some general technical principles to guide surgery in this challenging area.

General Clinical and Surgical Considerations

Various surgical approaches are available to gain access to the different sections of the brainstem (Fig. 1). A comprehensive description of these well-established approaches is beyond the scope of this review. For each location, we will describe and illustrate the specific surface anatomy encountered by the surgeon after exposure of the particular area and briefly discuss the pros and cons of the various routes. Various approaches can be used to remove a given lesion, and multiple considerations play a role in choosing the correct approach. These include the following: clinical presentation, lesion location, area to which the lesion comes closest to the surface, clinical functions of specific areas, pattern and distribution of associated hemorrhage, relationships to the adjacent DVA, and last but not least the degree of comfort of the individual surgeon with a specific approach. For educative and logistical purposes we will try to schematize the surgical considerations as they relate to a specific area. It is important, however, to understand that no dogma exists and the approach as well as the surgical strategy must be tailored to the particular characteristics of the individual patient.

There is lack of agreement about the indications for surgery in patients with brainstem CMs. We usually recommend resection for symptomatic CMs after a recent first hemorrhage for superficial lesions. We tend to be more aggressive in patients with hemorrhagic lesions if the hemorrhage extends beyond the boundaries of the CM. It has been our anecdotal experience that these patients have a higher risk of bleeding.

Abbreviations used in this paper: BA = basilar artery; CM = cavernous malformation; CN = cranial nerve; DVA = developmental venous anomaly; FOZ = frontoorbitozygomatic; MLF = medial longitudinal fasciculus; PCA = posterior cerebral artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery; UMN = upper motor neuron.

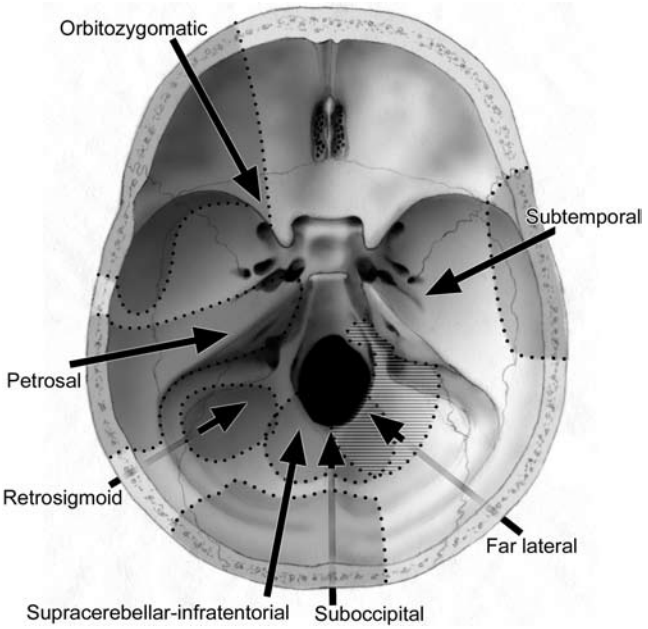

Fig. 1 Schematic drawing illustrating the most common surgical approaches used for different areas of the brainstem.

Surgery for brainstem CMs requires careful preoperative planning. Cavernous malformations compress and displace the surrounding parenchyma rather than infiltrating it. If the malformation abuts the pial or ependymal surface, it provides a direct and safe entry route[5] (Fig. 2). When the lesion is deep and separated from the surface by a thin parenchymal layer, surgery can still be performed safely by following a "safe entry zone;"[5,15,28,46,49,52] these are relatively safe but narrow surgical corridors into the brainstem parenchyma where "critical neural structures are sparse and no perforating arteries are encountered."[49]

Intraoperative monitoring is helpful in identifying safe entry zones especially in the presence of large underlying lesions that distort normal anatomy. With intraoperative monitoring, structures such as the corticospinal tract in the cerebral peduncle, CN nuclei (CNs VII, IX, X, and XII), the facial colliculus, and hypoglossal and vagal trigones on the floor of the fourth ventricle can be identified.[51] Frameless stereotaxy registered to the focus of the surgical microscope is also very helpful, especially when the CM is hidden under a very thin layer of normal-appearing parenchyma.

The goal of surgery for brainstem CMs is radical removal of the lesion. Partial removal is associated with a persistent and probably higher risk of recurrent hemorrhage from the residual lesion. We recommend delaying surgery after a symptomatic hemorrhage if possible for 2–3 weeks. This delay allows for partial liquefaction of the hematoma, providing a natural buffer that diminishes surgery-related trauma. We also try to avoid operating months after a symptomatic bleed when hematoma retraction and organization lead to tight adherence between the CM and the surrounding parenchyma, which increases the likelihood of mechanical trauma from surgical manipulation.

Brainstem CMs are usually removed through an incision smaller than the lesion itself. This makes internal decompression and piecemeal removal necessary[30] (Fig. 3). "En bloc" resection is usually neither safe nor feasible in this location. In contrast to the situation with supratentorial CMs, after resection of a brainstem CM the hemosiderin-stained parenchyma is not disturbed and is left in situ. Every attempt must be made to preserve any associated DVA[30,43,46,48] (Fig. 4); the presence of a DVA should be suspected even when the preoperative MR imaging does not show one. Sacrifice of the DVA will invariably lead to a venous infarct with disastrous clinical sequelae.[32,46,50,53] Developmental venous anomalies are usually absent in patients with familial CMs.[44]

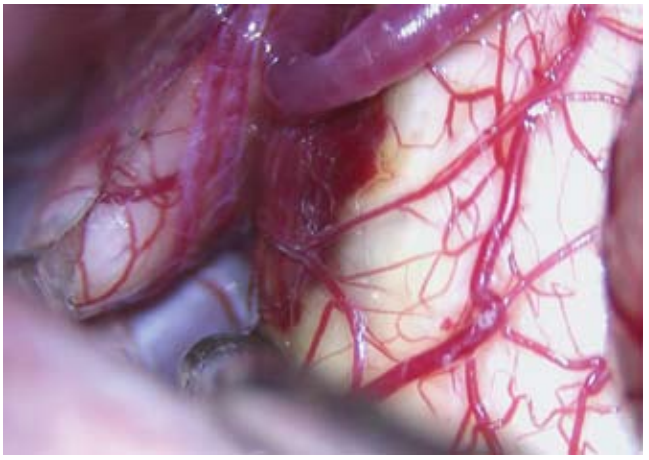

Fig. 2. Intraoperative photograph showing a posterolateral CM of the left medulla abutting the pial surface. The CM was exposed through a posterior suboccipital approach after elevation of the ipsilateral tonsil. The PICA loop and the vertebral artery (deeper in the *left corner*) are visible. The superficial portion of the CM in this case provided a natural and atraumatic entry route.

Anatomical, Clinical, and Surgical Considerations in Relation to Common Brainstem Locations

Midbrain: Internal and Functional Anatomy

The anterior midbrain contains the crus cerebri, which are composed of cortical projections to the brainstem and spinal cord (Fig. 5). Projections to the pontine nuclei from the parietal, occipital, and temporal lobes are found later-

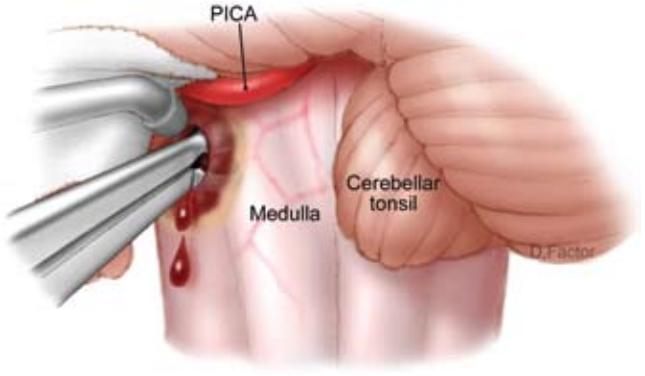

Fig. 3. Artist's illustration showing internal emptying of the same CM as in Fig. 2 and piecemeal removal with a pituitary forceps through a small opening.

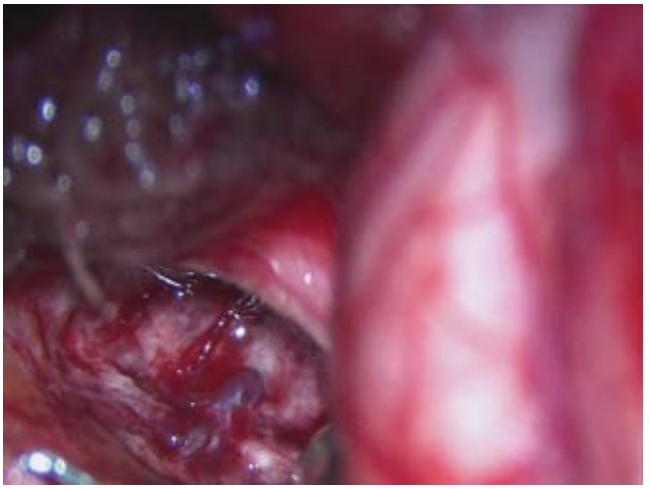

Fig. 4. Intraoperative photograph obtained after resection of the CM shown in Figs. 2 and 3. A typical DVA is visible along the inferior wall of the surgical cavity although no clear-cut evidence of a DVA was visible on the preoperative MR images.

ally, whereas frontal projections are found medially. At the center of the crus cerebri is the corticospinal tract and medial to that the corticobulbar tract.

Dorsal to the crus, the substantia nigra extends the width of the crus and separates it from the midbrain tegmentum. Containing dopaminergic and GABAergic cells, the substantia nigra contains reciprocal projections with the striatum, as well as efferents to the brainstem and thalamus.

Progressing dorsally, the red nucleus lies medially and the medial lemniscus lies laterally in the cross-section. The red nucleus is facilitatory to upper extremity flexors and is thought to be responsible for the upper extremity flexor pattern that occurs in classic decorticate posturing. The red nucleus exerts its influence on the musculoskeletal system through the rubrospinal tract, which descends to the contralateral spinal cord. The medial lemniscus carries proprioception, vibration, and discriminative touch information from the contralateral spinal cord to the ventral posterior lateral nucleus of the thalamus.

In more caudal sections, the decussation of the superior cerebellar peduncle lies centrally and medially instead of the more rostrally located red nucleus.

Continuing dorsally, CN nuclei are located medially and the spinothalamic tract (anterolateral system) laterally. The CN nuclei found in the midbrain are the oculomotor nuclear complex and Edinger-Westphal nucleus rostrally and the trochlear nucleus caudally.

The nuclei of CN III, the oculomotor nuclei and Edinger-Westphal nucleus, are found primarily at the level of the superior colliculus. The oculomotor nuclei supply the somatic innervation to the superior, inferior, and medial rectus; the inferior oblique; and the levator palpebrae muscles. The Edinger-Westphal nucleus supplies the parasympathetic innervation to the intraocular muscles for the accommodation reflex (pupillary constriction and ciliary muscle activation to change the shape of the lens allowing for near vision).

The trochlear nucleus (motor to the contralateral superior oblique muscle) is located caudal to the nuclei of CN III and at the level of the inferior colliculus.

The CNs III and IV nuclei are connected by the medial longitudinal fasciculus (MLF). It is positioned lateral to those nuclei, and within its most rostral portion is found the vertical gaze center, the rostral interstitial nucleus of the MLF. Deficits of upward gaze result from lesions of the uppermost portion of this nucleus, whereas deficits of

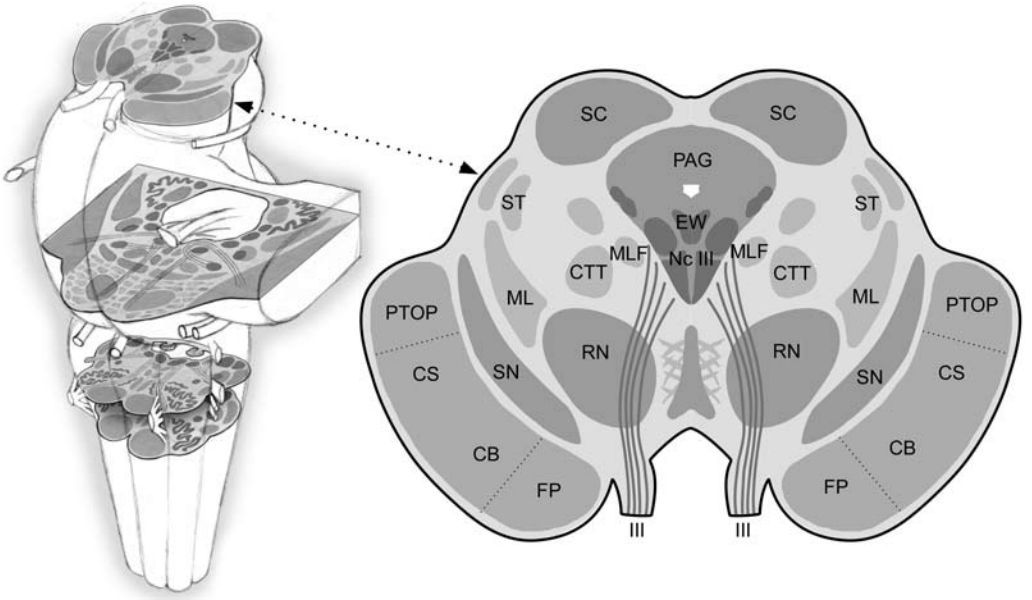

Fig. 5. Schematic 3D illustration **(left)** and axial view at the level of the superior colliculus **(right)** of the nuclei and fascicles in the midbrain. CB = corticobulbar tract; CS = corticospinal tract; CTT = central tegmental tract; EW = Edinger-Westphal nucleus; FP = frontopontine fibers; III = CN III; ML = medial lemniscus; MLF = medial longitudinal fasciculus; Nc III = CN III (oculomotor nerve) nuclei; PAG = periaqueductal gray matter; PTOP = parietotemporooccipitopontine tract; RN = red nucleus; SC = superior colliculus; SN = substantia nigra; ST = spinothalamic tract.

downward gaze occur when the caudal part of the nucleus is damaged.

Central and dorsal in location to the CN nuclei is the cerebral aqueduct, connecting the third and fourth ventricles. Impingement of the aqueduct will result in hydrocephalus. The cerebral aqueduct is surrounded by the periaqueductal gray matter, which manufactures various neurotransmitters and projects to the spinal cord to inhibit ascending pain transmission. The locus ceruleus is found laterally in this region and contains norepinephrine.

The corpora quadrigemina rounds out the dorsal aspect of the midbrain. Rostrally, the superior colliculus serves as the "orientation center." All sensory input projects to the superior colliculus, which in turn projects efferents to extraocular motor nuclei and gaze centers, as well as the upper cervical and thoracic spinal cord (via the tectospinal tract) to orient the eyes and head to sensory stimuli.

The inferior colliculus receives auditory sensory input through a series of relay nuclei that convey this information from bilateral dorsal and ventral cochlear nuclei. Unilateral damage usually results in no deficits, since auditory information ascends through the CNS in a bilateral fashion.

The various nuclei and fascicles in the midbrain are illustrated in Fig. 5.

Midbrain: Clinical Correlations

The clinical correlates of the midbrain structures are summarized in Table 1.

Midbrain: Surface Surgical Anatomy, Clinical-Anatomical Correlations, and Illustrative Cases

Ventral and Ventrolateral Midbrain CMs

Surface Surgical Anatomy of the Ventral and Ven-

TABLE 1: Midbrain nuclei and structures listed by anatomical location, function, and dysfunction*

Structure	Location (ventral to dorsal, medial to lat)	Function	Dysfunction
crus cerebri	ventral, lat	transmits descending corticopontines, corticospinals, corticobulbars	contralat UMN signs, weakness
substantia nigra	ventral, lat	dopaminergic input to striatum, GABAergic input to thalamus & brainstem	parkinsonism[38,40]
red nucleus	central, medial, rostral	facilitatory to UE flexors	contralat ataxia, rubral tremor[54]
superior cerebellar peduncle & decussation	central, medial, caudal	transmits ascending rostral & anterior spinocerebellar input to bilat cerebellar hemispheres, dentatothalamic tract from cerebellum to contralat thalamus	contralat cerebellar ataxia & tremor
medial lemniscus	central, lat	transmits incoming proprioceptive, vibratory, & discrim touch info from contralat spinal cord	contralat hemianesthesia of trunk & extremities
spinothalamic tract (anterolat system)	dorsal, lat	transmits incoming pain & temp info from contralat spinal cord	contralat loss of pain & temp sensation in trunk & extremities
ventral trigeminothalamic tract	dorsal, lat (along mediodorsal edge of medial lemniscus)	transmits sensory input from contralat face to the ventral pst medial nucleus of thalamus	hemianesthesia of contralat face
medial longitudinal fasciculus	dorsal, medial	pathway btwn extraocular motor nuclei & gaze centers	internuclear ophthalmoplegia
oculomotor nucleus	dorsal, medial, rostral	innervates ipsilat superior, medial, inferior rectus muscles, inferior oblique & levator palpebrae muscles	ipsilat oculomotor ophthalmoplegia
Edinger-Westphal nucleus	dorsal, medial, rostral	parasymp innervation to eye	ipsilat loss of pupillary constriction, difficulty focusing
trochlear nucleus	dorsal, medial, caudal	innervates contralat superior oblique	difficulty moving contralat eye down & inward
rostral interstitial nucleus of MLF	dorsal, medial	vertical gaze center	problems w/ vertical gaze, contralesional torsional nystagmus[7]
periaqueductal gray	dorsal, medial	produces multiple neurotransmitters, role in micturition[23]	none reported
cerebral aqueduct	dorsal, medial	transmits CSF	hydrocephalus
superior colliculus	dorsal, rostral	reflex movements of eyes & head	pupillary disturbances, vertical gaze deficits, gaze palsy
inferior colliculus	dorsal, caudal	auditory relay nucleus	difficulty localizing sounds in space[17], hypoacusia[59]

* discrim = discriminative; info = information; LE = lower extremity; parasymp = parasympathetic; pst = posterior; symp = sympathetic; temp = temperature; UE = upper extremity.

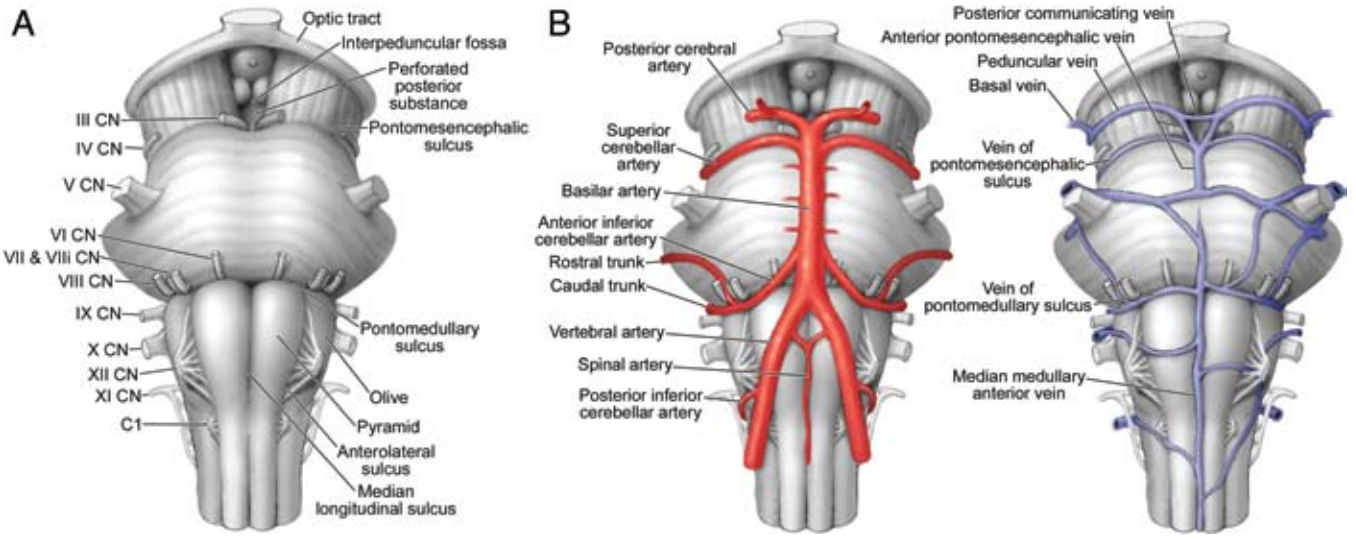

Fig. 6. A: Schematic illustration of the surface anatomy of the ventral brainstem. **B:** Schematic illustration of the arterial **(left)** and venous **(right)** anatomy

trolateral Midbrain. The surface anatomy of the ventral midbrain is illustrated in Fig. 6. Grossly, the midbrain is composed of the cerebral peduncles, the tegmentum, and the tectum. Its superior limit is the optic tract, while its inferior limit is the pontomesencephalic sulcus, which runs posteriorly to meet the lateral mesencephalic sulcus. The lateral mesencephalic sulcus extends from the medial geniculate body superiorly to the pontomesencephalic sulcus inferiorly. This sulcus is considered the posterior limit of the ventrolateral mesencephalon,[49] separating the cerebral peduncle surface from the tegmentum surface.[35] The depression between the cerebral peduncles and the root of CN III, containing the posterior perforated substance, is the interpeduncular fossa.

The BA divides into the 2 PCAs in the interpeduncular cistern. Blood supply to the midbrain comes from penetrating branches of the BA, the PCA, and the SCA. The peduncular vein of each side arises from the interpeduncular fossa and anastomoses with the contralateral vein, forming the posterior communicating vein, which crosses the interpeduncular fossa. The peduncular vein drains into the basal vein of Rosenthal together with the lateral mesencephalic vein after curving around the cerebral peduncle below the optic tract.[35] The anterior pontomesencephalic vein, running on the ventral midline surface of the pons as a single trunk, is usually a paired vein in its mesencephalic course. The vein of the pontomesencephalic sulcus runs on the homonymous sulcus.

Surgical Approaches to the Ventral and Ventrolateral Midbrain. The more central CMs of the midbrain (anterior and interpeduncular) can be reached through a transsylvian route with the classic pterional[58] or the frontoorbitozygomatic (FOZ) craniotomy[20,25,42] (Fig. 7) with one of its numerous modifications. The FOZ approach of-

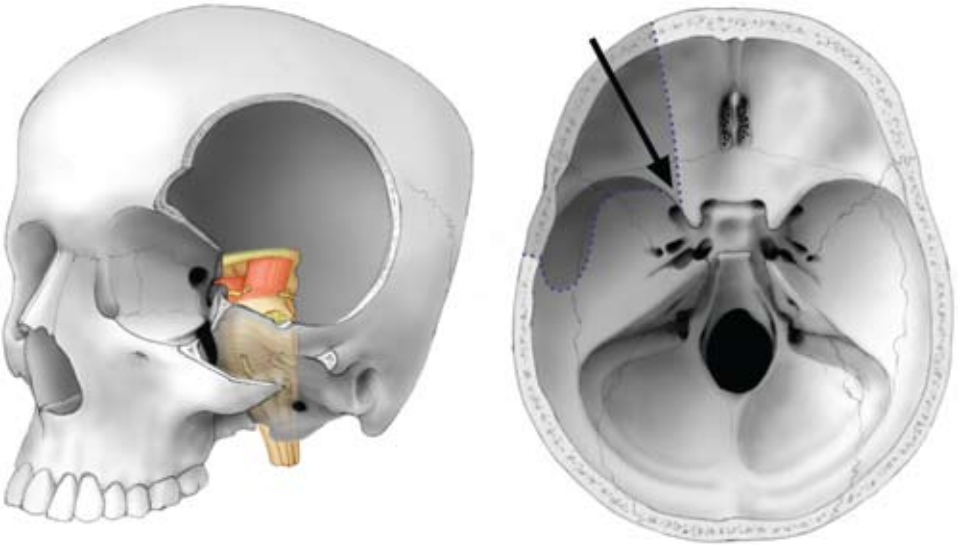

Fig. 7. Illustrations of the FOZ approach. Schematic 3D view of the skull after craniotomy, showing the region of the brainstem that can be approached **(left),** and axial view of the skull **(right)** showing the area of the craniotomy *(dotted lines). Arrow* indicates the surgical trajectory.

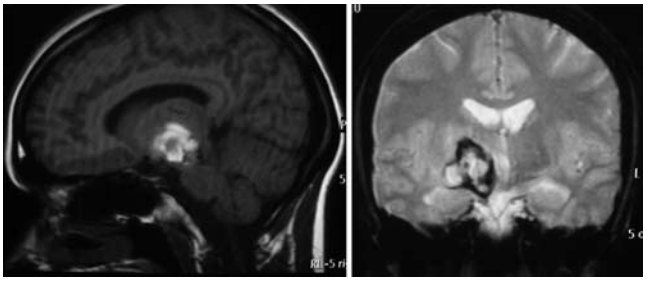

Fig. 8. Sagittal **(left)** and coronal **(right)** MR images obtained in a 24-year-old woman with sudden onset of facial numbness and left hand weakness showing a hemorrhagic CM extending from the upper midbrain to the ipsilateral thalamus.

fers the surgeon a flatter view of the midbrain and of the interpeduncular fossa by the transsylvian approach than the pterional approach.[45] A fairly safe entry zone has been described by Bricolo and Turazzi[6] as a narrow corridor lateral to the emergence of CN III between the SCA and the PCA, and medial to the pyramidal tract (Fig. 6).

Ventrolateral CMs of the midbrain can be reached either through the transsylvian route or though the subtemporal transtentorial approach.[12,13] Placement of a lumbar drain preoperatively in such cases decreases the amount of temporal lobe retraction required for the exposure with the subtemporal approach. Known complications of the subtemporal route include ophthalmoparesis secondary to mechanical manipulation of CNs III and IV and the risk of retraction injury and/or venous infarct from damage to the vein of Labbé complex. These complications are a major drawback especially when the dominant hemisphere is considered. Ventrolateral midbrain CMs, especially those extending caudally (see *Illustrative Case 2*) can also be approached via more complex skull base transpetrosal approaches that afford a wider and more lateral exposure for the lower midbrain, pons, and higher medulla. These approaches, though, carry the risk of complications such as hearing loss, CN VII deficit, or CFS leakage.[19]

It can be difficult to achieve complete resection of lesions centered in the ventral and ventrolateral midbrain, as extension of the CM into other compartments (primarily the thalamus) is not uncommon (Fig. 8). In a recent systematic review of 745 patients from 56 surgical series of brainstem CMs, the subgroup with ventral and ventrolateral midbrain lesions displayed the highest percentage of incomplete resections with subsequent persistent risk of rebleeding at follow-up.[19]

Clinical Correlates of a Ventral Midbrain CM. For a CM located in the central midbrain–cerebral peduncle as shown in Fig. 9, the more likely clinical presentations/possible sequelae from surgery include contralateral facial weakness from the compression of the corticobulbar tract, contralateral ataxia or tremor from compression of the red nucleus, and ipsilateral oculomotor ophthalmoplegia from compression of CN III. Larger lesions may also cause contralateral weakness and upper motor neuron (UMN) signs due to compression of the corticospinal tract.

Illustrative Case 1: CM of the Ventral Midbrain. This 49-year-old man developed transient right ptosis. Magnetic resonance imaging (Fig. 10) showed a central brainstem CM, likely involving the fibers and nuclei of the right CN III. Because the CM did not come to the pial surface but was separated by a thin layer of parenchyma and the symptoms completely resolved, surgery was not considered.

Clinical Correlates of a Ventrolateral Midbrain CM. For a CM located in the ventrolateral midbrain as shown in Fig. 11, the more likely clinical presentations or possible sequelae from surgery include contralateral weakness and UMN signs due to compression of the corticospinal tract, and contralateral facial weakness due to compression of corticobulbar tract. Larger lesions can cause contralateral

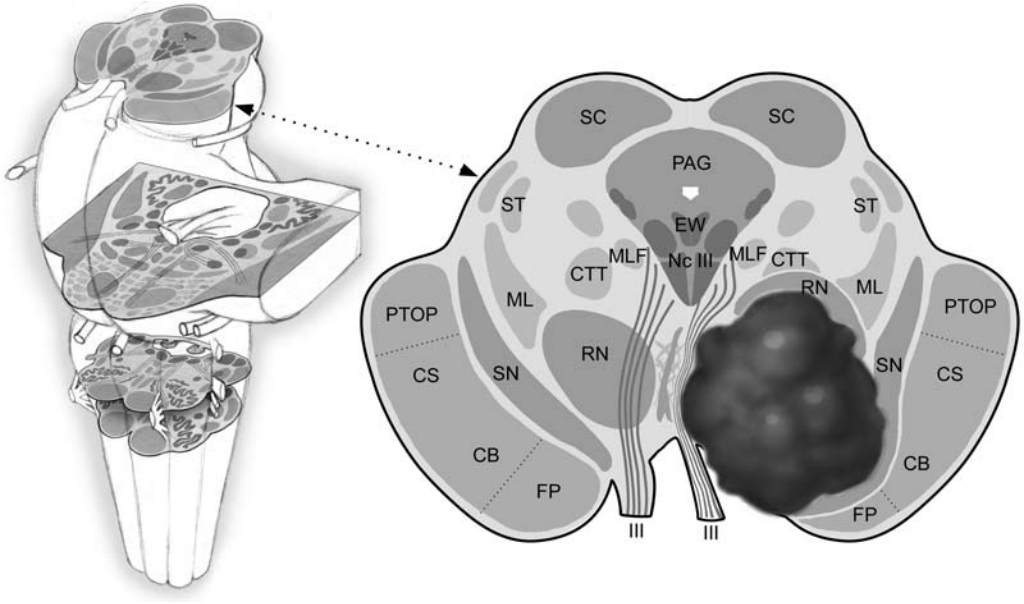

Fig. 9. Schematic 3D illustration of the anatomy of the midbrain **(left)** and axial view of a ventral midbrain CM displacing internal structures **(right)**.

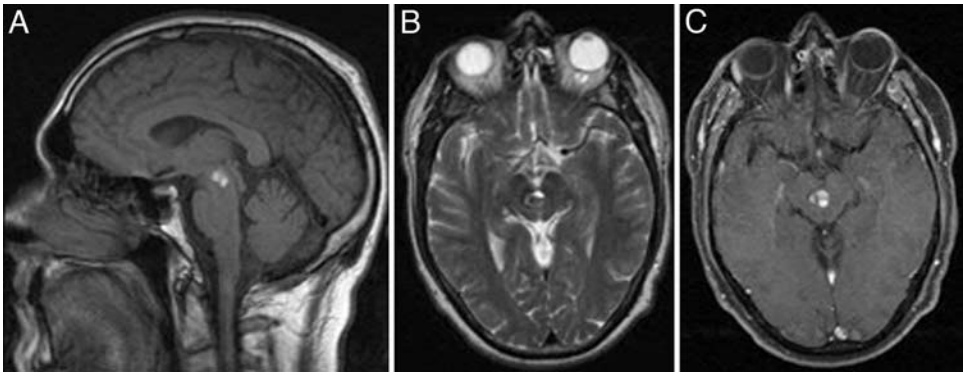

Fig. 10. Illustrative Case 1: CM in the central midbrain. Sagittal T1-weighted **(A)**, axial T2-weighted **(B)**, and Gd-enhanced axial T1-weighted **(C)** MR images demonstrating a CM in the central midbrain. The lesion is hyperintense on T1-weighted images **(A)**, heterogeneous on T2-weighted images with a fluid-fluid/debris level **(B)**, and nonenhancing **(C)**.

loss of tactile sensation from trunk and extremities due to medial lemniscus compression and/or contralateral ataxia due to compression of the red nucleus.

Illustrative Case 2: CM of the Ventrolateral Midbrain. This 39-year-old woman experienced acute right-sided hearing loss that led to the diagnosis of a CM of the right ventrolateral midbrain and upper pons (Fig. 12). Resection was performed through a subtemporal/presigmoid approach with partial petrosectomy.

Posterior Midbrain CMs

Surface Surgical Anatomy of the Posterior Midbrain. The lateral mesencephalic sulcus is considered the limit between the so-called anterolateral midbrain and the posterior midbrain (Figs. 13 and 14). The sulcus, as explained above, is located in the posterior aspect of the midbrain; it runs from the medial geniculate body above to the pontomesencephalic sulcus. The quadrigeminal plate, with the paired superior and inferior colliculi is posteromedial to the lateral mesencephalic sulcus. The CN IV decussates into the medullary velum and exits just below the inferior colliculus running anteriorly between the PCA and SCA.

Surgical Approaches to the Posterior Midbrain. Cavernous malformations involving the posterior midbrain are approached through a supracerebellar infratentorial route, which allows an adequate view of the posterior and posterolateral surface of the midbrain and quadrigeminal plate, as well as the posterolateral surface of the upper pons. This approach includes median, paramedian, and extreme lateral variants,[10] which provide access to different parts of the posterior midbrain. Moreover, their convergent trajectory to similar regions allows the surgeon to choose the most convenient trajectory to CMs in analogous sites but approach the pial or ependymal surface in different points.[10] We prefer the sitting position because it maximizes the effects of gravity by allowing the superior aspect of the cerebellum to "fall down," obviating the need for retraction. The occipital transtentorial approach is an alternative for patients with a steep tentorial slope.[19]

The median supracerebellar infratentorial approach[2,

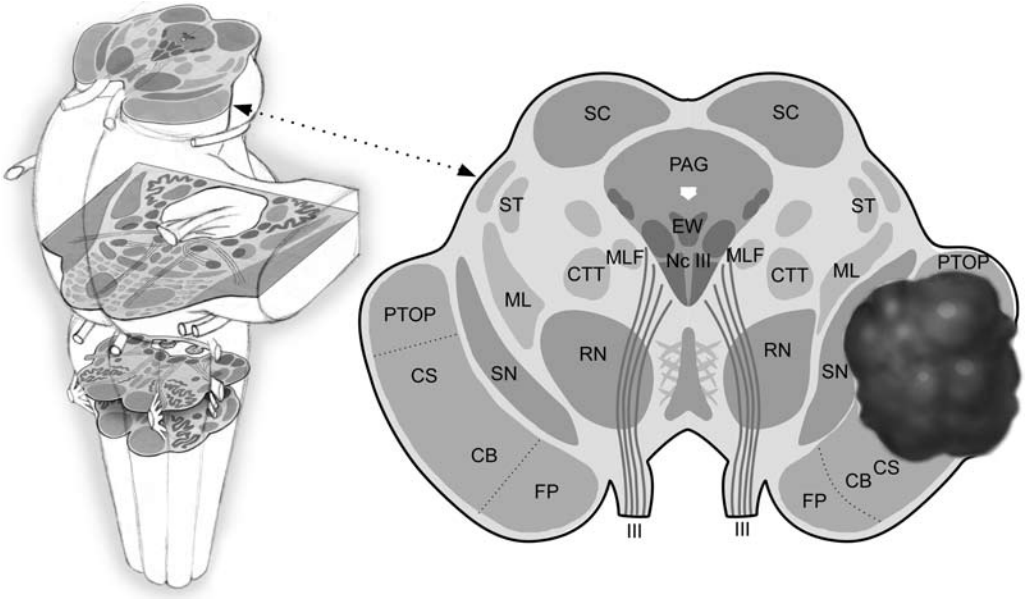

Fig. 11. Schematic 3D illustration of the anatomy of the midbrain **(left)** and axial view of a ventrolateral midbrain CM displacing internal structures **(right)**.

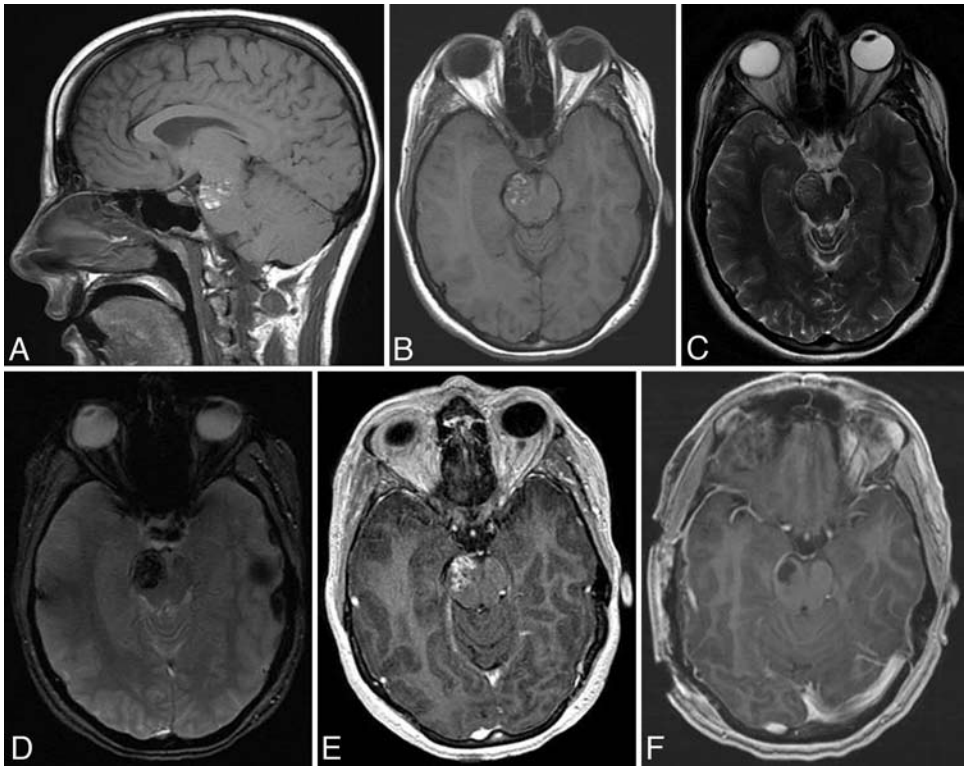

Fig. 12. Illustrative Case 2: CM in the right ventrolateral midbrain and upper pons. **A–E:** Preoperative sagittal T1-weighted **(A)**, axial T1-weighted **(B)**, axial T2-weighted **(C)**, axial gradient echo (GRE) **(D)**, and axial T1-weighted Gd-enhanced **(E)** MR images demonstrating a CM involving the right anterolateral midbrain and upper pons, extending to the surface. Note the pre-contrast T1 hyperintensity **(A and B)**; speckled, "popcorn" morphology **(A and B)**; extensive blooming on GRE sequence due to magnetic susceptibility artifact **(D)**; and minimal enhancement **(E)**. **F:** Postoperative axial T1-weighted Gd-enhanced image demonstrating resection of the CM, with a resection cavity at the operative site and no residual enhancement.

[33,55,56] requires a craniotomy exposing the entire width of the transverse sinus as well as the confluence of sinuses to increase the angle of view by upward retraction of the sinus. In doing so, care must be taken to avoid excessive retraction of the sinus to prevent sinus thrombosis. Small veins running from the superior aspect of the cerebellum to the tentorium can be coagulated and divided close to the cerebellar surface.[10] After opening the posterior wall of the quadrigeminal cistern, the precentral cerebellar veins draining to the vein of Galen are visible. Whenever

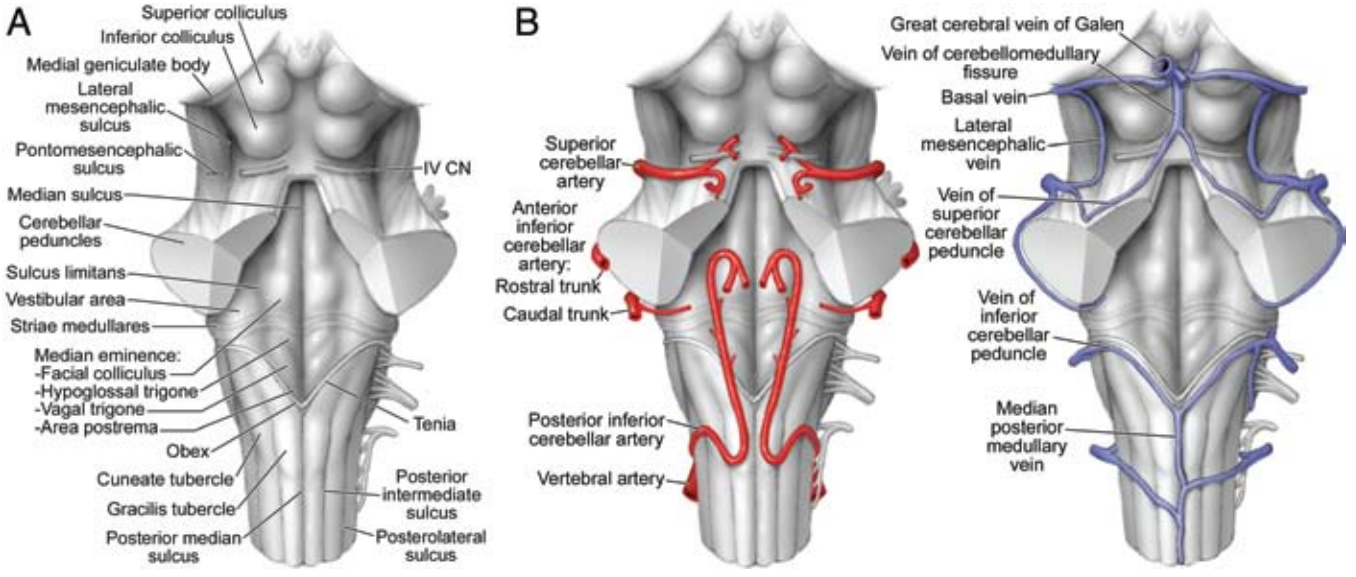

Fig. 13. A: Schematic illustration of the surface anatomy of the dorsal brainstem. **B:** Schematic illustration of the arterial **(left)** and venous **(right)** brainstem anatomy.

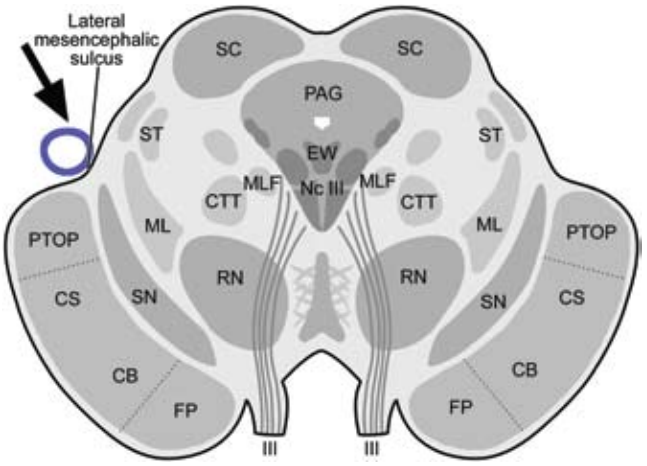

Fig. 14. Axial view of the midbrain showing the surgical route through the lateral mesencephalic sulcus, covered by the lateral mesencephalic vein *(blue circle)*. This safe entry zone allows a trajectory *(arrow)* of approach between the substantia nigra (SN) and the medial lemniscus (ML) posterior to the cerebral peduncle.

possible we prefer to avoid coagulation and division of the precentral cerebellar vein, and we try work around it. Sharp opening of the cerebellomesencephalic fissure under high magnification leads to exposure of the corpora quadrigemina.

The lateral supracerebellar infratentorial approach requires a paramedian craniotomy, again exposing the entire width of the transverse sinus. This provides access to the posterior portion of the ambient cistern, including the proximal portion of the trochlear nerve, the SCA, and the posterolateral aspect of the midbrain, with the lateral mesencephalic vein running in the lateral mesencephalic sulcus. The lateral mesencephalic vein, as discussed later, is an important landmark for identifying a safe entry zone in this area[2] (Figs. 14 and 15).

The extreme-lateral supracerebellar infratentorial approach is performed through a classical retrosigmoid craniectomy, with full exposure of the transverse/sigmoid sinus junction. It allows for a more lateral view of the posterolateral midbrain than the lateral approach.[10]

In the posterior midbrain, the lateral mesencephalic sulcus is a relatively safe entry zone (Figs. 13–15). This sulcus represents the anatomical surface separation between the colliculi and the cerebral peduncle and runs from the medial geniculate body superiorly to cross inferiorly, almost at a right angle, the pontomesencephalic sulcus. The lateral mesencephalic vein runs into the lateral mesencephalic sulcus, thus representing an easily identifiable surface landmark for this structure. Entry into the posterolateral midbrain through the lateral mesencephalic sulcus minimizes the risk of damaging the cerebral peduncles. A vertical incision in this sulcus provides a narrow corridor between the substantia nigra ventrally and the medial lemniscus dorsally[49] (Fig. 14). This area can be reached also through a subtemporal route with the limitations and possible risks of this approach as previously discussed.[49]

In the more medial posterior midbrain, Bricolo[5] described 2 safe entry zones at the level of the supracollicular and infracollicular areas (Fig. 15). These are 2 narrow horizontal lines immediately above and below the lamina quadrigemina.

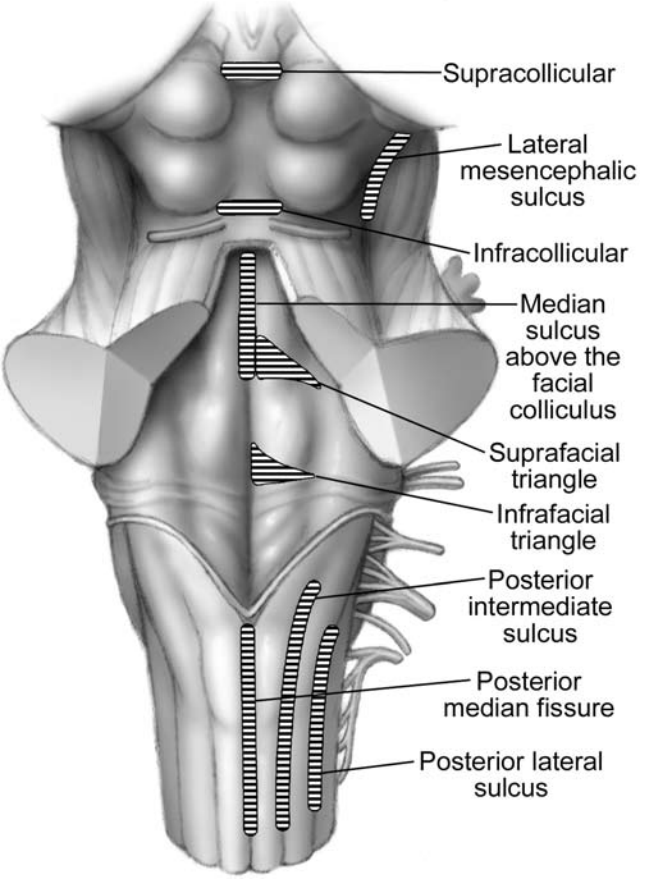

Fig. 15. Posterior view of the brainstem showing the various safe entry zones.

Usually CMs of the posterior midbrain can be resected with good results, the most common complication being a CN III paresis.[19]

Clinical Correlates of a Posterior Midbrain CM. For a CM located in the posterior midbrain as shown in Fig. 16, the more likely clinical presentations or possible sequelae of surgery include difficulty tracking and contralateral neglect due to compression of the superior colliculus; hydrocephalus due to impingement of the aqueductus; pupillary changes (large, irregular) and accommodation impairment due to compression of the Edinger-Westphal nucleus; and, in patients with larger lesions, ipsilateral oculomotor ophthalmoplegia due to compression of the CN III nuclei, vertical gaze palsy from compression of MLF, and torsional nystagmus (rostral interstitial nucleus).

Pons: Internal and Functional Anatomy

The ventral (basilar) pons contains pontine nuclei throughout its structure. Within this region the corticospinal tract is found ventromedially in each hemisection. The corticobulbar tracts are closely associated with the most dorsal corticospinal fibers.

The medial lemniscus runs medially to laterally in

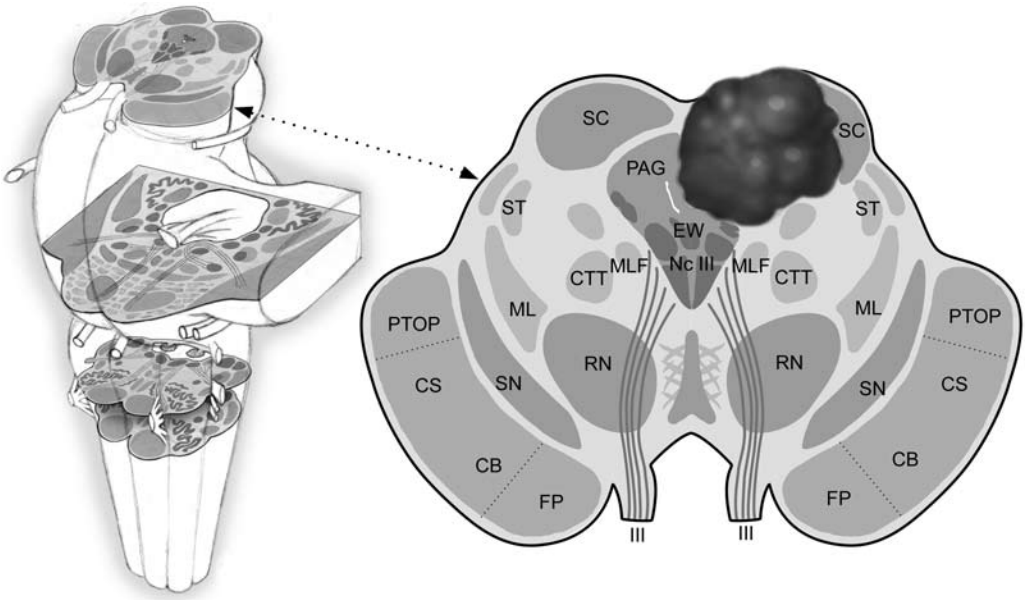

Fig. 16. Schematic 3D illustration of the midbrain **(left)** and axial view of a posterior midbrain CM displacing internal structures **(right)**.

the pons, in effect separating the basilar region from the dorsally located tegmentum.

Lateral and in the same plane as the medial lemniscus is the spinothalamic tract (anterolateral system).

Moving dorsally in the section and in a midline position is the tectospinal tract and posterior to that the medial longitudinal fasciculus (MLF). The MLF connects the nuclei of CNs III, IV, and VI to coordinate extraocular movements. Lateral to these axonal pathways is the central tegmental tract. Multiple connections involving the reticular formation and brainstem nuclei occur through the central tegmental tract.

The branchial arch motor nuclei (trigeminal and facial motor nuclei) can be seen lateral to the central tegmental tract. The trigeminal motor nucleus innervates the muscles of mastication and is located rostrally. The facial motor nucleus innervates the muscles of facial expression and is found caudally.

Most dorsal in the pons and medially located is the abducent nucleus, which innervates the ipsilateral lateral rectus. The paramedian pontine reticular formation, responsible for initiating horizontal gaze, is found just lateral to the abducent nucleus.

The trigeminal sensory nuclei (spinal trigeminal nucleus, mesencephalic nucleus, and chief sensory nucleus) are found far laterally in the cross-section at the level of the rostral pons. The vestibular nuclei are also far lateral and dorsal to the trigeminal nuclei.

Laterally, the pons is bordered by the middle cerebellar peduncle, which carries fibers into the cerebellar hemisphere from the contralateral pontine nuclei. The inferior border of the middle cerebellar peduncle shares an intimate relationship with the inferior cerebellar peduncle.

The various nuclei and fascicles in the pons are illustrated in Fig. 17.

Pons: Clinical Correlations

Clinical correlates of pontine nuclei and tracts are summarized in Table 2.

Pons: Surface Surgical Anatomy, Clinical-Anatomical Correlations, and Illustrative Cases

Ventral and Ventrolateral Pons CMs

Surface Surgical Anatomy of the Ventral and Ventrolateral Pons. The ventral pons is convex and is indented along the midline by the basilar sulcus (Fig. 6). The emergence of the trigeminal nerve defines the limit between the pons proper medially and the middle cerebellar peduncle laterally. Inferiorly, the pontomedullary sulcus separates the pons from the medulla. Cranial nerves VII and VIII emerge from the pontomedullary sulcus at the level of the supraolivary fossette. During its course in the basilar sulcus, the BA sends several perforating branches to the ventral pons.[35]

On the ventral surface of the pons, the pontine portion of the median anterior pontomesencephalic vein anastomoses with a transverse pontine vein before continuing on the medulla as the median anterior medullary vein. The vein of the pontomedullary sulcus courses along the pontomedullary sulcus.[35]

Surgical Approaches to the Ventral and Ventrolateral Pons. Truly ventral pontine lesions pose a significant surgical challenge and usually require invasive skull base approaches. However, exclusively ventral pontine CMs are rare, and more often the CM has a more lateral extension. For ventrolateral and lateral pontine lesions we prefer a classical retrosigmoid approach and usually enter the brainstem between CNs V and VII. For more ventral lesions, this approach can be extended by anterior mobiliza-

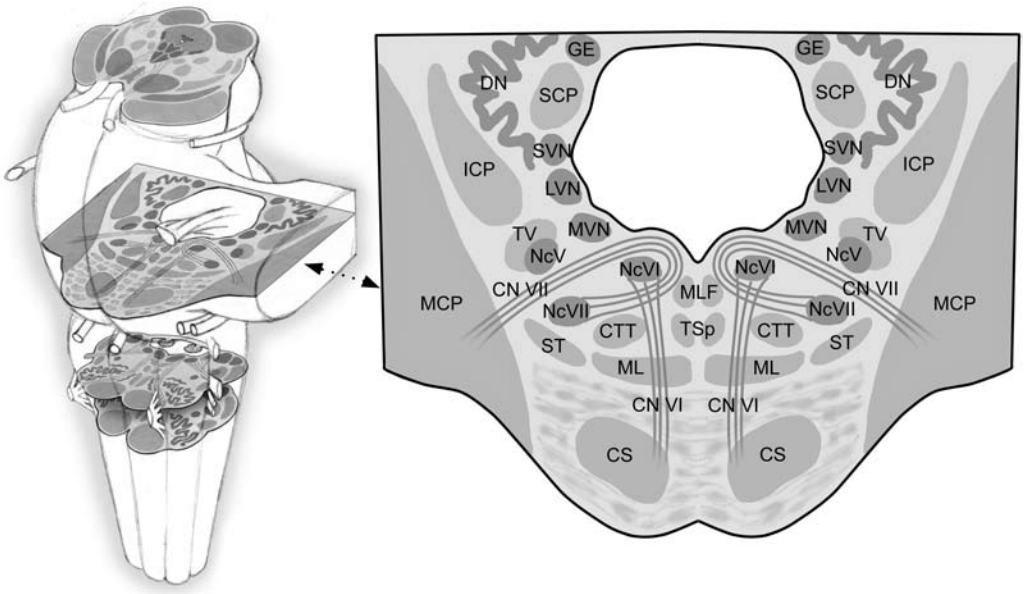

Fig. 17. Schematic 3D illustration **(left)** and axial view of the pontine nuclei and fascicles in a section at the level of the facial colliculus **(right)**. CN VI = abducent nerve fibers; CN VII = facial nerve fibers; DN = dentate nucleus; GE = globose end emboliform nuclei; ICP = inferior cerebellar peduncle; LVN = lateral vestibular nucleus; MCP = middle cerebellar peduncle; MVN = medial vestibular nucleus; NcV = spinal nucleus of trigeminal nerve; NcVI = abducent nerve nucleus; NcVII = facial nerve nucleus; SCP = superior cerebellar peduncle; SVN = superior vestibular nucleus; TSp = tectospinal tract; TV = spinal tract of trigeminal nerve.

tion of the skeletonized sigmoid sinus.[47] Alternatives to the retrosigmoid approach for lateral and ventrolateral pontine lesions include the subtemporal transtentorial route (for lesions with more rostral extension) or the presigmoid route, which provides a more lateral and direct view to the lesion.[21] Combination of various approaches is rarely necessary and useful only in a few exceptional cases of giant lesions spanning multiple compartments.

Transpetrosal approaches[1,26,36] are also useful for lesions in these locations, but in our opinion their application is limited by their invasive nature and potential complications. A detailed review of the pros and cons of the various transpetrosal skull base approaches to this region is beyond the scope of this review, and the reader is referred to various publications on the topic.[4,9,18,24,26,31]

A well-established safe entry zone into the lateral pons is the so-called "peritrigeminal area" (Fig. 18) between the emergence of CNs V and VII. This is an area located medially to the CN V and laterally to the pyramidal tract.[49] This area is adequately exposed with any of the aforementioned approaches.

Clinical Correlations of a CM of the Ventral Pons. For a CM located in the ventral pons as shown in Fig. 19, the more likely clinical presentations/possible sequelae of surgery include contralateral weakness and UMN signs due to compression of the corticospinal tract; ipsilateral CN VI palsy due to compression of the nerve fibers; and contralateral loss of tactile sensation from the trunk and extremities due to compression of the medial lemniscus. In larger lesions, ipsilateral hemifacial weakness due to compression of the CN VII nucleus is possible and central tegmental tract compression may result in nystagmus and intention tremor.

Illustrative Case 3: CM of the Ventrolateral Pons. This 27-year-old woman developed intractable nausea, vomiting, ataxia, bilateral (right greater than left) weakness and loss of sensitivity, left eye-abduction weakness, and a complete left facial palsy. Magnetic resonance imaging (Fig. 20) showed a large CM extensively involving the ventrolateral pons. Using a classic retrosigmoid approach, the brainstem was entered between CNs V and VII at a point where the hemorrhage had reached the surface. The CM was completely removed.

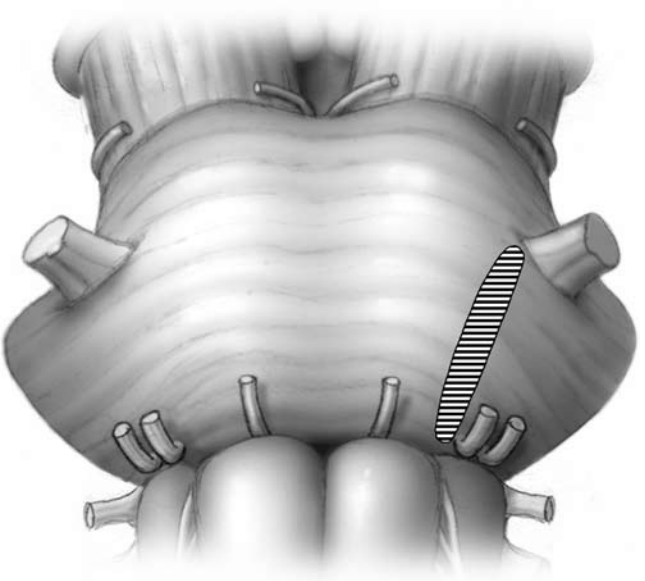

Fig. 18. Peritrigeminal safe entry zone in the ventrolateral pons.

TABLE 2: Pontine nuclei and structures listed by anatomical location, function, and dysfunction

Structure	Location (ventral to dorsal, medial to lat)	Function	Dysfunction
pontine nuclei	scattered throughout ventral half of cross-section	relay input from ipsilat cerebral cortex to contralat cerebellum	contralat hemiataxia, but may be masked by UMN weakness if corticospinal tract is also involved
corticospinal tract	ventral, medial	UMN from cortex to contralat spinal cord	contralat UMN signs, weakness
medial lemniscus	central, medial	transmits incoming proprioceptive, vibratory, & discrim touch info from contralat spinal cord	contralat hemianesthesia of trunk & extremities
ventral trigeminothalamic tract	central, medial (along dorsal edge of medial lemniscus)	transmits sensory input from contralat face to ventral pst medial nucleus of thalamus	hemianesthesia of contralat face
spinothalamic tract (anterolat system)	central, lat	transmits incoming pain & temp info from contralat spinal cord	contralat loss of pain & temp sensation in trunk & extremities
hypothalamospinal tract (not shown)	central, lat near spinothalamic tract	carries symp projections from hypothalamus to spinal cord	Horner syndrome
tectospinal tract	central-dorsal, medial	reflex movement of head & neck	unappreciable
medial longitudinal fasciculus	dorsal, medial	pathway btwn extraocular motor nuclei, vestibular nuclei, & gaze centers	internuclear ophthalmoplegia
central tegmental tract	central	connects multiple reticular formation & brainstem nuclei	nystagmus,[34] intention tremor[16]
trigeminal motor nucleus	central, lat, rostral	innervation of muscles of mastication	paralysis of ipsilat muscles of mastication
facial motor nucleus	central, lat, caudal	innervation of ipsilat muscles of facial expression	lower motor neuron facial weakness
abducent nucleus	dorsal, medial, caudal	innervates ipsilat lat rectus	loss of ipsilat eye abduction, possible ipsilat gaze palsy
spinal trigeminal nucleus & tract	dorsal, lat	transmits pain & temp info from face, sensory input from around external auditory meatus, & pharynx	ipsilat loss of pain & temp sensation in areas around ear, decreased sensation in ipsilat oropharynx
chief (principal) sensory nucleus	dorsal, lat	receives sensory input from face	loss of tactile sensation in ipsilat face
vestibular nuclei	dorsal, lat	vestibular relay nuclei, integrates sensory input	dizziness/vertigo, postural instability, eye movement disorders
middle cerebellar peduncle	lat	carries projections from contralat pontine nuclei to ipsilat cerebellar hemisphere	ipsilat hemiataxia

Dorsal Pons CMs

Surface Surgical Anatomy of the Dorsal Pons and Dorsal Medulla (Floor of the Fourth Ventricle). The floor of the fourth ventricle (Fig. 13) is also known as the rhomboid fossa because of its shape. The rhomboid fossa is divided into a larger upper triangle (pontine) and a smaller inferior triangle (medullary) by a line connecting the 2 foramina of Luschka.[35] The junctional part with the striae medullares lies between the 2 triangles. The intraventricular portion of the cerebellar peduncles forms the lateral boundaries of the upper triangle with the apex of the upper triangle located at the sylvian aqueduct. The teniae of the fourth ventricle form the lateral limit of the inferior triangle, and the obex forms its most inferior and medial limit.[39] The median sulcus runs in the midline along the extent of the rhomboid fossa. On each side of the median sulcus are the paired vertically oriented sulci limitans. The median eminence is situated on either side of the median sulcus and is medial to the sulcus limitans. The pontine (upper) portion of the median eminence includes the facial colliculus (an eminence formed by the genu of the facial nerve curving around the abducent nucleus). The medullary (lower) portion of the median eminence includes 3 triangular areas: the hypoglossal and vagal trigones and the area postrema. These areas are often included in a region that is called the "calamus scriptorius" because of its shape. In the pontine triangle, lateral to the sulcus limitans, there are 2 anatomical structures: the locus coeruleus rostrally and the vestibular area (a prominence corresponding to the vestibular nuclei) caudally. Lateral to the vestibular area, closer to the lateral recess, the acoustic tubercle overlies the dorsal cochlear nucleus.[39]

The most important vascular structures of this region (Fig. 13) are the PICA and veins of the cerebellomedullary fissure.

Surgical Approaches to the Floor of the Fourth Ventricle. Dorsally located lesions involving the pons and up-

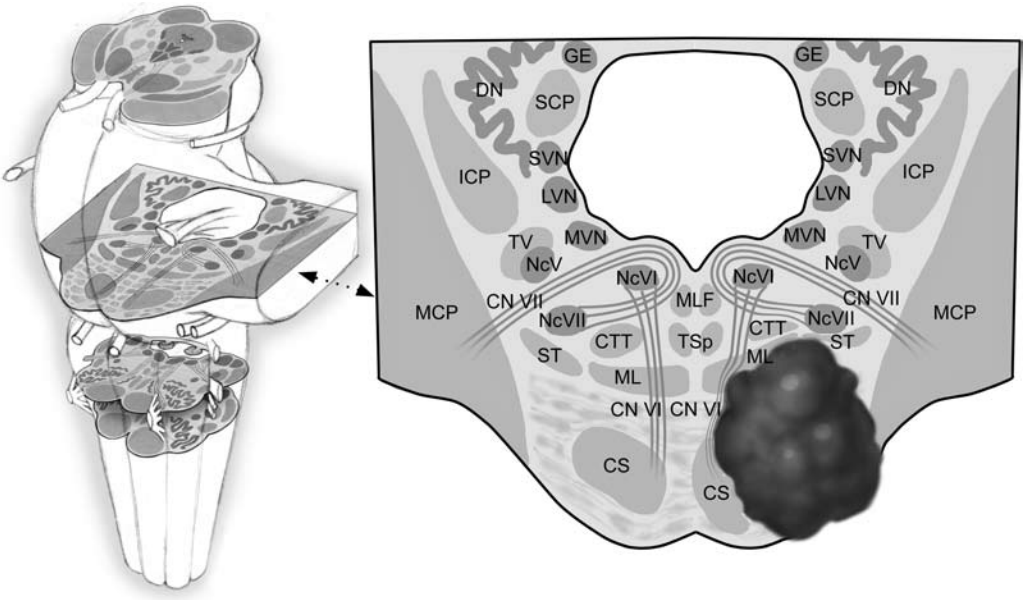

Fig. 19. Schematic 3D illustration of the pons **(left)** and axial view at the level of the facial colliculus of a ventral pontine CM displacing internal structures **(right)**.

per medulla can be reached through the floor of the fourth ventricle. This area can be exposed through the telovelar transcerebellar-medullary fissure or the transvermian approaches after a suboccipital midline craniectomy or craniotomy. We prefer the sitting position although the prone position is a good alternative. Both in the semisitting and prone positions a maximal flexion is required to allow for ideal exposure of the floor of the fourth ventricle. In many instances, resection of the vermis (with the underlying risk of postoperative truncal ataxia) is not necessary. Instead the surgical corridor can be maximized by enlarging the opening into the fourth ventricle by dividing the tela chorioidea. If access to the superior half of the floor of the fourth ventricle is necessary, then division of the inferior medullary velum provides access to the entire floor of the fourth ventricle up to the aqueduct.

The median suboccipital vermis–splitting approach is an alternative route to this region. This approach affords better exposure and a more direct view of the uppermost part of the fourth ventricle as compared with the telovelar approach.[11]

However, due to the risk of trunk ataxia with the transvermian approach,[22,57] the telovelar approach is preferred.[3,19,39] It is not unusual that a minimal division of the

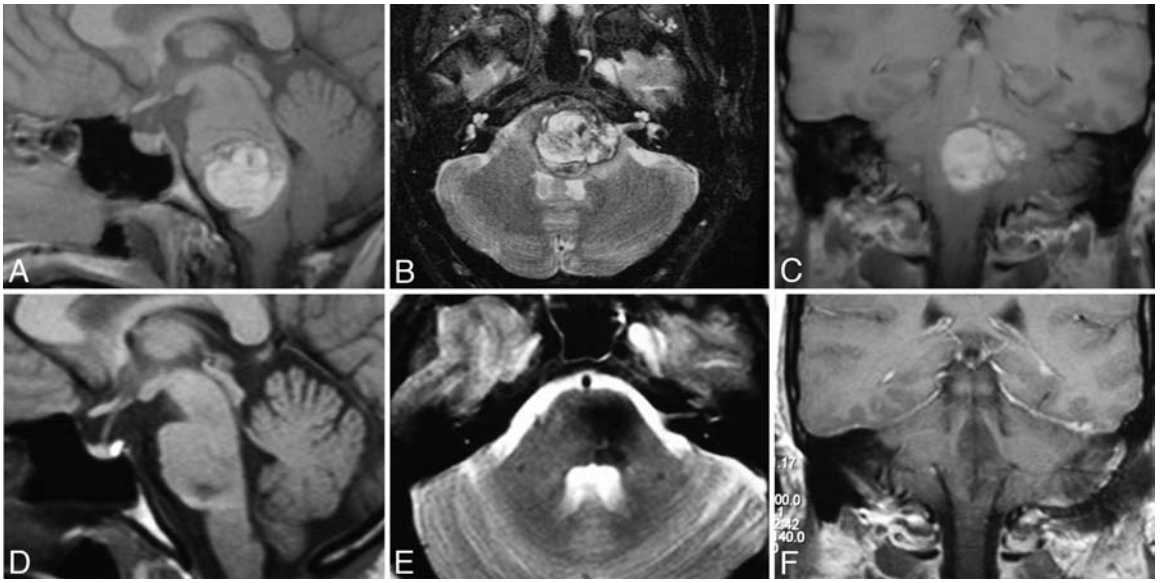

Fig. 20. Illustrative Case 3: CM in the pons. **A–C:** Sagittal T1-weighted **(A)**, axial T2-weighted **(B)**, and Gd-enhanced coronal T1-weighted **(C)** MR images demonstrating a large CM centered in the left ventrolateral aspect of the pons. The lesion is hyperintense on T1-weighted imaging **(A)**, heterogeneous on T2-weighted imaging with surrounding vasogenic edema **(B)**, and nonenhancing **(C)**. **D–F:** Postoperative correlative images demonstrating complete resection of the lesion.

inferior vermis is needed in conjunction with the telovelar approach for more cranial lesions. Removal of the posterior arch of C-1 maximizes the exposure obtained with the telovelar approach.[11]

Although safe entry zones through the floor of the fourth ventricle have been described,[28] because of the potential for morbidity we approach CMs of the dorsal pons through the floor of the fourth ventricle only if the lesion comes to the surface or the hemorrhage has created a natural corridor (see *Illustrative Case 4*). For completeness, we describe these safe entry zones that are located in the upper half of the floor of the fourth ventricle: the median sulcus above the facial colliculus, the suprafacial triangle, and the infrafacial triangles (Fig. 15). In those exceptional cases of lesions not approaching the surface of the rhomboid fossa, intraoperative electrophysiological monitoring and mapping of the floor are indispensable tools for identifying the best area to enter.

The median sulcus above the facial colliculus is a virtual passage between the 2 parallel medial longitudinal fascicles. Sharp dissection along the median sulcus (similar to the dissection used to reach intramedullary spinal cord lesions) is possible as there are no crossing fibers above the facial colliculus.[5] Damage of the MLF results in internuclear ophthalmoplegia.

On the lateral surface of the floor of the fourth ventricle there are 2 relatively safe entry zones. One, the suprafacial triangle, is located immediately above the facial colliculus between the MLF (medially) and the cerebellar peduncles (laterally).[28] The second one, the infrafacial triangle, is immediately below the facial colliculus, lateral to the MLF, and is bordered inferiorly by the striae medullares and superolaterally by the facial nerve.[28]

The region of the calamus scriptorius must be avoided to prevent dysphagia and cardiorespiratory disturbances related to damage of the vagal and hypoglossal triangles. Damage to the slightly more lateral nucleus ambiguus (which sends fibers to CNs IX, X, and XI) will cause palatal, pharyngeal and laryngeal palsy.

Lesions of this portion of the pons can be resected completely in 95% of patients and the overall results are generally good.[19] However, there is a significant transient morbidity related to the numerous vital structures present in this area. The most common reported deficits are internuclear ophthalmoplegia and CN VI and VII deficits. Up to 20% of patients with CMs in this location may need a tracheostomy and/or a feeding tube.[19]

Clinical Correlates of a Dorsal Pons CM. For a CM located in the dorsal pons, as shown in Fig. 21, the more likely clinical presentations or possible sequelae of surgery include: ipsilateral hemifacial weakness from compression of the intraaxial CN VII fibers; ipsilateral CN VI palsy from compression of CN VI nucleus; ipsilateral loss of horizontal gaze from involvement of the paramedian pontine reticular formation; possible weakness of right face due to impingement of the intraaxial CN VII fibers on the right.

Illustrative Case 4: CM of the Dorsal Pons. This 52-year-old man was initially conservatively followed up after bleeding of an upper pons–lower midbrain CM (Fig. 22), which was diagnosed after the patient noted hemibody numbness (medial lemniscus), inability to look up (MLF), and ataxia (red nucleus).

A subsequent bleed resulted in significant neurological deterioration. A new MR imaging study (Fig. 23) surprisingly showed that the second bleed occurred from a separate CM in the pons. The patient's new symptoms included bilateral CN VI palsy (bilateral abducent nuclei), bilateral pain/temperature and fine touch sensory deficits (spinothalamic tract and medial lemniscus), and facial numbness (chief sensory nucleus of CN V).

The CM was abutting the floor of the fourth ventricle

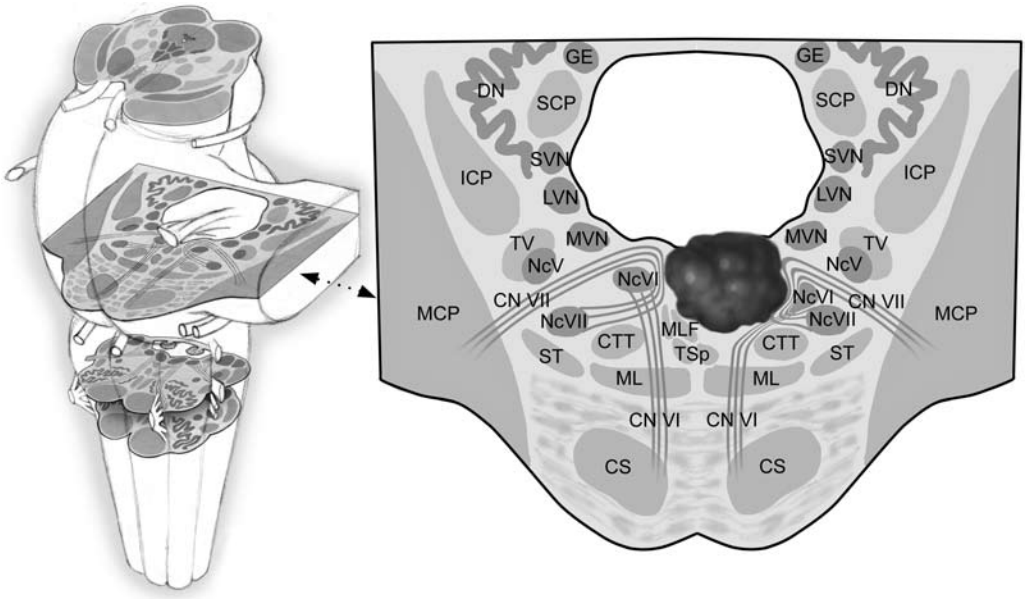

Fig. 21. Schematic 3D illustration of the pons **(left)** and axial view at the level of the facial colliculus showing a dorsal pontine CM displacing internal structures **(right)**.

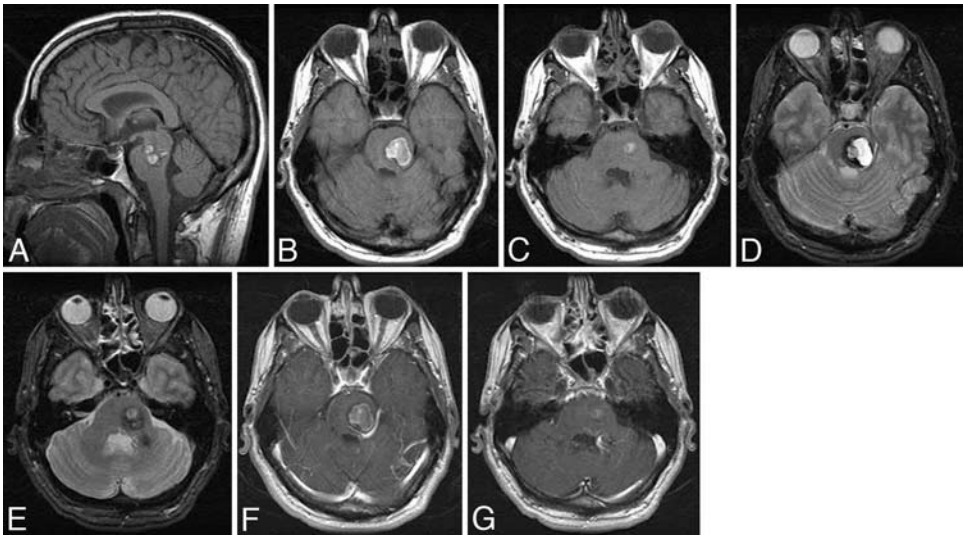

Fig. 22. Illustrative Case 4: CM in the midbrain–upper pons and right middle cerebellar peduncle. Sagittal T1-weighted **(A)**, axial T1-weighted **(B and C)**, axial T2-weighted **(D and E)**, and axial T1-weighted Gd-enhanced **(F and G)** MR images demonstrating a large CM in the left midbrain–upper pons **(A, B, D, and F)**, with predominantly T1 and T2 hyperintensity, subacute blood products, and a hypointense hemosiderin ring. A smaller focal area of hemosiderin related to prior hemorrhage is seen in the left middle cerebellar peduncle **(C and E)**. Both areas of hemorrhage are in the drainage field of a moderately sized DVA **(F and G)**.

at the level of the pontomesencephalic junction and was resected through a left-sided telovelotonsillar approach to the floor of the fourth ventricle (Fig. 24). A very small inferior vermian incision was required to obtain optimal exposure of the uppermost portion of the floor of the fourth ventricle.

The CM was entered at the point where it was abutting the ependyma without violating any normal nerve structures in the rhomboid fossa.

Medulla: Internal and Functional Anatomy

Approaching the medulla's ventral surface, the prominent medially placed pyramid extends rostrally to caudally, containing the corticospinal tract. The lateral corticospinal tract crosses at the pyramidal decussation at the most caudal section of the medulla.

Just dorsal to the pyramid and running in a ventral-dorsal orientation is the medial lemniscus. Sensory pro-

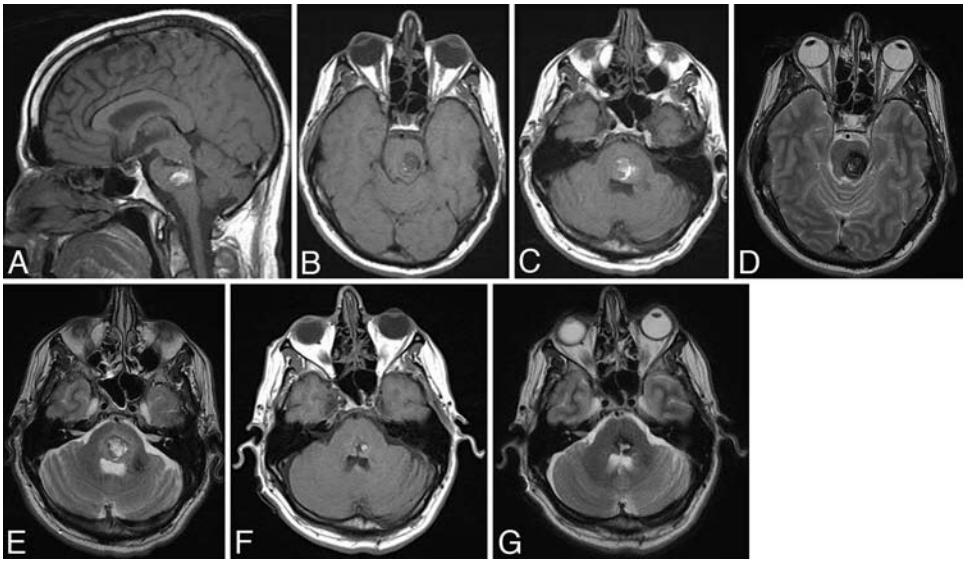

Fig. 23. Illustrative Case 4: new CM in the central pons. Sagittal T1-weighted **(A)**, axial T1-weighted **(B, C, and F)**, and axial T2-weighted **(D, E, and G)** MR images obtained 16 months after the images in Fig. 22, demonstrating a new large CM in the left central pons **(A, C, and E)**, with predominantly T1-hyperintense, subacute blood products. Moderate vasogenic edema with mild effacement of the fourth ventricle is associated **(E)**. The previously seen midbrain–upper pontine CM has undergone temporal evolution of blood products, and is now predominantly T1 and T2 hypointense, compatible with hemosiderin. A stable smaller focal area of hemosiderin related to prior hemorrhage is seen in the left middle cerebellar peduncle **(C and E)**. All 3 areas of hemorrhage are in the drainage field of the previously seen DVA.

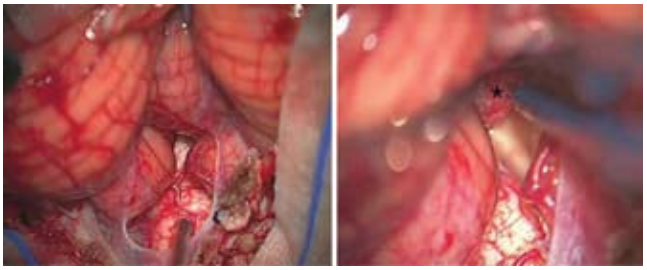

Fig. 24. Illustrative Case 4: intraoperative photographs. **Left:** Initial steps of the telovelar approach to the floor of the fourth ventricle. After opening the cisterna magna, the cerebellar hemispheres, the tonsils and the uvula of the vermis are visible. **Right:** After sharp opening of the telovelotonsillar cleft, the tela choroidea is exposed *(black asterisk)*. The floor of the fourth ventricle is visible in the depth of the operative field. Division of the tela choroidea (not shown) further opens the field of view into the fourth ventricle.

jections from the uppermost cervical spine lie most dorsal, whereas those from the sacral cord are most ventral.

Two other white matter tracts can be found just dorsal to the medial lemniscus: the tectospinal tract (from the superior colliculus) and the MLF. At this level, the MLF contains descending projections from the medial vestibular nucleus, forming the medial vestibulospinal tract. This is important in coordinating eye and neck movement.

Lateral to the medial lemniscus and dorsolateral to the pyramid is the inferior olivary nucleus, which receives input from the ipsilateral red nucleus (as well as other areas) and projects fibers to the contralateral cerebellar hemisphere.

Dorsal to the inferior olivary nucleus is the nucleus ambiguus. This nucleus houses efferent neuronal cell bodies that innervate laryngeal, pharyngeal, and palatal muscles, primarily by way of the vagus nerve (the glossopharyngeal nerve innervates only the stylopharyngeus).

A cluster of white matter tracts are found lateral in the medulla. They are the spinothalamic tract (anterolateral system), the rubrospinal tract (from the red nucleus), and the anterior spinocerebellar tract, carrying unconscious proprioceptive input to the ipsilateral cerebellar hemisphere. The spinal trigeminal tract lies dorsal to this cluster and carries nociceptive input from CNs VII, IX, and X from various structures around the external auditory canal and oropharynx.

Various nuclei fill most of the dorsal region of the cross-section. Beginning most medially is the hypoglossal nucleus, containing efferent motor neurons whose projections run in CN XII. A lesion here will result in ipsilateral tongue weakness. This nucleus is responsible for the formation of the hypoglossal trigone found medially in the caudal rhomboid fossa.

Laterally, the next nucleus is the dorsal motor nucleus of the vagus, accounting for most of the body's parasympathetic nervous system innervation. This nucleus is responsible for the formation of the vagal trigone found laterally in the caudal rhomboid fossa.

Continuing laterally, the solitary nucleus can be found. Rostral functioning involves the transmission of taste sensation. Caudal function concerns the afferent processing from CNs IX and X regarding chemo- and baroreception.

Most lateral are the vestibular nuclei, which extend rostrally into the dorsolateral pons, and the inferior cerebellar peduncle. The inferior cerebellar peduncle contains reciprocal connections to and from the ipsilateral cerebellum. Although it is associated with the medulla, it borders the inferior margin of the middle cerebellar peduncle as it connects to the cerebellum. The dorsal and ventral cochlear nuclei are adjacent to the inferior cerebellar peduncle at this rostral-most level.

The various nuclei and fascicles in the upper and lower medulla are illustrated in Figs. 25 and 26.

Medulla: Clinical Correlations

The clinical correlations of the nuclei and tracts of the medulla are summarized in Table 3.

Medulla: Surface Surgical Anatomy, Clinical-Anatomical Correlations, and Illustrative Cases

Upper (Ventricular) Dorsal Medulla CMs

Surface Surgical Anatomy and Surgical Approaches to the Upper (Ventricular) Dorsal Medulla. The surface surgical anatomy and the surgical approaches to the upper part (intraventricular) of the dorsal medulla have been described above (floor of the fourth ventricle).

Clinical Correlates of a CM of the Posterior Upper (Ventricular) Dorsal Medulla. For a CM located in the upper dorsal medulla, as shown in Fig. 27, the more likely clinical presentations or possible sequelae of surgery include: ipsilateral tongue weakness or CN XII palsy due to compression of the CN XII nucleus; cardiac and respiratory irregularities or instability due to compression of the CN X nucleus; and possible problems coordinating eye and head movement due to MLF or medial vestibulospinal tract involvement.

Lower Dorsal Medulla CMs

Surface Surgical Anatomy of the Lower Dorsal Medulla. The inferior part of the dorsal medulla is divided in 2 lateral parts by the posterior median sulcus, which is continuous with the median sulcus separating the posterior columns in the spinal cord (Fig. 13). The gracile fasciculus underlying the homonymous tubercle is lateral to the median sulcus on either side. The posterior intermediate sulcus separates the gracile fasciculus (medially) from the lateral cuneate fasciculus (laterally), which underlies the homonymous tubercle. The more lateral posterolateral sulcus delineates the cuneate fasciculus.

Surgical Approaches to the Lower Dorsal Medulla. The posterior medulla is usually approached by a median suboccipital craniotomy.

Bricolo[5] describes 3 safe entry zones for the posterior medulla (Fig. 15): the posterior median fissure below the obex, the posterior intermediate sulcus between the gracile and cuneate fascicles, and the posterior lateral sulcus between the cuneate fascicle medially and the spinal trigeminal tract and nucleus laterally.

Clinical Correlates of a CM of the Lower Dorsal Medulla. For a CM located in the lower dorsal medulla, as shown in Fig. 28, the more likely clinical presentations

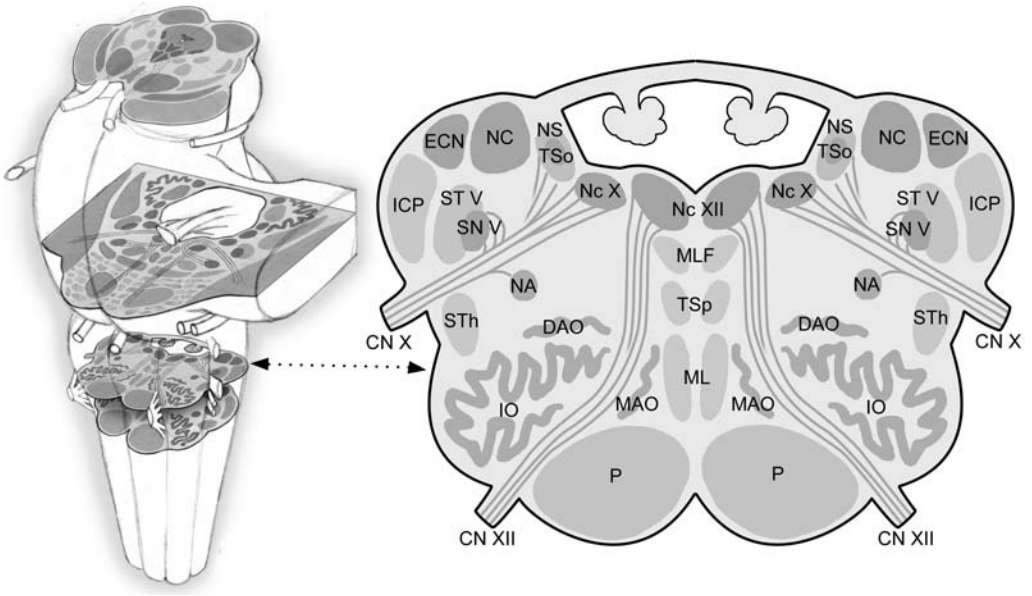

Fig. 25. Schematic 3D illustration **(left)** and axial orientation **(right)** of nuclei and fascicles in the upper medulla. CN X = vagus nerve fibers; CN XII = hypoglossal nerve fibers; DAO = dorsal accessory olivary nucleus; ECN = external cuneate nucleus; IO = inferior olivary nucleus; MAO = medial accessory olivary nucleus; NA nucleus ambiguus; NC = nucleus cuneatus; Nc X = dorsal motor nucleus of vagal nerve; Nc XII = hypoglossal nerve nucleus; NS = nucleus solitarius; P = pyramid; SN V = spinal nucleus of trigeminal nerve; STh = spinothalamic tract; ST V = spinal tract of trigeminal nerve; TSo = tractus solitarius.

or possible sequelae of surgery include the following: ipsilateral loss of tactile sensation from the mid-trunk and below due to compression of the nucleus gracilis; ipsilateral loss of tactile sensation from the mid-trunk and above due to compression of the nucleus cuneatus; possible cardiac/respiratory instability due to compression of the solitary nucleus and dorsal motor nucleus of the vagus; and possible ipsilateral tongue weakness due to compression of the CN XII nucleus.

Illustrative Case 5: CM of the Lower Dorsal Medulla. This 34-year-old woman developed sudden nausea with severe headache and numbness in her left arm and leg and dysmetria involving the left arm with gait ataxia (involvement of the inferior cerebellar peduncle). Imaging studies (Fig. 29) showed a CM of the left posterior medulla with evidence of recent and recurrent hemorrhage. She underwent a suboccipital craniotomy in the semisitting position and complete resection of the lesion. Intraopera-

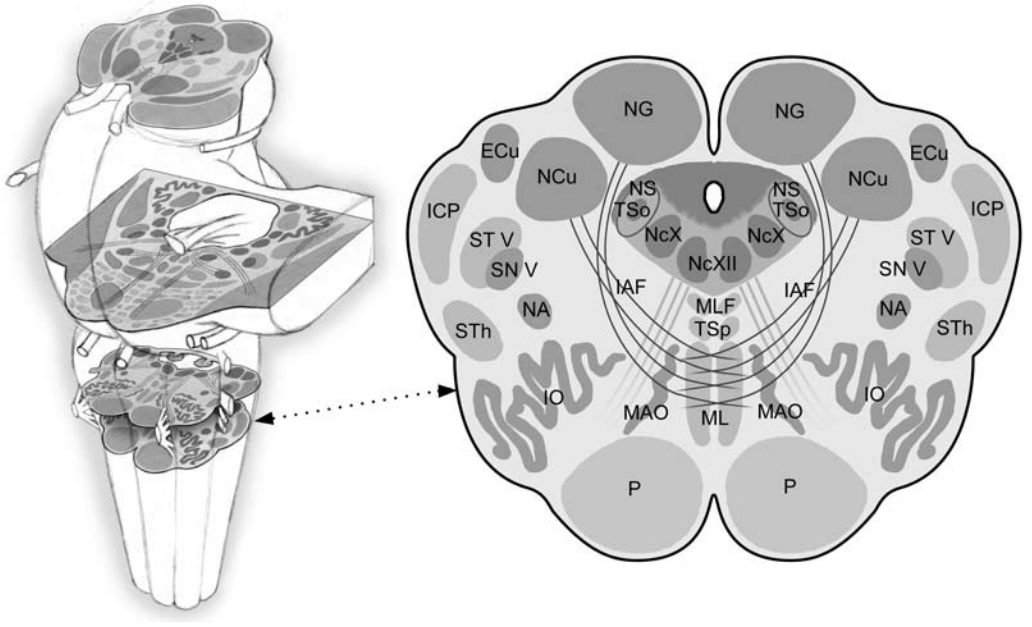

Fig. 26. Schematic 3D illustration **(left)** and axial view **(right)** of nuclei and fascicles in the lower medulla. ECu = external cuneate nucleus; IAF = internal arcuate fibers; NCu = nucleus cuneatus; NG = nucleus gracilis.

TABLE 3: Medullary nuclei and structures listed by anatomical location, function, and dysfunction

Structure	Location (ventral to dorsal, medial to lat)	Function	Dysfunction
pyramid	ventral, medial	upper motor neuron from cortex to contralat spinal cord	contralat UMN signs, weakness
inferior olivary nucleus	ventral, lat	relay nucleus to the contralat cerebellum	tremor[27] & possible cerebellar signs
medial lemniscus	ventral, medial	transmits incoming proprioceptive, vibratory, & discrim touch info from contralat spinal cord	contralat hemianesthesia of trunk & extremities
tectospinal tract	central, medial	reflex movement of head & neck	unappreciable
medial longitudinal fasciculus	central, medial	pathway btwn extraocular motor nuclei & gaze centers	unappreciable
nucleus ambiguus	central, lat	innervates the muscles of palate, pharynx, larynx	ipsilat paralysis of palate, pharynx, larynx (dysphagia, vocal changes)
spinothalamic tract (anterolat system)	central, lat	transmits incoming pain & temp info from contralat spinal cord	contralat loss of pain & temp sensation in trunk & extremities
hypothalamospinal tract (not shown)	central, lat near the spinothalamic tract	carries symp projections from hypothalamus to spinal cord	Horner syndrome
spinal trigeminal nucleus/tract	dorsal, lat	transmits pain & temp info from face, sensory input from around external auditory meatus & orophayrnx	ipsilat loss of pain & temp sensation in areas around ear, decreased sensation in ipsilat oropharynx
hypoglossal nucleus	dorsal, medial	innervation of most intrinsic & extrinsic muscles of tongue	ipsilat tongue weakness, tongue deviates ipsilaterally
dorsal motor nucleus of the vagus nerve	dorsal, central	parasymp innervation to level of the transverse colon	ipsilat loss of taste & increased heart rate
solitary nucleus tract (tract ascends throughout lat brainstem, though not shown)	dorsal, lat	receives incoming taste, chemo/baroreceptor sensation	loss of taste sensation,[14] intractable hiccup & nausea,[37] sleep apnea[41]
vestibular nuclei	dorsal, lat	vestibular relay, integrates sensory input	dizziness/vertigo, postural instability, eye movement disorders
inferior cerebellar peduncle	dorsal, lat	transmits vestibular & proprioceptive input to ipsilat cerebellum, inferior olivary nucleus input to contralat cerebellum	ipsilat ataxia, hearing loss
nucleus gracilis	dorsal, medial, caudal	transmits ipsilat LE proprioceptive, vibratory, discrim touch sensory input	ipsilat loss of tactile & vibratory input from LE (below T-6 level)
nucleus cuneatus	dorsal, centra, caudal	transmits ipsilat UE proprioceptive, vibratory, discrim touch sensory input	ipsilat loss of tactile & vibratory input from UE (above T-6 level)

tive photographs are shown in Figs. 2 and 4 and an artistic representation in Fig. 3.

Cavernous Malformations of the Ventrolateral Medulla

Surface Surgical Anatomy of the Ventrolateral Medulla. The ventral aspect of the medulla (Fig. 6) presents a median longitudinal sulcus, the anterior median fissure, which divides the 2 pyramids. An additional sulcus lateral to the main anterior median fissure is the anterolateral sulcus. The anterolateral sulcus contains the origin of CN XII and separates the medial pyramid from the lateral olive. Dorsolaterally to the olive, CNs IX and X arise from the posterolateral sulcus.

Surgical Approaches to the Ventrolateral Medulla. Cavernous malformations located in the ventrolateral medulla can be resected through a far-lateral approach, which offers an anterolateral trajectory to the lower brainstem. This approach requires a lateral suboccipital craniectomy, resection of the posterior arch of the atlas, and partial drilling of the posterior third of the occipital condyle. For more ventral lesions, additional drilling of the occipital condyle may be required to achieve optimal exposure.[19] This approach offers a lateral view of the medulla, the vertebral artery and the origin and proximal portion of the PICA and CNs IX, X, and XI emerging from the retro-olivary area, the origin of the fascicles of CN XII, and the C-1 spinal nerve.[8,29]

A safe entry zone has been described in this region at the level of the retro-olivary sulcus[49] or between CN XII and C-1 in the anterolateral sulcus.[8] However, because of the small diameter of the medulla, most symptomatic CMs come to the surface and provide a direct route of attack without the need to violate normal parenchyma.

Clinical Correlates of a CM of the Ventrolateral Medulla. For a CM located in the ventrolateral medulla, as

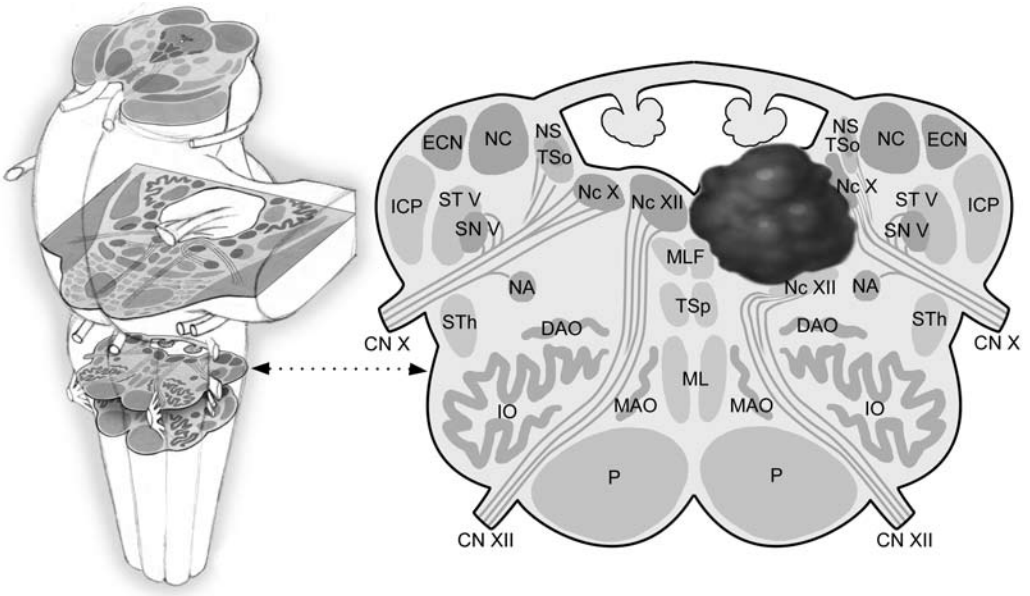

Fig. 27. Schematic 3D illustration of the medulla **(left)** and axial view of an upper dorsal medullary CM displacing internal structures **(right)**.

shown in Fig. 30, the more likely clinical presentations/possible sequelae of surgery include: ipsilateral tongue weakness or CN XII nerve palsy due to compression of the CN XII nucleus; loss or weakness of the gag reflex due to compression of the nucleus ambiguus; change in voice quality due to nucleus ambiguus compression; possible loss of pain/temperature sensation in the contralateral trunk and extremities due to compression of the spinothalamic tract; and contralateral loss of tactile sensation in the trunk and extremities due to compression of the medial lemniscus.

Illustrative Case 6: CM of the Ventrolateral Medulla. This 27-year-old woman experienced sudden hemiparesis and decreased sensation. The MR imaging study (Fig. 31) demonstrated a left CM of the ventrolateral medulla. The CM appeared to be compressing the left pyramid (causing right hemiparesis) and the medial lemniscus (causing right hemianesthesia).

Conclusions

The increasingly widespread availability of noninvasive imaging and the known morbidity of brainstem CMs, together with modern technologies such as intra-

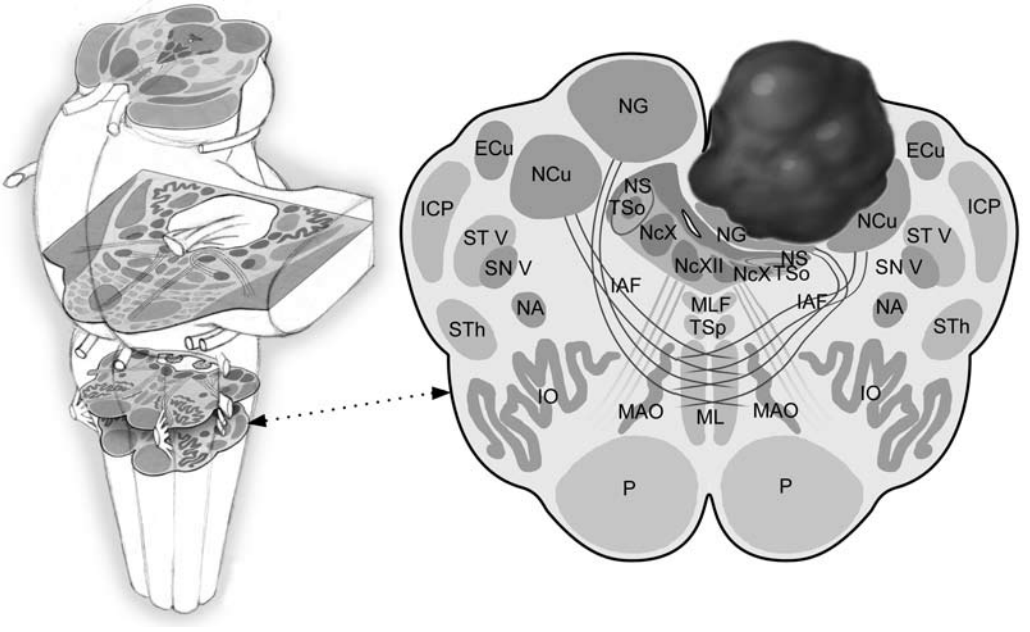

Fig. 28. Schematic 3D illustration of the medulla **(left)** and axial view of a lower dorsal medulla CM displacing internal structures **(right)**.

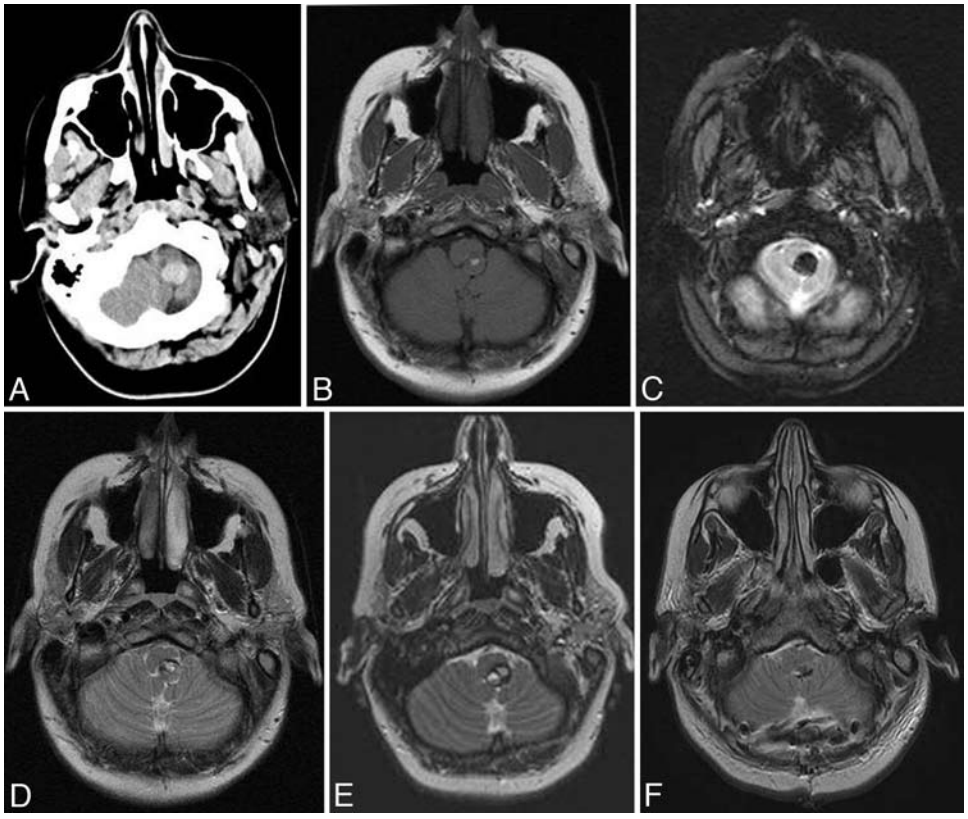

Fig. 29. Illustrative Case 5: CM of the dorsal medulla. **A–D:** Initial imaging studies. Axial noncontrast CT **(A)** and T1-weighted **(B)**, GRE **(C)**, and T2-weighted **(D)** MR images demonstrating an exophytic CM at the left-posterior aspect of the medulla. The lesion is hyperdense on CT **(A)**. There is mild T1 hyperintensity **(B)**, significant "blooming" **(C)**, and T2 heterogeneity **(D)**. **E:** Axial T2-weighted image obtained 4 weeks later showing that the lesion has slightly increased size and developed a peripheral hypointense hemosiderin rim. **F:** Postoperative axial T2-weighted MR image demonstrating that the cavernoma has been resected, with a small amount of residual T2 hypointense hemosiderin at the operative site.

operative monitoring and frameless stereotaxy, have led to an aggressive management of symptomatic brainstem CMs. Thorough knowledge of the surgical and functional anatomy of the brainstem is an indispensible prerequisite to establish proper indications and minimize the surgical morbidity related to such a challenging procedure.

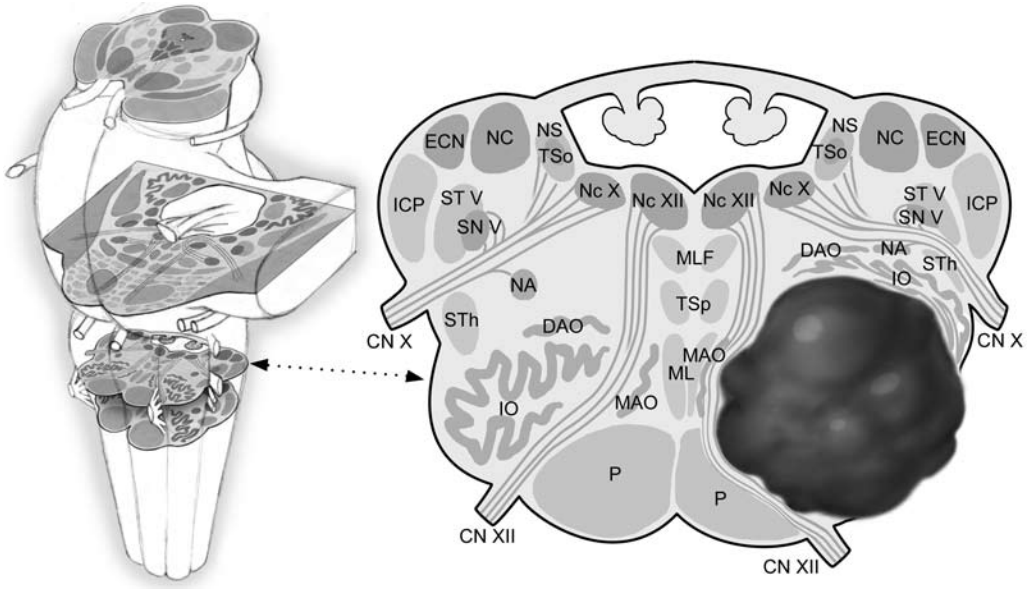

Fig. 30. Schematic 3D illustration of the medulla **(left)** and axial view of a ventrolateral medulla CM displacing internal structures **(right)**.

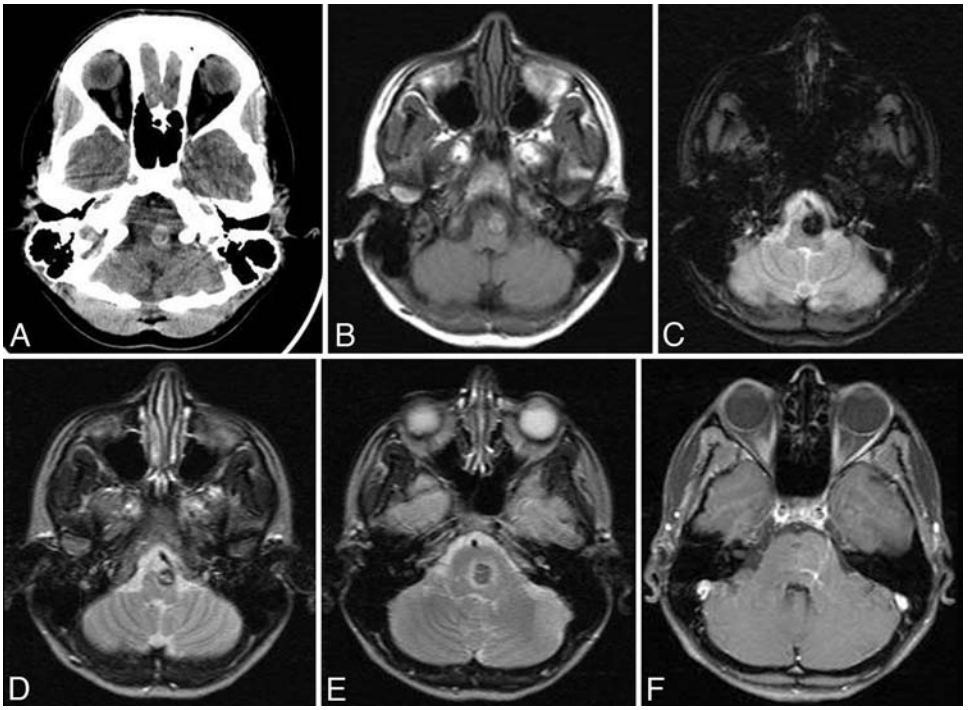

Fig. 31. Illustrative Case 6: CM of the ventrolateral medulla. **A–E:** Axial noncontrast CT **(A)** and T1-weighted **(B)**, GRE **(C)**, and T2-weighted **(D and E)** MR images demonstrating an exophytic CM at the left-ventral aspect of the medulla. The lesion is hyperdense on CT **(A)**. There is mild T1 hyperintensity **(B)**, significant "blooming" **(C)**, and T2 heterogeneity **(D)**. The lesion extends into the lower pons **(E)**. **F:** Axial T1-weighted Gd-enhanced MR image demonstrating an associated DVA.

Disclosure

Dr. Lanzino reports that he is a consultant for Edge Therapeutics and Actelion, Inc. He also reports receiving clinical or research report for this study from ev3, Inc., and Synthes.

Author contributions to the study and manuscript preparation include the following. Conception and design: G Lanzino, Giliberto. Acquisition of data: Giliberto. Analysis and interpretation of data: Giliberto, DJ Lanzino, Diehn. Drafting the article: Giliberto. Critically revising the article: Giliberto, DJ Lanzino, Flemming. Reviewed final version of the manuscript and approved it for submission: G Lanzino. Study supervision: G Lanzino. Illustrations: Factor.

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Manuscript submitted May 14, 2010.
Accepted June 3, 2010.

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Neurosurg Focus 29 (3):E10, 2010

Operative management of brainstem cavernous malformations

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Brainstem cavernous malformations (CMs) are complex lesions associated with hemorrhage and neurological deficit. In this review, the authors describe the anatomical nuances relating to the operative techniques for these challenging lesions. The resection of brainstem CMs in properly selected patients has been demonstrated to reduce the risk of rehemorrhage and can be achieved relatively safely in experienced hands.
(DOI: 10.3171/2010.6.FOCUS10134)

Key Words • **cavernous malformation** • **brainstem** • **review**

Cavernous malformations are vascular lesions of the CNS with an estimated prevalence of 0.4–0.9% in the general population.[14,29,38,46] The proportion of CMs occurring in the brainstem is difficult to determine precisely, as brainstem lesions are more likely to be symptomatic than similar lesions in the cerebral hemispheres. Therefore, it is presumed that a disproportionate number of brainstem CMs come to clinical attention.

Cavernous malformations are believed to cause symptoms in several ways. They are implicated in the etiology of a patient's new symptoms when there is radiographic evidence of recent hemorrhage (on MR imaging, usually) as well as a correlation between the location of the lesion and the patient's neurological deficit. Hemorrhages can be entirely intralesional, in which case new clinical findings probably represent increasing pressure on adjacent neural structures by the expanding capsule. Alternatively, hemorrhages can extravasate outside the bounds of the malformation, in which case symptoms may be caused by the direct interaction of adjacent structures with blood and its breakdown products as well as by local mass effect.[66] Over time, because of repeated hemorrhage—many of which are suspected to be clinically silent—CMs develop a hemosiderin-laden margin. This injured tissue may contribute to the symptomatology; supporting this theory are hemispheric CMs associated with seizures, in which the complete resection of surrounding hemosiderin-laden tissue has been found to yield better seizure control.[8]

The clinical presentation of brainstem CMs often correlates with their anatomical location. Somatic motor and sensory symptoms predominate, as would be expected given the presence of these tracts along the entire axis of the brainstem.[9,36] Oculomotor abnormalities are more common with lesions of the mesencephalon compared with other portions of the brainstem.[36] Ataxia, meanwhile, has been reported more commonly with lesions situated toward the medulla—although this is not always the case, as cerebellar long tracts and cerebellar peduncles are present in all segments of the brainstem.[22,36] Vertigo and nausea have been noted in conjunction with pontine lesions.[36] Trigeminal neuralgia has been documented with intraaxial lesions at the root of CN V.[46,56] Headache, too, is a common associated complaint; in the absence of hydrocephalus, however, the degree to which these headaches are etiologically related to the CM is unknown.[2,46] Lesions can also be completely asymptomatic; presumably more frequently than previously thought given the increased use of neuroimaging for nonspecific symptoms, such as headache, during screening for metastatic lesions in cancer patients or after a minor head injury.

Abbreviations used in this paper: CM = cavernous malformation; CN = cranial nerve; MLF = medial longitudinal fasciculus.

Clinical Decision Making

The decision to pursue operative intervention for brainstem CMs must take into account the lesion location and size, patient age, the nature of the presenting signs and symptoms, and the potential neurological deficits associated with surgery. Experience at many centers suggests that there are indeed safe ways to proceed. For example, a retrospective review of 87 patients who underwent resection of a brainstem CM revealed that 78 (90%) were neurologically stable or improved at a later follow-up.[46] Note, however, that at least transient postoperative neurological signs or symptoms are very common and occur in the majority of patients.[9,46]

When a patient presents with a brainstem CM, either incidentally or through the appearance of new neurological signs or symptoms, the decision to recommend intervention depends primarily on 3 core factors: 1) the estimated risk of future hemorrhage, that is, the natural history of the lesion; 2) the form of neurological injury predicted to occur with such a hemorrhage; and 3) the patient's clinical status, specifically, his or her current neurological condition and age and the size and location of the lesion.

The risk of brainstem CM bleeding is generally reported to be higher than the risk of hemorrhage from a CM situated elsewhere.[45,46] This phenomenon may be explained by the likelihood that lesions located outside the brainstem generally occur in less densely eloquent areas of the brain and are therefore more apt to be clinically silent when hemorrhage occurs. Nevertheless, lesions occurring in different areas may have different underlying pathophysiology, and variations in local anatomical structure can, in theory, influence their likelihood of hemorrhage. In general, the annual risk of hemorrhage for a brainstem CM is reported to be between 2% and 21%.[33,57] This generalization, however, is usually agreed to be insufficient on its own to determine the absolute need for operative intervention when such a lesion is incidentally discovered.

Establishing the risk of future hemorrhage is a complex task and multifactorial in nature. The history of a prior hemorrhage influences the calculation of a future risk because hemorrhagic events for a given CM tend to cluster in time; in other words, the probability of a hemorrhage is increased in the setting of a prior, recent hemorrhage. The time window of this increased risk is estimated to be about 2 years.[7] In addition, the magnitude of this increased risk is higher in younger patients.[7,33] Similarly, the risk of rehemorrhage and progressive neurological deterioration from a CM discovered in infancy or early childhood is generally considered to be very high.[15,16]

Other factors may also influence the risk of hemorrhage but are less certain. For example, pregnancy is often cited as potentially increasing the risk of CM hemorrhage.[3,5,47,51] Indeed, a disproportionate fraction (11%) of females referred to 1 center after hemorrhagic events were pregnant.[46] Whether this increased risk during pregnancy is real and whether it is related to hormonal alterations, circulatory changes (for example, venous hypertension), or other variables are currently unknown. Another uncertain contributor to hemorrhage is the local vascular anatomy. For instance, the presence of an associated developmental venous anomaly is commonly observed—and in some reports, is seen to be universal.[46] It is not unreasonable to suspect that the precise nature of the association between a CM and the venous anatomy would influence its likelihood of hemorrhage.[27] Not surprisingly, recent increases in the size of a lesion as well as its absolute size are often considered relevant to its future hemorrhage risk, as the former probably represents 1 or more episodes of intraluminal hemorrhage and the latter may be proportional to the cumulative volume of prior hemorrhages.[33] Finally, hereditary CMs have been linked with an increased propensity to bleed.[47]

For any individual, the estimated risk of injury from the hemorrhage of a brainstem CM is usually estimated from its specific location with respect to brainstem tracts and nuclei, and—most usefully, perhaps—from that individual's relevant neurological history. While the effects of a lesion can be predicted with reasonable accuracy on anatomical grounds alone, the surest guide is each patient's particular experience. Therefore, if prior symptoms consisted entirely of a tolerable deficit such as somatic sensory disturbances, then the low-pressure, low-volume forms of hemorrhage common with CMs make sudden devastating deficits as a result of a rehemorrhage less likely. Nonetheless, there is some evidence that when hemorrhage is accompanied by new neurological symptoms, early surgery to resect the brainstem CM might yield better outcomes.[9,36]

In addition to the risk of future hemorrhage, an individual's current functional status is important when establishing an assessment of risks and benefits. Where someone lies on the neurological spectrum—from asymptomatic and fully independent to symptomatic and dependent—determines his or her marginal risk. For instance, someone who is moderately disabled yet retains just enough function to be somewhat independent may have little tolerance for a slight worsening of symptoms. In such a case, intervention would be considered to prevent any further decline. Conversely, persistent symptoms, with or without evidence of hemorrhage, may be a result of mass effect; in these cases, removing the lesion could result in an improvement of neurological functioning. A full assessment of these factors, along with common sense considerations of a patient's overall health and age as well as his or her individual preferences, informs the decision to observe and follow or to recommend intervention.

Treatment

There is usually agreement that an incidentally discovered brainstem CM in an asymptomatic individual is not a candidate for resection. On the other hand, if intervention is desirable (for example, in a person with multiple symptomatic hemorrhages causing additive deficits), the particular surgical approach depends on the accessibility of the lesion and on the patient's ability and desire to tolerate an operation and its associated risks. If these factors are unfavorable, radiosurgery is sometimes considered; however, the true efficacy of radiosurgery in

reducing future rehemorrhages is difficult to assess. Any radiation-derived benefits are expected to occur in a delayed fashion (beginning many months after treatment), typified by the radiobiological effect following single-fraction therapy precedence seen elsewhere in the human cerebrum. Of note, the natural history of CMs suggests that after the same time period, a patient's risk for rehemorrhage will spontaneously decline.[7] Therefore, studies that document a reduction in the risk of hemorrhage by radiosurgery, particularly after 2 or more years from the preceding hemorrhage, do not necessarily indicate an effect of treatment but may simply chart the natural course of these lesions.[4,23,32,44] The possibility remains that radiosurgery offers a risk reduction over and above that due merely to the passage of time. A prospective study comparing radiosurgically treated patients with untreated controls will therefore be required to measure its true benefit.

In light of the remaining uncertainties regarding the efficacy of radiosurgery and the potential complications associated with radiation administered to the brainstem, operative resection represents the generally accepted method for reducing the probability of future hemorrhage from a CM.[9,52,58,66] The relative complexity of resection for a particular brainstem lesion is dependent on its location and intrinsic characteristics. These factors are each considered in turn.

A lesion that abuts a pial or ependymal surface is often directly accessible without the need for traversing normal brainstem tissue. One that lies deeper entails a potentially increased risk in proportion to its distance from a pial or ependymal surface and in relation to those brainstem nuclei or tracts lying superficial to it. In experienced hands, however, outcomes after the resection of deeper lesions can be comparable with those following the resection of lesions rising to meet a pial surface.[46] Obstacles to the excision of a deep-seated lesion are implicit given the lesion's position within the known standard anatomy of the brainstem, but if necessary can be made more explicit with the aide of MR imaging. While typical MR imaging sequences do not provide discrimination of brainstem structures with significant contrast, newer methodologies, if locally available, can provide useful anatomical detail. Functional MR imaging, for example, is capable of revealing the locations of lower CN nuclei.[31] The complementary technique of diffuser tensor imaging may resolve the positions of axonal tracts within the brainstem and can be used to guide the surgical approach to a CM.[28,59] While the highly conserved nature of brainstem anatomy across individuals usually renders more exhaustive neuroimaging in any particular case unnecessary, these diagnostic studies might be useful because of their potential to reveal the true positions of structures displaced by larger lesions; knowing whether a motor tract is displaced medially or laterally by a lesion in the medulla, for example, could help determine the most advantageous pial point of entry. The integration of these imaging techniques with intraoperative neuronavigation technologies will likely improve safety during the resection of CMs juxtaposed to white matter tracts and nuclei.[13]

A deep-seated lesion is typically less accessible because it may not be associated with any surface irregularities (for example, distortion of the contour of surface structures or hemosiderin staining) that help reveal its location intraoperatively. The potential difficulty in localizing the lesion intraoperatively must therefore be considered preoperatively and appropriate measures taken in advance to reduce uncertainty during the procedure. In many cases, dead reckoning can be used to correlate a lesion's radiographic position with normal anatomical features that are clearly identifiable on the surface of the brainstem. If dead reckoning proves insufficient or is uncertain for any reason, other strategies are available. Ultrasonography has been shown to be a relatively sensitive methodology to locate CMs, although the surgeon's experience with this technique will determine its specificity.[36,69] Intraoperative localization of a lesion can be achieved with the use of frameless stereotaxy as well. Because the need to minimize registration error is paramount in the brainstem, and because many brainstem approaches require prone positioning in which the highly contoured face is largely inaccessible, the use of fiducial markers is recommended. With these markers, the relatively featureless occiput can be populated with unambiguous landmarks. These fiducials can be applied prior to imaging and are subsequently used intraoperatively to register the images with the operative field. Finally, intraoperative neuroimaging can be used in cases of brainstem lesions. This process can help guide the surgeon during resection if manipulation causes a change in the positions of critical structures.

Operative Approaches and Techniques

Because the brainstem is a large and diverse structure, the selection of a particular operative approach out of the many that are possible is dependent on the particular location of the lesion and the experience of the surgeon (Table 1). Ideally, the cranial approach should allow for a line of sight in which the surgeon, the pial incision, and the lesion itself are all collinear. This alignment will provide the best view of the lesion while minimizing the need for brainstem retraction. Meanwhile, the pial incision should be chosen to minimize the distance to the lesion while avoiding critical nuclei and tracts.

The intrinsic characteristics of a CM influence the ease with which it is removed and determine the extent of the exposure and the degree to which it will be hemorrhagic. Calcified lesions with a solid, mineralized portion may necessitate a larger surface incision for removal. Meanwhile, previously irradiated lesions are seen to be more friable and hemorrhagic.[58]

Mesencephalic Lesions

In general, operative resection of mesencephalic lesions is considered high risk and is undertaken in only the most compelling circumstances. If an individual is symptomatic primarily because of compression of the cerebral aqueduct by a lesion, supratentorial CSF shunting is the preferred interventional modality. If, on the other hand, an individual is suffering from multiple, progressive neurological deficits attributable to a mesencephalic lesion

TABLE 1: Various approaches to the brainstem depending on the lesion location

Lesion Location	Anterior	Lateral	Posterior
midbrain	pterional orbitozygomatic subtemporal	lateral infratentorial/supracerebellar	lateral infratentorial/supracerebellar
pons	pterional orbitozygomatic subtemporal	far lateral suboccipital retrosigmoid	midline suboccipital/4th ventricular
medulla	subtemporal far lateral suboccipital transcondylar	lateral suboccipital retrosigmoid	midline suboccipital/4th ventricular

abutting a pial surface, resection is undertaken only with the understanding that further neurological deficits are very likely, at least in the short-term.

Lesions of the dorsal mesencephalon in the vicinity of the colliculi can be accessed via a supratentorial, infratentorial, or combined approach (Fig. 1). The patient can be positioned prone or in a semisitting position allowing gravity to aid retraction of the cerebellum inferiorly. If the latter position is selected, precordial Doppler ultrasonography and central venous access are recommended to detect and evacuate potential air emboli. Cavernous malformations that occur next to the pial surface are resected through a small incision precisely over the area of yellowish discoloration. However, if the lesion is deep and not associated with surface irregularities, this operative intervention is treacherous. The direction of the incision should be parallel to the nearest underlying fibers. One must keep in mind that in this region, CN IV, visualized caudal to the inferior colliculi, decussates just beneath the pial surface within the superior medullary velum; an anteroposterior midline incision here would transect both nerves, resulting in bilateral trochlear nerve palsies. Meanwhile, more rostrally and laterally, fibers of the brachium of the superior and inferior colliculi also travel horizontally, carrying afferents from the geniculate nuclei. When resecting a lesion here, care must be taken to remain within the tectum. Medially, one must avoid entrance into the cerebral aqueduct and certainly should not violate the floor of this structure, which contains the third and fourth CN nuclei. More laterally, lying at the border of the colliculi and the periaqueductal gray matter, one will encounter the mesencephalic trigeminal tract, which carries proprioceptive information. This tract is involved in the masseter reflex arc; damage to it does not necessarily lead to loss of facial sensation or motor function.[65]

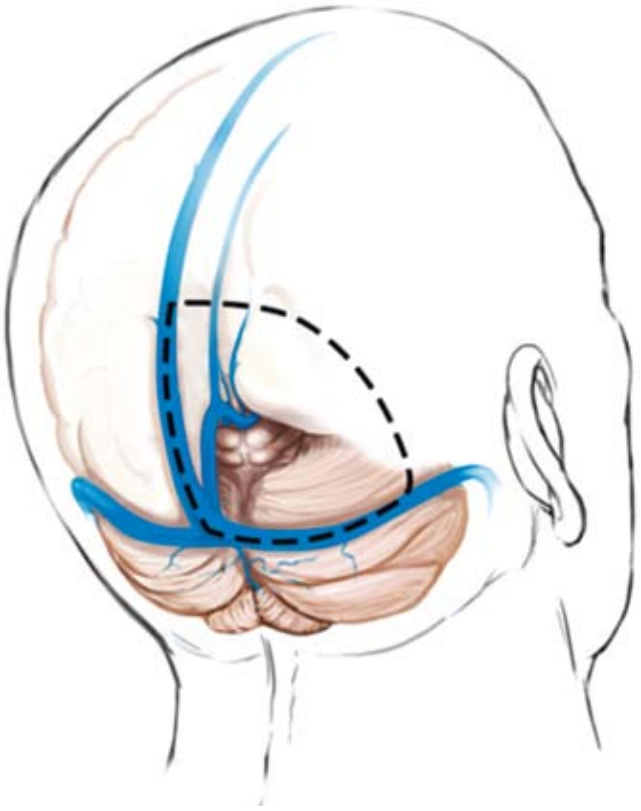

Fig. 1. Drawing showing the approach to the dorsal midbrain.

Electrophysiological recording of the oculomotor system can be performed to map these important structures prior to resection of the CM.[55] However, there is less certainty regarding the predictive ability of mechanically evoked electromyographic activity in the extraocular muscles to signify injury to the brainstem oculomotor system.[54] Therefore, the oculomotor system is more easily mapped than monitored. In general, this technique requires placement of an electrode into 1 or more extraocular muscles (usually by an ophthalmologist after the induction of anesthesia) to monitor contraction when the relevant midbrain oculomotor nuclei or tracts are electrically stimulated by the surgeon. This stimulation can be delivered using a bipolar device across a small gap (for example, 1 mm) with low current (approximately 1.0 mA) and low frequency (1–5 Hz). In this way, the oculomotor structures can be mapped and avoided so that postoperative deficits can be minimized.

The ventral mesencephalon is also a high-risk operative region; it contains the cerebral peduncles laterally, the substantia nigra just dorsal to them, and the red nuclei forming the bulk of the intraaxial mass. Lesions here can be accessed via a modified pterional craniotomy. A modified pterional craniotomy, in which the posterior arc is exaggerated, extending just beyond the level of the external auditory meatus, will afford better exposure than a standard pterional craniotomy by allowing the temporal lobe to be retracted posteriorly to reveal the floor of the middle cranial fossa. Meanwhile, an orbitozygomatic modification, which involves removal of the orbital roof, provides good exposure of the interpeduncular and prepontine cisterns via a shallower approach along the floor of the middle cranial fossa.[70] A subtemporal transpetrosal route is also available to provide increased exposure of the caudal mesencephalon/rostral pons (Fig. 2).[34]

At least 1 group has described the successful resec-

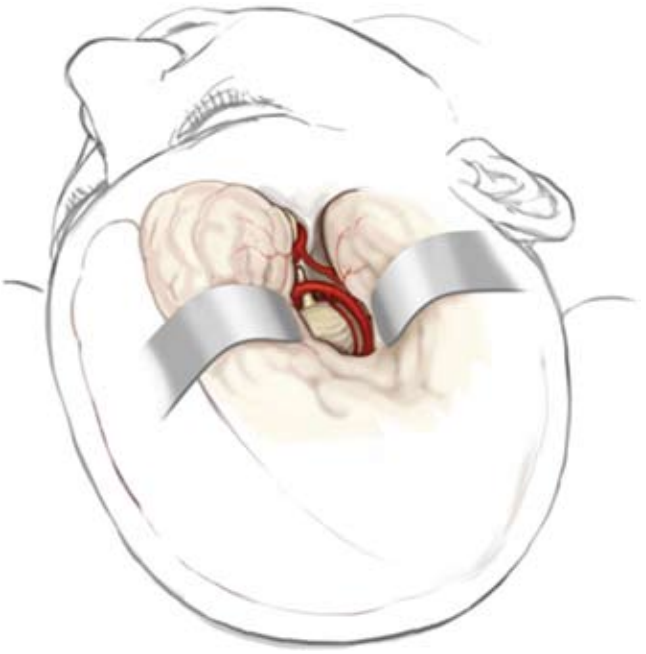

Fig. 2. Illustration of the approach to the ventral midbrain.

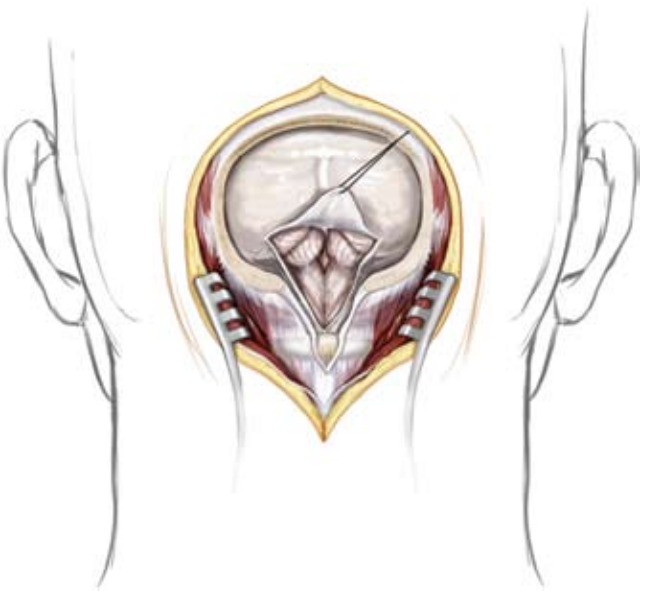

Fig. 3. Drawing of the suboccipital approach to the dorsal brainstem.

tion of a CM in this region by utilizing intraoperative monitoring of motor evoked potentials generated by direct bipolar stimulation of the cerebral peduncles as well as by transcranial motor evoked potentials.[49] The homunculus is oriented medially to laterally, face to leg, along the surface of the peduncles; the appropriate muscles can be monitored depending on the location of the lesion. If the underlying lesion is sufficiently superficial, the overlying corticospinal tracts may have functional gaps created by the displacement of fibers or by direct damage resulting from compression or chemical irritation by the lesion. Furthermore, based on knowledge of the homunculus, regions corresponding to a patient's established deficit can be mapped. A myelotomy can then be made in an anterior-to-posterior direction at a medial-to-lateral position chosen to minimize injury to remaining functional tissue.

In general, even when a lesion appears to present directly to the pial surface in the region of a known motor pathway, preoperative arrangements to perform electrophysiological monitoring are useful because standard anatomical MR imaging alone is an insufficient guide to the extent and nature of the overlying tissue, especially when that tissue consists of axonal tracts, which can be very thin yet functionally significant.

Metencephalic Lesions

Cavernous malformations located in the metencephalon can be accessed either through the floor of the fourth ventricle dorsally or via the pons ventrally. The former is achieved through a midline suboccipital approach, traversing the obex toward the rhomboid fossa. The latter is approached most commonly through a lateral suboccipital craniotomy (Fig. 3).

Lesions within the floor of the fourth ventricle are generally considered resectable if they present to or through the floor's surface (Fig. 4). Careful planning with respect to the relevant anatomy can minimize the risk of neurological injury, particularly when considering access to deeper lesions causing progressive deficits. The critical structures to avoid are clustered into 2 groups represented on the surface of the floor of the fourth ventricle by the facial and hypoglossal colliculi. The facial colliculi, formed by the sixth CN nuclei and the overlying traversing fibers of the seventh CN, are located in the base of the

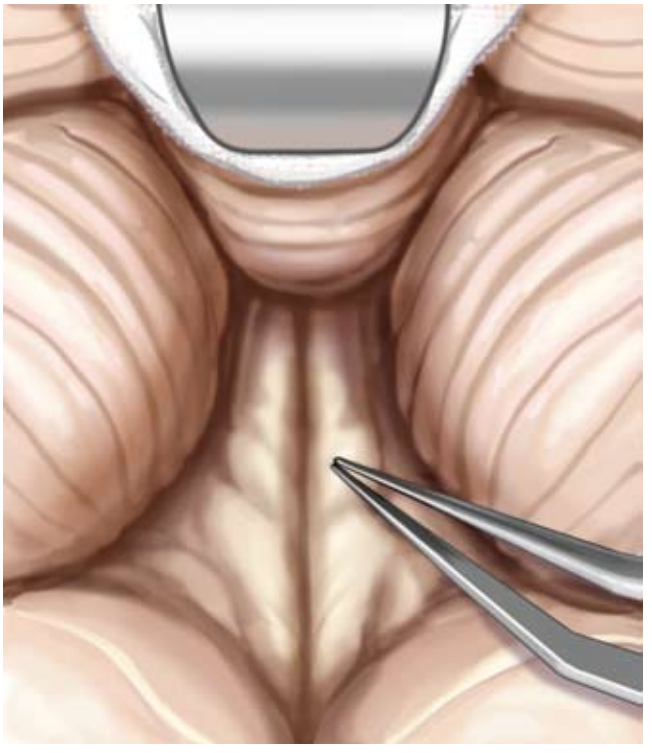

Fig. 4. Illustration of the floor of the fourth ventricle.

rostral triangle of the rhomboid fossa. These structures are within 2–4 millimeters of the surface. More caudally, the hypoglossal colliculi are less prominent than the facial colliculi; they represent the rostral portion of the hypoglossal nuclei, which are long structures (approximately 11–12 mm) crossing the pontomedullary junction. Running parallel to the midline sulcus is the MLF, anteriorly composed of fibers from the sixth nerve nucleus and vestibular nuclei, which mediate coordinated voluntary eye movements as well as the vestibuloocular reflex, and posteriorly composed of fibers that likely mediate head movements associated with gaze shifts.

In addition, there are many important structures not immediately evident externally but whose position can be inferred from external landmarks. In close association with the hypoglossal nucleus is the dorsal parasympathetic motor nucleus of the vagus nerve. This nucleus is just lateral to the rostral head of the hypoglossal nucleus but courses dorsomedially to lie more superficially in the medulla. Lateral to this nucleus is the solitary nucleus. Most laterally, at the ventrolateral angle of the rhomboid fossa and extending caudally into the medulla, the vestibular nuclei are found. They are situated between the fourth ventricle and the cerebellar peduncles more laterally. The motor and principal sensory trigeminal nuclei are also near the lateral angles of the fourth ventricle, just ventral to the superior vestibular nuclei.

With this anatomical knowledge in mind, the 2 visible structures—the facial and hypoglossal colliculi—serve as landmarks for 2 approaches into the dorsal metencephalon.[61,62]

The first of these approaches is oriented rostral and lateral to the facial colliculi. A paramedian approach is necessary to avoid injury to the ascending MLF. The rostral limit of this approach is defined by the decussation of the trochlear nerves in the superior medullary velum; vigilance is necessary to avoid retraction injury to this structure.[61] This approach leads into nuclei of the ascending pontine reticular formation. While bilateral imaging abnormalities of this region have been associated with sleep disturbances,[43] unilateral damage to these structures during resection of a brainstem CM reportedly does not interfere with level of consciousness or the sleep-wake cycle.[17]

The second approach enters into the region of the descending reticular formation between the level of the facial and hypoglossal colliculi. A paramedian entry is also necessary here to avoid injury to the descending MLF. The descending reticular formation, through efferent nerves that inhibit the spinal cord, is involved in REM (rapid eye movement) sleep paralysis. While bilateral manipulation of this structure in animal models is associated with altered sleep,[25] unilateral damage in humans during surgery has not been reported to cause significant dysfunction. The major structures ventral to the reticular formation at this level but still dorsal to the pontine nuclei are sensory and special sensory in nature. These structures include the medial lemniscus (somatosensory), lateral lemniscus (auditory), trigeminal pathways, and the central tegmental tract (taste).

Electrophysiological monitoring and direct stimulation can be applied to identify and preserve many of these important neural structures and pathways.[12,20,39,40] As previously mentioned, oculomotor monitoring can be used to identify the location and extent of relevant structures. Here, the electrically evoked activity of the abducens nucleus can be tested using recording electrodes in the lateral rectus muscles. Localization of the overlying facial nerve fibers can be achieved by recording motor evoked potentials from the orbicularis oris and the orbicularis oculi. Importantly, as appears to be true for the other oculomotor CNs, there is no clear predictive relationship between electromyographic activity in the lateral rectus muscle and preserved CN VI function;[21] interestingly, activity of the lateral rectus did suggest damage to the facial nerve. When working laterally, the motor trigeminal nucleus can be monitored with recording electrodes in the masseter. Meanwhile, stimulation in the region of the hypoglossal nucleus can be detected by electrodes placed in the tongue. Here, care must be taken with regard to possible current spread into the nearby dorsal motor nucleus of the vagus, causing bradycardia. In all cases, one must keep in mind the potential to directly injure stimulated tissue. In general, higher currents will be required if using monopolar (> 1–2 mA) versus bipolar (< 1 mA) stimulation. However, it should be remembered that the risk of injury is a function of not just current intensity, but also the charge delivered per unit of time and per unit of electrode surface area.

Pontine lesions can also be approached ventrolaterally at times. Either a far lateral suboccipital craniotomy or a larger craniotomy for a combined supra-/infratentorial approach can be used to gain access to the ventrolateral surface of the lower brainstem.[6] In addition, a subtemporal approach is possible for anteriorly situated lesions that may not be accessible from a ventrolateral angle;[53] however, this approach involves drilling into the petrous temporal bone to expose and then mobilize the petrous carotid artery. Furthermore, a transpeduncular approach to the rostral pons has also been described (Fig. 5).[24]

Within the pons, the descending motor fibers of the corticospinal and corticobulbar tracts lie clustered within the interspersed and surrounding pontine nuclei. These fibers do not rise to the surface at the level of the pons; rather, pontocerebellar fibers arise ventrally and curve dorsolaterally along the ventrolateral surface. A paramedian incision into the ventral pons is therefore generally considered optimal unless the lesion rises to the pial surface elsewhere.[11] Indeed, the occurrence of significant or lasting new postoperative deficits has been found by some to be lowest when the location of a CM allowed for this particular anterolateral approach.[18] The use of transcranial motor evoked potentials may help further minimize risks to the motor pathways.[48] Nonetheless, there are risks to the interspersed motor fibers as well as to corticocerebellar pathways that traverse this region. For instance, there is a report of transient postoperative mutism in a child with a pontine CM resected via this anterolateral approach.[19] (Others have reported postoperative mutism after the resection of dorsal mesencephalic CMs, suggesting that the observation of this deficit may reflect 1 of multiple forms of damage possible to cerebellar input/output.[60,68])

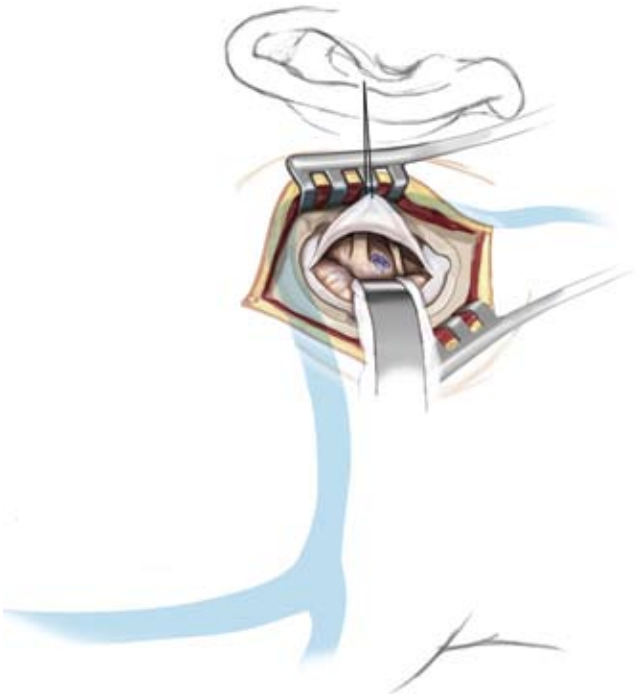

Fig. 5. Drawing of approaches to the ventral pons and medulla.

Medullary Lesions

Medullary CMs can be resected using the same principles described above. However, the higher density of long tracts and lower CN nuclei within this region makes the resection of deep lesions more treacherous. This region can be approached dorsally from a midline suboccipital craniotomy (with or without a C-1 laminectomy depending on the extent of required exposure) or ventrolaterally from a far lateral suboccipital craniotomy (craniotomy from the transverse sinus superiorly to the sigmoid sinus laterally and to the ipsilateral occipital condyle ventrally).

As is generally the case for operative resection of intrinsic brainstem lesions, new or worsened neurological symptoms will develop in many patients in the immediate postoperative period. Fortunately, experience with brainstem glioma surgery has shown that many of these lower CN deficits will improve with time.[26] There is no wide consensus regarding the safest ways to violate the surface of the medulla, and few surgeons are comfortable doing so if the lesion does not itself contact the surface. Externally salient features of the medulla include the midline sulcus between the protuberances of the fasciculi gracili, the shallower protuberances of the cuneate fascicles more laterally, the bulges of the inferior olivary nuclei laterally, and the corticospinal tracts with their pyramidal decussation ventrally. Less clearly evident are the spinal trigeminal tract immediately ventrolateral to the cuneate fasciculus below the level of the inferior cerebellar peduncle and the dorsal and ventral spinocerebellar tracts at the lateral margin of the medulla.

Favorably placed dorsal medullary lesions may be resected with the aid of electrophysiological monitoring. Monitoring of lower CN function is believed to be a reliable operative guide to postoperative function.[20] Cranial nerve IX can be monitored with electrodes in the posterior wall of the pharynx, and one can assess the status of CN XII with electrodes in the tongue. To prevent damage to the nucleus ambiguous and avoid vagal-mediated deficits, particularly dysphagia, evoked movements of the vocal cords can be monitored with electrodes on the surface of the endotracheal tube.[37] Alternatively, the cords can be directly visualized with a laryngoscope;[64] however, it is not yet known whether continuous observation of the spontaneous vocal cord movements accompanying respiration are a reliable sign of intact CN X function.

Ventral lesions are more difficult in terms of both the cranial approach and the details of the local anatomy. Access to the ventral medulla is achieved using the same approaches described for the pons—although a transoral transclival approach to ventrally situated CMs has been described in 2 patients.[50] The general utility and safety of this technique is not yet clear, especially as it relates to the potential incidence of meningitis. Once the ventral medulla is exposed, the choice of an entry point is critical. While it is preferable to avoid entering into the long tracts directly, especially the motor tracts, working ventrally between these tracts is generally not feasible given the presence of exiting nerve rootlets. Therefore, entering directly into lesions that rise to the ventral surface and either displace or damage these tracts is the least likely route to lead to further deficits (motor deficits, if working ventrally; or ataxia, if working more laterally). There is at least 1 case report of entry into the ventrolateral medulla through the inferior olive to resect a superficially located CM without subsequent observation of a new deficit.[41]

The goals of operative intervention, regardless of the lesion location, are complete resection of the CM and preservation of any associated venous anomaly. The former is achieved by entering the lesion to internally decompress it and then working outward toward the margins. Using low rather than high bipolar currents is generally preferred. The incomplete resection of a CM is likely to be a risk factor for recurrence; any residual endothelial cells are believed able to proliferate and recreate the lesion.[67] Indeed, some authors have reported worse overall outcomes when lesions have been only partially resected.[30] However, in contrast to the resection of supratentorial lesions for which a further goal may be to remove the surrounding rim of gliotic tissue, it is important to remain within the vascular portion of a brainstem lesion given the dense apposition of critical structures. Whether this results in the persistence of neurological deficits that could otherwise be alleviated by removing this pathological tissue is not known.

The presence of an associated venous anomaly must be noted to preserve that structure. The experience of many surgeons has shown that these veins drain normal tissue, and their obliteration can lead to venous infarcts. In many cases, these venous anomalies can be preoperatively studied with MR venography or traditional catheter angiography.[27] While venous anomalies are often observed radiographically or intraoperatively in association with a CM,[1] one group has reported a 100% correlation (86 of 86) based on intraoperative assessment.[46]

Furthermore, some authors have suggested that the presence of a venous anomaly is mechanistically related to the development of a CM.[10,35,42,63] Therefore, given these considerations, the inspection of all CMs, preoperatively and intraoperatively, for the presence of a nearby venous anomaly is warranted. When resection is undertaken, great care is used in trying to avoid manipulation of the venous anomaly. In such cases, the CM is separated from the venous anomaly as the resection proceeds.

Illustrative Case

History and Examination. A 27-year-old man presented with a 3-day history of double vision on right gaze and symptoms of sinus pressure with frontal headaches. Convergence insufficiency had been diagnosed 1 year earlier for the intermittent blurriness he noticed while looking left. The patient denied any history of trauma or infection, and a review of his systems was nondiagnostic. Evaluation at the outside hospital emergency ward revealed a left internuclear ophthalmoplegia. A noncontrast CT scan of the head and an MR image of the brain demonstrated a left pontine lesion, which did not enhance. A CT angiogram and formal angiogram were obtained, although neither revealed any vascular pathology. The patient was transferred to our institution for further evaluation.

On presentation to our institution, he was noted to have left internuclear ophthalmoplegia, impaired adduction of the left eye, limited abduction of the right eye, and diplopia on right lateral gaze. He was evaluated by the neuroophthalmology service, which confirmed that these findings were consistent with damage to the left intramedullary fascicle of the right sixth nerve and involvement of the left MLF. An MR image of the brain with contrast revealed a T1 and T2 hyperintense nonenhancing lesion in the left upper dorsal pons extending into the left midbrain, notable for a surrounding hemosiderin ring and mass effect as well as displacement of the fourth ventricle without hydrocephalus (Fig. 6 left). The patient elected to undergo resection of the lesion.

Operation. A suboccipital craniotomy with microsurgical removal of the CM through the floor of the fourth ventricle was performed using frameless stereotactic guidance (BrainLAB VectorVision2 navigation system). Complete resection was achieved (Fig. 6 right).

Postoperative Course. Postoperatively, the patient was noted to have a left facial palsy and slight improvement of his diplopia. At the 1-month follow-up, his facial weakness improved such that he was able to completely close his eyes. A neuroophthalmological evaluation during follow-up revealed marked improvement in the diplopia, with mild and slight left fascicular nerve palsy.

Conclusions

A brainstem CM is a potential candidate for operative resection if there is a history of neurological deficit attributable to previous hemorrhage and if the risk of future hemorrhage is unacceptable. The acceptability of risk in any particular case is a function of patient preference, his or her neurological status, and lesion characteristics (size, location, and intrinsic features). Operative resection of brainstem CMs has been demonstrated to reduce the risk of rehemorrhage and can be achieved relatively safely in experienced hands. The possibility of at least transient focal deficits should be anticipated. Once resection is elected, careful consideration of the local anatomy and possible surgical approaches is necessary to obtain the most useful preoperative studies and to arrange for the proper intraoperative monitoring. During the operation, identification and preservation of abnormal venous structures is a goal on par with gross-total resection of the malformation. In the future, as the aggregate experience of neurosurgeons accrues and as surgical technology improves, the range of patients for whom surgery is a viable option to prevent devastating hemorrhage may expand.

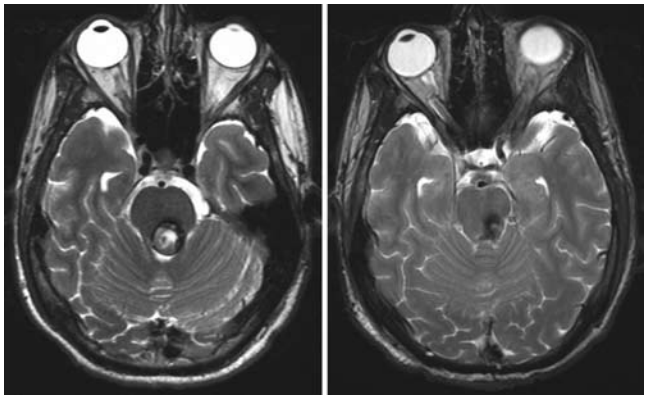

Fig. 6. Preoperative **(left)** and postoperative **(right)** MR images demonstrating complete resection of a brainstem CM.

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: Asaad, Ogilvy. Acquisition of data: Asaad, Ogilvy. Analysis and interpretation of data: Asaad, Ogilvy. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Ogilvy.

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Manuscript submitted May 14, 2010.
Accepted June 21, 2010.
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Neurosurg Focus 29 (3):E11, 2010

Stereotactic radiosurgery for the treatment of symptomatic brainstem cavernous malformations

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Object. The authors performed a retrospective review of prospectively collected data to evaluate the safety and efficacy of stereotactic radiosurgery (SRS) for the treatment of patients harboring symptomatic solitary cavernous malformations (CMs) of the brainstem that bleed repeatedly and are high risk for resection.

Methods. Between 1988 and 2005, 68 patients (34 males and 34 females) with solitary, symptomatic CMs of the brainstem underwent Gamma Knife surgery. The mean patient age was 41.2 years, and all patients had suffered at least 2 symptomatic hemorrhages (range 2–12 events) before radiosurgery. Prior to SRS, 15 patients (22.1%) had undergone attempted resection. The mean volume of the malformation treated was 1.19 ml, and the mean prescribed marginal radiation dose was 16 Gy.

Results. The mean follow-up period was 5.2 years (range 0.6–12.4 years). The pre-SRS annual hemorrhage rate was 32.38%, or 125 hemorrhages, excluding the first hemorrhage, over a total of 386 patient-years. Following SRS, 11 hemorrhages were observed within the first 2 years of follow-up (8.22% annual hemorrhage rate) and 3 hemorrhages were observed in the period after the first 2 years of follow-up (1.37% annual hemorrhage rate). A significant reduction ($p < 0.0001$) in the risk of brainstem CM hemorrhages was observed following radiosurgical treatment, as well as in latency period of 2 years after SRS ($p < 0.0447$). Eight patients (11.8%) experienced new neurological deficits as a result of adverse radiation effects following SRS.

Conclusions. The results of this study support a role for the use of SRS for symptomatic CMs of the brainstem, as it is relatively safe and appears to reduce rebleeding rates in this high-surgical-risk location.
(DOI: 10.3171/2010.7.FOCUS10151)

Key Words • cavernous malformation • brainstem • Gamma Knife • cerebral hemorrhage • stereotactic radiosurgery

Symptomatic, multiply hemorrhagic CMs of the brainstem present a vexing clinical problem, as they are often not amenable to resection with acceptable risk. While CMs of the brain occur in 0.1%–4.0% of the population, they comprise 8%–15% of all its vascular lesions.[3,18,23,27,38] These angiographically occult vascular abnormalities typically occur supratentorially; however, those isolated to the brainstem have been reported to account for 9%–35% of all CMs.[7,16,36] A number of causes have been identified for CMs, including genetic, congenital, postsurgical, and postirradiation effects.[6,13,29] Up to one-third of patients harboring CMs possess associated DVAs.[17,20,26,27,31]

The near ubiquity of MR imaging has increased the frequency with which CMs are diagnosed and has better elucidated the epidemiology and natural history of these lesions.[1,9,17,18,21,24,28,33,34] Presentation symptoms correspond with lesion location, and while supratentorial CMs are often identified incidentally or after seizures, those in the brainstem typically produce focal neurological deficits. The annual hemorrhage risk has been estimated to be 0.1%–2.5% per lesion-year and 0.25%–16.5% per patient-year, but this risk is substantially higher (up to 34% annual risk) for patients with prior hemorrhagic events.[4,12]

Symptomatic CMs of the brainstem can be managed microsurgically, and several centers have documented

Abbreviations used in this paper: ARE = adverse radiation effect; CM = cavernous malformation; DVA = developmental venous anomaly; SRS = stereotactic radiosurgery.

acceptable outcomes.[2,25,30,32] However, microsurgery for CMs in this location carries with it high rates of morbidity (up to 35%), demands complete resection, and is only reasonably suited for those lesions that present to an ependymal or pial surface.[24,33,37]

Methods

Patient Population

After receiving approval from the University of Pittsburgh institutional review board, we retrospectively analyzed our prospectively collected pre- and post-SRS data obtained in 68 patients (whose brainstem CMs were treated between 1988 and 2005). The average age of patients in this analysis was 41.2 years (range 5–79 years). All patients had previously experienced at least 2 hemorrhagic events, and 36.8% had suffered 3 or more hemorrhages (range 3–12). Bleeding events were defined as the development of a new neurological deficit with coexisting imaging evidence of new blood products in a newly discovered or previously identified CM. Information pertaining to clinical events was obtained via discussions with patients and/or their treating physicians combined with review of all available imaging studies. The diagnosis of CM was made by CT prior to 1990 and by MR imaging after 1990. Sixty-four patients (94.1%) presented with preexisting neurological deficits resulting from CM hemorrhages. Fifteen patients (22.1%) had previously undergone partial microsurgical resection. Half of the patients underwent angiography prior to SRS. These studies failed to identify a vascular abnormality. Only 1 patient (1.47%) was found to have an associated DVA. A summary of the patient characteristics is shown in Table 1.

Radiosurgical Technique

Radiosurgical treatment of CMs was performed as previously described in our reports.[10,15] Briefly, the Leksell Model G stereotactic frame (Elekta Instruments) was applied to the patients head after the administration of local anesthetic and, as needed, conscious sedation. For the 3 patients under the age of 12 years, frame application and SRS were performed after induction of general anesthesia. Through 1990, CT scanning was used for dose planning (17 patients), whereas stereotactic MR imaging was used since 1991. Upon the administration of a single-dose of paramagnetic contrast medium (0.1 mmol/kg), we obtained a 3D volume acquisition spoiled gradient recalled in steady-state sequence (1- to 1.5-mm-thick slices). An additional variable echo multiplanar (3/0 thickness) sequence was obtained to identify the hemosiderin signal surrounding the CM. Images were exported to dose-planning workstations for the U, B, C, or 4C Gamma Knife instruments (Elekta Instruments). These immediate pretreatment dose-planning images served as the baseline for future comparison with follow-up images.

Radiosurgery dose plans, with single or multiple isocenters (range 1–9), were created to yield highly conformal (to the lesion's 3D geometry) and selective (rapid dose fall-off outside the CM margin) dosing (Fig. 1). The targeted edge of the CM was considered to be the region characterized by mixed signal change within the T2-weighted signal–defined hemosiderin ring. This margin served as the 50% or greater isodose line. In general, targeting of accumulated blood products was avoided because iron breakdown products are potential radiation sensitizers. Dose planning details are summarized in Table 2. Stereotactic radiosurgery was performed with a 201 ^{60}Co source Gamma Knife. Following completion of SRS, each patient received a single 40-mg dose of methylprednisolone. All patients were discharged from the hospital within 24 hours.

TABLE 1: Summary of characteristics in 68 patients with brainstem CMs

Characteristics	No. of Patients (%)
sex	
male	34 (50)
female	34 (50)
preop hemorrhage events	
2	43 (63.24)
≥3	25 (36.76)
preop neurological deficit	
yes	64 (94.12)
no	4 (5.88)
follow-up after SRS (yrs)	
≤5	42 (61.76)
>5–10	17 (25)
>10–20	9 (13.24)

Follow-Up

Clinical follow-up data were obtained from patients, their caregivers, or referring physicians. Follow-up MR imaging was requested at 6-month intervals during the first 2 years after SRS, after which it was recommended on an annual basis. Sixty-six patients (97.1%) had follow-up of at least 2 years, 40 (58.8%) had follow-up from 2–5 years, 17 (25%) had follow-up from 5–10, and 9 (13.2%) had follow-up for more than 10 years.

Statistical Analysis

Hemorrhage was defined as imaging evidence of a new area of blood density corresponding to a new neurological sign or symptom. The annual hemorrhage rate was calculated using the following formula: total number of hemorrhages in all patients/total number of patient-years observed. Hemorrhage rates were compared before and after SRS using a paired t-test.

Results

Pretreatment Hemorrhage Rate

Pretreatment observation comprised the time from the first symptomatic, image-documented hemorrhage to the time of SRS. Thus, a total of 386 patient-years were observed with a mean pretreatment observation period of 5.68 years (range 1–38 years). There were 193 hemorrhages documented during this time (2.84 per patient). All

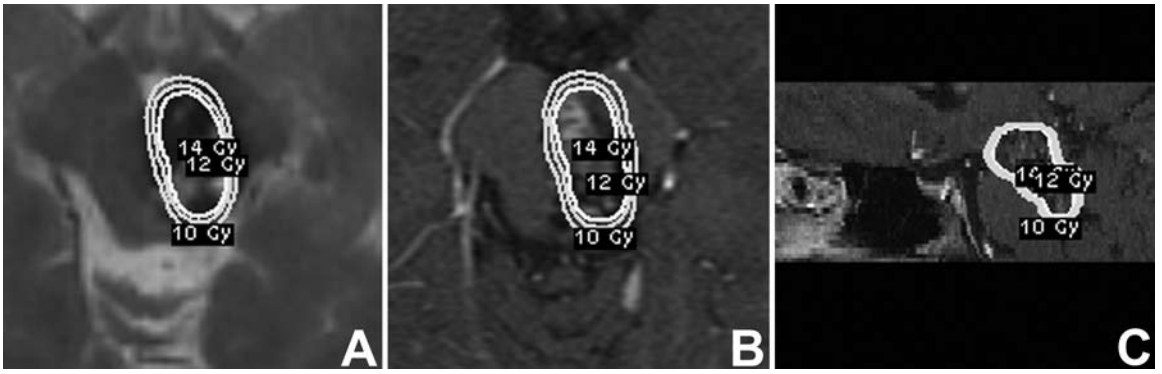

Fig. 1. Magnetic resonance imaging-based SRS dose plan obtained in a 14-year-old boy who had suffered 2 previous symptomatic hemorrhages of a CM of the midbrain and pons. A portion of the dose plan is shown on axial T2- **(A)** and T1-weighted **(B)** MR images illustrating the limited dosing to hemosiderin-stained adjacent brainstem parenchyma. Radiosurgery was performed, as shown in a midsagittal MR image **(C),** with a margin dose of 14 Gy, a maximal dose of 30 Gy, to a total volume of 2.3 ml.

patients had at least 2 hemorrhages prior to SRS (range 2–12). After exclusion of the first hemorrhage (193–68 = 125 hemorrhages), the calculated annual hemorrhage rate was 32.38% (125 hemorrhages in 386 patient-years observed).

Posttreatment Hemorrhage Rate

The observation period following radiosurgery was considered to be the time following treatment until either of the following: most recent clinical follow-up, surgical intervention, or death. Thus, postradiosurgical follow-up averaged 5.17 years per patient (range 0.58–12.41 years) with an overall observation period of 353 patient-years. During follow-up after SRS, 7 patients died (10.3%). Two patients died in the setting of subsequent microsurgical resection of lesions that rebled, and the remaining 5 died of either unknown causes or causes unrelated to their CMs (1 myocardial infarction, 3 cancer related, and 1 unknown). There were no deaths directly attributable to SRS.

Fourteen hemorrhages in 13 patients were documented during this period (0.21 hemorrhages per patient). Eleven of these hemorrhages occurred in 10 patients within a 2-year latency period after SRS, while only 3 were identified after 2 years. The annual hemorrhage rate during the first 2 years after SRS was calculated to be 8.22% (11 hemorrhages/133.75 patient-years). The annual hemorrhage rate after the initial 2-year follow-up was calculated to be 1.37% (3 hemorrhages/219.25 patient-years). Statistical analysis revealed a significant reduction ($p < 0.0001$) in the annual hemorrhage rate after SRS (32.38% before SRS compared with 8.22% after SRS, respectively; Fig. 2), as well as a reduction in the mean number of hemorrhages per patient (2.84 before compared with 0.21 after SRS, respectively; $p < 0.0001$). Furthermore, we confirmed a statistically significant reduction ($p < 0.0447$) in the annual hemorrhage rate following the 2-year latency after SRS treatment (8.22% compared with 1.37%, respectively).

TABLE 2: Summary of brainstem CM radiosurgery dose planning

Parameter	Mean	Range
malformation vol (ml)	1.19	0.12–6.8
no. of isocenters	3.38	1–9
margin dose (Gy)	15.84	12–32
maximum dose (Gy)	29.52	16–40

Adverse Radiation Effects

Eight patients (11.8%) had new neurological symptoms following SRS in the absence of a new hemorrhage. In all but 1 of these patients, the neurological worsening was transient and responded fully to a short course of corticosteroids. The remaining patient suffered a permanent new neurological deficit and went on to undergo microsurgical resection. Two additional patients (2.94%) were discovered to have new T2 signal abnormality surrounding their CMs, but the patients were neurologically asymptomatic. Overall, at the most recent follow-up, the neurological condition was either stable or improved in 79.4% of the patients following SRS.

Discussion

It has been observed by our group,[10] and by others,[11,33,37] that symptomatic brainstem CMs have a high rate of rehemorrhage (up to a 60% annual risk) and corresponding neurological deficits. Indeed, brainstem CMs are of unique interest because even bleeding events too

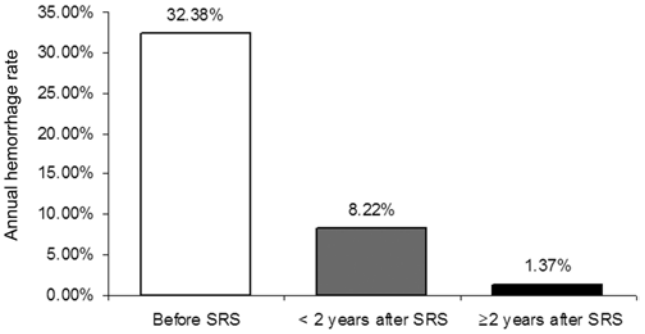

Fig. 2. Bar graph showing the annual hemorrhage rates in the 68 patients with symptomatic multiple hemorrhagic brainstem CMs before SRS, during the first 2 years after SRS, and after a latency period of 2 or more years.

small to be detected with modern imaging can cause profound neurological sequelae. Multiply hemorrhagic, symptomatic CMs of the brainstem are admittedly a rare entity with only a few hundred patients presented in several retrospective series. As such, management of this neurologically devastating problem is not clearly defined. Herein, we have shown that in a highly selective group of patients with surgically high risk symptomatic CMs of the brainstem, SRS is a reasonable alternative treatment with a safety profile similar to or better than other treatment approaches.

Although the treatment of choice for most symptomatic CMs is microsurgical resection, when the lesions are discovered in locations like the brainstem the risks are not trivial. Porter et al.[33] reviewed a series of 86 patients who underwent surgery for brainstem CMs. Fifty-two percent of the CMs in this series reached the pial surface. Following surgery, 33% of patients had new cranial nerve deficits, 30% exhibited cerebellar findings, and 29% had new-onset weakness. The overall rate of temporary and/or permanent morbidity and mortality was 35%. Overall mortality rate was 8% and all-cause 30-day mortality rate was 3.5%. Twelve percent of patients had permanent or severe deficits. Eleven patients required additional surgery to either retreat the target lesion or address a complication.

Mathiesen et al.[24] reported on a series of patients with deep-seated CMs, including 40 patients with CMs confined to the brainstem, 17 of whom underwent microsurgical resection. They reported a 69% incidence of transient and an 8% risk of permanent neurological deterioration. There was a 15% rate of rehemorrhage after surgery, in each case attributed to subtotal resection. From these data it was concluded that microsurgery for symptomatic lesions was feasible as long a radical resection could be confidently and safely achieved. In a retrospective series of 137 patients with brainstem CMs treated by microsurgery, Wang et al.[37] reported that 4.6% of patients harbored residual CM after surgery and 27.7% experienced deterioration after surgery or developed new neurological deficits. Hauck et al.[11] reported on 44 microsurgically treated patients with brainstem CMs, all of whom had symptomatic hemorrhages. Postoperatively, 1 patient was found to have residual a CM and went on to suffer a subsequent hemorrhage. Fourteen percent of the patients experienced increased cranial nerve deficits, 7% had worsened hemiparesis, and 4% had new deafness. In a series of 45 patients with brainstem CMs treated surgically via a supracerebellar infratentorial approach, de Oliveira et al.[5] found that 44% of patients had new postoperative deficits with almost half of these being permanent. Twenty-nine percent of patients experienced treatment-related complications including hydrocephalus, CSF leakage, meningitis, and a pseudomeningocele. Four patients required placement of a tracheostomy and feeding tube. Despite postoperative MR imaging that confirmed gross-total resection in 100% of the patients, 7 presented with recurrence, 4 of whom underwent reoperation.

We have previously reported our data on the treatment of surgically high-risk cavernomas[10,15,22] but never exclusively on lesions localized to the brainstem (midbrain, pons, and medulla). With the continued evolution of imaging techniques, treatment planning, and dose selection we wished to test the hypothesis that SRS for surgically high-risk symptomatic CMs of the brainstem is efficacious and safe. We first identified SRS as being associated with a significant reduction on hemorrhage rates for symptomatic CMs in 1995.[15] In our most up-to-date report,[22] we showed that in 103 patients with surgically high-risk CMs the rate of rehemorrhage significantly declined from a pre-SRS annual rate of 32.5% to 10.8% in the 2 years following treatment, and to an annual rate of 1.06% thereafter. Adverse radiation effects were observed in 13.5% of patients, with most being transient and most occurring early in the experience. The data presented herein are in good agreement with our previous observations, showing a decrease in the annual hemorrhage rates of symptomatic CMs located exclusively in the brainstem from 32.38% before SRS to 8.22% in the first 2 years after treatment, and 1.37% thereafter. Similar reductions in annual hemorrhage rates have been documented in the literature.

In 57 patients harboring surgically inaccessible CMs, Chang et al.[3] observed a pre-SRS hemorrhage annual rate of 9.4% that declined to 1.6% 36 months after treatment. Only 7% of these patients suffered AREs. Using stereotactic Bragg-peak proton beam therapy, Amin-Hanjani et al.[2] treated 95 patients with 98 CMs. They observed a reduction in the hemorrhage rate from a pretreatment annual rate of 17.5% to 4.5% after a 2-year latency period. They did, however, have 16% of patients suffer permanent neurological dysfunction and 3% die. Liu et al.[21] treated 125 patients with a reduction in the annual hemorrhage rate from 10.3% pretreatment to 3.3% posttreatment. Seventeen (13.1%) of these patients experienced AREs. In a smaller study of 22 patients with CMs treated by SRS, Kim et al.[14] documented an annual hemorrhage rate reduction of 35.5%–3.55%, with 6 patients demonstrating AREs. Finally, García-Muñoz et al.[8] reported 15 patients treated with SRS and showed that the annual hemorrhage rate decreased from 34.45% to 7.17%. Other reports have failed to reproduce similar reductions in hemorrhage risk but are limited by either their size, details of treatment, and/or limited follow-up.[24,33,35]

Although Pollock and colleagues[31] treated 17 patients and showed a reduction in annual hemorrhage rates from 40% pre-SRS to 2.9% after a 2-year latency period post-SRS, they did not conclude that radiosurgery was protective against hemorrhage. Indeed, 59% of these patients had evidence of AREs, a finding possibly attributable to a high median target dose of 18 Gy causing toxicity in the radiation-sensitized adjacent hemosiderin-containing brain. Some other authors have expressed concerns related to the high risk of reactive edema around treated CMs.[19,24] However, this may be the result of adverse effects on coexistent DVAs, as many of the patients in these reports harbored DVAs. Far fewer patients in the current series experienced AREs, with only 11.8% of patients being symptomatic. Surrounding a CM is parenchyma containing hemosiderin, a potential radiation sensitizer. We have previously proposed that radiation dosing to the tissue surrounding the CM may injure this adjacent tis-

sue, causing AREs.[22] Using multiple small isocenters to deliver a highly conformal dose with greater selectivity to the CM target within the T2-defined hemosiderin-stained brain appears to be critical. With such a strategy, we have shown before a decrease in the rate of ARE risk from 18.5% to 8%. In the current study, the mean marginal dose was limited to 15.84 Gy and the mean number of isocenters was 3.38.

We have hypothesized that the radiobiological effect of SRS on CMs is similar to that for arteriovenous malformations: progressive endothelial cell proliferation and hyalinization yielding luminal closure. Gewirtz et al.[9] reviewed the histopathological changes in 8 CMs in patient who underwent resection after failed SRS treatment (with 18–26-Gy equivalents). These lesions demonstrated fibrinoid necrosis compared with untreated controls but still possessed patent vascular channels. Nyáry et al.[28] identified endothelial cell destruction and marked fibrosis in the connective tissue stroma of a thalamic CM 1 year after 40-Gy irradiation. Taken together with clinical data, these reports suggest that CMs may respond to SRS in a fashion similar to other vascular lesions via delayed luminal closure of vascular channels.

Our study, as with previously published reports on this topic, is limited by its retrospective nature and by the relative rarity of brainstem CMs. Selection bias is likely to contribute to the results of such studies. In this instance, only patients with brainstem CMs who had 2 or more hemorrhages confirmed by the observation of new neurological findings and new MR imaging evidence were evaluated. At our multidisciplinary conference, all patients were judged to have excessive risks for a microsurgical resection based on CM location, size, and lack of contact with a pial or ependymal surface. Unlike the ability one has to observe arteriovenous malformation obliteration with imaging, no such imaging correlate has been identified for CMs. As such, only clinical outcomes serve as the measure of effectiveness. Importantly, the natural history of brainstem CMs has not been fully elucidated. As such, our data, and those of others, cannot refute the possibility that some CMs may bleed repeatedly and then cease to bleed. If such a phenomenon were identified, it would certainly call into question our observations.

Conclusions

The current study lends further support to the role of SRS in the management of a selective group of patients with surgically high-risk symptomatic CMs that repeatedly bleed as an alternative to observation alone. In particular, when these CMs are within the brainstem, highly conformal SRS may reduce the annual hemorrhage rates substantially with an acceptable safety profile and few permanent AREs.

Disclosure

Drs. Lunsford, Kondziolka, and Niranjan are consultants with AB Elekta. Dr. Lunsford is also a stockholder in AB Elekta.

Conception and design: Lunsford, Monaco, Kano, Kondziolka, Flickinger. Acquisition of data: Lunsford, Niranjan, Kano, Kondziolka, Flickinger. Analysis and interpretation of data: Lunsford, Monaco, Khan, Kano, Kondziolka. Drafting the article: Monaco, Khan, Grandhi. Critically revising the article: Lunsford, Monaco, Niranjan, Kano, Grandhi. Reviewed final version of the manuscript and approved it for submission: Lunsford, Monaco, Niranjan, Kano, Grandhi, Kondziolka, Flickinger. Statistical analysis: Monaco, Khan, Kano. Administrative/technical/material support: Lunsford, Khan, Niranjan, Kano, Grandhi, Kondziolka, Flickinger. Study supervision: Lunsford, Niranjan, Kondziolka, Flickinger.

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Manuscript submitted May 31, 2010.
Accepted July 6, 2010.
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Neurosurg Focus 29 (3):E12, 2010

Clinical presentation and surgical management of intramedullary spinal cord cavernous malformations

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Object. Intramedullary cavernous malformation (CM) is a rare entity, accounting for 5% of all intraspinal lesions. The objective in this study was to define the clinical characteristics of this disease, detail the surgical approach and technique, and present the clinical outcome.

Methods. Retrospective chart review was performed in 22 patients with histologically confirmed CMs. The authors used a laminectomy approach for midline dorsal lesions, with unilateral radical facetectomy and dentate ligament resection for laterally or ventrally located lesions. Patient profiles, operative indications, surgical approaches, operative findings, complications, and long-term follow-up were reviewed.

Results. The average age of patients in the cohort was 43 ± 14 years, the average duration of symptoms was 7 ± 7 months, and the average follow-up was 6 ± 4 years. The average size of the lesion was 1 ± 0.4 cm, the average surgical time was 4 ± 0.96 hours, and the average estimated blood loss was 350 ± 131 ml. The rate of complication was 5% (1 patient; due to a wound infection). According to the McCormick classification, the score for the cohort was 1.8 ± 1.2 preoperatively, 2.1 ± 1.2 postoperatively, and 1.3 ± 0.65 at late follow-up. (All preceding values are given as the mean ± SD.) There was a significant neurological improvement at follow-up compared with the preoperative state ($p < 0.05$). The majority of patients (50%) had a stable outcome compared with their preoperative state, with a large proportion (41%) having an improved outcome. A minority of patients (9%) had a worsened outcome due to dysesthetic pain. Patients with dysesthesia had a longer duration of clinical symptoms prior to surgery compared with patients without dysesthesia ($p < 0.05$).

Conclusions. The authors demonstrated the safety, efficacy, and durability of their surgical approach for resection of spinal intramedullary CM. Proper examination, preoperative imaging, and prompt surgical intervention were necessary for a satisfactory outcome. *(DOI: 10.3171/2010.6.FOCUS10139)*

Key Words • cavernous malformation • spine • intramedullary lesion • vascular malformation

Cavernous malformations are well-circumscribed lesions that consist of closely packed, capillary-like vessels, without intervening neural tissue. These lesions are angiographically occult and are assessed using MR imaging, which often reveals mixed signal intensity on T1-weighted images, along with a low-signal-intensity ring surrounding the lesions on T1- and T2-weighted imaging; this ring represents hemosiderin deposits.[1,3,4,8] They are characterized by sinusoidal channels under magnification, and have a mulberry-like appearance grossly.

Spinal cord cavernomas are considered rare, accounting for 5% of all spinal cord lesions. The spinal types account for 5% of all CMs, and are histologically identical to their intracranial counterpart.[6] However, unlike intracranial CMs, compression or irritation of neural tissue in the spinal cord by an intramedullary CM readily causes neurological symptoms due to the higher density of eloquent structures in the spinal cord.

In this report, we present our series of 22 cases of intramedullary CMs, with emphasis on the surgical technique and long-term clinical outcome.

Methods

Study Design and Data Collection

Our study was approved by the Institutional Review Board and conducted in compliance with Health Insurance Portability and Accountability Act regulations. Pa-

Abbreviations used in this paper: CM = cavernous malformation; EBL = estimated blood loss; LE = lower extremity; MEP = motor evoked potential; SSEP = somatosensory evoked potential; UCSF = University of California San Francisco.

tients with spinal intramedullary CM treated with resection were identified using the cerebrovascular database at UCSF.

Our data were gathered retrospectively from medical records, radiographic reports and images, intraoperative photographs, neurological examinations, pre- and postoperative clinical visits, and telephone calls. Statistical analysis was performed using the Student t-test method, with $p < 0.05$ deemed as significant.

The McCormick classification[10] distinguishes 4 functional stages, as follows: Grade 1 denotes neurologically normal, mild focal deficit not significantly affecting function of involved limb, and normal gait; Grade 2 a sensorimotor deficit affecting function of the involved limb, mild to moderate gait difficulty, although patient still can walk independently; Grade 3 designates more severe neurological deficiencies, patient requires a cane/brace for ambulation, and may or may not be independent; Grade 4, signifies severe deficit, patient requires wheelchair or has bilateral upper-extremity impairment, and usually is not independent.

Surgical Technique

The patients were placed prone on the operating room table (with the head fixated using a Mayfield headholder for cervical lesions), and electrophysiological monitoring was used in all patients. Localization was performed with intraoperative fluoroscopy. Midline incisions were made spanning the affected levels. Laminectomies were performed overlying the area of interest and extending a single spinal level above and below the CM for lateral and ventral lesions. Wide laminectomies were performed for dorsal midline lesions, preserving much of the facets. For ventrally or laterally located lesions, wide facetectomies were performed on the side of the lesion, flush with the pedicle. With microscopic assistance, midline dural incisions were made. For lateral and ventral lesions, the spinal cord was released by cutting the dentate ligaments bilaterally at the level of the lesion as well as above and below it. This maneuver enabled the spinal cord to rotate to allow us to visualize the CM, allowing for spinal cord rotation of up to 90°.

For dorsal lesions, myelotomies were performed in the midline posterior median sulcus with a No. 11 blade, and extended with microscissors. For lesions that come to the surface, incisions were made overlying the CM. Round knives were used to separate the malformations from the surrounding tissue. For lesions with a hematoma component, the hematoma was drained to decompress the spinal cord at this time. The CM was pulled into the center of the cavity and separated from the surrounding spinal cord. For larger lesions, the CMs were removed in piecemeal fashion to accommodate the opening and to minimize cord traction.

After inspection for residual malformation, the gliotic, hemosiderin-stained walls were left. The dura mater was closed in a watertight fashion with a continuous suture, which was sewn with the aid of the microscope.

Illustrative Cases

Case 17

History and Examination. This 53-year-old woman presented to her primary care physician with left leg numbness, dyscoordination, and gait difficulty. Motor examination revealed left LE weakness (4-/5 in hip flexion) and increased tone in the legs bilaterally. Admission MR imaging demonstrated an intramedullary hemorrhage at T1–2. She was referred to the UCSF vascular neurosurgery service for further evaluation and treatment.

Operation and Postoperative Course. A dorsally located spinal CM was confirmed. The patient underwent a T1–2 laminectomy to expose the spinal cord CM. On dural opening, this lesion was apparent (Fig. 1). A pial incision in the midline accessed the hematoma, which was evacuated to decompress the spinal cord and remove the remainder of the CM in piecemeal fashion, teasing the malformation into the cavity previously occupied by the hematoma. During this maneuver, there was fluctuation of the MEP. Surgical manipulation of the cord was briefly suspended and the cord was irrigated with saline; the MEP ultimately returned, albeit lower than baseline. Her LE neurological function was stable immediately after surgery, and imaging confirmed gross-total resection.

Case 19

History and Examination. This 62-year-old man presented with a long history of a burning sensation of his right toe and ankle, and recent gait instability. Admission MR imaging of his lumbar spine revealed a T2–3 ventrolateral CM. The patient was referred to UCSF for treatment. Examination revealed 3/5 strength in the right leg.

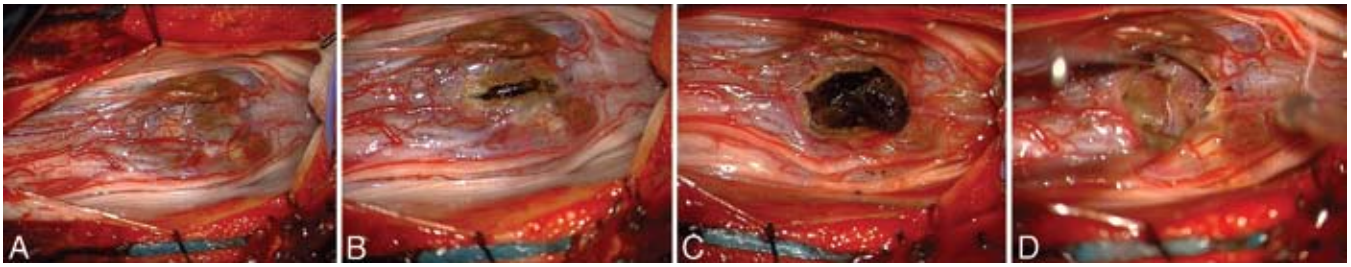

Fig. 1. Case 17. Intraoperative photographs. **A:** After dural incision, the CM was seen at the dorsal midline surface. **B:** A midline pial incision exposed the underlying CM associated with hematoma. **C:** Microsurgical dissection with round knives freed the CM from its adhesions to surrounding spinal cord, and it was removed along with the hematoma. **D:** After evacuation of the hematoma and resection of the CM, the hemosiderin-stained and gliotic wall was explored carefully for residual CM.

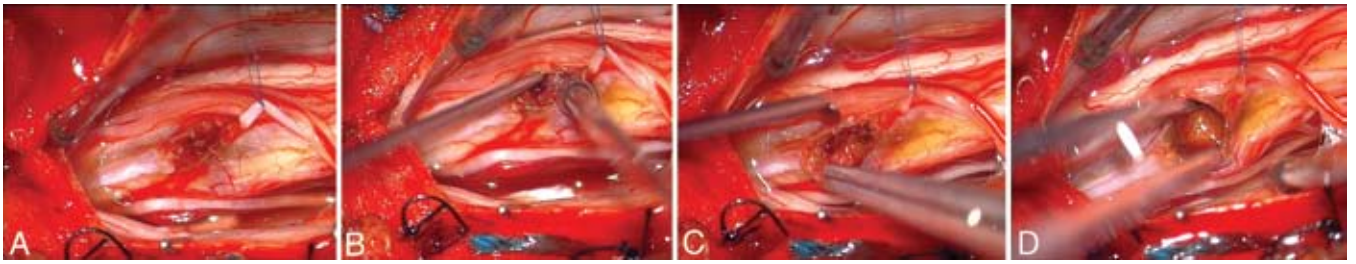

Fig. 2. Case 19. Intraoperative photographs. **A:** The spinal cord was rotated by cutting the dentate ligaments bilaterally at T-2 and T-3, tying a suture to its free end, and gently applying lateral traction. The CM was apparent on the lateral spinal cord surface, right underneath the dentate ligament. **B:** A myelotomy exposed the underlying CM and hematoma. **C:** Dissection with round knives freed the malformation and it was removed completely. **D:** After removal of the CM, the hemosiderin-stained cavity was carefully inspected to ensure complete removal.

Operation and Postoperative Course. The patient underwent a T2–3 laminectomy and radical facetectomy of T-2. A midline dural incision was made and the dentate ligaments at T-2 and T-3 were cut (Fig. 2). A prolene suture was placed on the right dentate ligament to facilitate cord rotation. On rotation of the cord, a hemosiderin stain on its surface was identified, and an incision was made overlying the CM. A hematoma associated with the malformation was removed. The CM was dissected within this cavity and removed en bloc. There were no changes in readings on electrophysiological monitoring. Immediately after surgery, the patient's LE strength and pain improved, and he progressively recovered to full strength and complete resolution of pain at long-term follow-up. Postoperative imaging revealed gross-total resection.

Results

Twenty-two patients who were surgically treated by the senior author (M.T.L.) at UCSF were included. The patient profiles are presented in Table 1. The average age at surgery was 43 years (range 19–67 years), and the male/female ratio was 1.4:1 (Tables 1 and 2). The most common presenting symptoms were sensory deficit (45%), motor weakness (36%), and dysesthesia (32%), with an average duration of 7 months (range 0–30 months). Three patients

TABLE 1: Summary of 22 patients with CMs*

Case No.	Age (yrs), Sex	Presenting Symptoms	Duration of Clinical Symptoms (mos)	Previous Op	Familial CM	FU (yrs)
1	34, F	sensory deficits	3	no	no	14
2	45, M	sensory deficits	7	no	no	14
3	23, M	quadriplegia	0	no	no	13
4	55, M	paraparesis	3	yes	no	11
5	30, F	radiculopathy, dysesthesia	5	no	yes	9
6	26, F	sensory deficits, dysesthesia	6	no	no	8
7	45, M	dysesthesia	5	no	no	7
8	63, F	dysesthesia	8	no	no	7
9	32, F	dysesthesia	12	no	no	7
10	35, M	paraparesis, sensory deficits	6	no	no	7
11	67, M	rt LE weakness	30	yes	yes	5
12	35, F	sensory deficits	1	no	no	7
13	29, M	sensory deficits	5	no	no	5
14	47, F	sensory deficits	9	no	no	4
15	45, M	paraparesis, sensory deficits	20	yes	no	4
16	60, M	dysesthesia	8	no	no	3
17	53, F	lt LE weakness	5	no	no	3
18	36, M	sensory deficits	4	no	no	3
19	62, M	rt LE weakness, dysesthesia	9	no	no	2
20	50, M	lt LE weakness	7	no	no	1
21	19, M	radiculopathy	4	no	yes	1
22	33, F	sensory deficits	3	no	no	1

* FU = follow-up.

TABLE 2: Summary of characteristics in patient cohort

Characteristic	Value*
age (yrs)	43 ± 14
duration of clinical symptoms (mos)	7 ± 7
FU (yrs)	6 ± 4
lesion size (cm)	1 ± 0.4
EBL (ml)	350 ± 131
op time (hrs)	4 ± 0.96
complication rate (%)	5
McCormick grade	
preop	1.8 ± 1.2
postop	2.1 ± 1.2
FU	1.3 ± 0.65

* All but the complication rate are given as the mean ± SD.

had undergone surgeries at another institution, and 14% of the patients had familial form of CM. The average follow-up duration was 6 years (range 1–14 years).

The lesions were located in the thoracic region in 73% of the patients, and in the cervical region in 27% (Table 3). The majority of the lesions (64%) involved a single level, whereas 36% encompassed 2 levels on MR imaging, and the average lesion size was 1 cm (range 0.3–1.6 cm). A single-level laminectomy was performed for 1 patient, a 2-level laminectomy for 11 patients, a 3-level laminectomy for 8 patients, and a 4-level laminectomy for 2 patients. The majority of patients (73%) had dorsally located lesions, whereas 27% of patients had ventrally located lesions; radical facetectomy was performed for all ventrally located lesions. Additionally, dentate ligament release was performed in all patients with ventral CMs, whereas it was performed in 18% of dorsal CMs. Sixty-eight percent of patients had blood clot within the CM that was evacuated during surgery. The average EBL was 350 ml (range 100–600 ml), the average operating time was 4 hours (range 3–6 hours), and excision was complete in all patients, as confirmed on MR imaging (Tables 2 and 3). Analyzed by location of lesion, ventrally located lesions had an average EBL of 483 ± 75 ml versus 322 ± 127 ml ($p < 0.005$) for dorsally located lesions, and an average operating time of 5.3 ± 0.5 hours versus 3.8 ± 0.86 hours ($p < 0.0005$), respectively. The patient in Case 20 suffered from a wound infection that required wound washout and antibiotic treatment, giving rise to a complication rate of 5% in this cohort.

In terms of outcome as assessed according to the McCormick classification, 11 patients (50%) had stable outcome, 9 (41%) had improved outcome, and 2 (9%)

TABLE 3: Summary of surgical procedures in 22 patients with CMs*

Case No.	Lesion Level	Laminectomy Level	Lesion Orientation	Radical Facetectomy	Dentate Ligament Resection	Lesion Size (cm)	Δ on Intraop Electrophys Tests	Blood Clot Evac	EBL (ml)	OR Time (hrs)	Compli-cation
1	T8–9	T7–10	ventrolat	yes	yes	0.8	none	yes	400	6	no
2	T-3	T2–4	dorsal	no	no	0.9	none	no	300	3	no
3	C3–4	C2–4	dorsal	no	yes	1.2	none	yes	500	3	no
4	T-5	T3–6	dorsal	no	yes	1.4	none	yes	300	6	no
5	C5–6	C4–6	dorsal	no	yes	0.6	none	no	250	3	no
6	T2–3	T2–3	dorsal	no	no	0.7	none	yes	300	4	no
7	T-1	C7–T2	ventrolat	yes	yes	1.1	none	no	500	5	no
8	T11–12	T10–12	dorsal	no	no	1.5	none	yes	400	4	no
9	C-4	C3–4	ventrolat	yes	yes	1.3	none	yes	400	5	no
10	T-8	T7– 9	ventrolat	yes	yes	1.3	none	yes	600	6	no
11	T-2	T1– 3	dorsal	no	yes	0.3	MEP & SSEP	no	100	5	no
12	T-12	T-12	dorsal	no	no	0.8	none	no	100	3.5	no
13	T-7	T6–7	dorsal	no	no	0.8	SSEP	yes	200	3	no
14	C-6	C5–6	dorsal	no	no	1.0	none	no	200	3	no
15	T-12	T12–L1	dorsal	no	no	0.7	none	yes	300	4	no
16	T5–6	T5–6	ventral	yes	yes	1.0	none	yes	500	5	no
17	T1–2	T1–2	dorsal	no	no	1.6	MEP	yes	300	3	no
18	C-7	C6–7	dorsal	no	no	0.9	none	yes	300	4	no
19	T2–3	T2–3	ventrolat	yes	yes	0.8	none	yes	400	4	no
20	T-12	T11–L1	dorsal	no	no	1.2	none	yes	350	3.5	WI
21	T-2	T1–2	dorsal	no	no	0.7	none	yes	500	5	no
22	C-6	C5–6	dorsal	no	no	1.4	none	no	500	4	no

* All lesions were completely excised. Abbreviations: Electrophys = electrophysiological; Evac = evacuation; OR = operating room; WI = wound infection; Δ = change.

had worsened outcome (Table 4). The average McCormick classification at follow-up was 1.3 ± 0.65, which was significantly improved compared with 1.8 ± 1.2 before surgery ($p < 0.05$; Table 2). Although there was a slight worsening of the McCormick grade at postoperative assessment (2.1 ± 1.2), this did not reach significance compared with the preoperative state ($p > 0.05$).

Of the 2 patients with worsened outcome, both cases were due to severe dysesthetic pain (Table 4). Dysesthesia was present in 5 patients (23%) at follow-up; this dysesthetic cohort appears to have a longer duration of clinical symptoms prior to surgery when compared with the cohort of patients who did not have dysesthesia at follow-up (7.6 ± 2.9 months vs 4.9 ± 2.7 months, respectively [$p < 0.05$]; excluding the patients who underwent a second operation). There was no incidence of postlaminectomy kyphosis.

Discussion

In our study, surgery improved condition in a large proportion of our patients (41%); in fact, 2 patients had a debilitating McCormick classification of Grade 4 at preoperative assessment and made a full functional recovery to a classification of Grade 1 on follow-up evaluation. A large proportion (50%) has stable function; in fact, 45% of patients had a stable full McCormick classification of Grade 1 before and after surgery. Two patients had worsened McCormick classification upon follow-up; this was due to worsening of dysesthetic pain.

TABLE 4: Clinical outcome in 22 patients with CMs

Case No.	McCormick Classification*			Dysesthesia	Postlaminectomy Kyphosis
	Preop	Postop	On FU		
1	1	1	1	no	no
2	1	1	1	no	no
3	4	4	3	no	no
4	4	4	3	no	no
5	1	1	1	no	no
6	1	1	2	yes	no
7	1	3	2	yes	no
8	2	3	1	no	no
9	1	1	1	yes	no
10	1	2	1	yes	no
11	2	4	2	no	no
12	1	1	1	no	no
13	1	1	1	no	no
14	1	1	1	yes	no
15	2	2	1	no	no
16	1	2	1	no	no
17	2	2	1	no	no
18	4	4	1	no	no
19	2	2	1	no	no
20	4	3	1	no	no
21	1	1	1	no	no
22	3	2	1	no	no

* McCormick classifications are defined as follows: Grade 1—neurologically normal, mild focal deficit not significantly affecting function of involved limb, normal gait; Grade 2—sensorimotor deficit affecting function of involved limb, mild to moderate gait difficulty, still walks independently; Grade 3—more severe neurological deficiencies, patient requires cane/brace for ambulation, may or may not be independent; Grade 4—severe deficit, patient requires wheelchair or has bilateral upper-extremity impairment, and is usually not independent.

The development of dysesthetic pain, part of the spectrum of neuropathic pain syndrome, does not appear to be related to the age or sex of the patient, location or size of the lesion, presence of hematoma, preoperative McCormick score, previous surgery, changes in intraoperative electrophysiology findings, operating time, EBL, or surgical technique; and all symptoms of dysesthetic pain on follow-up were present during presentation. Interestingly, there was a significant difference in the duration of clinical symptoms in the cohort that had dysesthesia at follow-up compared with patients who did not, with a longer duration of clinical symptoms in the patients with dysesthetic pain. This argues for a posthemorrhagic effect that induces dysesthesia that is probably associated with perturbation to the spinothalamic tract, and may suggest that early surgical intervention may be important to prevent this pain syndrome, contrary to a previous study in which an optimal time for surgery of 4–6 weeks after hemorrhage was suggested.[12] Although previous studies did not specifically report dysesthetic pain associated with CMs, such a symptom may be broadly categorized as sensory deficits. We specifically categorized it thus, because in 2 of our patients (Cases 6 and 7) the long-term outcome was negatively impacted; dysesthesia was present in 7 patients, 5 of whom had improvement or resolution of their dysesthetic pain. Our study's results are consistent with previous reports[5,11] that have suggested the role of timely surgery in improving outcome.

In the majority of cases with a dorsally located lesion, the CM came to the surface and myelotomy was not required (see Illustrative Case 17). Five of the dorsally located lesions required a midline myelotomy (Cases 2, 11, 13, 14, and 15). Of these 5 cases, there were SSEP changes during surgery in 2 (Cases 11 and 13). For the patient in Case 11, this occurred during lesion resection and not when myelotomy was performed. For the patient in Case 13, there was fluctuation of SSEP during myelotomy and lesion resection, but this did not lead to any postoperative deficits. It appears that midline myelotomy was only needed in a minority of the cases, and led to SSEP changes in 9% of the patients in our series (2 of 22). Postoperative posterior column deficits were recorded, but were not attributed to the myelotomy. In Case 11 there was a decline in McCormick score after surgery, but that was attributed to cord manipulation. The others (Cases 2, 13, 14, and 15) had stable sensory and propioceptive deficits compared with the preoperative state. It appears that midline myelotomy had minimal impact on posterior column function; however, this may be masked by preoperative sensory deficits. Perturbations imparted by midline myelotomy were not substantial enough to affect the McCormick score.

Five patients had a worsened McCormick score immediately following surgical intervention; this value is within published rates.[2,7,9] Intraoperative neuromonitoring did not necessarily predict a postoperative deficit. In fact, in only 1 of 3 cases with an intraoperative electrophysiology change was there a postoperative deficit. The case with both SSEP and MEP changes (Case 11) had a new postoperative deficit that ultimately resolved at long-term follow-up. There are reasons for this: some patients may have preoperative deficits in which the motor and sensory pathways are perturbed, and therefore electrophysiological monitoring was not adequately sensitive. In cases with electrophysiological change, such changes may not reach the threshold of permanent neural damage. Therefore, we recommend the use of electrophysiological monitoring during resection of spinal cord CMs, but that it be used to guide rather than abort the resection. Often a pause in the resection, with irrigation of the spinal cord or relaxation of any cord rotation, will restore the electrophysiological signals.

In our study cohort, we did not encounter any patients with a postoperative motor deficit, even in more ventrally located lesions that may be close to the corticospinal tracts. Resection of the dentate ligaments for ventrally and laterally located lesions allows for safe manipulation of the spinal cord and direct access to the CM as it approaches the surface of the spinal cord.

Consistent with the doctrine of minimizing spinal cord manipulation, we performed unilateral radical facetectomies in cases in which ventral access was necessary. By resecting much of the facet and part of the medial pedicle, a complete lateral view of the spinal cord was possible; and along with cord rotation afforded by dentate ligament resection, ventrally located lesions could be accessed. The technique of accessing a ventrally located lesion by radical facetectomy and cord rotation by dentate ligament release does lead to a longer operating time and greater blood loss. Although radical facetectomy could be potentially destabilizing, we found that when it was performed at a single level and unilaterally, stability was preserved.

Although postlaminectomy kyphosis is a concern, particularly for the cervical and lumbar spine, where there is no rib cage to act as an internal brace, we did not encounter any patients who required fusion procedures in our long-term follow-up. Furthermore, laminectomy did not appear to destabilize the spine even when crossing the cervicothoracic (1 case) or thoracolumbar junction (2 cases). Based on our data, we suggest that fusion is not an absolute necessity in this setting.

Conclusions

Our experience demonstrates the safety of resecting intramedullary spinal cord CMs through simple posterior approaches. This study is limited by its retrospective design and the fact that it represents just one surgeon's experience. Although a prospective randomized trial comparing different surgical techniques may be useful, such a study is limited by the rarity of intramedullary CMs.

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: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed final version of the manuscript and approved it for submission: both authors. Statistical analysis: Lu.

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Manuscript submitted May 15, 2010.
Accepted June 10, 2010.

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Neurosurg Focus 29 (3):E13, 2010

Prognostic factors for the outcome of surgical and conservative treatment of symptomatic spinal cord cavernous malformations: a review of a series of 20 patients

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Object. In this study, the authors present a review of a series of 20 intramedullary spinal cord cavernous malformations (SCCMs) with particular focus on MR imaging and prognostic factors.

Methods. Between 1994 and 2009, 20 patients with SCCM were treated under the care of the senior author. The diagnosis was made in all patients after the onset of clinical symptoms. The age of the 9 men and 11 women ranged between 26 and 71 years (median 38.5 years). The duration of symptoms prior to referral ranged from 1 week to 9 years (median 6.5 months). At the time of referral, 4 patients had no significant neurological deficits, 10 patients suffered significant functional restrictions, and 6 patients presented with severe paraparesis and loss of functional strength. None of the patients had complete paraplegia. Seventeen patients underwent microsurgical removal, while 3 patients opted for conservative therapy. For the present analysis, the medical records and MR images and/or reports were reviewed. Classification of length of history, pretreatment status, MR imaging pattern, and treatment modality was done and correlated with outcome.

Results. The cavernoma was located at the cervical level in 8 patients and between T-1 and L-1 in 12 patients. The cavernoma appeared as mainly T2 hyperintense on MR images in 7 patients, mainly T2 hypointense in 2 patients, and mixed in the remaining 10 patients. The craniocaudal extension of the core varied between 5 and 45 mm. In 2 patients with cervical cavernomas, a distinct T2 signal of the spinal cord cranial and distal to the cavernoma was seen, and in a patient with a large thoracic cavernoma, T2 extinction cranial and caudal to the cavernoma was seen as a sign of hemosiderosis. Neurological deficits improved postoperatively in 12 of the surgically treated patients, remained stable in 2, and deteriorated in 3. The 3 patients who were conservatively treated remained stable over a follow-up of 3–9 years. Postoperative improvement was seen in 5 of 7 surgical patients with a history of symptoms of 2 months or less, 5 of 6 patients with a history of 2–24 months, and in 2 of 4 patients with a history of more than 2 years. Two of the 3 patients with postoperative deterioration had a history of more than 2 years and the third a short history of 1 month.

Conclusions. Although a satisfactory outcome can be achieved through surgical treatment of SCCMs, some patients worsen after surgery or during the postoperative course. Long-term stability is possible in oligosymptomatic conservatively treated patients. The prevalence and pathophysiological importance of segmental spinal cord edema and hemosiderosis is incompletely understood at the present time. *(DOI: 10.3171/2010.6.FOCUS10123)*

Key Words • cavernoma • spinal cord • intramedullary • magnetic resonance imaging • outcome • prognostic factors

Spinal cord cavernous malformations are rare lesions with a frequency of approximately 5%–10% of the cranial counterpart. Prevalence and incidence correspond roughly to spinal hemangioblastomas as estimated on the basis of reported cases. Awareness of the entity increased with the advance of the resolution of spinal MR imaging. Spinal cord cavernous malformations could be differentiated into intramedullary and into central and superficial localizations. In addition, spinal cavernomas can be located epidurally and become clinically symptomatic with epidural hemorrhage or as a space-occupying mass.[2,23]

The real incidence of SCCM is unknown. Knowledge of the pathodynamics is mostly based on the reported series consisting of surgical cases and a few autopsy reports of partially ante mortem unknown lesions.[4,17–22,24] Limited data are available on the natural course of incidentally detected asymptomatic lesions, that is, the risk of growth and hemorrhage. Ten years ago, it was expected that high-resolution MR imaging would lead to the diagnosis of many asymptomatic SCCMs. This fear turned out to be unjustified. At least at our institution, most of the patients present for consultation with the diagnosis of

Abbreviation used in this paper: SCCM = spinal cord cavernous malformation.

SCCM and related symptoms, which are the reasons for MR imaging. Nonetheless, a conclusive answer regarding the frequency of asymptomatic SCCM appears premature in view of the rarity of the entity.

There are now a number of reports available of cases or small series of surgically managed SCCM. Most agree that the outcome is not uniformly positive. The purpose of the present update is to analyze our experience in light of prognostic factors. The main focus is on surgically treated patients, but the experience with some patients who underwent conservative treatment allows for discussion of this issue in the context of the limited literature on conservative management.

Methods

Between 1994 and 2009, 20 patients with SCCM were treated by the senior author (H.J.S.). The diagnosis was made in all patients after the onset of clinical symptoms. We did not include asymptomatic lesions diagnosed in patients with multiple cavernomas. One patient in the series also had multiple intracranial cavernomas but no known family history. The remaining patients had a monofocal spinal pathology and no known family history. The clinical characteristics of the individual patients are summarized in Table 1. The data regarding the patients in Cases 1–9 have been published in part in an earlier publication.[24] The age of the patients ranged between 26 and 71 years (median 38.5 years). Sex was slightly unbalanced with 9 men and 11 women.

Seven patients had an acute onset of sensorimotor deficits and a pretreatment history of 1 week to 2 months. Six patients complained of slow or stepwise progression and had a duration of symptoms between 2 and 24 months before being referred for treatment. Four patients sought treatment with progressing deficits more than 2 years after symptom onset. Overall, the duration of symptoms ranged from 1 week to 9 years (median 6.5 months).

We used the Frankel grading to quantify the functional status at the time of admission and at follow-up (Grade A, complete motor and sensory loss below spinal cord injury; Grade B, complete motor and incomplete sensory loss; Grade C, incomplete motor loss with nonfunctional strength; Grade D, incomplete motor loss with functional strength; and Grade E, grossly normal motor and sensory function).[7] At the time of referral, 4 patients had no significant objective neurological deficits (Frankel Grade E). Ten patients suffered significant functional restrictions (Frankel Grade D), and 6 patients presented with severe paraparesis and loss of functional strength (Frankel Grade C). None of the patients had complete paraplegia (Frankel Grades A and B).

The cavernoma was located at the cervical level in 8 patients and between T-1 and L-1 in 12 patients. Diagnostic MR imaging varied with regard to field strength and sequences. For all patients, T1- and T2-weighted sequences were available, although the parameters varied to some degree. For the present review, comparison of the MR imaging characteristics was based on T2-weighted imaging.

During the first years, surgical management was recommended to all symptomatic patients, assuming that there was a progressive natural history. Three patients in the series opted for conservative management. Surgical procedures were done under intraoperative electrophysiological monitoring with somatosensory and motor evoked potentials and electromyography of the concerned muscle groups.

Dorsal and central cavernomas were approached dorsally. Even the lateral and ventrolateral cavernomas were amenable to a dorsal exposure.[13] Laminectomy was avoided in view of the younger age of these patients and the benign nature of the pathological entity. Laminotomy with reinsertion and fixation of the laminae was used for large cavernomas, but we preferred a unilateral approach by an extended interlaminar fenestration or hemilaminectomy for smaller lesions with a unilateral surface contact. One ventral midline cervical SCCM was approached by a ventral corporectomy approach (Case 13).[3,16] Following appropriate bony exposure and dural opening, the cavernoma was identified on the surface whenever possible. Most often, hemosiderin discoloration was seen on the surface overlying the cavernoma (see Fig. 2). The pia mater was then opened, and the cavernoma was exposed. The cavernoma was carefully shrunk with low-power bipolar coagulation and removed if necessary in several pieces. Clearly abnormal vascular tangles in the cavernoma bed were carefully coagulated with reduced power and fine forceps. The gliotic periphery was left in place. The dura was closed in a watertight fashion, and bony reconstruction was performed as appropriate. Dexamethasone was given perioperatively at a dosage of 3 × 4 mg/day, usually for 3 days.

Mobilization was not restricted postoperatively. Stability of the spinal column was generally not affected by the surgical procedure. If laminotomy with reattachment of the laminae or corpectomy and reconstruction for certain anterior approaches were necessary, CT or native imaging was done prior to discharge from the hospital to document stable position of the implants.

For the present analysis, the medical records and MR images and/or reports were reviewed and analyzed. Classification of length of history, pretreatment status, and MR imaging pattern was done and correlated with outcome.

Results

The age of the 20 patients, 11 women and 9 men, ranged from 26 to 71 years with a median value of 38.5 years. Seven patients were admitted after an initial acute episode of partial sensomotor deficits. The other 13 patients were admitted after slowly progressive dysfunction or recurrent episodes of functional deterioration over a period of several months up to almost 10 years.

Eight cavernomas were located in the cervical region, 11 at the thoracic level, and 1 lesion was located at L-1. For the present review, comparison of the MR imaging characteristics was based on the T2-weighted images. The MR imaging data of the patients are also summarized in Table 1. A predominately T2 hyperintense lesion was seen in 7 patients, a mainly T2 hypointense lesion in 2 patients, and a mixed appearance in the remaining 10

TABLE 1: Summary of patient characteristics and follow-up*

Case No.	Age (yrs), Sex	Level	Clinical Presentation (Frankel grade)	Sx Duration	Treatment	FU (Frankel grade)	FU Length (yrs)	Preoperative MRI Findings	FU MRI
1	43, F	L-1	LE unilat sensory deficit (D)	9 mos	conservative	complete recovery (E)	4	predom T2 hyperintense	NA
2	60, F	C-6	unilat arm & leg sensory deficit (C)	9 yrs	CR	residual unilat hand numbness (D)	3	predom T2 hyperintense	NA
3	25, M	C-6	progressive rt hemiparesis (C)	2 yrs	CR	improved (D)	4	predom T2 hypointense	NA
4	30, F	C-1	unilat arm & leg sensory deficit (D)	9 yrs	CR	worse w/ gait ataxia (C)	3	predom T2 hyperintense, max 6 mm	small defect
5	45, M	T-4	unilat LE sensomotor deficit (C)	1 mo	CR	improved (D)	2	predom T2 hyperintense	small defect
6	31, F	T-4	acute unilat leg weakness & urinary retention (D)	1 mo	CR	function stable, pain improved (D)	2	T2 hypointense, max 25 mm	NA
7	49, F	T1–2	acute spastic paraparesis (C), multiple IC cavernomas	2 wks	CR	improved (D)	1	predom T2 hypointense, max 5 mm	NA
8	31, M	T-3	gait ataxia & sensory deficit (D)	7 mos	conservative	complete recovery (E)	1	predom T2 hyperintense	NA
9	30, M	T7–8	acute LE sensomotor deficit (C)	3 mos	CR	improved (D)	2	T2 mixed intensity, max 20 mm	NA
10	31, M	T-4	acute paraparesis (D)	2 mos	CR	improved (E)	2	predom T2 hyperintense, max 25 mm	no visible defect
11	40, F	T-6	LE unilat sensory deficit (E)	6 mos	CR	improved (E)	3	T2 mixed intensity, max 5 mm	local defect
12	43, F	T-12	urinary retention (D)	1 mo	CR	postop worsening, stable during FU (D)	2	T2 mixed intensity, max 10 mm	local defect
13	43, M	C-7	UE unilat sensory deficit (E)	2 mos	CR	improved (E)	4	T2 mixed intensity, max 10 mm	small defect
14	26, F	T-7	progressive gait ataxia deficit (D)	2 yrs	CR	improved (D)	3	predom T2 hyperintense, max 10 mm	small defect
15	45, F	C2–3	UE unilat sensorimotor deficit (D)	15 mos	CR	improved (E)	3	mixed T2, max 15 mm	small defect
16	31, M	C-3	acute tetraparesis (C)	1 wk	CR	improved (E)	2	T2 mixed intensity, max 20 mm, adjacent myelopathy	local defect, myelopathy decreased
17	71, M	T3–4	secondary posttraumatic gait ataxia (D)	3 yrs	CR	deteriorating, additional cervical myelopathy (C)	3	T2 mixed intensity, max 15 mm	small defect & cervical myelopathy
18	45, F	T4–6	progressive parapresis & LE sensory deficit (D)	3 yrs	CR	improved (D)	3	T2 mixed intensity, max 45 mm	residual hemosiderosis, dorsal thethering
19	28, F	C7–T1	UE unilat sensory deficit (E)	6 mos	conservative	stable (E)	9	mixed T2, max 15 mm	predominantly T2 hyperintense, max 13 mm
20	37, M	C-5	bilat sensory deficit (E)	3 mos	CR	stable (E)	1	mixed T2, max 16 mm	local defect

* CR = complete resection; FU = follow-up; IC = intracranial; LE = lower-extremity; predom = predominantly; UE = upper-extremity.

patients (Figs. 1 and 2). The craniocaudal extension of the core varied between 5 and 45 mm. In 2 patients with cervical cavernomas, a distinct T2 elevation of the spinal cord cranial and distal to the cavernoma was seen, indicating cord edema or myelopathy. In a patient with a large thoracic cavernoma, clear T2 extinction cranial and caudal to the cavernoma was seen as a sign of hemosiderosis (Figs. 2 and 3). The quality of the earlier images did not, however, allow for systematic analysis of the signal pattern in the adjacent spinal cord.

Seventeen patients underwent resection. Postoperatively, neurological deficits improved in 12 patients, remained stable in 2, and deteriorated in 3. The Frankel grades at the time of follow-up are given in Table 1. Most patients with postoperative improvement gained maximally 1 point on the Frankel scale. Only one patient admitted with a 1-week history of severe tetraparesis recovered from Grade C to E. One of the patients with secondary deterioration had additional spondylotic cervical myelopathy, which was an additional factor for the secondary deterioration. One woman with an extensive cavernoma had a fluctuating course during the 15-month follow-up (Case 18, Figs. 2 and 3). Follow-up MR imaging showed pronounced hemosiderosis and possible dorsal tethering of the spinal cord.

The correlation of the duration of pretreatment clinical symptoms and outcome is given in Table 2. Postoperative improvement was seen in 5 of 7 surgical patients with a symptom history of 2 months or less, 5 of 6 patients with a history of 2–24 months, and in 2 of 4 patients with a history of more than 2 years. Two of the 3 patients with postoperative deterioration had a history of more than 2 years, and the third a short history of 1 month.

Three patients opted for conservative treatment. All 3 improved or remained stable over the follow-up time of 3–9 years.

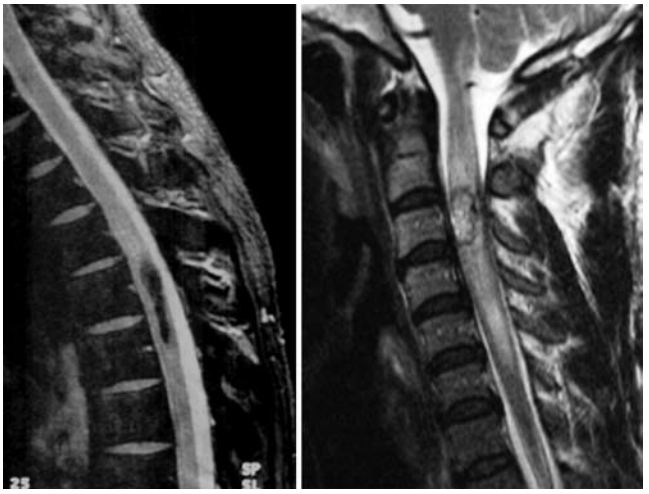

Fig. 1. Various patterns of the T2-weighted MR imaging appearance. **Left:** Case 10. Predominant T2 extinction is seen in a patient with a 2-month history of Brown-Séquard syndrome and a cavernoma at T-4. **Right:** Case 16. Mixed T2 signal and segmental cord edema is seen in a patient who was admitted with a 1-week history of severe tetraparesis and a cavernoma at C-3.

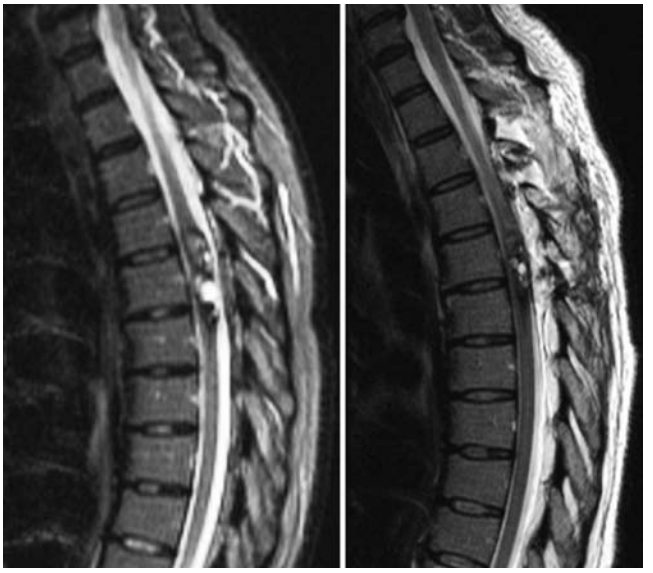

Fig. 2. Case 18. Sagittal MR images showing a thoracic intramedullary cavernoma presenting with a 3-year history of stepwise progression spastic paraparesis. **Left:** A T2-weighted image showing an extensive cavernoma with a mixed signal pattern adjacent cord hemosiderosis. **Right:** Early postoperative T2-weighted image depicting persistent cord hemosiderosis.

Discussion

A substantial number of small series on surgical management has been published during the past 2 decades. The principal feasibility of surgical treatment has been accepted, and the patterns of clinical manifestations have been recognized.[24] If the cavernoma lies on the surface of

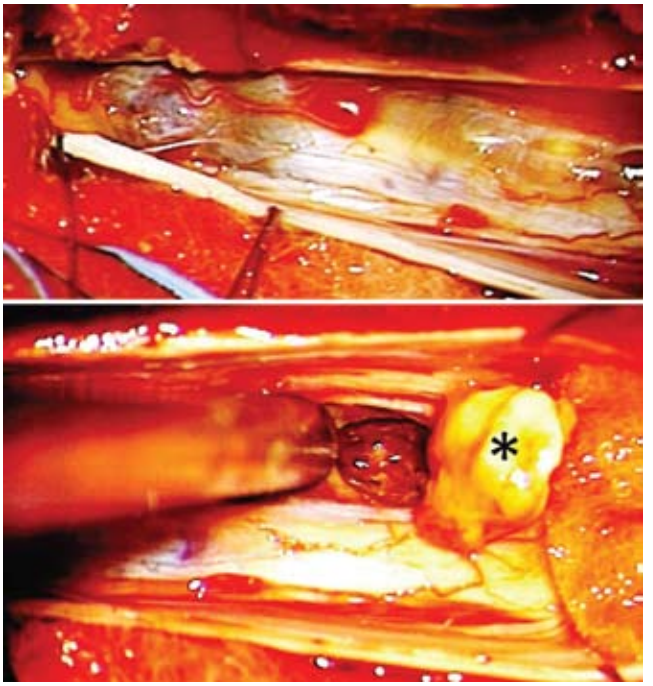

Fig. 3. Case 18. Intraoperative photographs. **Upper:** Diffuse hemosiderosis is apparent after exposure of the surface. **Lower:** The cavernoma was partially fibrous. The *asterisk* identifies a thrombosed and organized large cavern.

TABLE 2: Correlation of duration of symptoms and outcome

Duration of Symptoms (mos)	No. of Patients		
	Better	Stable	Worse
<2	5	1	1
2–24	5	1	0
>24	2	0	2

the spinal cord, in the subdural space, or if hemorrhage leaks through to the surface, the SCCM may present with subarachnoid hemorrhage, which is associated with prominent pain in the back and neck.[12,14] Most cases present with continually or stepwise progressive neurological deficits. Partial recovery is common between episodes of progression. The duration of symptoms ranges from a few days up to more than 25 years. Corresponding to cranial cavernous malformations, the average age at presentation is around 40 years, and women appear to be affected somewhat more frequently.

Since diagnosis of SCCMs became practically only possible with the widespread availability of MR imaging, the experience with the entity is still limited. In the light of the often-dramatic clinical presentation, surgical management was traditionally favored with the result that the data on the natural history are still scarce. In our series, we included 3 patients who opted for conservative management after initial neurological manifestation. All 3 remained stable over the follow-up period of 3–9 years. A small series of 10 conservatively managed SCCM was reported by Kharkar and coworkers.[11] For these patients, the mean duration of symptoms before presentation was 10 months. The mean duration of follow-up from the time of presentation was 80 months. The median McCormick grade for conservatively treated patients at presentation was Grade II, corresponding to a moderate deficit (Frankel Grade D). During this period, none of the conservatively treated patients had an acute intramedullary hemorrhage. In 9 patients, the McCormick grade at the last follow-up evaluation was the same as or better than the score at presentation. In another follow-up study on conservatively managed SCCMs, Cohen-Gadol and coworkers[6] made similar observations. Data obtained during the long-term follow-up period (mean 9.7 years, total of 319 patient-years) were available for 33 of the 42 patients with an SCCM who did not undergo surgery. Five symptomatic lesional hemorrhages (neurological events), 4 of which were documented on neuroimaging studies, occurred during the follow-up period, for an overall event rate of 1.6% per patient per year. No patient experienced clinically significant neurological deficits due to recurrent hemorrhage. The results of these case series confer with our experience that long-term stability is possible after initial manifestation. Nonetheless, we have to be aware that the conservatively treated patients in our series as well as the reported studies represent a selected group of patients.

Traditionally, the risk of hemorrhage was regarded as the most relevant prognostic factor for cavernomas. This concept was developed in analogy to arteriovenous malformations. In the earlier literature review of reported spinal cord cavernomas by Zevgaridis et al.,[24] we had estimated the hemorrhage rate as 1.4% per year, assuming a constant yearly risk since birth. This estimation was based on the number of rather distinct episodes of clinical worsening, which seems to be the mode of manifestation in approximately one-third of the patients. Since almost 50% of the reported cases show a slow worsening, we no longer believe that the concept of bleeding risk is adequate to capture the natural risk of spinal cord cavernomas.

The question of how SCCMs develop and progress is still not well understood. Some conclusions can be inferred from the experience with familial cavernomas that amount to some 20% of cases of CNS cavernomas. Three genes (*CCM1*, *CCM2*, and *CCM3*) have been identified since 1999, 2 on chromosome 7 (1 on each arm) and 1 on the short arm of chromosome 3. Glading and coworkers[8] suggested that defective endothelial junctions are the primary anomaly eventually leading to CNS cavernous malformations. They proposed that autosomal dominant *CCM1* mutations cause loss of KRIT-1 protein function. KRIT-1 binds to Rap1, a guanosine triphosphatase that maintains the integrity of endothelial junctions. They found that KRIT-1 protein is expressed in cultured arterial and venous endothelial cells and is present in cell-cell junctions. KRIT-1 was colocalized and was physically associated with junctional proteins. Rap1 activity regulated the junctional localization of KRIT-1 and its physical association with junction proteins.

Spinal cord cavernous malformations and brainstem cavernomas become symptomatic at an earlier developmental stage than hemispheric cavernomas, often after a first small hemorrhage. It is commonly assumed that cavernomas originate from congenital vascular precursor lesions, such as telangiectasias. In a number of the SCCMs that we surgically treated early after initial manifestation, we did not see the classic mulberry aspect but a rather limited vascular tangle at the border of a subacute hematoma. Similar observations with brainstem cavernomas principally corroborate that these small vascular tangles may be the precursor lesion. If we accept the aforementioned pathophysiological concept of a primary dysfunctional endothelial junction, it must be considered that also the visible abnormal vasculature of early stage cavernomas is a secondary lesion.

In the case of genetically determined cavernomas, additional local and transient systemic factors must be postulated as cofactors for the development of cavernomas. In the situation of sporadic cavernoma, the main cause must be sought locally. Increased venous pressure and hormonal changes have been suggested as temporary factors during pregnancy.[1,9] With regard to local factors, we can potentially draw some conclusions from the reported cavernomas developing after radiation.[1,10,15] For example, chronic ischemia induced by radiation or other causes could be a local cofactor.

In our analysis, the preoperative functional grade was the most important prognostic factor for the functional outcome. In this series, we saw improvement of neurological function in some cases even after a history of several years. Our previous meta-analysis already provided the notion that patients with a history of symptoms lasting more than 3 years fared worse than patients with a short-

er duration of symptoms.[24] Our experience suggests that the postoperative course is unsatisfactory in 2 groups of patients: those who present after an initial manifestation and harbor a small lesion without contact to the surface, and those with a year-long history and severe deficits. The reason for the questionable results in patients with small central cavernomas must be sought in the inevitable access-related sensory deficits. With larger cavernomas or cavernomas with contact to the surface, the risk of additional sensory deficits is less pronounced.

Although imaging quality during the earlier years of the current series does not allow detailed analysis, the current data suggest that that the secondary changes in the vicinity vary substantially. We saw 2 patients with a cervical SCCM and a distinct high T2 signal cranial and caudal to the cavernoma in the sense of cord edema or myelopathy. Both patients recovered and remained stable over the follow-up period. Nonetheless, we must assume that the prognosis after removal of spinal cord cavernomas is comparable to the prognosis after decompression for spondylotic cervical myelopathy and that some 30% of the patients deteriorate in the long range despite adequate decompression. Furthermore, a pronounced myelopathy signal on MR imaging around an SCCM appears to predict an unfavorable outcome comparable to the myelopathy signal in cervical spondylosis.[25] With regard to the importance of adjacent spinal cord hemosiderosis, no data are available.[5] In this series, one patient had a large cavernoma and pronounced adjacent hemosiderosis. It appears likely that adjacent hemosiderosis is mainly seen in patients with a longer history of symptoms, that is, an unfavorable factor. A potential toxic effect of hemosiderin remains hypothetical at the present time.

To define criteria for surgery of an SCCM, the risk of the procedure has to be related to the risk of progression. As mentioned, chronic or stepwise progression of deficits is common, but our experience with conservative management and the literature suggest that long-lasting spontaneous regression of symptoms after initial manifestation can occur. In our experience and among the reported series, it appears that two-thirds of the patients improve after surgery. The reported risk of neurological deterioration after surgery amounts to some 6%.[24] It is unclear whether the risk of surgery is smaller for spinal cord cavernomas than for brainstem cavernomas. The currently available data are too small for a final assessment. In this light, it appears to be a reasonable basis to demand repeated or progressive symptoms for the surgical indication in patients without substantial deficits. For patients with substantial deficits, we recommend surgical treatment without further delay.

Conclusions

Although a satisfactory outcome can be achieved through surgery for SCCM, some patients worsen after surgery or during the further course. Long-term stability is possible in oligosymptomatic patients who are conservatively treated. The frequency and pathophysiological importance of segmental spinal cord edema and hemosiderosis is incompletely understood at the present time.

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: Steiger. Acquisition of data: Turowski. Analysis and interpretation of data: Turowski, Hanggi. Drafting the article: Steiger. Critically revising the article: Turowski, Hanggi. Reviewed final version of the manuscript and approved it for submission: Turowski, Hanggi.

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Manuscript submitted May 11, 2010.
Accepted June 21, 2010.

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Neurosurg Focus 29 (3):E14, 2010

Intramedullary spinal cord cavernous malformations

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Although originally the subject of rare case reports, intramedullary spinal cord cavernous malformations (CMs) have recently surfaced in an increasing number of case series and natural history reports in the literature. The authors reviewed 27 publications with 352 patients to consolidate modern epidemiological, natural history, and clinical and surgical data to facilitate decision making when managing these challenging vascular malformations. The mean age at presentation was 42 years without a sex predilection. Thirty-eight percent of the cases were cervical, 57% thoracic, 4% lumbar, and 1% unspecified location. Nine percent of the patients had a family history of CNS CMs. Twenty-seven percent of the patients had an associated cranial CM. On presentation 63% of the patients had motor deficits, 65% had sensory deficits, 27% had pain, and 11% had bowel or bladder dysfunction. Presentation was acute in 30%, recurrent in 16%, and progressive in 54% of cases. An overall annual hemorrhage rate was calculated as 2.5% for 92 patients followed up for a total of 2571 patient-years. Across 24 reviewed surgical series, a 91% complete resection rate was found. Transient morbidity was seen in 36% of cases. Sixty-one percent of patients improved, 27% were unchanged, and 12% were worse at the long-term follow-up. Using this information, the authors review surgical nuances in treating these lesions and propose a management algorithm. *(DOI: 10.3171/2010.6.FOCUS10144)*

Key Words • **cavernous malformation** • **cavernoma** • **intramedullary lesion** • **spine** • **natural history** • **hemorrhage**

Cavernous malformations of the spinal cord are a potential source of significant morbidity and should always be considered in the differential diagnosis for spinal intramedullary lesions. They account for 5–12% of all spinal vascular tumors.[24,31,38] Surgical series of these lesions began to appear in the late 1980s concomitant with the introduction and growing use of MR imaging. Early reviews focused on case reports and small surgical series;[6,34,52] in recent years, however, more sizable series of these relatively rare lesions have been reported,[3,10,23,25,28,30,36,50] allowing for the possibility of a meaningful review. Herein, we comprehensively analyze the epidemiology, natural history, clinical presentation, and surgical results of these lesions.

Methods

A PubMed search was performed using the terms "spinal," "intramedullary," "cavernoma," "cavernous malformation," and "cavernous hemangioma." Surgically and conservatively treated patient series were selected for review to amalgamate data on the natural history, clinical presentation, and surgical results for these lesions. For comprehensiveness, references within pertinent articles were also perused and included if appropriate. Series with at least 3 lesions were included to minimize bias. In cases in which institutions reported multiple series over time, the most recent, inclusive series was used.

Natural History and Clinical Presentation

Twenty-seven series with 352 patients were reviewed to elucidate the epidemiological, natural history, and clinical data on these lesions (Table 1). Combined results were summarized in Table 2. The average age at presentation was 42.0 years. Contrary to early reports[6,52] and more consistent with contemporary larger series,[25,26,28] the overall male/female ratio was 1.0 (173 males:175 females). The lesions were primarily located in the cervical and thoracic regions: cervical, 134 lesions (38%); thoracic, 200 lesions (57%); lumbar, 14 (4%); unspecified location, 4 (1%). Six reports provided data on family history; 12 (9%) of 129 patients evaluated for a family history of these lesions had at least 1 family member with at least 1 CM.[7,10,23,25,31,39] Fifty-one (27%) of 187 patients described in 13 series had associated intracranial CMs.[3,7,9,10,23,25,28,29,31,38,39,49,52] At least 23 (45%) of these 51 cases with both intracranial and spinal CMs were associated with a family history of a CNS CM.

Seventeen series with 205 patients provided infor-

Abbreviations used in this paper: AVM = arteriovenous malformation; CM = cavernous malformation.

TABLE 1: Epidemiological and clinical data from series of intramedullary CMs*

Authors & Year	No. of Patients	Mean Age (yrs)	M/F Ratio	Lesion Location, No. of Lesions	Clinical Presentation, No. of Patients	Onset, No. of Patients
Cosgrove et al., 1988	5	41.4	2:3	cervical, 1; thoracic, 4	weakness, 5; sensory deficit, 4; pain, 2; B/B, 1	progressive, 5
McCormick et al., 1988	6	32.7	4:2	cervical, 1; thoracic, 5	weakness, 6; sensory deficit, 6; pain, 3; B/B, 3; respiratory difficulty, 1	acute, 1; recurrent, 4; progressive, 1
Villani et al., 1989	3	38.0	1:2	cervical, 1; thoracic, 2		progressive, 3
Lunardi et al., 1994	5	42.4	2:3	cervical, 2; thoracic, 3		acute, 3; recurrent, 1; progressive, 1
Samii & Klekamp, 1994	4	45.0		thoracic, 4		
Cantore et al., 1995	6	53.5	5:1	cervical, 2; thoracic, 4	weakness, 5; sensory deficit, 5; B/B, 2	recurrent, 2; progressive, 4
Gordon et al., 1995	3	43.0	1:2	thoracic, 2; lumbar, 1	weakness, 3; sensory deficit, 3; pain, 2; B/B, 1	recurrent, 1; progressive, 2
Turjman et al., 1995	11	49.1	2:9	cervical, 2; thoracic, 6; lumbar, 3		acute, 3; progressive, 7; not denoted, 1
Furuya et al., 1996	4	45.0	2:2	cervical, 2; thoracic, 2	weakness, 4; sensory deficit, 4; pain, 2; B/B, 2	recurrent, 1; progressive, 3
Padovani et al., 1997	4	46.0	3:1			acute, 1; progressive, 3
Vishteh et al., 1997	17	40.1	8:9	cervical, 8; thoracic, 8; lumbar, 1	radiculopathy, 6; myelopathy, 10; conus syndrome, 1	acute, 6; progressive, 11
Cristante & Hermann, 1998	12	33.5	4:8	cervical, 8; thoracic, 4	weakness, 7; sensory deficit, 11; pain, 6	acute, 4; recurrent, 3; progressive, 5
Chabert et al., 1999	5	43.0	1:4	cervical, 3; thoracic, 2	weakness, 4; sensory deficit, 5; pain, 2; B/B, 1	acute, 2; recurrent, 2; progressive, 1
Ghogawala & Ogilvy, 1999†	9	44.1	5:4	cervical, 6; thoracic, 3		acute, 1; recurrent, 5; progressive, 3
Tu et al., 1999	7	30.1	5:2	cervical, 4; thoracic, 3	weakness, 6; sensory deficit, 2; pain, 2; B/B, 2; respiratory difficulty, 1	acute, 1; recurrent, 1; progressive, 5
Zevgaridis et al., 1999	9	38.2	4:5	cervical, 3; thoracic, 5; lumbar, 1	weakness, 5; sensory deficit, 5; pain, 3; B/B, 1	acute, 5; recurrent, 3; progressive, 1
Sandalcioglu et al., 2003	10	34.5	3:7	cervical, 5; thoracic, 5		acute, 4; recurrent, 6
Santoro et al., 2004	10	40.9	5:5	cervical, 5; thoracic, 5	weakness, 8; sensory deficit, 8; B/B, 4	
Weinzierl et al., 2004‡	12	44.3	6:6	cervical, 5; thoracic, 7	weakness, 7; sensory deficit, 2; pain, 10	
Cohen-Gadol et al., 2006	67	50.0	35:32	cervical, 28; thoracic, 37; lumbar, 2	asymptomatic, 7	
Jallo et al., 2006§	26	38.0	17:9	cervical, 8; thoracic, 18	weakness, 15; sensory deficit, 5; pain, 5; B/B, 2	acute, 12; progressive, 14
Nishikawa et al., 2006	3	48.3	1:2	cervical, 3	sensory deficit, 3	
Kharkar et al., 2007	14	42.0	8:6	cervical, 4; thoracic, 8; lumbar, 2	weakness, 9; sensory deficit, 5; pain, 13; B/B, 2; involuntary mvmts, 1	
Labauge et al., 2008	53	40.2	26:27	cervical, 12; thoracic, 41	weakness, 28; sensory deficit, 37; asymptomatic, 1	acute, 20; progressive, 32; asymptomatic, 1
Bian et al., 2009	16	38.0	7:9	cervical, 9; thoracic, 7	weakness, 8; sensory deficit, 14; pain, 5; B/B, 2	recurrent, 3; progressive, 13
Matsuyama et al., 2009	17	41.6	7:10	cervical, 8; thoracic, 8; lumbar, 1		

(continued)

TABLE 1: Epidemiological and clinical data from series of intramedullary CMs* *(continued)*

Authors & Year	No. of Patients	Mean Age (yrs)	M/F Ratio	Lesion Location, No. of Lesions	Clinical Presentation, No. of Patients	Onset, No. of Patients
Park et al., 2009	14	34.3	9:5	cervical, 4; thoracic, 7; lumbar, 3	weakness, 9; sensory deficit, 14	acute, 3; recurrent, 4; progressive, 7

* B/B = bowel or bladder dysfunction; mvmts = movements.
† Includes prior series of Ogilvy et al., 1992, and Amin-Hanjani et al., 1998.
‡ Includes prior series of Spetzger et al., 1995, and Huffman et al., 1998.
§ Includes prior series of Deutsch et al., 2000.

mation on patient clinical presentations. One hundred twenty-nine patients (63%) presented with motor weakness, 133 patients (65%) had at least 1 sensory deficit, at least 55 patients (27%) had pain, and 23 patients (11%) had bowel or bladder dysfunction. Two patients had respiratory compromise, and 1 patient presented with involuntary movements. Three differing modes of presentation were apparent in reviewing these cases: 1) acute presentation with neurological deficit, 2) recurrent episodes of neurological deficits with varying degrees of recovery, or 3) progressive neurological decline. Using this classification for 20 series with 223 patients revealed 66 patients (30%) who presented acutely, 36 patients (16%) with recurrent episodes, and 121 patients (54%) with progressive neurological decline.

Theories on the mechanisms underlying these various modes of presentation generally converge on progressive deterioration occurring due to microhemorrhage, hyalinization/wall thickening, gliosis, microcirculatory changes, and/or partial thrombosis.[3,10,17,25] Acute or recurrent events are thought to be attributable to frank CM hemorrhage. Table 3 summarizes annual rates of hemorrhage from intramedullary CMs. Aside from the observed cohorts in the studies by Cohen-Gadol et al.[10] and Kharkar et al.,[25] rates were calculated retrospectively, assuming lesion presence since birth. Annual hemorrhage rates varied from 0 to 4.5%. Over 2571 patient-years for 92 patients in these 6 studies, 63 bleeds occurred, yielding an overall annual hemorrhage rate of 2.5%.

TABLE 2: Natural history and clinical presentation of spinal intramedullary CMs

Characteristic	Value
mean age at presentation in yrs	42
M/F ratio	1.0
lesion location (%)	
cervical	38
thoracic	57
lumbar	4
% patients w/ positive family history	9
% patients w/ associated intracranial CMs	27*
% patients w/ associated venous anomaly	34
presentation (% patients)	
motor weakness	63
sensory deficit(s)	65
pain	27
B/B	11
symptom onset (% patients)	
acute	30
recurrent episodes	16
progressive decline	54
annual hemorrhage rate†	2.5

* Forty-five percent of these patients with both spinal and intracranial CMs had a family history of at least 1 CM.
† Rate calculated from retrospective data assuming lesion presence since birth.

Imaging Characteristics and Differential Diagnosis

The deposition of hemosiderin resulting in a hypointense rim around a mixed signal intensity leads to the pathognomonic appearance of CMs on T2-weighted MR imaging.[14,45] Cavernous malformations must remain in the differential diagnosis of intradural intramedullary lesions. Infrequently, they may take a more homogeneous hyper- or hypointense appearance.[45] In 24 (34%) of 70 patients (range 0–94% per series) in 6 series, venous malformations were observed.[3,11,38,39,48,50] Calcification is seen less frequently with these lesions as compared with their intracranial counterparts (2 of 15 lesions across the series of Cosgrove et al.[11] and Ghogawala and Ogilvy[17]). Distin-

TABLE 3: Annual hemorrhage rates of intramedullary CMs*

Study	No. of Patients	No. of Bleeds	Patient-Yrs	Annual Hemorrhage Rate
Sandalcioglu et al., 2003	10	17	375	4.5
Cantu et al., 2005	5	4	173	2.3
Cohen-Gadol et al., 2006	33	5†	319	1.6
Kharkar et al., 2007	14	10	556	1.8
	10 observed	0	67	0.0
Bian et al., 2009	16	19	611	3.1
Park et al., 2009	14	8	470	1.7

* With the exception of the 10 observed patients in the series of Kharkar et al., all rates were derived from retrospective data, assuming lesion presence since birth.
† These were described as "clinical events."

guishing CMs from multiple sclerosis on MR imaging can be difficult because inactive lesions may not enhance and can demonstrate mixed or hyperintense signal intensity. Clinical histories of progressive or recurrent episodes of the neurological decline seen with CMs also mimic multiple sclerosis; however, a distinguishing feature for these lesions in contrast to multiple sclerosis is a symptomatology that is referable to only 1 location of the neuraxis. In addition, demyelinating lesions will more consistently respond to steroids and tend to have more rapid changes in appearance on serial imaging. The broader differential includes spinal ependymomas, astrocytomas, metastatic disease, hemangioblastomas, spinal AVMs, and transverse myelitis. A lack of enhancement can help distinguish CMs from most of these lesions, and cranial MR imaging demonstrating additional CMs can also help elucidate the diagnosis. Angiography will facilitate the diagnosis of a spinal AVM or hemangioblastoma.

Illustrative Case

History and Examination. This 37-year-old healthy man with a family history of CMs presented after an episode of left upper-extremity numbness that left him with residual finger numbness and dysesthesias. Physical examination was remarkable for right biceps muscle weakness and diminished sensation to light touch in his entire left upper extremity distally. Magnetic resonance imaging demonstrated a nonenhancing exophytic lesion at C4–5 with heterogeneous signal intensity, supporting the diagnosis of a spinal intramedullary CM (Fig. 1). As a healthy young patient with a symptomatic exophytic lesion, the patient was deemed to be an ideal surgical candidate.

Operation. In the operating room, laminectomies from C-4 through C-6 were performed. After opening the dura mater, the exophytic malformation was clearly seen, spreading the posterior columns laterally. It was entered and circumferentially dissected away from the cord, leaving the hemosiderin margin as a guide for the cleavage plane of the lesion. Careful inspection of the cavity after lesion removal revealed no residual malformation. No changes in somatosensory or motor evoked potentials were seen during the case.

Postoperative Course. Postoperatively, transient weakness developed on right wrist dorsiflexion, as did a mild lower-extremity proprioceptive deficit and a worsening of the patient's right upper-extremity sensory deficit. One month after surgery, his motor examination was entirely normal, his dysesthesias had improved, and he was left with only residual finger numbness that had been present at his preoperative examination. Cervical spine MR imaging at 6 months postsurgery demonstrated no residual lesion (Fig. 2).

Results

Across 24 series with 208 patients, 190 CMs (91%) were totally resected (Table 4). Four of 18 residual lesions rebled on follow-up, and 1 patient suffered further neurological decline without a repeat hemorrhage. Transient early postoperative morbidity was reported in 15 series, with rates ranging from 0–100% and a mean of 36% (62 of 171 patients). At the long-term follow-up mentioned in 22 series, 143 patients were improved (61%), 62 (27%) were unchanged, and 28 (12%) were worse, as compared with their preoperative status. These overall results are summarized in Table 5.

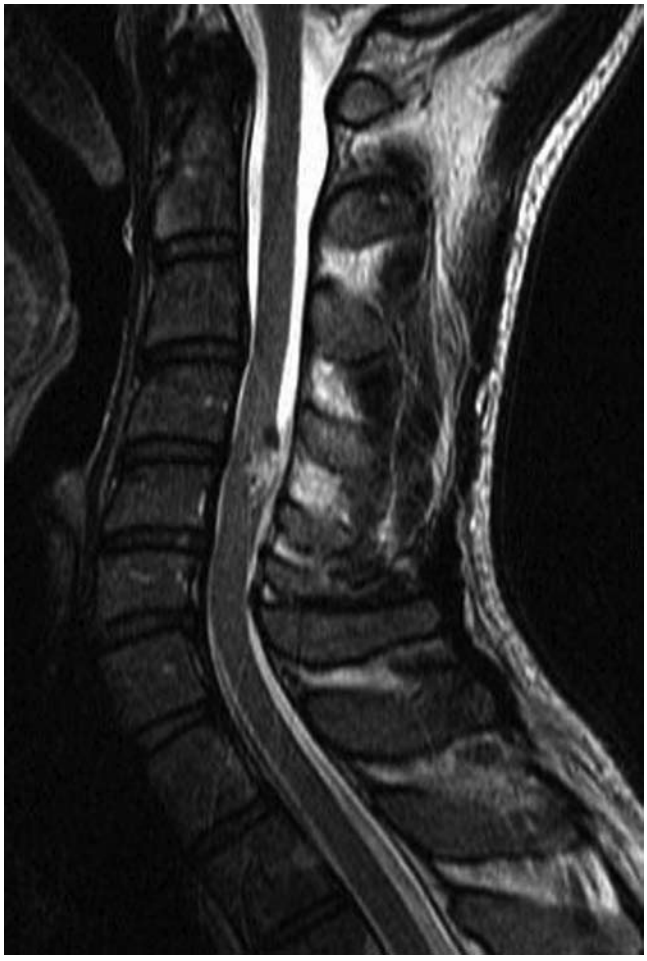

Fig. 1. Sagittal T2-weighted MR image demonstrating a C4–5 exophytic CM. Note the heterogeneous mixed signal intensity.

Discussion

The entity of spinal intramedullary CMs was first reported in 1903 in an autopsy study of a 35-year-old woman with a lesion at L-1 that had bled.[21] In 1912 the first successful excision of an intramedullary CM was performed.[40] Resection was complete and the patient's condition improved postoperatively. In the ensuing decades, additional small surgical series and autopsy reports accumulated[2,4,18,24,33,41,43,46,51] until Cosgrove et al.[11] presented the first surgical series of 5 patients in 1988. At that time, most patients still underwent only partial resection or biopsy, and the epidemiology of these lesions was poorly understood.

Natural History and Clinical Presentation

Our findings were mostly consistent with conclusions

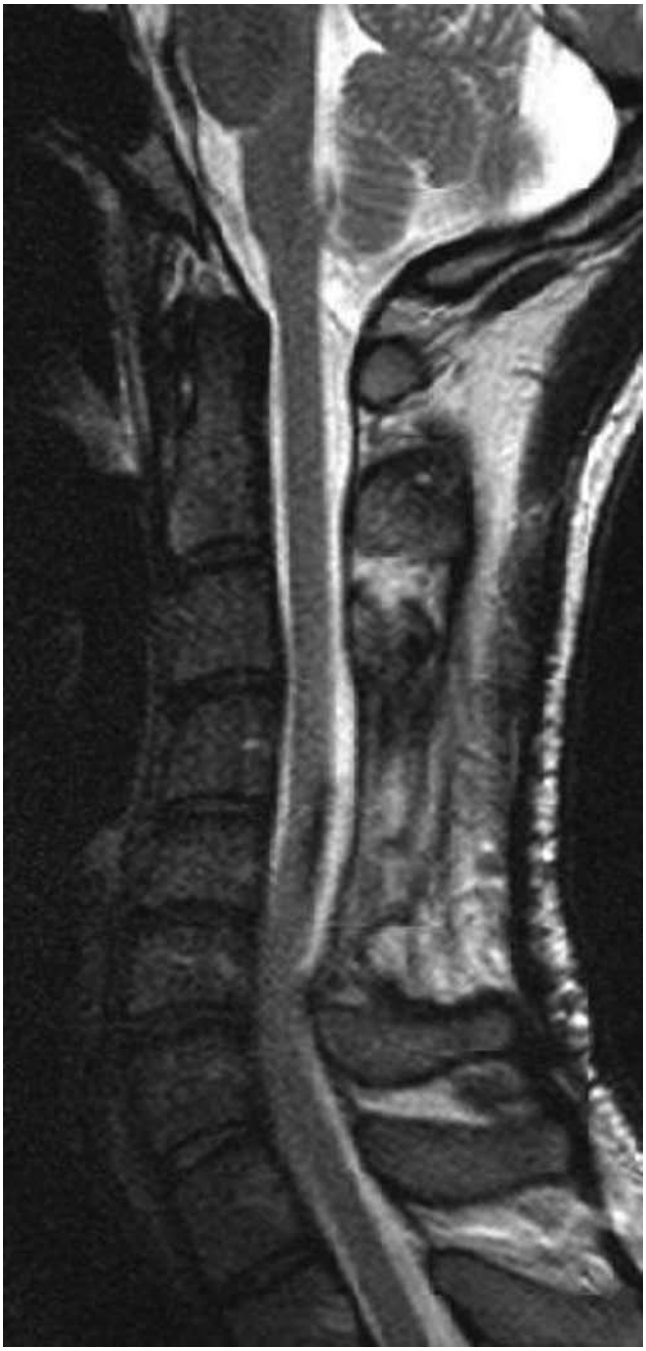

Fig. 2. Postoperative sagittal T2-weighted MR image showing no residual lesion, but simply hemosiderin staining of the parenchyma.

from prior studies with regard to patient age at presentation, distribution of lesion location, annual hemorrhage rate, and modes of clinical presentation (Table 2).[6,52] Early observations of a female preponderance (female/male ratios ranging from 1.5 to 2.2)[6,52] have been refuted in more recent series[25,26,28] with a balance to a more even distribution without a clear sex predilection. Twenty-seven percent of patients had an associated intracranial CM, with approximately 45% of these patients having a family history of CMs. This phenomenon was carefully analyzed in 2 series. Cohen-Gadol et al.[10] obtained cerebral MR images in 33 of 67 cases of spinal intramedullary CMs at their institution, finding 14 with associated cranial and spinal lesions. The mean age in this patient group was 40 years, 12 of the patients were Caucasian, and 8 of the patients had a family history of CMs. Vishteh et al.[49] found that 8 (47%) of 17 patients with spinal intramedullary CMs had at least 1 intracranial lesion as well. The mean age in this patient group was 36 years (as compared with 47 years for those without cranial CMs), with 4 patients (50%) having a family history of CMs. The greater rates of associated cerebral CMs documented in these studies is likely due to selection bias, as only selected patients underwent additional cranial imaging. Nevertheless, these observations encourage imaging of the entire neuraxis when a spinal CM is found—not only in the interest of diagnosing intracranial lesions, but also to facilitate narrowing of the differential diagnosis for spinal lesions that may not have a convincing or characteristic appearance of a CM and avoiding potentially unnecessary angiography.

The clinical presentation of spinal intramedullary CMs can be confused with demyelinating disease, transverse myelitis, intramedullary neoplasms, and spinal AVMs. In their review of 107 patients with 108 lesions, Zevgaridis et al.[52] found that 30% of patients had a stepwise deterioration, 41% a progressive deterioration, and 26% an acute presentation. These rates are similar to our rates of 16%, 54%, and 30%, respectively. As mentioned, progressive decline is likely due to subtle changes in the lesion such as hyalinization/wall thickening, gliosis, microcirculatory changes, partial thrombosis, or microhemorrhage.[34,42] Acute neurological decline or recurrent episodes of acute decline with varying degrees of recovery are likely due to frank hemorrhage from the lesion. Our review of natural history studies revealed an overall 2.5% annual hemorrhage rate (range 0–4.5%),[3,10,25,36,38] similar to brainstem cavernomas.[5,8,15,20,27] Prior reviews of primarily case reports and small case series revealed retrospective annual hemorrhage rates of 1.4–1.6%.[6,52] Of note, these hemorrhage rates assuming lesion presence since birth are probably underestimates given the potential for de novo CM development.[20]

Surgical Selection and Technique

Symptoms associated with intramedullary CMs and lesion location will often dictate the course of management. Figure 3 provides a management algorithm for these lesions. Asymptomatic lesions that do not abut a pial surface should be observed. Given that even our 2.5% annual hemorrhage rate is likely an underestimate, as it assumes lesion presence since birth, asymptomatic lesions that are exophytic should be excised to avoid potential future deterioration. Symptomatic lesions that are exophytic should be excised. Symptomatic lesions that are intrinsic should be observed if the findings are minor, transient, or improving. If the patient has recurrent or progressive deficits, these lesions should also be excised using methods such as ultrasonography for intraoperative guidance. The surgeon should be aware that preoperative MR imaging is imperfect in defining whether a lesion is superficial or deep. Vishteh et al.[48] reported a 17.6% false-positive rate for CMs that appeared to abut a pial surface on MR imaging but were actu-

TABLE 4: Surgical series of intramedullary CMs*

Authors & Year	No. of Patients	Total Resection Rate	Early Transient Morbidity	Mean FU in Yrs (range)	Long-Term Outcome, No. of Patients
Cosgrove et al., 1988	5	0/5	1/5		improved, 1; same, 3; worse, 1
McCormick et al., 1988	6	5/6	1/5	3.0 (0.3–7)	improved, 5; same, 1
Villani et al., 1989	3	3/3			improved, 3
Lunardi et al., 1994	5	5/5			
Samii & Klekamp, 1994	4	3/4			
Cantore et al., 1995	6	6/6			improved, 2; same, 3; worse, 1
Gordon et al., 1995	3	3/3			improved, 2; worse, 1
Furuya et al., 1996	4	4/4		3.7 (1.8–7.7)	improved, 4
Padovani et al., 1997	4	4/4		2.0	improved, 3; same, 1
Vishteh et al., 1997	17	14/17	4/17	4.0 (1.2–5.9)	improved, 10; same, 6; worse, 1
Cristante & Hermann, 1998	12	12/12	12/12	4.5 (0.4–8.5)	improved, 7; same, 3; worse, 2
Huffmann et al., 1998	12	11/12†	7/12		improved, 9; same, 3
Chabert et al., 1999	4	4/4			improved, 2; same, 1; worse, 1
Ghogawala & Ogilvy, 1999	9	9/9	2/9‡		improved, 8; same, 1
Tu et al., 1999	7	7/7	4/7		improved, 6; same, 1
Zevgaridis et al., 1999	7	7/7	2/7		improved, 6; worse, 1
Sandalcioglu et al., 2003	10	10/10	5/10	0.9 (0.4–2.7)	improved, 4; same, 6
Santoro et al., 2004	10	10/10	2/10	5.7 (2.2–9.2)	improved, 9; same, 1
Jallo et al., 2006§	26	25/26	13/26	4.5 (0.3–10)	improved, 12; same, 12; worse, 2
Nishikawa et al., 2006	3	3/3	1/3		improved, 3
Kharkar et al., 2007	4	3/4		3.5 (0.2–12.4)	improved, 1; same, 2; worse, 1
Labauge et al., 2008	37			7.3 (0.4–50)	improved, 20; same, 6; worse, 11
Bian et al., 2009	16	16/16	0/16	1.9 (0.1–6.5)	improved, 12; same, 4
Matsuyama et al., 2009	17	12/17	5/17	5.5 (2–10)	improved, 6; same, 8; worse, 3
Park et al., 2009	14	14/14	3/14	4.6 (0.3–10.8)	improved, 11; worse, 3

* FU = follow-up.
† Extrapolated from Weinzierl et al., 2004, and includes prior series of Spetzger et al., 1995.
‡ Extrapolated from Amin-Hanjani et al., 1998, and includes prior series of Ogilvy et al., 1992.
§ Includes prior series of Deutsch et al., 2000.

ally found to be intrinsic intraoperatively. Weinzierl et al.[50] found that T1-weighted imaging correctly demonstrated 6 of 7 lesions as deep, while T2-weighted imaging correctly showed only 3 of 7 lesions as deep. These findings, likely due to a blooming artifact from the ferromagnetic properties of iron, serve as valuable cautionary observations.

The general approach to these lesions involves a laminectomy or hemilaminectomy over the appropriate spinal level(s). Nishikawa et al.[32] have also described the use of partial vertebrectomy in approaching ventral cervical lesions. Intraoperative somatosensory and motor evoked potential monitoring is used. Exophytic lesions or staining/bulging of the pial surface can dictate the sagittal plane of entry into the spinal cord. Intrinsic lesions can be approached through a midline myelotomy or through the dorsal root entry zone with intraoperative real-time image guidance (ultrasonography). Such adjuncts not only facilitate lesion localization but also can be used at the conclusion of the operation to confirm complete lesion resection.[29] Once the lesion is reached, the bipolar cautery and microscissors are used to disconnect potential arterial feeders and draining veins. A cleavage plane is defined and the lesion can be removed en bloc or piecemeal using bipolar cautery with a small cottonoid placed between the malformation and hemosiderin-stained parenchyma, leaving this ring of tissue intact. Up to 94% of intramedullary CMs (mean 34% in our review) may have an associated venous malformation that should be preserved.[48] Persistent bleeding that cannot be controlled with simple irrigation should prompt a search for residual cavernoma.[7] After lesion removal, the resection cavity

TABLE 5: Summary of results across surgical series of spinal intramedullary CMs

Characteristic	Percentage
total resection rate	91
transient morbidity	36
long-term outcome	
improved	61
unchanged	27
worse	12

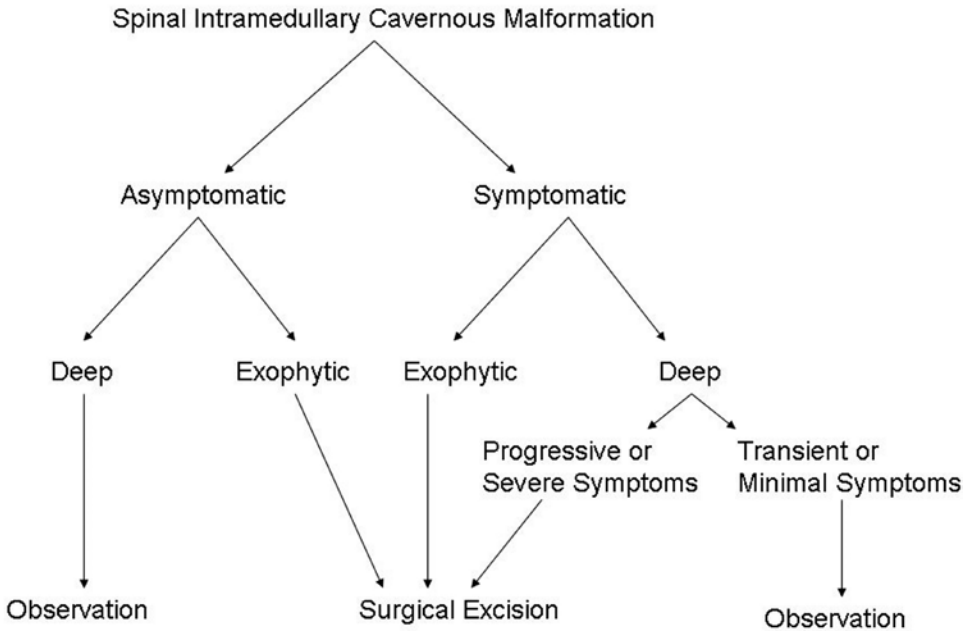

Fig. 3. Management algorithm for spinal intramedullary CMs.

should be inspected and ultrasonography used to investigate for residual matter. The dura is then closed in a watertight fashion. Postoperative MR imaging is performed 3–6 months after excision, because early postoperative blood products can obscure whether the lesion has been completely excised.

Surgical Results

In early reports of surgical management for intramedullary CMs, lesions were often sampled for biopsy or partially resected.[4,11,41,43] In an early review of 43 surgical case reports and small surgical series, Canavero et al.[6] reported a 74% rate of complete resection. This rate has improved to 91% in our study since the goal of surgery has become complete resection. All 3 patients with partially resected lesions in the series of Vishteh et al.[48] experienced rebleeding, underscoring the validity of this modern practice standard.

Transient worsening of sensorimotor symptoms is often seen and occurs in approximately one-third of patients. The large series of Jallo et al.,[23] Vishteh et al.,[48] and Matsuyama et al.[30] reported rates ranging from 24–50%. In particular, lesions approached via myelotomy through the dorsal root entry zone will often be associated with postoperative paresthesias and dysesthesias in the distribution of the nerve emerging from that entry zone. This was seen both in patients undergoing this approach in the series of Cristante and Hermann[12] and in 1 of 3 patients in the series of Park et al.[36]

We found that 61% of patients improved, 27% were unchanged, and 12% were worse at the long-term follow-up, as compared with their preoperative status. Several studies have demonstrated that a shorter duration of preoperative symptoms[7,23,52] and a less compromised preoperative status[1,6,12,37] are correlated with improved postoperative outcomes. Although they did not find a correlation between postoperative outcome and the timing of surgery or initial lesion grade, Labauge et al.[28] found that ventral location correlated with poorer outcomes. Patient age, sex, and lesion size have not correlated with postoperative outcome.[1,6,28,52] Patients with preoperative sensory disturbances had a tendency to improve more slowly and less frequently than those with motor deficits.[12] Park et al.[36] reported a 45% rate of complete resolution of motor deficits as opposed to a 7% rate of complete resolution of preoperative sensory deficits. All patients in the series of Furuya et al.[16] experienced improvement in motor function as opposed to only 50% who had improvement in sensory deficits. Kim et al.[26] specifically evaluated resolution of preoperative pain in 23 patients, noting improvement in 78% of patients immediately after surgery but in only 48% of patients at the long-term follow-up.

Conclusions

Intramedullary spinal cord CMs can clinically and radiographically masquerade as demyelinating or neoplastic processes. Our review has demonstrated that these malformations affect middle-aged men and women in an equal proportion with at least 27% of patients harboring additional cranial lesions. Approximately one-half of patients present with progressive deficits while others present acutely or with recurrent symptomatology. We recommend complete resection for exophytic lesions. Deep lesions that do not abut the pial surface should only be resected if the patient has progressive, recurrent, or significant initial symptoms. The majority of lesions can be completely resected with only 12% of patients suffering long-term morbidity.

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: all authors. Acquisition of data: Gross. Analysis and interpretation of data: all authors. Drafting the article: Gross. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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Manuscript submitted May 15, 2010.
Accepted June 21, 2010.
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Neurosurg Focus 29 (3):E15, 2010

Pain outcomes after surgery in patients with intramedullary spinal cord cavernous malformations

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Object. The objective of the study was to quantify the improvement in pain levels for patients who have undergone surgery for intramedullary spinal cord cavernous malformations (SCCMs).

Methods. The author reviewed medical records of patients who underwent surgery for an intramedullary SCCM between 2003 and 2010. Numerical pain scores (range 0–10) were recorded preoperatively and at follow-up. The follow-up period exceeded 1 year. Neurological status and subjective outcomes were assessed. Each patient underwent follow-up MR imaging.

Results. Five patients were identified with SCCMs who underwent surgery: 4 with thoracic and 1 with cervical lesions. Patients had been conservatively managed for an average of 5 years prior to surgery, and none had a history of acute hemorrhage or neurological deterioration during the observation period. The primary indication for surgery in each patient was pain, although 4 of 5 patients had some evidence of myelopathy on examination. Pain improved from a mean preoperative score of 8.6 to mean score of 2.0 ($p < 0.01$) at 1 month. Pain scores then increased to 3.7 ($p < 0.01$) at 1 year. All patients had some improvement in pain. No new motor weakness was noted, but all patients had increased symptoms of posterior-column dysfunction and numbness after surgery.

Conclusions. Spinal cord intramedullary cavernous malformations are increasingly being diagnosed early with patients presenting with mostly pain symptoms. Removal of the lesion is reliably associated with improvement in pain scores but often the pain improvement is transient. While long-term worsening of pain scores occurs, at 1-year follow-up, patients reported pain scores were improved over preoperative scores. In all patients some degree of postoperative posterior-column dysfunction was present. Some of the immediate pain relief may be due to analgesia related to the myelotomy of newly described posterior column pain pathways. In patients with severe pain, surgery to remove SCCMs reduced the overall pain level at 1 year. *(DOI: 10.3171/2010.6.FOCUS10108)*

Key Words • **intramedullary spinal cord cavernous malformation** • **cavernous malformation** • **pain**

Spinal cord cavernous malformations are increasingly detected with the widespread availability of MR imaging.[3] Initially, most cavernomas were detected in patients with significant neurological deficits. With even more widespread availability of MR imaging, SCCMs are more frequently detected in patients presenting with axial pain. Natural history studies have shown the rate of hemorrhage in SCCMs is low and progression of neurological deficit is slow.[5] Most SCCMs can be managed conservatively. Recent studies have cast doubt whether resection of an SCCM significantly affects overall pain in the long term.[6] While initial results in pain improvement are noted, puzzlingly, long-term pain often recurs. In patients with relatively intact neurological status but severe pain, the treatment decision is difficult. The morbidity related to surgical removal and postoperative posterior-column dysfunction must be weighed against the desired pain improvement.[2] The purpose of this study was to quantitatively evaluate the effectiveness of pain relief with surgery for SCCMs.

Abbreviations used in this paper: NPS = numerical pain scale; SCCM = spinal cord cavernous malformation.

Methods

The charts of 5 patients who had undergone resection of SCCMs were reviewed retrospectively. Patients underwent surgery at our institution between 2003 and 2009. All patients had pain as the primary complaint, although 4 had evidence of myelopathy on physical examination. The SSCMs were localized in the thoracic spine in 4 patients and in the cervical spine in 1 patient. All patients had a McCormick Scale grade of I or II on presentation. Extensive nonoperative pain management failed in all patients. Magnetic resonance imaging with and without contrast medium was performed in all patients (Fig. 1). Patients underwent a thoracic or cervical laminectomy and lesion resection via a midline posterior myelotomy. The operative microscope was used. Both somatosensory evoked potentials and motor evoked potentials were monitored. Gross-total resection was achieved

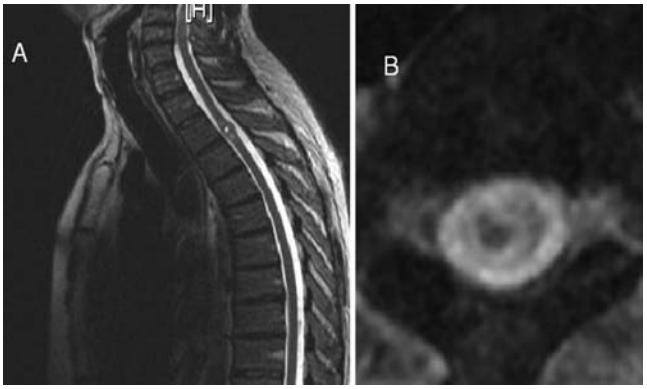

Fig. 1. Sagittal midline **(A)** and axial **(B)** T2-weighted MR images of a C7–T1 SCCM.

in each case. The diagnosis of an SCCM was confirmed on pathology reports. Postoperative MR images were obtained in all patients. Table 1 lists patient demographic data. Pain score data are listed in Table 2.

Numerical pain scale scores were collected preoperatively and following surgery at 2 weeks, 3 months, and 1 year. A paired t-test was used to assess the statistical significance of the numerical pain scores. We compared immediate postoperative and the baseline scores. Baseline and 1-year scores were also compared. The NPS scores are verbal patient-reported pain scores that range from 0 to 10. The 11-point NPS was used instead of a visual analog scale 100-mm scale. Studies have shown a high correlation between the 11-point NPS scale and the visual analog scale. Some questions exist whether patient cognitive issues and cognitive issues in the perioperative period affect visual analog scale precision.[9]

Results

Patient characteristics are listed in Table 1. Five patients were identified with intramedullary SCCMs who underwent surgery. Four patients had thoracic intramedullary lesions and 1 had a cervical lesion. Patients had received conservative treatment for an average of 5 years prior to surgery and no patients had a history of an acute hemorrhage or neurological deterioration during the observation period.

The primary indication for surgery in each patient was pain although 4 of 5 patients had some evidence of myelopathy on examination. Pain improved from a mean NPS score of 8.6 prior to surgery to 2.0 ($p < 0.01$) at 1 month. Pain scores then increased to 3.7 ($p < 0.01$) at 1-year follow-up. (Fig. 2) All patients had some quantitative improvement in pain scores. No new motor weakness was noted, but all patients had increased symptoms of posterior-column dysfunction and numbness after surgery. McCormick Scale scores at 1 year were all unchanged, but 4 of 5 patients worsened immediately after surgery by 1 grade due to posterior-column deficits.

TABLE 1: Patient characteristics

Characteristic	Value
mean age (yrs)	56
male/female ratio	3:2
mean symptom duration (mos)	62
mean NPS score	
preop	8.6
1 yr postop	3.7

TABLE 2: Summary of results by case

Case No.	Age (yrs)	NPS Score			
		Baseline	1 Mo	3 Mos	1 Yr
1	37	8	3	5	5
2	75	7	2	3	4
3	58	9	0	1	2
4	65	10	5	3	4
5	45	9	0	3	3.5

Discussion

Spinal cord cavernous malformations are increasingly diagnosed in patients presenting with primarily pain symptoms because of increased MR imaging usage.[3] Natural history studies of SCCM suggest a low risk of neurological symptom progression.[11] Kharkar et al.[5] reported on the conservative management of intramedullary cavernomas in 10 patients over an average on 42 months. While 50% of patients presented with motor weakness and 30% exhibited myelopathy, there was no significant progression of neurological deficit in the patients followed.

In patients with neurological deficits, improvement is often noted in less than 50% of patients. Deutsch et al.[3] noted modest neurological improvement in 57% of patients in a literature meta-analysis. Park et al.[12] noted no improvement in sensory symptoms after surgery for SCCMs. In this series, while patients did not have a new motor deficit, significant posterior-column deficits after surgery resulted in a transient increase in the McCormick Scale score after surgery in 4 of 5 patients. Considering the morbidity associated with surgery for a SCCM, nonoperative treatment is preferable in most cases of axial pain.[1,2]

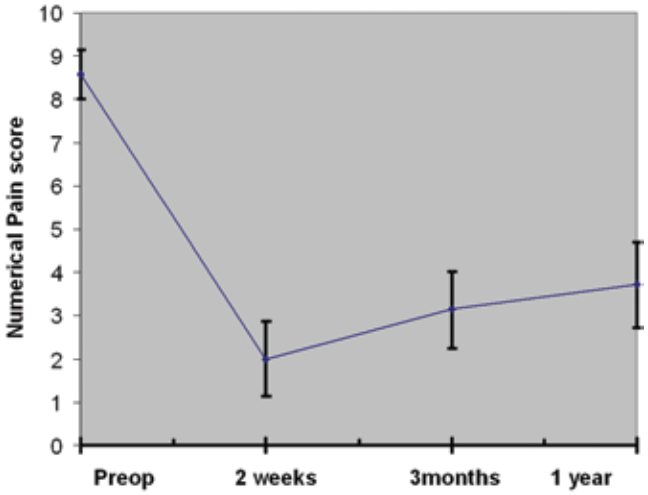

Fig. 2. Graph showing the NPS scores (range 0–10) versus time.

In patients with severe axial pain, the question arises whether SCCM excision will relieve pain-related symptoms. Literature regarding SCCMs is limited to case reports and small case series because SCCMs are relatively rare.[4,8] In the series reported by Kharkar et al.,[5] 40% of patients presented with significant pain. Of the 4 patients who underwent surgery, all had pain as a significant finding. After surgery, 1 of 4 patients had complete pain relief and the other 3 had some degree of residual pain.

Kim et al.[6] reported on 23 patients with spinal cord cavernoma who had pain as part of their presentation. Only 6 patients had pain as a primary complaint. Twelve patients had axial pain while the rest had some form of radicular pain. Pain improvement was noted in 78% of patients acutely, but only 52% of patients had sustained improvement after 1 year. Transient motor weakness was noted in 35% of patients. Neurological improvement after surgery was rare (20%). Visteh and colleagues[13] initially reported good outcome with regard to pain resolution in several patients, but Kim et al.[6] presented longer-term outcome for the same patients. Long-term pain improvement was not sustained in 2 patients. The reason pain returned several months after surgery was unclear.

While transient results for pain relief are good, long-term pain recurrence has been noted in the literature. The small series presented here supports the transient pain improvement described by Kim et al.[6] Patients often presented at later follow-up with increased pain compared with immediately after surgery. A proposed explanation for the transient pain relief may be that the midline myelotomy and dissection around the SCCM yields disruption of a newly reported dorsal midline pain pathway. Dorsal midline visceral pain pathways were recently described in rat anatomical studies.[7] Nauta et al.[10] recently described the use of a midline dorsal-column myelotomy to effectively treat oncological visceral pain. The transient improvement and timeframe noted is consistent with pain improvement results obtained in the past for percutaneous cordotomy procedures.

Previous SCCM series reported in the literature have been mainly focused on neurological outcome. Pain outcomes were reported in a categorical fashion. Patients either have pain or they do not have pain. In this series numerical pain scores were used to evaluate patient-expressed pain. The results indicate that while 4 of 5 patients had persistent long-term axial pain, patients felt pain was improved at 1 year. Pain improved from NPS score of 8.6 to 3.7 at 1-year follow-up. Some of the long-term pain complaints are related to dysesthetic pain mediated by permanent posterior-column loss of function. Understanding the postoperative morbidity and likely outcome with regard to pain improvement will better allow surgeons and patients to make choices regarding surgery for SCCMs.

Conclusions

Patients with SCCMs frequently present with axial pain as a significant complaint. The natural history of SCCMs indicates a low risk for further neurological deterioration. Resection of an SCCM can carry significant morbidity. Therefore, most SCCMs are best managed nonoperatively. Previous studies have shown that improvement in pain with SCCM surgery may be transient. This study demonstrates while pain worsens with long-term follow-up, patients report improvement in overall pain levels with surgery. The transient improvement in pain perception after surgery may be related to disruption of newly described posterior-column pain pathways.

Disclosure

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

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Manuscript submitted April 15, 2010.
Accepted June 10, 2010.

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Patient-assessed satisfaction and outcome after microsurgical resection of cavernomas causing epilepsy

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Object. Microsurgical resection of supratentorial cavernomas associated with intractable epilepsy is performed frequently. Despite its common occurrence, little is known about patient perceptions of microsurgical resection for cavernomas. This survey study was performed to investigate patient perceived outcome after surgery for cavernomas associated with intractable epilepsy.

Methods. The authors' surgical database was searched for cavernoma resection performed between 1971 and July of 2006. Of the initial 173 patients identified, 102 met criteria for medically intractable seizures. These 102 patients were then mailed a survey to determine follow-up and patient satisfaction. Thirty-nine surveys were returned as undeliverable, and 30 (48%) of the remaining 63 patients responded.

Results. The average age at surgery for patients responding to this survey was 40 ± 16 years compared with 35 ± 15 years for all 102 patients. At prolonged follow-up, 87% of patients reported being seizure-free. Of those with seizures, 2 (7%) reported being nearly seizure-free (rare disabling seizures), 2 (7%) believed they had a worthwhile improvement in seizure frequency, and no patient (0%) in this series believed they did not have a worthwhile improvement in seizure frequency. Ninety percent of responders stated they definitely, and 10% probably, would have surgery again. No patient responded that they probably or definitely would not have epilepsy surgery. Mean clinical follow-up was 36 ± 8 months and survey follow-up was 97 ± 13 months for these 30 patients. Use of the mail-in survey increased follow-up length 2.7 times longer compared with clinical follow-up.

Conclusions. It is clear from this select group of survey responders that patients undergoing surgery for cavernomas associated with medically intractable epilepsy are happy they underwent surgery (100%) and had excellent surgical outcomes (87% seizure-free) at prolonged follow-up of 97 ± 13 months. These survey results support that microsurgical resection for cavernomas is highly effective and significantly improves these patients' quality of life.
(DOI: 10.3171/2010.6.FOCUS10127)

Key Words • cavernoma • epilepsy • survey • patient outcome • postal questionnaire

Cavernomas (cavernous hemangiomas) present in a relatively diverse fashion in the CNS. Infratentorial lesions typically present with stepwise deterioration in neurological function as the result of hemorrhage. Supratentorial lesions may present incidentally with hemorrhage, or most typically, with seizures (40%–70%).[1,12] Previously, we have reported outcomes of supratentorial cavernomas in patients presenting with intractable seizures.[20] These outcomes, as in all studies to date, are based on clinician assessment of the patient's last clinic presentation.[1,2,5–9,12,13,15,19,20,22]

As government interests and insurance control become slowly integrated into health care in the US and globally, it is clear that patient-centered comparative effectiveness research outcomes will be used to guide payment decisions.[10] Comparative effectiveness research or patient-assessed satisfaction/outcome is a relatively soft concept (subjectively evaluated) and infrequently reported in relation to neurosurgical procedures. There is no current literature regarding microsurgical resection of cavernous hemangiomas and patient-assessed satisfaction. Therefore, this study was undertaken to detail patient-assessed outcomes and satisfaction in microsurgical resection of cavernomas associated with epilepsy.

Abbreviation used in this paper: HRQOL = health-related quality of life.

Methods

Inclusion Criteria

This study was approved by the Mayo Clinic Institutional Review Board. The Mayo Clinic surgical databases contained records on 173 patients who underwent

cavernoma resection between 1971 and July of 2006. All records were screened for neuropathological confirmation of cavernous hemangioma and then determined to meet criteria for medically intractable seizures (failure to control seizures while receiving 2 antiepileptic medications at therapeutic dosing). Of the initial 173 patients, 102 met criteria for medically intractable seizures. These 102 patients were then mailed a survey to determine follow-up and patient satisfaction; 39 were returned as undeliverable. Thirty patients responded, giving a response rate of 48% (30 of 63 possible).

Demographic Evaluation

Patient sex, age at operation, lobular lesion location, and size were abstracted from the clinical charts.

Survey Design

A 2-page survey (Fig. 1) designed to assess seizure type (based on semiology), outcome from epilepsy surgery (based on Engel classification and International League Against Epilepsy outcome scale score), and patient perceived satisfaction was used.[21] The survey was designed with the goal of creating a useful tool for outcome follow-up that would not represent a significant burden for patients to respond. The 2-page survey was sent by US mail to all patients.

Analysis of Follow-Up

Follow-up was determined by date of initial surgery to date of clinic follow-up or survey follow-up postal marking. Follow-up calculations were based on a 360-day year and a 30-day month. Furthermore, Engel seizure outcome classifications were based on last clinic visit with a neurologist subspecializing in epilepsy. Our Engel classification of these patients has been previously described.[20]

Results

Patient Demographics

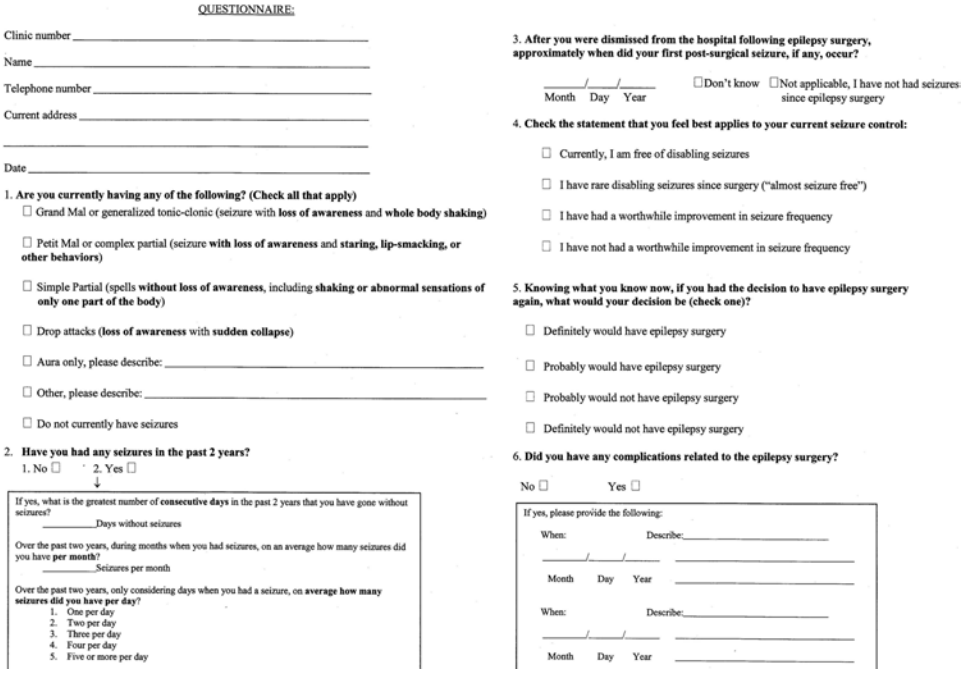
The average age of the patients responding to this survey (survey group) was 40 ± 16 years old compared with 35 ± 15 years old in all 102 patients asked to participate (total patient pool). In the survey group, 14 (47%) of 30 were women compared with 57 (56%) of 102 in the total patient pool. Average lesion sizes were 1.9 ± 1 cm in the survey group compared with 1.8 ± 1 cm in the total patient pool. In the survey group there were 13 left-sided lesions (43%) versus 51 (50%) in the total patient pool. Table 1 lists the locations of resected cavernomas in the survey and total patient pool groups.

Surgical Procedure

All patients undergoing resection outside the temporal lobe underwent lesionectomy alone. Two patients are currently not seizure free. One patient harbored a frontal lesion bordering motor cortex, and he has experienced an improvement in seizure status and further resection would result in weakness. The second patient has a parietal lesion residing in sensory cortex abutting motor cortex, and further surgery would result in a worsening of present deficits; these patients have elected to continue medical therapy. Eight patients underwent resection of mesial temporal lobe cavernomas. Of these 8 patients, 6 underwent anterior temporal lobectomy with amygdalohippocampectomy, and 2 underwent lesionectomy alone. Nine patients harbored neocortical temporal cavernomas. Seven of these 9 patients underwent lesionectomy alone, and 2 did not have prolonged seizure-free status and required repeat surgery (detailed below).

Repeat Surgery

Two patients in this series received repeat operations



QUESTIONNAIRE:

Clinic number _____

Name _____

Telephone number _____

Current address _____

_____

Date _____

1. **Are you currently having any of the following? (Check all that apply)**
- ☐ Grand Mal or generalized tonic-clonic (seizure with **loss of awareness** and **whole body shaking**)
- ☐ Petit Mal or complex partial (seizure **with loss of awareness** and **staring, lip-smacking, or other behaviors**)
- ☐ Simple Partial (spells **without loss of awareness**, including **shaking or abnormal sensations of only one part of the body**)
- ☐ Drop attacks (**loss of awareness** with **sudden collapse**)
- ☐ Aura only, please describe: _____
- ☐ Other, please describe: _____
- ☐ Do not currently have seizures

2. **Have you had any seizures in the past 2 years?**
1. No ☐ 2. Yes ☐

If yes, what is the greatest number of **consecutive days** in the past 2 years that you have gone without seizures?
_____Days without seizures

Over the past two years, during months when you had seizures, on an average how many seizures did you have **per month**?
_____Seizures per month

Over the past two years, only considering days when you had a seizure, on **average how many seizures did you have per day**?
1. One per day
2. Two per day
3. Three per day
4. Four per day
5. Five or more per day

3. **After you were dismissed from the hospital following epilepsy surgery, approximately when did your first post-surgical seizure, if any, occur?**

_____/_____/_____ ☐Don't know ☐Not applicable, I have not had seizures since epilepsy surgery
Month Day Year

4. **Check the statement that you feel best applies to your current seizure control:**
- ☐ Currently, I am free of disabling seizures
- ☐ I have rare disabling seizures since surgery ("almost seizure free")
- ☐ I have had a worthwhile improvement in seizure frequency
- ☐ I have not had a worthwhile improvement in seizure frequency

5. **Knowing what you know now, if you had the decision to have epilepsy surgery again, what would your decision be (check one)?**
- ☐ Definitely would have epilepsy surgery
- ☐ Probably would have epilepsy surgery
- ☐ Probably would not have epilepsy surgery
- ☐ Definitely would not have epilepsy surgery

6. **Did you have any complications related to the epilepsy surgery?**

No ☐ Yes ☐

If yes, please provide the following:

When: Describe:_____

_____/_____/_____ _____
Month Day Year _____

When: Describe:_____

_____/_____/_____ _____
Month Day Year _____

Fig. 1. Survey form used in the study.

TABLE 1: Location of cavernomas according to group

Lesion Location	No. in Each Group (%)	
	Survey	Total Patient Pool
temporal	17 (57)	61 (60)
mesial	8 (27)	35 (34)
neocortical	9 (30)	26 (25)
frontal	6 (20)	21 (20)
parietal	5 (17)	14 (14)
occipital	2 (7)	6 (6)
total	30	102

(1 man and 1 woman). The lesions were 1.2- and 5-cm cavernomas, respectively. The first patient was seizure-free for 4 years until recurrence, then after a medication trial underwent mesial structure resection. She is currently seizure free. The second patient experienced a partial reduction in seizures during the first year after surgery, but was considered Engel Class IV. After repeat surgery, he was seizure-free after surgery for 35 days and now continues to experiences seizures, but these have been simple partial seizures without generalization. Both patients' cavernomas were left neocortical temporal. Their repeat operation was a completion anterior temporal lobectomy with amygdalohippocampectomy. Neither patient underwent electrocorticography at the time of their initial surgery.

Survey Responses

In response to the first question on the survey ("Are you currently having any of the following"), 26 (87%) did not currently have seizures, 3 (10%) had complex partial seizures, and 1 (3%) had simple partial seizures (Table 2). In response to the second question ("Have you had any seizures in the past 2 years?"), 26 (87%) said no. Of the 4 (13%) that said yes, their greatest number of days without a seizure over the last 2 years was 120, 35, 50, and 21 days, respectively, and their average number of seizures per month was 3, 2, 2, and 8 seizures, respectively. In response to Question 4 ("Check the statement that you feel best applies to your current seizure control"), 26 (87%) were currently free of disabling seizures, 2 (7%) were almost seizure free (rare disabling seizures), 2 (7%) believed they experienced a worthwhile improvement in seizure frequency (Engel Class III), and no patient (0%) in this survey group believed they did not have a worthwhile improvement in seizure frequency. Regarding the fifth question ("Knowing what you know now, if you had the decision to have epilepsy surgery again, what would your decision be?"), 27 (90%) definitely would have surgery again, 3 (10%) probably would have surgery again, and no patient (0%) responded they probably or definitely would not have epilepsy surgery. Lastly, in response to the sixth question ("Did you have any complications related to the epilepsy surgery?"), 4 (13%) believed they suffered a complication related to epilepsy surgery. The write-in responses for what they considered complications were poor facial recall, incisional headache, mild unilateral weakness, and mild unilateral sensory loss (last 2 complications in the same patient).

Follow-Up

Mean clinical follow-up was 36 ± 8 months (range 0–164 months) for these 30 patients. Survey follow-up was 97 ± 13 months (range 9–317 months). Follow-up by mail-in survey increased follow-up duration 2.7 times longer. Of the 30 responders, 6 returned to their home institutions for follow-up and therefore had unknown outcome at our institution. Of 24 patients with known follow-up, 22 were seizure-free (92%) and 2 were not. Of the 6 patients without any known clinical follow-up, 1 reported seizures. Interestingly, 1 of the 24 patients followed clinically reported simple partial seizures. She had been followed clinically for more than 5 years and these "seizures" were determined to be amnestic spells with an unknown cause and negative electroencephalographic findings for epileptiform activity. Agreement was high ($\kappa = 0.78$) between reported seizure-free rates and the clinically determined rate.

Discussion

Microsurgical resection of cavernomas responsible for intractable epilepsy is evidently a heterogeneous procedure in the literature.[5,12,20,22] This is likely due to the ongoing debate as to the extent of tissue surrounding the cavernoma that needs to be removed to achieve the best outcome for the patient.[2,5,12,19,20,22] Ultimately, approximately 90% of patients realize a decrease in seizure frequency and 60% to 90% achieve seizure freedom depending on the surgical approach used.[2,5,7,12,13,15,19,20] Interestingly, 87% of our survey responders were seizure free, which is imperative when one considers the average follow-up interval of more than 8 years. This data suggests that not only is microsurgical resection of cavernomas successful in the long-term, it likely has a significant impact on the HRQOL. The evaluation of HRQOL is increasingly being accepted as a vital component of clinical care and outcome appraisal. Given that these patients are typically 20 to 40 years of age, the HRQOL impact for society appears to be very significant.

Health-related quality of life has been evaluated in neurosurgery, with the most information available in surgical epilepsy. Stavem et al.[18] compared medically and surgically treated patients with focal epilepsy in an age- and sex-matched retrospective cohort, noting seizure-free outcomes and results on the Quality of Life in Epilepsy Inventory 89 questionnaire. In this study, postsurgical patients were seizure-free in 48% of cases (and used less medications) compared with 19% of controls.[18] Health-related quality of life was higher in 5 of 17 dimensions and worse in none compared with controls with an average of more than 15 years of follow-up.[18] In a long-term outcome study with similar patients, Spencer et al.[17] demonstrated HRQOL improved after resection regardless of outcome. These studies support that surgical treatment for focal epilepsy improves HRQOL, as this report implies.

There are currently no data pertaining to the patient's perception on outcome and satisfaction in relation to CNS cavernomas.[1] Furthermore, an extensive literature search reveals no published information on comparative effectiveness research in neurosurgery for any procedure. Per-

TABLE 2: Responses to survey questions

Survey Question	Percentage
are you currently having any of the following:	
grand mal or generalized tonic-clonic seizure	0
petit mal or complex partial seizure	10
simple partial seizure	3
drop attacks	0
aura only	0
other	0
do not currently have seizures	87
have you had any seizures in the past 2 years:	
yes	13
no	87
check the statement that you feel best applies to your current seizure control:	
currently, I am free of disabling seizures	87
I have rare disabling seizures since surgery	7
I have had a worthwhile improvement in seizure frequency	7
I have not had a worthwhile improvement in seizures	0
would you have epilepsy surgery again:	
definitely would	90
probably would	10
probably would not	0
definitely would not	0

haps this is due to the subjective nature of the data, but it is becoming more and more important that we begin to consider patients' feelings regarding their operations postoperatively as this may guide reimbursements in the future. Furthermore, implications beyond seizure freedom such as depression, return to work, and driver's licensure will need to be documented to justify these procedures.

Patient satisfaction with the procedure performed is also infrequently reported in the literature, but it is present in surgical epilepsy series.[3] In a series of 42 children undergoing temporal lobe resection for various pathologies, including 3 cavernomas, evaluation of satisfaction found that most families were very satisfied. Furthermore, of those who were seizure free, all were satisfied with the procedure, and of those with poor Engel classes (III or IV, minimal improvement in seizure control), most were neutral regarding surgery.[3] It should be noted that half of these patients underwent tumor resections and therefore it may be difficult to generalize this study to our current study.[3] Postsurgically, 82% of these patients were not taking anticonvulsants.[3] Other studies have validated that HRQOL in epilepsy patients who underwent surgery is related to seizure-free outcome, medications, and driver status postsurgically.[4,11]

It is difficult to assess why mailed-in response rates are so low in this study (48%). We were unable to reliably detect whether there was a change in address or if mail was not returned for another reason. Likely due to the prolonged time period of the study, as well as the referral pattern of our hospital, many of our patients were not able to be tracked. Other postal survey outcome studies have experienced similar reported response rates (between 30% and 50%).[11,14,16] The relatively low response rate may introduce a reporting bias in which dissatisfied patients did not respond.

Conclusions

It is clear from this select group of survey responders that patients undergoing surgery for cavernomas associated with medically intractable epilepsy are happy they underwent surgery (100%) and had excellent surgical outcomes (87% seizure free) at prolonged follow-up of 97 ± 13 months. These data indicate that microsurgical resection for cavernomas is likely highly effective and supports that the procedure significantly improves the patients' quality of life.

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: all authors. Acquisition of data: Worrell, Van Gompel. Analysis and interpretation of data: Worrell, Van Gompel. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Van Gompel. Study supervision: Worrell, Marsh, Meyer.

Acknowledgments

The authors would like to thank Karla Crockett for her administrative support of our epilepsy surgery database and tireless patient care, as well as Dr. Aaron Cohen-Gadol for his development of the epilepsy surgery database.

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Manuscript submitted May 13, 2010.
Accepted June 3, 2010.

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Neurosurg Focus 29 (3):E17, 2010

Cavernous malformations of the optic pathway and hypothalamus: analysis of 65 cases in the literature

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Object. Cavernous malformations (CMs) of the optic pathway and hypothalamus (OPH) are extremely rare. Patients with these lesions typically present with chiasmal apoplexy, characterized by sudden visual loss, acute headaches, retroorbital pain, and nausea. Surgical removal is the recommended treatment to restore or preserve vision and to eliminate the risk of future hemorrhage. However, the anatomical location and eloquence of nearby neural structures can make these lesions difficult to access and remove. In this study, the authors review the literature for reported cases of OPH CMs to analyze clinical and radiographic presentations as well as surgical approaches and neurological outcomes.

Methods. A MEDLINE/PubMed search was performed, revealing 64 cases of OPH CMs. The authors report an additional case in the study, making a total of 65 cases. Each case was analyzed for clinical presentation, lesion location, radiographic features, treatment method, and visual outcome.

Results. In 65 patients with OPH CMs, the optic chiasm was affected in 54 cases, the optic nerve(s) in 35, the optic tract in 13, and the hypothalamus in 5. Loss of visual field and acuity was the most common presenting symptom (98%), followed by headache (60%). The onset of symptoms was acute in 58% of patients, subacute in 15%, and chronic progressive in 26%. Computed tomography scans revealed hyperdense suprasellar lesions, with calcification visible in 56% of cases. Magnetic resonance imaging typically demonstrated a heterogeneous lesion with mixed signal intensities suggestive of blood of different ages. The lesion was often surrounded by a peripheral rim of hypointensity on T2-weighted images in 60% of cases. Minimal or no enhancement occurred after the administration of gadolinium. Hemorrhage was reported in 82% of cases. Most patients were surgically treated (97%) using gross-total resection (60%), subtotal resection (6%), biopsy procedure alone (6%), biopsy procedure with decompression (23%), and biopsy procedure followed by radiation (2%). Those patients who underwent gross-total resection had the highest rate of visual improvement (85%). Two patients were treated conservatively, resulting in complete blindness in 1 patient and spontaneous recovery of vision in the other patient.

Conclusions. Cavernous malformations of the OPH are rare and challenging lesions. Gross-total resection of these lesions is associated with favorable visual outcomes. Emergent surgery is warranted in patients presenting with chiasmal apoplexy to prevent permanent damage to the visual pathway. *(DOI: 10.3171/2010.5.FOCUS10129)*

Key Words • **cavernous malformation** • **optic pathway** • **hypothalamus** • **suprasellar lesion**

Cavernous malformations are low-flow vascular lesions, which are typically angiographically occult. On histological examination, the wall of the vascular channels consists of a single layer of endothelial cells that lacks any muscle cells. These lesions are well circumscribed with no intervening brain parenchyma,[33,53] having an incidence of 0.3 to 0.7% in the general population and representing 10–20% of all vascular malformations.[43,50] The distribution of CMs within the CNS is proportional to the volume of the various compartments. Most occur in the supratentorial compartment (80%), followed by the infratentorial compartment (15%); the remaining 5% occur in the spinal cord. Cavernous malformations of the OPH are extremely rare, representing 1% or less of all CMs.[21] The earliest reported lesion was described in 1979 by Klein et al.[29]

Patients with CMs of the OPH typically present with chiasmal apoplexy, characterized by sudden visual disturbance, headache, retroorbital pain, and nausea.[36] Apoplectic symptoms are frequently preceded by transient

Abbreviations used in this paper: CM = cavernous malformation; GTR = gross-total resection; OPH = optic pathway and hypothalamus; STR = subtotal resection.

blurred vision and headache weeks or months beforehand. Although some episodes are self-limiting, permanent damage can occur from neural compression of the optic nerve, chiasm, or tract. Surgical removal is the recommended treatment to restore or preserve vision, to decompress the visual apparatus, and to eliminate the risk of future hemorrhages. However, the anatomical location and eloquence of intrinsic neural structures can make these formidable lesions difficult to surgically access and remove. In this study, we evaluated 65 cases of OPH CMs in the literature, including a newly reported case from our institution. We also analyzed the clinical and radiographic characteristics and reviewed the surgical approaches and neurological and visual outcomes of OPH CMs.

Methods

A biomedical literature search for OPH CMs confined to the English language was performed using the MEDLINE/PubMed search engine. The search included the following key words: "cavernous malformation," "cavernoma," "cavernous hemangioma," "cavernous angioma," combined with "optic nerve," "optic chiasm," "optic tract," and "hypothalamus," for all possible combinations. All relevant articles pertaining to CMs of the OPH were reviewed. Additional cases were identified in the references of these articles, that is, references to articles that did not show up on the initial PubMed search. A total of 64 OPH CM cases were identified.[2,8–10,12–15,18,19,21,22,25–27,29–31,36–42,46–48,51,52,57–64,67,68] We also report an additional case in this paper, making a total of 65 cases that were reviewed. Each case was analyzed for clinical presentation, lesion location, radiographic features, surgical treatment, and neurological and visual outcome (Table 1).

Results

Among the 65 cases of OPH CMs, 60 lesions arose from the optic pathway and 5 from the hypothalamus. The optic chiasm was affected in 54 cases, the optic nerve(s) in 35, the optic tract in 13, and the hypothalamus in 5. Three cases occurred as a third ventricular mass. One case of a hypothalamic CM extended into the thalamus, and another extended into the basal ganglia. Among the 65 cases were 36 females and 29 males. The average age was 34 years (range 4–63 years). The majority of cases (73%) occurred in patients in their 2nd to 4th decade of life.

Clinical Characteristics

The most common presenting symptom was visual deficit (98%), including visual acuity loss, visual field deficit, or both. Bitemporal hemianopia was the most prevalent pattern of visual field loss from chiasmal involvement (16 cases [25%]), followed by homonymous hemianopia from optic tract involvement (12 cases [18%]). An afferent pupillary defect was present in 17 cases (26%). Sixteen patients (25%) experienced prior episodes of visual disturbance, and 7 (11%) of these had long-term fluctuation of their visual symptoms. Thirty-nine patients (60%) presented with a headache or retroorbital pain, and 15 of them (38%) had a history of headaches. Five patients presented with confusion, 4 with nausea, 2 with lethargy, 2 with gait disturbance, and 1 with endocrine disturbance. The onset of symptoms was acute (chiasmal apoplexy) in 38 patients (58%), subacute in 10 (15%), and progressive in 17 (26%). Nineteen of the 38 patients (50%) presenting with chiasmal apoplexy had prior episodes of acute headache and visual loss.

Radiographic Characteristics

In 39 patients with preoperative CT scans, the OPH CMs appeared as suprasellar hyperdense masses. Fifty-six percent of these lesions had calcification. Cerebral angiography studies for 33 patients did not reveal any arterial feeding vessels or early draining veins suggestive of arteriovenous malformations. Magnetic resonance imaging data were available for 52 patients, including T2 gradient echo scans in 32 instances. In 46 cases (88%), the lesion was described as heterogeneous with mixed signal intensities suggestive of different ages of blood. This appearance was often described as a "popcorn-like" lesion. A peripheral rim of hypointensity (hemosiderin ring) on T2-weighted images was reported in 31 cases (60%). Minimal or no enhancement occurred after the intravenous administration of Gd. Lesions of the optic nerve or tract tended to appear as a thickened nerve with an increase in diameter that was best seen on coronal images. Lesions of the chiasm or hypothalamus were characterized as focal and round suprasellar masses. Acute hemorrhage was reported in 35 patients (54%). Evidence of old or chronic bleeding, often discovered intraoperatively, was found in 18 patients (28%). Additional cerebral CMs were found in 10 patients (15%), including the patient newly described in this study. In this new case, there were multiple CMs within the OPH region: 1 from the optic chiasm and 1 from the left optic tract. Two patients presented with a subarachnoid hemorrhage, and 2 with intraventricular hemorrhage. Lesion sizes ranged from 0.5 to 4.0 cm.

In 22 (34%) of 65 patients, the initial preoperative radiographic diagnosis was difficult to make, and a CM was not suspected as the initial diagnosis. The differential diagnosis most commonly included craniopharyngioma, optic neuritis, or optic glioma.

Surgical Treatment and Outcomes

Most patients (97%) were treated surgically. Gross-total resection was performed in 39 cases (60%), STR in 4 (6%), biopsy procedure alone in 4 (6%), biopsy procedure with decompression of the hemorrhage in 15 (23%), and biopsy procedure followed by radiation in 1 case. Forty-three (75.4%) of 57 patients with outcome data experienced improvement in vision, 11 had stable vision (19.3%), and 3 had worsening vision (5.3%). For those who underwent GTR, 85% had visual improvement, 12% had no change, and 3% had worsened vision (Table 2). Of the 4 patients who underwent STR, 2 had visual improvement and 2 had no change. Biopsy procedure alone resulted in stable vision in 2 patients; there was no visual outcome data in the other 2 patients.[61] Biopsy procedure with decompression resulted in a 77% rate of visual improvement, 15% visual

TABLE 1: Literature review of 65 patients with OPH CMs*

Authors & Year	Age (yrs), Sex	Clinical Presentation	Lesion Location	Treatment	Outcome
Arrué et al., 1999	36, M	acute visual loss, headache	OC	observation	improved
	36, M	progressive visual loss, headache	OC, LOT	STR	improved
	55, F	acute visual loss, headache	OC, LON	GTR	improved
Castel et al., 1989	23, F	acute visual loss, headache	OC	GTR	improved
Cerase et al., 2010	30, F	fluctuating visual loss	LON	steroids	worsened
Christoforidis et al., 2000	38, M	subacute visual disturbance, headache	OC	GTR	NA
Corboy & Galetta, 1989	44, F	acute visual loss, headache	OC, LON, LOT	Bx	stable
Deshmukh et al., 2003	34, M	subacute visual loss	OC, LON	GTR	improved
	29, F	acute visual loss	OC, LON	GTR	improved
	28, F	progressive visual loss, headache	OC	GTR	improved
	29, F	acute visual loss	OC	GTR	improved
Escott et al., 2001	40, F	cardiac arrest	OC	NA	NA
Ferreira & Ferreira, 1992	8, M	acute visual loss, headache	OC, LON	GTR	stable
Glastonbury et al., 2003	25, F	acute visual loss, headache	OC, RON	GTR	NA
Hankey & Khangure, 1987	36, F	subacute visual loss	OC, LON	GTR	improved
	26, M	subacute visual loss, headache	OC	GTR	improved
Hasegawa et al., 1995	54, F	acute visual loss, headache, unsteady gait, convulsion	hypothalamus	STR	stable
Hassler et al., 1989[21]	24, F	progressive visual loss, headache	RON	GTR	improved
	16, M	subacute visual loss	OC, RON	GTR	improved
	35, M	acute visual loss, headache	ROT	GTR	improved
Hassler et al., 1989[20]	24, F	fluctuating visual loss, headache	RON	GTR	improved
Hempelmann et al., 2007	38, M	progressive visual loss, confusion, lethargy	OC	GTR	improved
Hufnagel & Cobbs, 1988	30, F	acute visual loss, headache	OC	GTR	improved
Hwang et al., 1993	42, M	acute visual loss, headache	OC, LON, LOT	BxD	improved
Iwai et al., 1999	31, F	acute visual loss, headache	OC, RON	GTR	improved
Kehagias, 2003	27, M	fluctuating visual loss	OC, RON	GTR	NA
Klein et al., 1979	30, M	subacute visual loss, headache	OC, LON, RON, ROT	BxD	improved
Kurokawa et al., 2001	27, F	progressive visual loss, headache	hypothalamus	GTR	stable
Lehner et al., 2006	39, F	acute visual loss, headache	OC, LOT	GTR	improved
Lejeune et al., 1990	26, F	acute visual loss, headache	OC	BxD	improved
Maitland et al., 1982	26, M	acute visual loss, headache, nausea, vomiting	OC	BxD	improved
	23, F	acute visual loss, headache	OC, LON, RON	BxD	improved
	63, F	subacute visual loss, headache	OC	BxD	NA
	15, F	progressive visual loss, headache	OC, LON	BxD	worsened
Malik et al., 1992	4, F	acute visual loss	OC, LON	STR	stable
Manz et al., 1979	30, M	acute visual loss, headache	OC, RON, ROT	BxD	improved
Maruoka et al., 1988	24, F	acute visual loss	OC, RON	GTR	improved
Mizoi et al., 1992	40, M	progressive visual loss	hypothalamus	GTR	improved
	60, M	dementia	hypothalamus	GTR	improved
Mizutani et al., 1981	36, F	acute visual loss, headache	OC, LON	BxD	improved
	26, M	acute visual loss	OC, LON, LOT	BxD	NA
Mohr et al., 1985	30, M	acute visual loss, confusion, lethargy	OC, LON, LOT	BxD	stable
Muta et al., 2006	14, M	progressive visual loss	LON, RON	Bx	stable
Newman et al., 2008	16, M	acute visual loss, headache	OC, LON	GTR	improved
Ozer et al., 2007	15, M	acute visual loss	OC, LON	GTR	improved
Paladino et al., 2001	58, F	progressive visual loss, headache	OC, RON	STR	improved
Regli et al., 1989	28, F	acute visual loss, headache	OC	GTR	improved

(continued)

TABLE 1: Literature review of 65 patients with OPH CMs* *(continued)*

Authors & Year	Age (yrs), Sex	Clinical Presentation	Lesion Location	Treatment	Outcome
Reilly & Oatey, 1986	31, F	acute visual loss, headache	OC, LON, LOT	BxD	improved
	36, F	acute visual loss, headache	OC, LON	BxD	improved
Shaikh et al., 2002	42, M	acute visual loss	OC, LON, RON	GTR	improved
Shibuya et al., 1995	18, F	subacute visual loss	OC	GTR	improved
	60, F	subacute visual loss, headache	OC, RON	GTR	improved
Son et al., 2008	39, F	acute visual loss, headache, nausea	OC	GTR	stable
Steinberg et al., 1990	58, M	acute visual loss, nausea	OC, ROT	BxD	stable
	33, F	acute visual loss, headache	OC, RON	GTR	improved
Suarez et al., 1994	41, M	progressive visual loss, headache	OC	Bx	NA
	52, M	progressive visual loss, headache	OC, RON	Bx	NA
Tien & Dillon, 1989	32, F	fluctuating visual loss	OC	Bx & rad	stable
Wang et al., 2003	62, F	progressive unsteady gait, LE weakness	hypothalamus	GTR	stable
Warner et al., 1996	32, F	acute visual loss, headache	OC	GTR	improved
Yoshimoto & Suzuki, 1986	37, M	acute visual loss	OC	BxD	improved
	43, M	subacute visual loss	OC, RON, ROT	GTR	worsened
	27, F	acute visual loss, headache	OC, RON	GTR	improved
Zentner et al., 1989	35, M	acute visual loss, headache	ROT	GTR	improved
present case	50, F	progressive visual loss	OC	GTR	improved

* Bx = biopsy; BxD = biopsy with decompression; LE = lower extremity; LON = left optic nerve; LOT = left optic tract; NA = not applicable; OC = optic chiasm; rad = radiation; RON = right optic nerve; ROT = right optic tract.

stabilization, and 8% visual worsening. Biopsy procedure followed by radiation therapy resulted in visual stabilization in 1 patient.

A variety of operative approaches were used for the surgical removal of OPH CMs. An anterolateral approach (pterional, orbitozygomatic, or frontotemporal) was used in 76% of patients, and a midline transcranial approach (transbasal subfrontal or transbasal interhemispheric) in 17%. One patient underwent a frontoparietal approach, 1 a transcortical transventricular approach, and 1 an eyebrow keyhole craniotomy approach. There were 9 reports of opening the lamina terminalis (including our new case) to access the CM within the third ventricle.

Two patients were not treated surgically.[2,8] One was treated with prednisone and acetazolamide for presumed optic neuritis with a fluctuating clinical course that ended in total blindness in 1 eye. The other patient was treated conservatively with observation for an unresectable lesion and experienced spontaneous total recovery of vision without surgical intervention. The duration of follow-up was available for just 26 cases described in the literature, with an average of 8 months (range 1 month–4 years).

Illustrative Case

History and Examination. This 50-year-old woman presented with progressive visual loss in both eyes (worse on the right) with a left temporal visual field deficit. Magnetic resonance imaging revealed a heterogeneously enhancing suprasellar mass involving the optic chiasm (Fig. 1). Gradient-echo sequences demonstrated blooming consistent with old hemorrhage. The radiographic diagnosis was consistent with a suprasellar CM of the optic chiasm

TABLE 2: Visual outcomes in patients with OPH CMs*

Treatment (no. of cases)	% w/ Visual Improvement (no.)	% w/ Visual Stabilization (no.)	% w/ Visual Worsening (no.)	No. w/ No Outcome Data
GTR (39)	85 (30)	12 (4)	3 (1)	4
STR (4)	50 (2)	50 (2)	—	—
Bx alone (4)	—	100 (2)	—	2
BxD (15)	77 (10)	15 (2)	8 (1)	2
Bx w/ rad (1)	—	100 (1)	—	—
nonsurgical treatment (2)	50 (1)	—	50 (1)	—
overall (65)	75.4 (43)	19.3 (11)	5.3 (3)	8

* Percentages are based on patients with outcome data. — = not applicable.

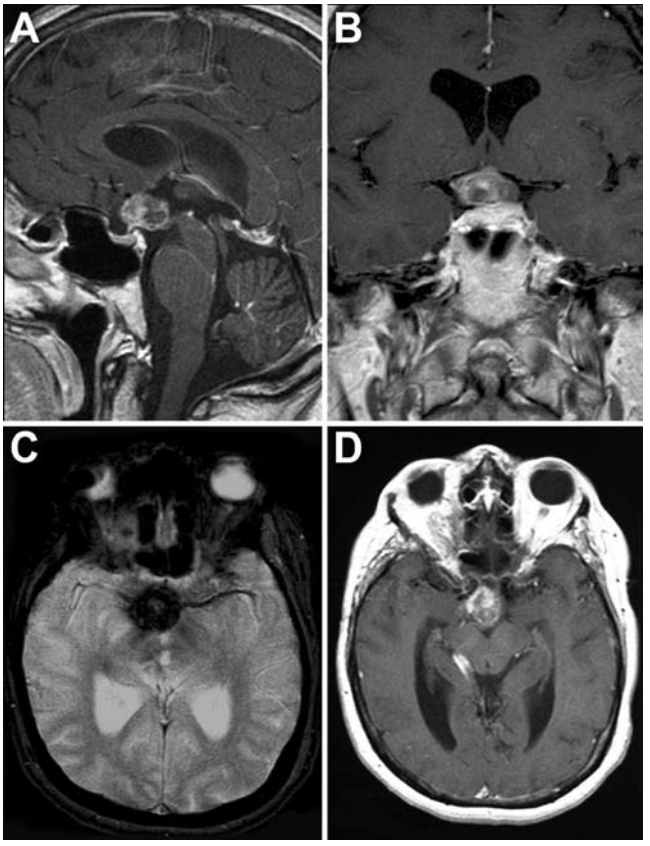

Fig. 1. Preoperative sagittal **(A)**, coronal **(B)**, and axial **(D)** post-Gd T1-weighted and axial gradient-echo **(C)** MR images demonstrating a heterogeneously enhancing suprasellar CM of the optic chiasm. Because the lesion was located within the third ventricle, a translamina terminalis approach was required to remove the lesion. Gradient-echo sequence **(C)** showing blooming consistent with hemosiderin deposition. There is an associated venous angioma located in the right posterolateral mesencephalon **(D)**.

located within the third ventricle. The patient also had an asymptomatic CM in the dorsal brainstem with an associated deep venous anomaly. Because the patient was losing vision in her right eye, resection was recommended.

Operation. A right pterional transsylvian approach was used to expose the optic chiasm, optic nerves, and suprasellar cistern. The chiasm appeared tinged with brown, consistent with old hemosiderin; however, no obvious CM was visible within the surgical exposure. The lamina terminalis was, therefore, opened to explore the third ventricle. Within the ventricle, an abnormal mulberry-like lesion consistent with a CM was noted. The lesion, which extended to the right optic chiasm, was totally resected via careful microdissection with preservation of the optic chiasm and optic nerves. Further exploration of the third ventricle revealed another separate CM arising from the left optic tract, which was surgically removed. Complete resection was achieved for both lesions.

Postoperative Course. Pathological examination confirmed that both lesions were CMs (Fig. 2). Each malformation was surrounded by reactive changes including inflammation, fibrosis, and hemosiderin. Immunohistochemical staining was positive for CD34, indicating the endothelial lining of the CM. Elastin stain was negative, indicating the absence of an arterial component and thereby ruling out an arteriovenous malformation.

Postoperatively, the patient's visual acuity improved to 20/20 in the left eye and 20/50 in the right eye. The left temporal field deficit remained stable. There were no neurological deficits. Follow-up MR imaging studies at 2 years demonstrated complete removal of the CMs without any evidence of recurrence (Fig. 3).

Discussion

Cavernous malformations have an incidence of 0.3–0.7% in the general population,[43,50] with < 1% of CMs appearing in the OPH region.[21] Most patients present with symptoms in their 2nd–4th decade of life.[54] There is generally no sex predilection, but hemorrhage reportedly occurs more frequently in females than in males (36 females:25 males[1]). Optic pathway and hypothalamic CMs are usually brought to clinical attention by visual deterioration. Chiasmal apoplexy is the most common clinical presentation, characterized by sudden visual disturbance, headache, retroorbital pain, and nausea. Apoplectic symptoms are often preceded by transient blurred vision and headaches that occur weeks or months beforehand. Symptoms can also occur in a chronic or progressive manner with intermittent episodes of headache and visual loss. Chiasmal apoplexy is nearly always associated with acute hemorrhage.[2] Transient or progressive symptoms are likely to result from recurrent episodes of hemorrhage and lesion growth;[8] however, the fluctuation of visual symptoms may not necessarily be associated with radiographic documentation of hemorrhage.[50]

Natural History

The natural history of OPH CMs specifically is not clear, as most reported cases have been surgically treated. Nonetheless, we can attempt to extrapolate the natural history from data acquired in cerebral and brainstem CMs. The rate of hemorrhage for CMs, in general, ranges from 0.7% to 3.1% per year.[43,54] Prior hemorrhage is a risk factor for subsequent bleeding, as rehemorrhage rates for cerebral CMs have been found to range from 3.8% to 22.9%.[1,28] There is evidence that the rehemorrhage rate for an untreated bleed is high in the first 2–3 years but decreases thereafter.[4] Although the hemorrhage and rehemorrhage rates for OPH CMs are not known, they are generally thought to be higher than those for cerebral lesions.[31,44] A large study of brainstem CMs revealed a 5% per year hemorrhage rate and a 30% per year rehemorrhage rate.[50] Other authors have reported brainstem rebleed rates of 17.7% per year with up to more than 1 hemorrhage per year.[6,55] The significantly higher rebleed rates seen with brainstem CMs may be partially due to the eloquent nature of the surrounding tissue. Therefore, each bleeding event is likely to result in a clinically apparent neurological deficit. It is reasonable to consider OPH CMs in a similar fashion with a higher rebleed rate because of the eloquent location of the visual apparatus. Therefore, each hemorrhagic event is likely to result in a symptomatic visual deficit.

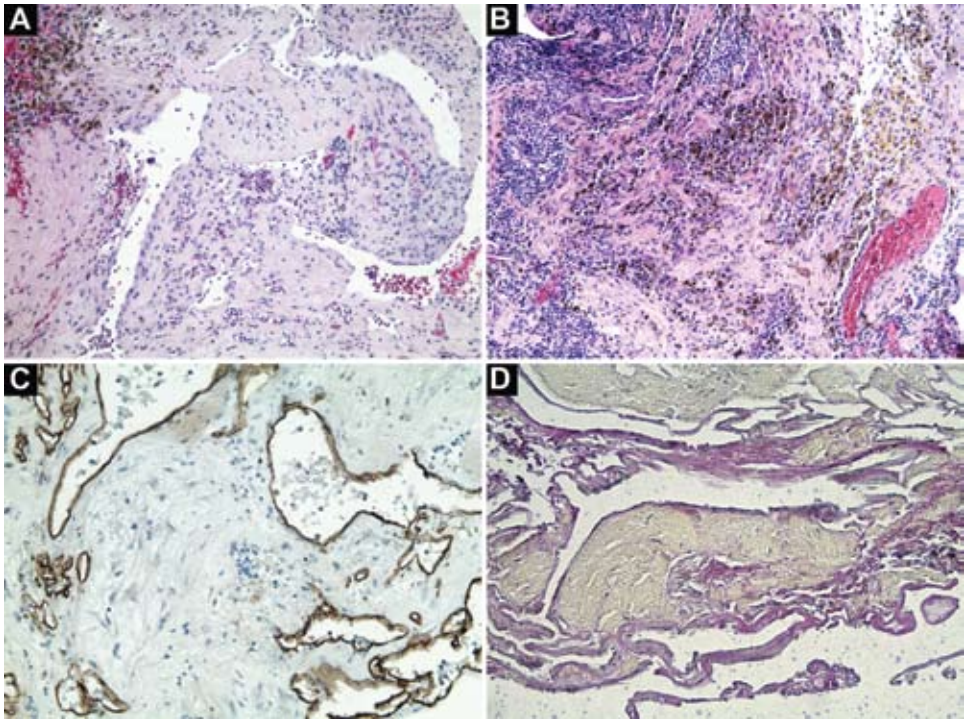

Fig. 2. Histopathological examination of the suprasellar lesion. **A:** Photomicrograph demonstrating the CM with red blood cells dispersed in the field. **B:** Photomicrograph showing the surrounding reactive changes including inflammation, fibrosis, and hemosiderin. **C:** Immunohistochemical staining showing positivity of CD34, indicating the endothelial lining of the CM. **D:** Histochemical staining showing negativity to elastin, indicating the absence of an arterial component to distinguish the CM from an arteriovenous malformation. H & E **(A and B)**, original magnification × 100 **(A and B)** and × 200 **(C and D)**.

Neuroimaging Studies

Magnetic resonance imaging is the most sensitive and specific imaging modality for identifying CMs.[53] These lesions usually appear as areas of mixed signal intensity with a hypointense rim. A typical "popcorn" appearance is characteristic of hemorrhagic components of different ages. Minimal or no enhancement occurs after the intravenous administration of Gd. Lesions of the optic nerve or tract may appear as nerve thickening on coronal views, whereas lesions in the chiasm or hypothalamus often appear as focal and round masses. Gradient-echo sequences are particularly sensitive to small hemorrhages and are ideal for detecting the presence of additional lesions in patients with multiple CMs.[31] The hemosiderin rim appears particularly dark on T2 gradient-echo sequences.[66] It is notable that peripheral hypointensity was not found in more than one-third of the cases providing detailed MR imaging information. The absence of the hemosiderin rim may have resulted from blood washout by CSF.[47] On CT scans, OPH CMs appear as areas of hyperdensity with or without calcification and can sometimes mimic the appearance of a tumor or thrombosed aneurysm.[58] Angiography does not typically show any pathological vessels. In some cases, however, an associated venous angioma (developmental venous anomaly) can be visualized.[20,21]

Differential Diagnosis

The differential diagnosis includes optic glioma, craniopharyngioma, meningioma, arteriovenous malformation, venous angioma, thrombosed aneurysm, pituitary apoplexy, and optic neuritis.[9,39,44] Optic gliomas can cause enlargement of the optic nerve or chiasm but usually do not exhibit signs of hemorrhage.[47] Intense enhancement after contrast administration is common for these lesions.[23] Meningiomas of the optic nerve sheath typically appear as tram-tracking patterns of enhancement around the nerve.[65] Craniopharyngiomas can appear cystic and/or solid with calcification on CT and typically enhance after contrast administration.[11] Arteriovenous malformations and aneurysms can be distinguished from CMs by their visibility on angiography. Venous angiomas are commonly associated with brainstem CMs and may have a role in inducing their formation.[5] Both contrast-enhanced MR imaging and angiography are useful in revealing associated venous angiomas (Fig. 1). The symptoms of pituitary apoplexy may resemble chiasmal apoplexy but can be distinguished by the presence of ocular paresis from cavernous sinus compression.[45] Optic neuritis, which can cause acute visual loss, appears as an intensely enhanced optic nerve on fat-suppressed post-Gd T1-weighted MR imaging.[3,8]

Surgical Treatment, Timing, and Visual Outcomes

Gross-total resection is the gold standard of treatment, as any residual malformation can be at risk for rebleeding.[12,22,31,44,47,59] Biopsy procedure alone is not recommended because of the risk of further bleeding and visual worsening.[12,47] While decompression without complete resection has resulted in visual improvement, this strat-

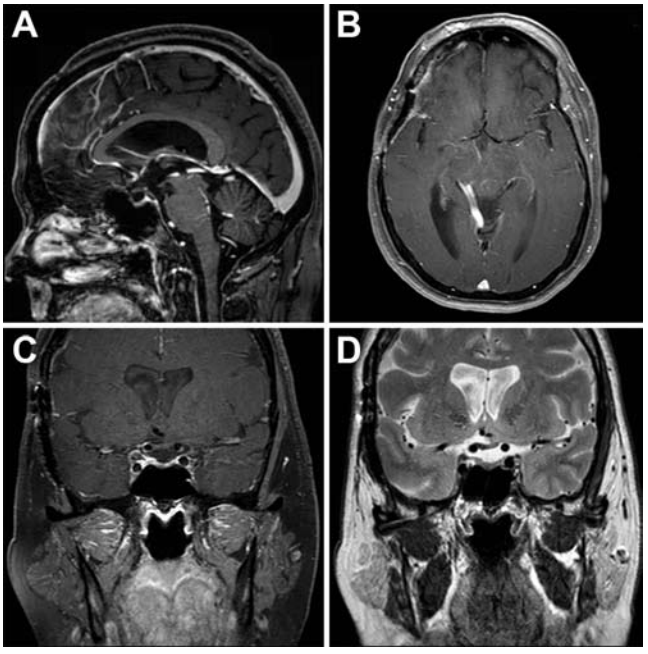

Fig. 3. Postoperative sagittal **(A)**, axial **(B)**, and coronal **(C)** post-Gd T1-weighted and coronal T2-weighted (**D**) MR images demonstrating complete resection of the optic chiasm CM. The optic chiasm is decompressed and well visualized on the coronal views **(C and D)**. The associated venous angioma is again shown in the right posterolateral aspect of the mesencephalon **(B)**.

egy does not eliminate the risk of recurrent hemorrhage. The lack of long-term follow-up data makes it difficult to evaluate rebleed rates or the durability of visual improvement following decompression or STR. Currently, there are not enough data to favor stereotactic radiosurgery as a primary treatment for OPH CM. The role of radiosurgery for CMs in general is still controversial. Recent evidence suggests that the risk of recurrent hemorrhage may be reduced after radiosurgery;[35] however, radiation-related complications are greater for CMs than for arteriovenous malformations, even when adjusting for lesion size and radiation dosage.[49] In cases of chiasmal apoplexy in which emergent surgical decompression of the optic apparatus is warranted, radiation therapy may not be the ideal form of treatment.

The timing for surgical intervention in OPH CMs may differ from that for malformations in other locations. For brainstem CMs in general, it has been advised to wait until 2 symptomatic hemorrhages have occurred before attempting resection. This strategy is based on the reasoning that only then will the risk of surgery be less than the risk of any morbidity associated with a subsequent hemorrhage.[17] In some cases, however, earlier intervention may be more appropriate for OPH CMs.[12,22,47] In patients with chiasmal apoplexy, emergent surgery (usually within 24 hours) is warranted to avoid permanent compressive damage to the visual pathway.[31] Rapid diagnosis is important, as even total visual loss can improve if decompression of the optic apparatus is achieved promptly.[46]

Despite the critical location, excellent surgical outcomes can be achieved. Ninety-four percent of the patients treated surgically in the present study experienced visual improvement or stabilization. Visual acuity and visual field improved simultaneously most of the time. In the present study, the highest rate of visual improvement (85%) was achieved in those who underwent GTR (Table 2). Only 2 patients experienced worsening of their vision after total resection.

Surgical Approach

Lesions of the OPH present an operative challenge because of their deep and eloquent location in the brain. The optimal surgical approach should provide maximal exposure of the optic chiasm with the shortest distance to the lesion while using minimal brain retraction. One should be prepared to open the lamina terminalis and explore the third ventricle, as some of these malformations are located intraventricularly. In our case included in the present study, the lesion was not visualized on initial exposure of the optic chiasm until the lamina terminalis was entered. Access to the lamina terminalis can be achieved using anterolateral approaches (pterional, supraorbital, or orbitozygomatic) and midline approaches (transbasal subfrontal, or transbasal interhemispheric). The majority of cases reviewed in this study involved an anterolateral approach (45% frontotemporal, 42% pterional, and 13% orbitozygomatic). The orbitozygomatic approach is a natural extension of the pterional approach and offers a wider exposure, shorter distance to the target, and more inferior-to-superior viewing trajectory.[16,56] The major disadvantage of anterolateral approaches to the lamina terminalis is the lack of midline orientation and lack of visualization of the ipsilateral wall of the third ventricle. In a midline approach to the lamina terminalis, both walls of the third ventricle and hypothalamus are well visualized for direct microdissection of the lesion.[34]

Conclusions

Cavernous malformations of the OPH are rare and challenging lesions. In cases of chiasmal apoplexy, emergent surgical removal is indicated to prevent permanent visual damage. Gross-total resection of these malformations is associated with favorable visual outcomes.

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: Liu, Delashaw. Acquisition of data: Liu, Lu, Raslan, Gultekin. Analysis and interpretation of data: all authors. Drafting the article: Liu, Lu, Raslan. Critically revising the article: Liu, Lu. Reviewed final version of the manuscript and approved it for submission: Liu, Delashaw. Statistical analysis: Liu.

Acknowledgments

The authors express their appreciation and thanks to Shirley McCartney, Ph.D., for editorial assistance, and Andy Rekito, M.S., for illustrative assistance.

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Manuscript submitted May 13, 2010.
Accepted May 27, 2010.
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Neurosurg Focus 29 (3):E18, 2010

Giant posterior fossa cavernous malformations in 2 infants with familial cerebral cavernomatosis: the case for early screening

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The author reports the details in 2 cases of infants with familial cerebral cavernomatosis who presented in dire condition from hemorrhagic posterior fossa cavernous malformations.

In Case 1, a 4-month-old boy presented with opisthotonos, gaze palsy, and lethargy. Magnetic resonance imaging revealed a multilobulated cavernous malformation in the fourth ventricle with evidence of bleeding and obstructive hydrocephalus. In Case 2, a 7-month-old girl presented with lethargy, followed by rapid neurological decline. Imaging demonstrated a large lesion involving both the brainstem and cerebellum, with obstructive hydrocephalus. Both patients required immediate surgical intervention, and external ventricular drainage and posterior fossa craniotomies were performed. Both patients made excellent recoveries. These cases suggest that infants in families with suspected or confirmed familial cerebral cavernomatosis should be screened at an early age.
(DOI: 10.3171/2010.5.FOCUS10119)

Key Words • **pediatric cavernoma** • **cavernous malformation** • **familial cerebral cavernomatosis** • **screening**

Cerebral cavernous malformations can be sporadic or familial in nature. In non-Hispanic populations, the familial form, familial cerebral cavernomatosis, constitutes a minority (10–20%) of the cases.[9–11] However, the familial form is responsible for a disproportionately large percentage of symptomatic events, likely due to the higher incidence of multiple lesions in these patients[7] and the propensity for de novo CCM formation.[3,5,6,11] Genetic testing for families with clinical histories consistent with familial cerebral cavernomatosis allows one to confirm the diagnosis, but there are no clear guidelines regarding routine imaging in these patients.[3,7–9] We present 2 cases of giant posterior fossa cavernous malformations in infants with familial cerebral cavernomatosis who presented in extremis. These cases and a review of the literature demonstrate the possibility of life-threatening hemorrhagic events in patients with familial CCM during infancy and support a strategy of early imaging.

Abbreviation used in this paper: CCM = cerebral cavernous malformation.

Case Reports

Case 1

This previously healthy 4-month-old boy presented to his pediatrician with a 2-week history of intermittent projectile vomiting. The presumptive diagnosis was gastroenteritis. The projectile vomiting persisted, and 2 days later the patient had a bulging fontanelle, opisthotonos, left gaze preference, and was lethargic. A CT scan of the head obtained at an outside hospital revealed a 4-cm-diameter hemorrhagic lesion effacing the fourth ventricle with obstructive hydrocephalus (Fig. 1A).

A right frontal external ventricular drain was urgently placed. The posturing and gaze preference resolved. Magnetic resonance imaging revealed a lobulated/cystic-appearing mass with subacute hemorrhage suspicious for vascular malformation (Fig. 1B). Angiography was performed to rule out an arteriovenous malformation. Three days after admission, he underwent a posterior fossa craniotomy for gross-total resection of the lesion, which arose from the superior aspect of the cerebellum. Histological features were consistent with a cavernous malformation.

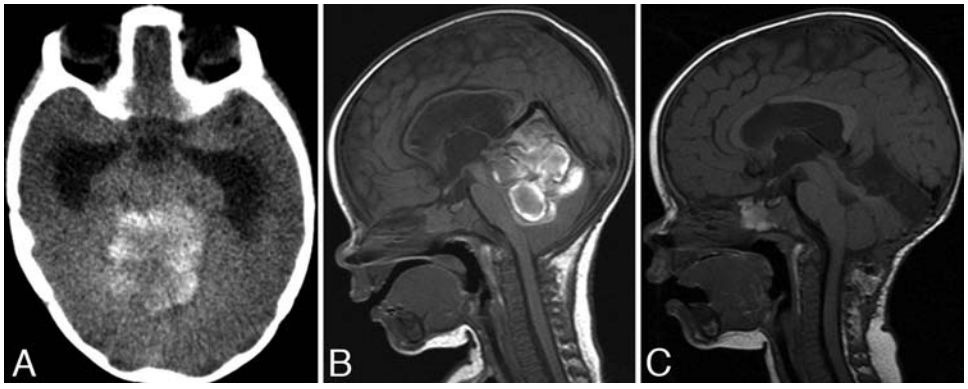

Fig. 1. Case 1. **A:** Axial noncontrast CT scan demonstrating a large fourth ventricular hemorrhagic mass with obstructive hydrocephalus and brainstem compression. **B:** Sagittal T1-weighted noncontrast MR image demonstrating the extent of the posterior fossa mass (after ventriculostomy). **C:** Sagittal T1-weighted noncontrast MR image obtained 6 months after resection.

The patient made a complete recovery, and follow-up visits for the next 3 years revealed normal psychomotor development, no neurological deficits, and no MR imaging evidence of residual cavernoma or local recurrence (Fig. 1C). We did observe subsequent development of small, asymptomatic supratentorial CCMs that are being followed conservatively. The patient's brother, mother, and maternal grandfather were subsequently found to be carriers for the *CCM1* gene mutation associated with familial cerebral cavernomatosis. His brother also harbors supratentorial lesions that remain small and asymptomatic.

Case 2

This previously healthy 7-month-old girl presented with a 3-day history of irritability and a 1-day history of progressive lethargy. On examination, she was noted to have a tense fontanelle but no focal neurological deficits. A CT scan of the head acquired at an outside institution demonstrated a very large right posterior fossa hemorrhagic mass, surrounding edema, brainstem compression, and obstructive hydrocephalus (Fig. 2 left). The patient was urgently intubated and transported by air to our institution. In flight, the patient exhibited periods of apnea, hypertension, and bradycardia. The patient's brother had been previously treated at our institution at the age of 4 years for a large hemorrhagic temporal CCM. Her father's history was suspicious for a cerebrovascular lesion, and we strongly suspected familial cerebral cavernomatosis, but the family had not undergone recommended genetic testing.

On arrival, the patient was taken immediately to surgery. A right frontal external ventricular drain was placed, and markedly elevated intraventricular pressure was demonstrated. A posterior fossa craniotomy was then performed, which revealed a large cavernous malformation involving the right cerebellar hemisphere, with extension into the brainstem causing obstruction and mesial displacement of the fourth ventricle. A gross-total resection was not attempted as the extent of brainstem involvement was not demonstrated on the CT scan (and the patient was not thought to be stable enough for preoperative MR imaging to be conducted). An aggressive debulking of the lesion was performed. The postoperative MR images demonstrated residual CCM within the pons (Fig. 2 right). The patient made a complete neurological recovery. Sixteen months after surgery, she remains developmentally normal and her lesions are being monitored by serial MR imaging. The patient's brother, father, paternal uncle, and paternal grandfather have a history consistent with familial cavernomatosis. Genetic testing has been recommended but as of yet not performed.

Discussion

There are a limited number of reports of giant cavernous malformations in infants. Braga and colleagues[2] reported on a 1-month-old girl who presented with macrocephaly and swallowing difficulties and was found to have a posterior fossa cavernoma arising from the brainstem. The lesion was followed until the patient reached the age of 9 months when progressive growth and neurological deterioration led to elective resection. It was not mentioned in this report if familial CCM was confirmed. Gezen and colleagues[4] reported a giant CCM in the left parietal lobe of a 10-month-old infant who presented with seizures. Ng and colleagues[8] described the case of an 8-week-old boy with familial CCM who presented with a month-long history of rapid head growth and decreased eye contact. Magnetic resonance imaging revealed a 2-cm lesion in the midbrain causing obstructive hydrocephalus.

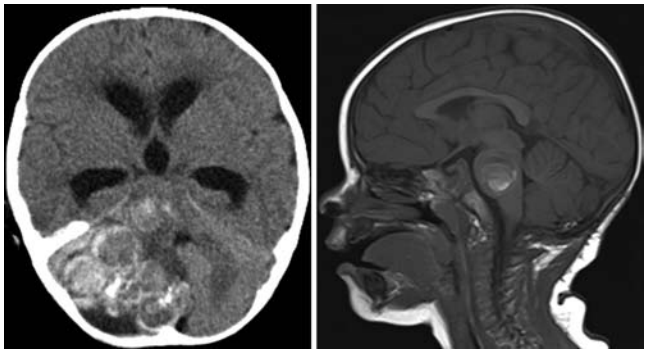

Fig. 2. Case 2. **Left:** Axial noncontrast CT scan demonstrating a hemorrhagic posterior fossa mass with obstructive hydrocephalus and brainstem compression. **Right:** Postoperative sagittal T1-weighted noncontrast MR image revealing a residual brainstem CCM.

Azam and O'Donovan[1] recently described a 50-hour-old neonate who presented with seizures and was found to have 2 right frontal cavernous malformations that were presumed to be the source of his epileptiform activity. The lesions did not have significant mass effect and the patient's seizures were successfully managed medically.

Our cases are unique as both patients presented in extremis, requiring emergency surgery due to hydrocephalus and brainstem compression. Placed in the context of previously described reports, it is clear that infants with familial CCM can develop large, symptomatic lesions early in life; these lesions are likely present at birth. Ideally, any surgical treatment would be performed electively, with the luxury of careful surgical planning and appropriate family counseling regarding the options of surgery and conservative management. To further this goal, we recommend routine cranial ultrasonography be performed early in life in patients with suspected or confirmed familial CCM. Although not as sensitive as CT or MR imaging, ultrasonography is likely to detect lesions that would be considered for elective surgical resection—that is, lesions causing hydrocephalus or those causing significant mass effect. Ultrasonography is cheaper, quicker, and does not expose the patient to the risks of anesthesia (MR imaging) or radiation (CT scanning). While the timing of any surveillance imaging is somewhat arbitrary, it seems reasonable to obtain a screening ultrasound during the neonatal period with follow-up in 3–6 months, after which consideration can be given to the use of MR imaging depending on clinical status, ultrasound findings, and genetic testing.

Although certainly rare, infants with familial cerebral cavernomatosis can present with symptomatic lesions early in life. Early recognition of giant lesions would likely reduce the incidence of life-threatening emergencies and allow for more elective management. Cranial ultrasound is recommended during the neonatal period for patients with suspected or confirmed familial cerebral cavernomatosis.

Disclosure

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

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Manuscript submitted May 7, 2010.
Accepted May 27, 2010.
Portions of this work were presented in poster form at the AANS/CNS Section on Pediatric Neurological Surgery Annual Meeting, Boston, Massachusetts, December 1, 2009.

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