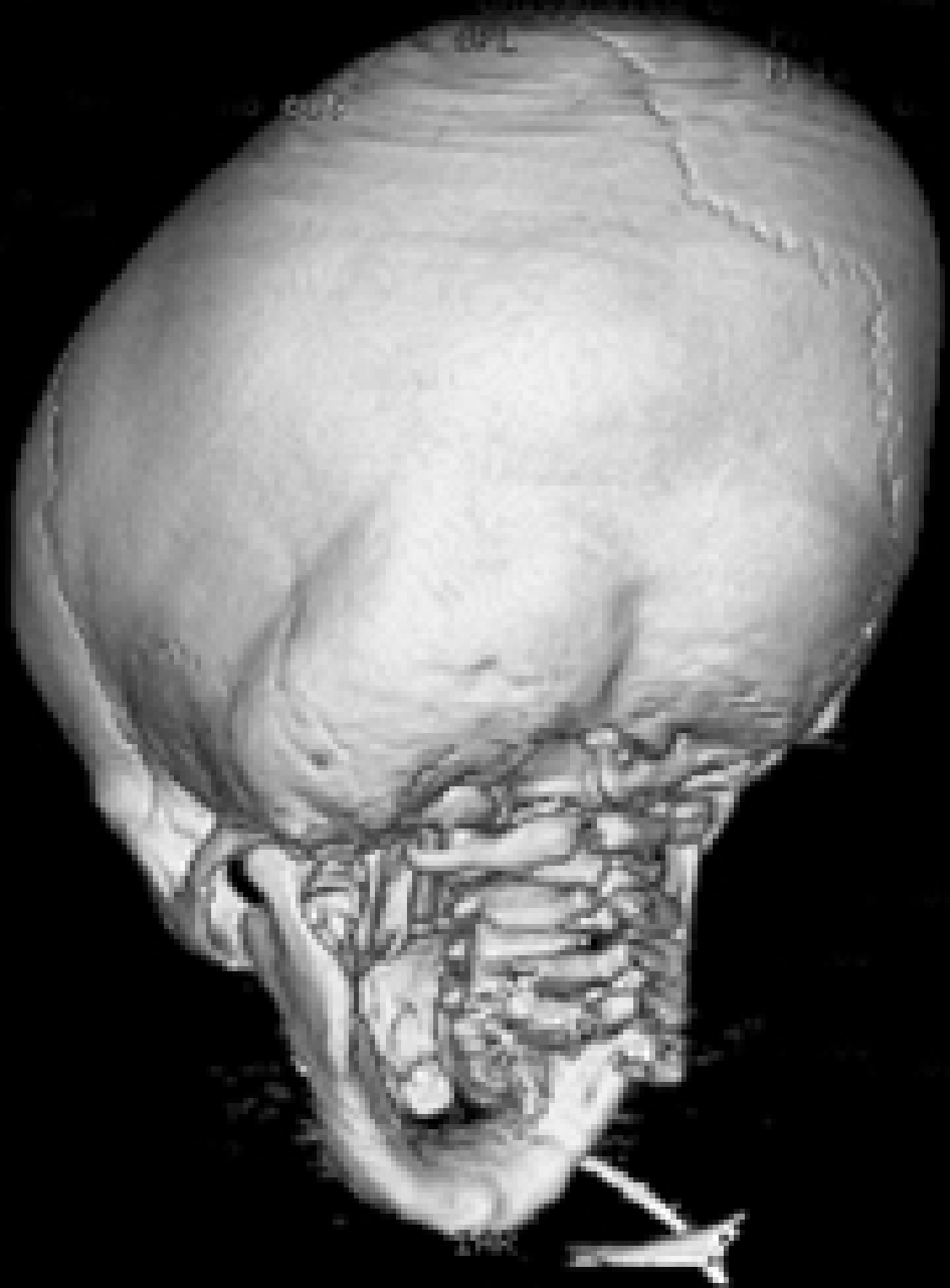

Introduction

Chiari malformation

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The treatment of Chiari malformation Type I is perhaps one of the more vexing and controversial topics in neurosurgery. There is a lack of agreement as to what defines the malformation, its symptoms, and its natural history. When treatment is necessary, a wide variety of surgical techniques have been proposed. For a field as complex as neurosurgery, it is ironic that there is such controversy regarding this so-called "simple" topic.

Why is Chiari malformation so difficult to wrap our heads around? First of all, it is a common incidental finding in the population, with estimates of true Chiari being present in about 0.75% of the population;[3,5] it is so common that some suggest it should be called the Chiari anomaly.[4] In fact, there is even a lack of agreement as to what constitutes a Chiari malformation Type I, with many authors accepting 5 mm of tonsillar descent as the minimum criteria, but others suggesting that 0–2 mm, or less, might still be consistent with pathological Chiari.[2] Second, Chiari symptoms are often common constitutional complaints, such as headache, but are sometimes extended to symptoms, such as lassitude or fatigue, that are seen in chronic fatigue syndrome. The Chiari malformation is, in fact, one of the few conditions for which the AANS (American Association of Neurological Surgeons) issued a position statement regarding the inappropriate use of surgery (AANS Position Statement on the Use of Cervical Decompression for Chronic Fatigue Syndrome, March 2000). When a patient presents with two common conditions, there is always going to be some degree of coincidental overlap, and we must be careful not to perform surgery in patients in whom there is little chance that the Chiari malformation is symptomatic. Third, do neurosurgeons really understand the natural history of the asymptomatic patient with a diagnosed Chiari malformation? Only recently have articles begun to address this issue, and the condition seems more benign than many had thought.[1,4,6] Finally, what is the appropriate treatment for Chiari malformation when surgery is indicated? Should it be a bone-only decompression? Should the dura be opened, and if so, should the dura be closed, and if so, how? One can also reasonably use a combination of different surgical approaches based on presentation, but there is little in the literature to guide this decision tree.

In this issue of *Neurosurgical Focus,* we try to clarify and provide evidence addressing some of the questions surrounding Chiari malformation and syringomyelia. Authors address topics such as familial Chiari malformation, its association with craniosynostosis and other associated disorders, and the use of newer imaging modalities that can help us establish the successful treatment of Chiari and syringomyelia. We hope that these papers will help to bring to our readers a degree of clarity regarding this complicated "simple" condition. *(DOI: 10.3171/2011.8.FOCUS11195)*

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Neurosurg Focus 31 (3):E1, 2011

Familial Chiari malformation: case series

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Chiari malformations (Types I–IV) are abnormalities of the posterior fossa that affect the cerebellum, brainstem, and the spinal cord with prevalence rates of 0.1%–0.5%. Case reports of familial aggregation of Chiari malformation, twin studies, cosegregation of Chiari malformation with known genetic conditions, and recent gene and genome-wide association studies provide strong evidence of the genetic underpinnings of familial Chiari malformation. The authors report on a series of 3 family pairs with Chiari malformation Type I: 2 mother-daughter pairs and 1 father-daughter pair. The specific genetic causes of familial Chiari malformation have yet to be fully elucidated. The authors review the literature and discuss several candidate genes. Recent advances in the understanding of the genetic influences and pathogenesis of familial Chiari malformation are expected to improve management of affected patients and monitoring of at-risk family members. *(DOI: 10.3171/2011.6.FOCUS11104)*

Key Words • **Chiari malformation** • **familial** • **genetic** • **posterior fossa** • **cerebellum** • **surgery**

Chiari malformation can be a congenital or acquired condition in which the cerebellar tonsils protrude through the foramen magnum, and the disorder has traditionally been defined as downward herniation of the tonsils of 5 mm or more.[3] The size of the posterior fossa and the degree of stenosis also play a role in the development of symptoms. Patients may be asymptomatic, even when there is significant descent of the tonsils. Conversely, symptoms can appear when relatively minimal cerebellar displacement exists. While the rate of progression can vary, most patients experience chronic or exertional headaches, ocular disturbances, neck pain, scoliosis, cerebellar ataxia, and vertigo. This condition can also result in hydrocephalus or syringomyelia as the result of CSF pathway obstruction. The mean age of presentation is 24.9 ± 15.8 years.[27] Estimates suggest that approximately 215,000 Americans may be affected with CM, with or without syringomyelia.[35] The incidence of CM ranges between 1/18,000 and 1/1280, not correcting for the suspected underdiagnosis of asymptomatic patients due to a lack universal neuroimaging.[25,33,35] An estimated 65%–80% of patients with CM present with syringomyelia.[11,27] Traditionally, combined surgical decompression and enlargement of the posterior fossa is a common method of treatment, although patients may require additional care for syringomyelia and hydrocephalus. The decision to proceed with surgical intervention often depends on disease severity and/or progression.

Chiari malformations have long been considered sporadic conditions, without a heritable etiology. However, there have been a number of case reports identifying familial aggregation and clustering of CM, suggesting a genetic basis.[1,6–9,13,15,17,22,27,28,34,37–40,42,44,45,49,51,52] A recent large retrospective series of 500 cases spanning the past 2 decades found the prevalence of familial CM to be about 3%,[41] and a past study of 364 patients with CM found that 12% of patients had a close relative with CM and/or syringomyelia.[27] We report on a series of 3 family pairs in whom a CM was present (Table 1).

Abbreviation used in this paper: CM = Chiari malformation.

TABLE 1: Cases of familial Chiari malformation*

Case No.	Age (yrs) at Presentation	Major Preop Symptoms	Syrinx	Cerebellar Tonsillar Descent (mm)	Postop Symptoms
1a	20	HA (tussive & exertional), paresthesias, hyperreflexia	no	9	hypertonia persists; paresthesias & HA resolved
1b	57	HA (tussive & exertional), paresthesias, ocular symptoms, LE dysesthesia	no	7	dysesthesia & HA resolved
2a	23	blurry vision, clonus, LE hypertonia, hyperreflexia, gait difficulty	no	17	no further deterioration of vision; all other symptoms resolved
2b	62	asymptomatic	no	6	no surgery
3a	24	HA (tussive & exertional), UE paresthesias, hearing changes	no	8	surgery scheduled
3b	44	paresthesias, HA, nystagmus, diplopia, balance & coordination problems	yes	8	chronic HA & dizziness

* HA = headache; LE = lower-extremity; UE = upper-extremity.

Case Series

Family 1

Case 1a. This 20-year-old woman presented with a several-year history of suboccipital tussive and exertional headaches worsening over 6 months and associated with a sensation of dizziness, upper-extremity paresthesias, and numbness. The patient was referred to our center by her mother, who had previously undergone CM decompression. Her symptoms had an insidious onset, and at the time of presentation, she was experiencing progressive and increasingly bothersome daily headaches. Secondary symptoms also included chronic headaches, anxiety, fatigue, and insomnia. Physical examination revealed diffuse spasticity in the upper extremities and abnormal coordination, with a decreased ability to perform rapidly alternating movements, worse on the left side. Passive movement of the extremities revealed marked hypertonia over the left knee greater than the right knee and over the ankles without sustained clonus. Reflexes were Grade $3^+/5$ over the right side and Grade $3^+/5$ with spread over the left side, including the biceps, triceps, brachial radialis, knee, and ankle.

Magnetic resonance imaging of the cervical spine demonstrated a CM in which the cerebellar tonsils extended 9 mm below the level of the foramen magnum down to the posterior arch of C-1. Cerebrospinal fluid was identified ventral but not dorsal to the spinal cord. The patient underwent a suboccipital craniectomy, C-1 laminectomy, and autologous expansion duraplasty. Postoperatively, the patient's symptoms remained stable. Rapid, alternating movements remained diminished at baseline over both upper extremities, and passive movement of the lower extremities demonstrated persistent hypertonia. Of note, this patient has a sister with typical CM symptoms who refuses to undergo neuroimaging.

Case 1b. This patient, the mother of the patient in Case 1a, originally presented at age 57 years with a long-standing history of multiple symptoms, including suboccipital headaches radiating upward, a burning sensation in the eyes, tearing, paresthesias radiating in both upper extremities in a vague distribution, numbness, and tussive and exertional headaches. Magnetic resonance imaging of the cervical spine demonstrated a CM with the cerebellar tonsils descending 7 mm below the level of the foramen magnum. The patient underwent a suboccipital craniotomy, C-1 laminectomy, and autologous expansion duraplasty. Postoperatively, the patient's symptoms resolved.

Family 2

Case 2a. This 23-year-old woman was referred by her ophthalmologist for blurry, deteriorating left-sided vision and left lower-extremity spasticity. Neurological examination demonstrated hypertonia, hyperreflexia of her lower extremities, clonus, and gait difficulties. Magnetic resonance imaging of the cervical spine demonstrated CM in which the cerebellar tonsils descended 17 mm below the level of the foramen magnum. The patient underwent a suboccipital craniectomy, C-1 laminectomy, and autologous expansion duraplasty. Postoperatively she had total resolution of her symptoms and plateauing of visual deterioration.

Case 2b. This 62-year-old mother of the patient in Case 2a presented at the urging of her daughter. She first noticed a decreased cervical range of motion without significant cervicalgia. Over the course of a year she developed pain bilaterally over the sternocleidomastoid and trapezius muscles and suffered an episode of nighttime dyspnea. She also experienced pain in her fingertips and arms, paresthesias, numbness, and coordination difficulties, as well as occasional problems with paraphasic errors while typing. Examination revealed decrease cervical range of motion, hyperreflexia, and decreased strength diffusely. Magnetic resonance imaging of the cervical spine identified CM in which the cerebellar tonsils descended 6 mm below the level of the foramen magnum and severe cervical spondylosis. The patient experienced significant relief of symptoms with nonsurgical management of her spondylosis; no CM decompression was performed.

Family 3

Case 3a. This 24-year-old woman presented with progressive symptoms of suboccipital headache, paresthesias, and tingling in her fingers, a sensation of abnormal hearing, and difficulty focusing while reading. She also had a history of other, migrainelike headaches over the frontal region, with the presence of visual auras. The symptoms were exacerbated by activity, including bearing down, bending over, and lifting objects, and the symptoms were alleviated with rest. Physical examination was significant for detecting mild hyperreflexia but no hypertonia on passive movement of the extremities. Magnetic resonance imaging of the cervical spine demonstrated CM in which the cerebellar tonsils descended 8 mm below the foramen magnum. The patient is scheduled to undergo a suboccipital craniectomy, C-1 laminectomy, and autologous expansion duraplasty.

Case 3b. This 44-year-old father of the patient in Case 3a presented with an 8-month history of worsening diplopia, incoordination, vertigo, and sensory complaints of left facial numbness and left-hand numbness. Just prior to his evaluation, he had experienced several weeks of constant vertigo and nystagmus resulting in vertical diplopia. The patient also described occasional suboccipital headaches with wet hair or a breeze against his head, as well as generalized weakness on his left side and a loss of left hand proprioception. Neurological examination revealed left to right rotary nystagmus in both eyes, worse with the left gaze, but present in all directions. With attempted fixation, his left eye was noted to drift upward with rotary nystagmus. Left-sided facial sensation was subjectively decreased to light touch and temperature. Reflexes and tone were noted to be normal bilaterally. Mild ataxia and a mild intentional tremor were also noted in the left hand. Magnetic resonance imaging of the cervical spine demonstrated CM in which the cerebellar tonsils descended 8 mm below the foramen magnum; there was associated syringomyelia.

The patient underwent a suboccipital craniectomy, C-1 laminectomy, and autologous expansion duraplasty. Postoperatively, a CSF leak developed and was treated with reoperation for primary closure. The patient also developed a supratentorial subdural hemorrhage that required bur hole drainage. His outcome was not ideal, with chronic complaints of headaches and dizziness persisting.

Discussion

Chiari malformation is associated with occipital hypoplasia resulting in posterior fossa overcrowding and in hindbrain and cerebellar herniation through the foramen magnum.[2,14,18,27,29,48] Two-thirds of patients with CM have posterior occipital bone anomalies with volumetric reduction.[9,31,48]

Chiari malformation has been thought to be related to the underdevelopment of the occipital somites that originate from the paraaxial mesoderm during nervous system development.[29] The craniovertebral junction and basicranium are formed predominantly by the sclerotomal cells of the C-1 and C-2 somites. The hypothesis of mesodermal origin has been supported by subsequent reports,[26,27] as well as early laboratory evidence: Following administration of large doses of vitamin A (a substance known to affect mesodermal development) to gestating hamsters, Marin-Padilla and Marin-Padilla[21] observed occipital hypoplasia, development of smaller than normal posterior fossae, and short basichondrocranium, with downward displacement of the cerebellum and medullary compression.

Chiari malformation, like other complex medical diseases, is likely the result of cascade of abnormalities attributable to 1 or more root genetic causes. Documented clustering in families often serves as a first step, followed by twin studies, segregation analysis, and genome-wide association studies once a critical mass of patients is available for research. Cosegregation of a condition with known genetic conditions can further corroborate a genetic basis, with the assumption that a common genetic root is responsible for the numerous abnormal phenotypes within the genetic syndrome.

Our institutional experience with familial clustering suggests an underlying genetic etiology. As with any familial clustering, there is the possibility of the observed phenotype being related to a common environmental exposure or chance—albeit, much less likely.

In twins, a genetically determined trait is expected to be concordant in monozygotic (identical) twins more frequently than dizygotic (fraternal) twins. Chiari malformation has been reported in the literature in numerous sets of twins or triplets.[1,7,15,28,34,38,40,43] In all but one of these case reports, the twins or triplets were monozygous, and in the outlier zygosity was undetermined.[15] The substantial concordance in monozygotic twins and the dearth of case reports for dizygotic twins further supports a genetic basis. In one of the twin studies, monozygotic twins are described as discordant for CM, but both are reported to have syringomyelia, and both experienced symptom alleviation after decompressive surgery.[43] A twin study by Speer et al.[35] in 2003 examined 6 additional sets of monozygotic and dizygotic twins, and similarly, the authors found a higher concordance between monozygotic twins than dizygotic twins.

Numerous inherited syndromes are associated with CM, including hypophosphatemic rickets, Klippel-Feil syndrome, Albright hereditary osteodystrophy (pseudohypoparathyroidism), X-linked aqueductal stenosis, Goldenhar syndrome, Williams syndrome, Shprintzen-Goldberg syndrome, achondroplasia, familial osteosclerosis, spondyloepiphyseal dysplasia tarda, velocardiofacial syndrome, primary basilar impression, and renal-coloboma syndrome, among many others.[36] For some of these conditions, associated genes have been identified and hypothesized to have pleiotropic effects influencing cerebellar tonsil herniation, occipital hypoplasia, syringomyelia, and other phenotypes.[36] Some of these syndromes lead to bone abnormalities (for example, achondroplasia and familial osteosclerosis); others affect pathways involved in axial mesodermal growth and differentiation (for example, Williams syndrome and Shprintzen-Goldberg syndrome), which adds support for the mesodermal origin hypothesis.

Past familial Chiari malformation pedigree studies

have found evidence consistent with vertical transmission and autosomal dominant inheritance patterns, but reduced penetrance and autosomal recessive patterns have also been observed.[27,36] Our institutional experience brings into question the potential influences of sex-controlled genes, the role of estrogen in bone growth and remodeling, and genomic imprinting in relevance to familial CM.

Despite growing evidence of genetic influences in familial Chiari malformation, the underlying culprit genes have not been fully elucidated. *PAX1*, a highly conserved gene mapped to chromosome 20p11.2, involved in segmentation and vertebral development during embryogenesis, has been suggested for future study.[35] It plays an important role in the segmentation of somites and the differentiation of sclerotomal cells,[4] and the gene is regulated by a complex balance of signaling factors during development.[24] *PAX1* mutations have been implicated in Klippel-Feil syndrome,[23] a condition in which Chiari malformations are common, making this gene a possible candidate. Klippel-Feil syndrome involves failed segmentation of the cervical vertebrae with the clinical sequelae in patients of a short, immobile neck and a low posterior hairline. Vertebral fusions may also occur elsewhere along the spine and other vertebral anomalies, such as hemivertebrae, may be present.[16] The *PAX* family of genes encodes for transcription factors that play a role in pattern formation during embryogenesis in vertebrates. Other studies have implicated *PAX2* mutations and *FGF2* mutations as potential culprit genes in the formation of Chiari malformations.[12,32] *PAX3* and *PAX6* have also been implicated in various developmental abnormalities,[20] and although studies in direct relevance to Chiari malformations are limited, these are also candidate genes.

Another biologically plausible gene is *Noggin*, a BMP antagonist required for growth and differentiation of the relevant somites.[24] A genetic study in 33 cases of CM identified no variants in the *Noggin* gene,[35] however, which makes this less likely as a major culprit gene. *Homeobox (Hox)* genes, involved in morphogenesis and vertebral segmentation, are also a logical potential culprits of vertebral fusion anomalies.[10]

Familial CM has been recently described in conjunction with craniofrontonasal dysplasia,[19] a rare X-linked syndrome linked to the *EFNB1* gene mapped on chromosome Xq12, which encodes ephrin B1.[46,47,50] The *EFNB1* gene encodes a member of the ephrin family of transmembrane ligands for Eph receptor tyrosine kinases, and heterozygous loss-of-function mutations are believed to lead to protein dysfunction, hyperostosis, and an increased amount of dense lamellated bone. In observing patients with craniofrontonasal dysplasia and CM, Mahore et al.[19] hypothesized that a spontaneous mutation may have occurred in a female patient, which manifested in both of the patients' daughters through X-linked Mendelian inheritance; this in turn is believed to have contributed to diffuse hyperostosis and sclerotic thickening of the skull base, promoting overcrowding of posterior fossa structures and hindbrain herniation through the foramen magnum.

In another recent genetic study of 3 patients with syringomyelia, Schaaf et al.[30] discovered rearrangements at 16p11.2, suggesting that genes (or a single gene) within the implicated interval may have significant roles in the pathogenesis of syringomyelia. One of the patients studied had CM, specifically with a 16p11.2 microdeletion. The patient's mother was negative for the deletion but the father was unavailable for testing. The authors suggested *TBX6* as a candidate gene because it lies within the implicated region. The gene encodes a transcription factor important in developmental processes and can have a role in congenital spinal anomalies.

To our knowledge, there has only been one genome-wide association study for familial CM. In 2006, Boyles et al.[5] studied 23 families with 71 affected individuals and analyzed over 10,000 single-nucleotide polymorphisms across the genome and found linkage to regions on chromosome 9 and chromosome 15, at loci 15q21.1-q22.3 and 9q22.31. Although no specific genes have been identified, chromosome 15 contains the gene for fibrillin-1, a biologically plausible gene for CM that has been implicated in Marfan syndrome and linked to Shprintzen-Goldberg syndrome, in which CM is common. The study further supports the presence of genetic influences in CM and suggests future comprehensive studies for finer genetic mapping of candidate genes in familial Chiari malformation.

Ultimately, one can surmise that various inheritable genetic perturbations can lead to phenotypic processes that have a final common pathway of CM. Although occipital hypoplasia has been reported as the underlying pathology in the majority of cases, familial CM has also been described in 4 generations of a family without reduced posterior cranial fossa volume.[42] Cases of familial syringomyelia have also been reported as well,[8,22,51,52] and although some believe that familial syringomyelia should be more accurately classified as familial CM with associated syringomyelia,[36] there is certainly no definitive consensus on diagnostic categorization.

The overlap of various inherited syndromes with CM, in addition, makes a distinction between syndromic familial CM and nonsyndromic familial CM relevant. In future studies of familial CM, it will be necessary to establish discrete phenotypic definitions and diagnostic categories to allow the completion of cohort studies in a scientifically beneficial manner.

Currently, there is an ongoing study (ClinicalTrials.gov Identifier: NCT00004738) recruiting patients with familial CM to better elucidate the genes involved in CM with or without syringomyelia. A better understanding of the genetic bases of familial CM has the potential to ultimately improve the treatment of patients through the use of targeted gene therapeutics. In addition, understanding the genetic bases may facilitate prediction of patient-specific anomalies and guide treatment approaches. In a series of asymptomatic first-degree relatives of affected patients in whom imaging studies were completed, 21% of tested relatives were diagnosed with CM and syringomelia.[21] Risk assessment, monitoring, and education of asymptomatic family members are important considerations during the management and treatment of patients with CM. Since the prevalence of CM is so great in the general population, and the normal distribution of cer-

ebellar descent is not a concrete value, care must be taken in the preoperative evaluation to identify patients who are truly symptomatic from a disease process (and thus would likely benefit from surgery).

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: Walcott, Coumans. Acquisition of data: Walcott, Coumans. Analysis and interpretation of data: Walcott, Kahle, Coumans. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Walcott. Study supervision: Coumans.

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Manuscript submitted May 12, 2011.
Accepted June 10, 2011.

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Neurosurg Focus 31 (3):E2, 2011

Chiari malformation associated with craniosynostosis

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Object. Chiari malformation (CM) Type I is frequently associated with craniosynostosis. Optimal management of CM in patients with craniosynostosis is not well-established. The goal of this study was to report on a series of pediatric patients with both craniosynostosis and CM and discuss their management.

Methods. The authors searched the medical records of 383 consecutive patients treated for craniosynostosis at a single institution over a 15-year period to identify those with CM. They recorded demographic data as well as surgical treatment and outcomes for these patients. When MR imaging was performed, cerebellar tonsillar descent was recorded and any other associated findings, such as hydrocephalus or spinal syringes, were noted.

Results. A total of 29 patients with both CM and craniosynostosis were identified. Of these cases, 28% had associated occipital venous abnormalities, 45% were syndromic, and 52% also had hydrocephalus. Chiari malformation was more likely to be present in those patients with isolated lambdoid synostosis (55%), multisuture synostosis (35%), and pansynostosis (80%), compared with patients with coronal synostosis (6%) or sagittal synostosis (3%). All patients underwent surgical repair of craniosynostosis: 16 had craniosynostosis repair as well as CM decompression, and 13 patients did not undergo CM decompression. Of the 7 patients in whom craniosynostosis repair alone was performed, 5 had decreased tonsillar ectopia postoperatively and 5 had improved CSF flow studies postoperatively. Both patients with a spinal syrinx had imaging-documented syrinx regression after craniosynostosis repair. In 12 patients in whom CM was diagnosed after primary craniosynostosis repair, 5 had multiple cranial vault expansions and evidence of elevated intracranial pressure. In 5 cases, de novo CM development was documented following craniosynostosis repair at a mean of 3.5 years after surgery.

Conclusions. Chiari malformation is frequently seen in patients with both multi- and single-suture lambdoid craniosynostosis. Chiari malformation, and even a spinal cord syrinx, will occasionally resolve following craniofacial repair. De novo development of CM after craniosynostosis repair is not unusual.
(DOI: 10.3171/2011.6.FOCUS11107)

Key Words • **Chiari malformation** • **craniosynostosis** • **surgical treatment**

The association between CM and craniosynostosis has been recognized for several decades.[36] Chiari malformation occurs in patients with both syndromic and nonsyndromic forms of craniosynostosis.[5,7,9,17,18,41,42] Up to 70% of individuals with Crouzon syndrome and 50%–82% of those with Pfeiffer syndrome have associated CM.[4,5,7] There are also several reports of CM with nonsyndromic synostosis involving the sagittal, coronal, and even the metopic sutures.[17,25,41] Cerebellar tonsillar ectopia in patients with craniosynostosis is thought to arise from disproportionately slow growth or the small size of the posterior fossa in many cases.[5] Hydrocephalus, venous hypertension, and associated congenital brain anomalies have also been proposed as possibly important factors leading to CM development in these patients.[5,34,39,40] The optimal management of CM in the setting of craniosynostosis is not well established. Some surgeons advocate simultaneous surgical correction of craniosynostosis and CM, and others suggest that CM should only be treated if it is symptomatic or associated with a syrinx.[5,7] We describe our experience with a group of children with synostoses of one or more cranial sutures and CM, and we propose a management strategy for these complex cases.

Methods

We performed a retrospective single-center review of all patients under 18 years of age who were treated for craniosynostosis between 1994 and 2009. The University of Michigan institutional review board granted approval for the study. For this analysis, craniosynostosis was defined as clinical or radiological evidence of premature fusion of at least one cranial suture. Chiari malformation was defined as cerebellar tonsillar descent greater than or equal to 5 mm below the foramen magnum.[23,29] In each

Abbreviations used in this paper: CM = Chiari malformation; CVR = cranial vault reconstruction; ICP = intracranial pressure; VP = ventriculoperitoneal.

TABLE 1: Preoperative and postoperative imaging in patients with craniosynostosis according to suture involvement

Craniosynostosis Type	No. of Patients	No. of Preop Studies (%)		No. of Postop Studies (%)		Mean MRI Follow-Up in Yrs (range)
		CT	MRI	CT	MRI	
sagittal	183	161 (88)	12 (7)	49 (27)	15 (8)	4.5 (0.1–15.2)
coronal	80	80 (100)	24 (30)	43 (54)	23 (29)	5.6 (0.4–15.9)
lambdoid	9	9 (100)	7 (78)	2 (22)	7 (78)	2.9 (0.3–9.1)
metopic	71	71 (100)	6 (8)	14 (20)	10 (14)	2.7 (0.4–6.8)
multisuture	40	40 (100)	20 (50)	29 (73)	24 (60)	7.2 (0.7–15)
w/ lambdoid involvement	21	21 (100)	14 (67)	18 (86)	16 (76)	8 (3–15)
w/o lambdoid involvement	19	19 (100)	6 (32)	11 (58)	8 (42)	5.7 (0.7–13.9)

case, we recorded demographic information, characteristics of the craniosynostosis including suture location, and the number of sutures involved. When pre- or postoperative imaging studies were performed (Table 1), we recorded characteristics of the CM including a measurement of tonsillar descent below the foramen magnum, CSF flow analysis data on cine MR imaging, and any associated findings on imaging including venous anomalies and hydrocephalus. Cerebrospinal fluid flow data were recorded for all patients in whom dedicated CSF flow sequences were shown on MR imaging. At our institution, changes in signal intensity on sagittal phase-contrast CSF flow studies are observed in the CSF spaces anteriorly and posteriorly at the level of the cervicomedullary junction. The alternating bright and dark signals seen in the CSF spaces in the cine mode are diminished or absent when there is abnormal flow. On the axial and sagittal phase-contrast images, any change in the signal intensity of the cerebellar tonsils in the cine mode suggests tonsillar pulsations. Cerebrospinal fluid flow was categorized as abnormal if flow was decreased anteriorly or posteriorly at the foramen magnum or decreased at the foramen magnum with abnormal tonsillar pulsations based on the initial report of the radiologist. Surgical results were recorded for those patients who underwent craniosynostosis repair with or without CM decompression.

Results

A total of 383 individual patients underwent surgical craniosynostosis repair over the specified time interval. Of these patients, 183 children were evaluated for isolated sagittal synostosis; 80 for isolated coronal synostosis; 71 for isolated metopic synostosis; 9 for isolated lambdoid synostosis; and 40 for multisuture craniosynostosis. Forty-six patients (12%) were diagnosed with a craniofacial syndrome. Specifically, 16 had Crouzon syndrome, 9 had Pfeiffer syndrome, 9 had Saethre-Chotzen syndrome, 2 had craniofacial dyssynostosis, and 1 had Norman-Roberts syndrome.

Chiari malformation was diagnosed in 29 (8%) of the patients treated for craniosynostosis (Table 2, Fig. 1). Children with single-suture lambdoid synostosis ($p < 0.001$) or multisuture craniosynostosis ($p < 0.001$) were much more likely to have associated CM than all other patients with craniosynostosis (Fig. 2). Of the 9 individuals with isolated lambdoid synostosis, 5 (56%) were diagnosed with CM (Figs. 3 and 4) in contrast to no patients (0%) of those 71 with isolated metopic synostosis, 5 (3%) of the 183 with isolated sagittal synostosis, and 5 (6%) of the 80 with isolated coronal synostosis. Of the 40 patients with multisuture synostosis, 5 had pansynostosis defined as premature closure of all sutures (metopic, coronal, sagittal, and lambdoid), and 4 (80%) of these patients were diagnosed with CM. In patients with multisuture synostosis, 14 (35%) of 40 had CM compared with 15 (4%) of the 343 with single-suture involvement ($p < 0.001$). Including 5 patients with single-suture lambdoid craniosynostosis as well as 12 patients with lambdoid suture involvement in multisuture craniosynostosis, lambdoid synostosis was found in 17 patients (59%) with CM. Multisuture craniosynostosis without lambdoid suture involvement was not significantly more likely to be associated with CM (Table 2) than single-suture disease ($p = 0.3$). Of the patients with CM, 15 (52%) had associated hydrocephalus. Of the 29 patients with craniosynostosis and CM, 10 (34%) also had syringomyelia and 8 (28%) had associated abnormalities of cerebral venous drainage.

Each of the 29 patients underwent surgical correction for their craniosynostosis. The mean age at time of craniosynostosis repair was 1.8 years (range 2 months to 9 years). Of the patients who underwent surgical craniosynostosis

TABLE 2: Incidence of CM according to suture involvement*

Craniosynostosis Type	Total No. of Patients	No. of Patients w/ CM (%)	p Value†
single-suture			
sagittal	183	5 (2.8)	NS
coronal	80	5 (6.3)	NS
metopic	71	0 (0)	0.05‡
lambdoid	9	5 (55.6)	<0.01
total	343	15 (4.4)	
multiple sutures			
w/ lambdoid involvement	21	12 (57.1)	<0.01
w/o lambdoid involvement	19	2 (10.5)	<0.01‡
total	40	14 (35)	

* NS = not significant.

† Single-suture cases compared with other single-suture cases and multiple-suture cases compared with other multiple-suture cases.

‡ Negatively correlated with CM.

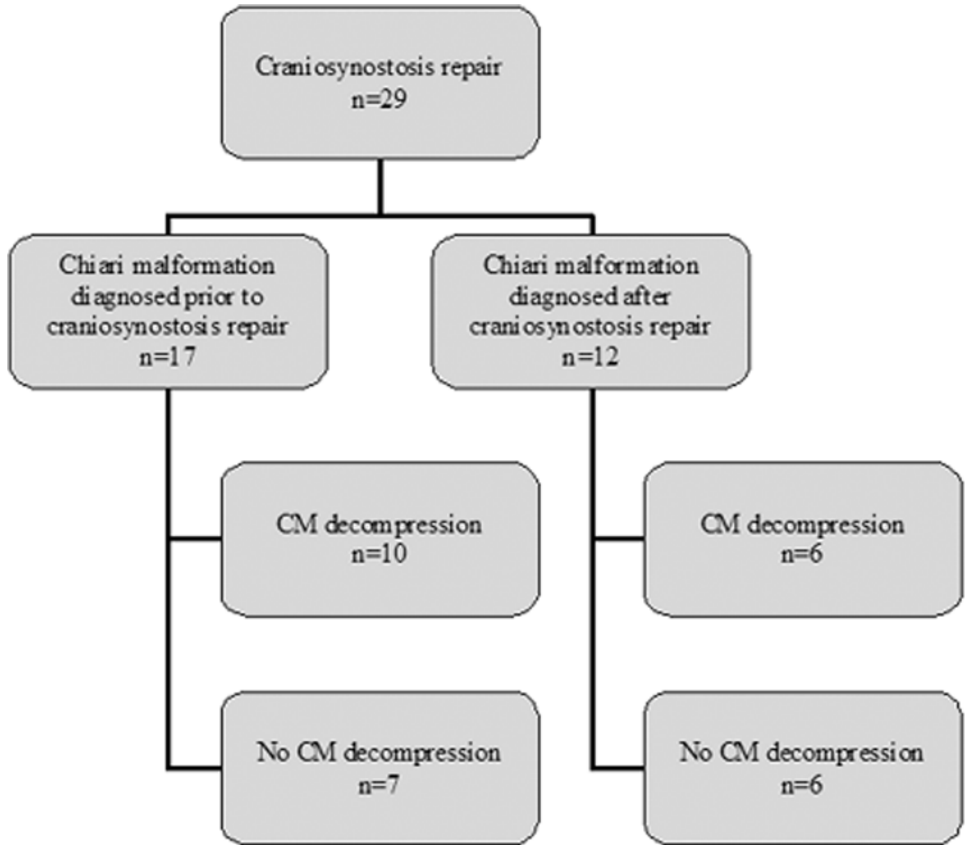

Fig. 1. Schematic treatment diagram for 29 patients with CM and craniosynostosis who underwent surgical repair of craniosynostosis.

repair, 17 were diagnosed with CM before undergoing surgical correction for craniosynostosis and 12 were diagnosed with CM following craniosynostosis repair.

Chiari Malformation Diagnosed Prior to Craniosynostosis Repair

Of the 17 patients diagnosed with CM prior to craniosynostosis repair, 10 underwent CM decompression. Five of these children were treated with simultaneous craniosynostosis repair and CM decompression. In each case, calvarial exposure of the posterior fossa was accomplished by reflecting the scalp posteriorly from a single bicoronal incision and performing a suboccipital craniectomy. In each case, the posterior arch of C-1 was never removed and the dura was never opened. In 3 patients, an initial craniosynostosis repair was followed by CM decompression, and in 2 CM decompression was performed prior to craniosynostosis repair. When CM decompression was carried out, either before or after craniosynostosis repair, the CM decompression was performed via a standard midline posterior scalp incision from the inion to the upper cervical spine, and a bony decompression was conducted. The dura mater was never opened. Seven patients diagnosed with CM prior to craniosynostosis repair did not undergo CM decompression at any time during the study period (Table 3). Of these, 6 had a decrease in tonsillar ectopia and 5 had improved CSF flow studies following craniosynostosis repair alone. The 2 patients in this group with syringes prior to craniosynostosis repair both had decreased syrinx width following craniosynostosis repair.

Chiari Malformation Diagnosed After Craniosynostosis Repair

Following craniosynostosis repair, 12 patients were diagnosed with CM. The mean age at time of CM diagnosis was 5.6 years (range 0–16 years) with a mean interval from the initial surgery of 3.7 years (range 197–2780 days). All of these patients underwent both cine MR imaging and spine MR imaging. At the time that CM was diagnosed, cine MR imaging revealed abnormal CSF flow in 10 (83%) of the 12 patients and spine MR imaging demonstrated a syrinx in 7 patients (58%). Five patients (42%) required more than 1 CVR procedure and 7 (58%) had increased ICP found after placement of an invasive ICP monitoring device. Six of these patients (50%) had tonsillar descent over 10 mm and CSF flow studies with restricted anterior and posterior flow at the foramen magnum. These patients ultimately underwent posterior fossa decompression at a mean interval of 3.4 years following the initial craniosynostosis repair.

Of the 12 patients diagnosed with CM following craniosynostosis repair, 5 had at least 1 prior MR imaging study that demonstrated normal tonsillar height, thus indicating de novo CM development. The mean interval between the initial repair and CM diagnosis in these patients was 3.5 years. Four of the patients with documented

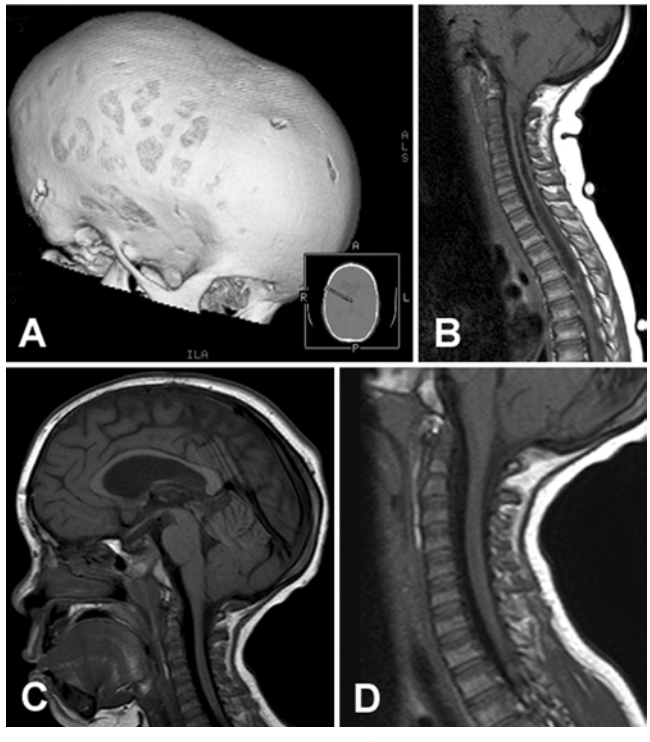

Fig. 2. Imaging studies obtained in a 3-year-old boy presenting with scaphocephaly. **A:** Reconstructed CT scan demonstrating fusion of the sagittal suture, coronal suture, and lambdoid sutures bilaterally, as well as lückenschädel of the skull. **Inset:** Two-dimensional depiction of the "viewing angle" that is depicted in the larger 3D image. **B:** Sagittal MR image showing cerebellar tonsillar descent with crowding at foramen magnum. The patient underwent cranial vault expansion and remodeling including frontoorbital advancement. No CM decompression was performed. **C:** Three years postoperatively, tonsillar descent has improved and there is less crowding at foramen magnum. **D:** The spinal syrinx has resolved.

de novo CM development had a history of hydrocephalus and VP shunt placement in the interim between craniosynostosis repair and CM diagnosis.

Discussion

An association between CM and craniosynostosis has been recognized for many years.[36] Chiari malformation is especially likely to be found in those with multisuture or syndromic craniosynostosis. Cinalli et al.[3,4] examined 95 patients with syndromic craniosynostosis and found CM in 70% of those with Crouzon syndrome, 75% of those with oxycephaly, 50% of those with Pfeiffer syndrome, and 100% of those with the Kleeblattschädel deformity.[26,43] Chiari malformation was found in only 1.9% of patients with Apert syndrome in that series.[4] Importantly, that group used cerebellar tonsillar descent of less than 2 mm below the basion-opisthion line as the diagnostic criterion, perhaps leading to a larger number of diagnosed cases of CM. Other reports, however, have confirmed the frequent association of CM with craniofacial syndromes.[7,9,33] Francis et al.[9] found an associated CM in 5 of 10 patients with Crouzon syndrome. Fearon and Rhodes[7] found that 84% of the 28 patients they treated for Pfeiffer syndrome had associated CM. Half of the children with

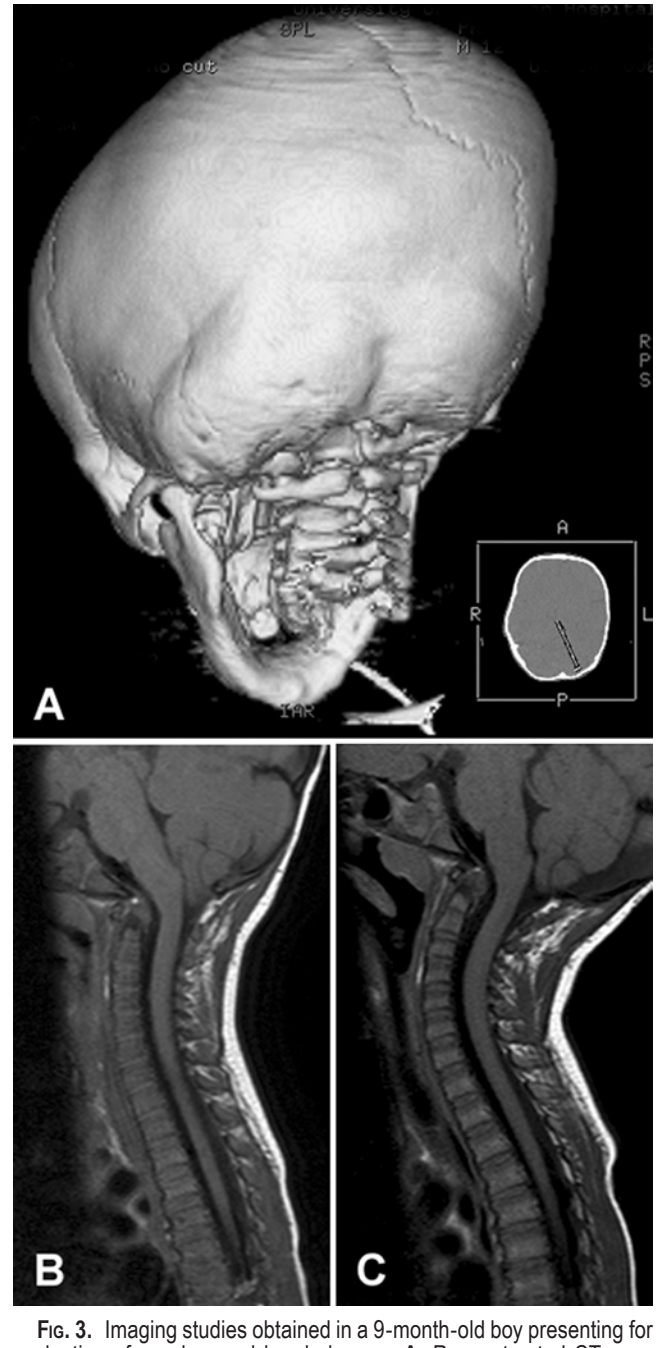

Fig. 3. Imaging studies obtained in a 9-month-old boy presenting for evaluation of an abnormal head shape. **A:** Reconstructed CT scan demonstrating synostosis of the left lambdoid suture. **Inset:** Two-dimensional depiction of the "viewing angle" that is depicted in the larger 3D image. **B:** Sagittal MR image showing cerebellar tonsillar descent to 5 mm below the foramen magnum. A posterior CVR with suboccipital craniectomy for CM decompression was performed. The dura was not opened. **C:** Two-year postoperative MR image revealing improvement in the degree of tonsillar descent and crowding at foramen magnum.

Pfeiffer syndrome underwent placement of a VP shunt for hydrocephalus, and CM was diagnosed in every patient in whom a VP shunt was placed. Because CM has been found so frequently in children with Pfeiffer syndrome, Fearon and Rhodes have advocated routine screening of these children with MR imaging.

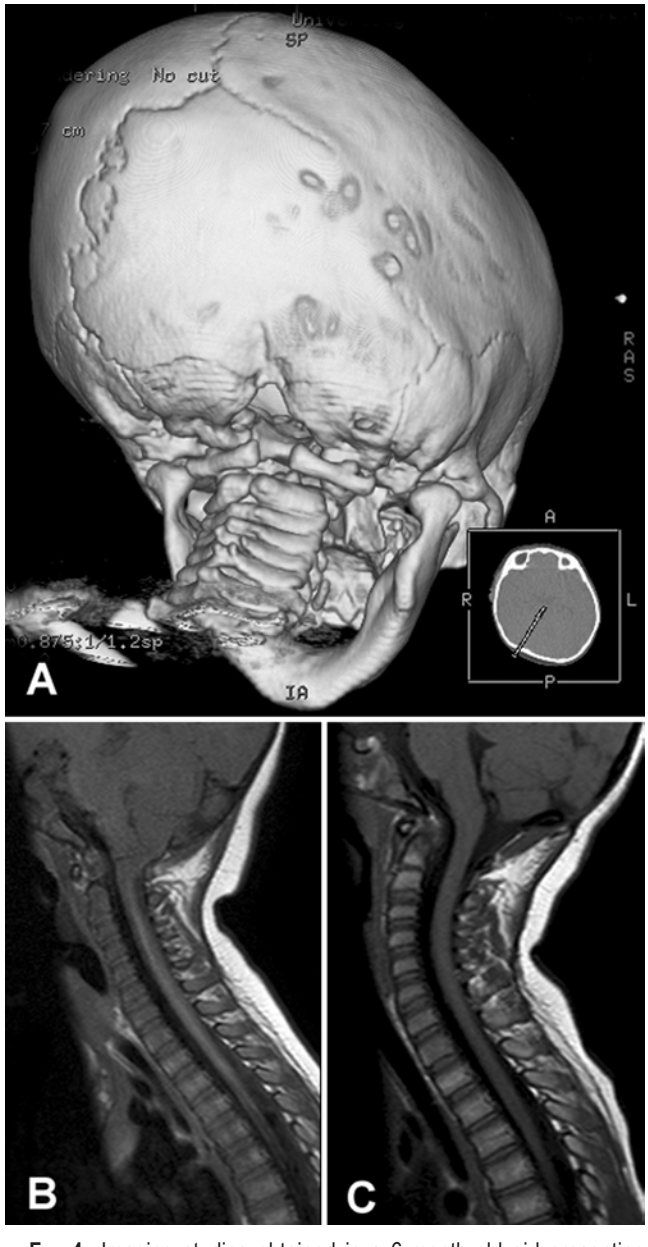

Fig. 4. Imaging studies obtained in a 6-month-old girl presenting for evaluation of severe plagiocephaly. **A:** Reconstructed CT scan confirming synostosis of the right lambdoid suture. **Inset:** Two-dimensional depiction of the "viewing angle" that is depicted in the larger 3D image. **B:** Sagittal MR image demonstrating cerebellar tonsillar descent in a pegged configuration consistent with a diagnosis of CM. The patient underwent posterior cranial vault reshaping including barrel-stave osteotomies and removal of suboccipital bone at the posterior rim of the foramen magnum. The dura was not opened and posterior arch of the first cervical vertebra was not removed. **C:** Two-year postoperative MR image demonstrating no evidence of a CM.

Many cases of single-suture nonsyndromic craniosynostosis associated with CM have also been reported.[2,17,25,41] Most of these cases involve the lambdoid suture, but CM has been reported even in conjunction with sagittal, metopic, and unilateral coronal synostosis.[2,17,25,41] Leikola et al.[17] reported on a series of 124 patients with single-suture craniosynostosis and, on imaging, found that 7 (5.6%) had CM. Sgouros et al.[38] showed that cranial base growth is altered in both multi- and single-suture craniosynostosis, even in cases that do not exhibit premature fusion of a cranial base synchondrosis. Tubbs et al.[41] found that 30% of those with metopic ridges had an associated CM, and they postulated that this may be the result of reduced anterior fossa volume. In our series, 15 (52%) of 29 patients with CM and craniosynostosis had single-suture disease, including syndromic and nonsyndromic cases. Five of these cases involved the lambdoid suture alone. We found CM in over half of all cases of isolated lambdoid synostosis. Chiari malformation was also found in isolated sagittal and coronal synostosis in 5 patients each when syndromic cases were included. Three patients with single-suture, nonsyndromic sagittal craniosynostosis and no patients with single-suture, nonsyndromic coronal craniosynostosis had associated CM. Because these sutures are involved much more often than the lambdoid suture, CM is significantly less associated with single-suture disease in these locations.

On the basis of the previously reported series and our own experience, we believe it is clear that syndromic and multisuture synostosis is frequently associated with CM. Furthermore, the frequent association of lambdoid synostosis with CM is well established.[4] Lambdoid suture involvement is predictive of CM formation even in patients with multisuture or syndromic forms of craniosynostosis.[4,43] Cinalli et al.[4] have postulated that CM is much more likely in patients with Crouzon syndrome than those with Apert syndrome, because the former is associated with significantly earlier closure of the sagittal and lambdoid sutures.

The frequency of CM in various types of craniosynostosis can guide the practitioner in the decision to obtain an MR imaging study to screen for CM. Cinalli et al.[5] found that approximately one-third of their patients who had CM associated with craniofacial disorders were either symptomatic or had a spinal cord syrinx. They advocated screening for CM in all patients with complex or syndromic craniosynostosis. We generally screen patients with syndromic craniosynostosis and patients with lambdoid synostosis with brain MR imaging prior to surgical correction of the craniosynostosis. We do not routinely screen asymptomatic individuals with single-suture craniosynostosis at locations other than the lambdoid suture.

Although some brain malformations associated with craniofacial disorders may be the primary result of a common genetic abnormality, most now believe that CM associated with craniosynostosis is acquired postnatally as a result of abnormal skull development.[27] Chiari malformation has been associated with underdevelopment of the occipital bone and a small posterior fossa,[21,22,24] as well as with primary bone disorders that affect the posterior fossa skull such as osteopetrosis and fibrous dysplasia.[30] Craniofacial disorders that lead to a small or deformed posterior fossa may result in crowding of posterior fossa contents and tonsillar descent in affected patients.[3] Most cases of CM associated with craniosynostosis are found after the prematurely fused suture has resulted in a significant skull deformity.[5] This assertion is supported by several reported cases of de novo CM formation follow-

TABLE 3: Effect of CVR without posterior fossa decompression on preoperatively diagnosed CM*

Case No.	Sex	Sutures	Pre-CVR			Post-CVR		
			Tonsillar Location†	CSF Flow‡	Syrinx	Tonsillar Location†	CSF Flow‡	Syrinx
1	F	coronal	C-1	decreased ant & pst	no	stable	improved	no
2	M	multiple	C-2	decreased pst	no	improved	improved	no
3	M	multiple	C-1	abnormal tonsillar motion	yes	improved	no change	decreased
4	M	multiple	C-2	decreased ant	no	improved	improved	no
5	M	multiple	C-2	decreased ant & pst	yes	improved	improved	decreased
6	M	multiple	unknown	unknown	no	improved	unknown	no
7	F	sagittal	C-2	decreased ant	no	improved	improved	no

* ant = anterior; pst = posterior.

† Tonsillar location is designated by vertebral level of tonsillar descent.

‡ Cerebrospinal fluid flow at the foramen magnum is described as decreased anterior, posterior, or demonstration of abnormal tonsillar motion.

ing diagnosis of a craniofacial syndrome. Hopkins and Haines[14] reported on a case of Seckel syndrome in a patient in whom rapid CM development was demonstrated on serial imaging. Ranger et al.[26] reported on a patient with Pfeiffer syndrome whose initial brain MR imaging findings were normal; 2 months after craniofacial reconstruction and VP shunt placement, however, MR imaging showed the development of CM, providing more evidence for an acquired pathogenesis. In patients with Crouzon syndrome, premature closure of the lambdoid suture is associated with an increased risk of CM.[4,11,20] Apert syndrome, however, which typically presents with a normal or larger than normal posterior fossa, is not associated with CM.[32]

Hydrocephalus is frequently associated with craniofacial anomalies and may occasionally play a role in CM pathogenesis in these patients.[4,9,10,43] Children with craniofacial disorders as well as hydrocephalus are more likely to have a CM than children with a craniofacial disorder in the absence of hydrocephalus.[4,9,34] Hydrocephalus has also been reported to develop after repair of craniosynostosis, with subsequent development of tonsillar herniation.[9,43] In our own series, 4 of the 5 patients with de novo CM on serial imaging developed hydrocephalus after craniosynostosis repair and were treated with VP shunt placement prior to the CM diagnosis. Our own results, combined with those of prior reports, suggest that hydrocephalus plays a role in the pathogenesis of CM in some cases.[4,9,10,34,43] We recommend routine screening for CM in patients with both craniosynostosis and hydrocephalus.

Craniofacial anomalies may be associated with venous outflow impairment that may lead to venous hypertension and increased ICP.[1,9,12,13,28,31,33,39,40] Some surgeons suggest that cerebellar tonsillar herniation may result from increased venous turgor.[9,28] Venous abnormalities are more often associated with complex and syndromic forms of craniosynostosis.[33,39] Abnormal venous anatomy must be accounted for when considering surgical treatment of CM associated with complex craniofacial syndromes. For this reason, we now screen all craniosynostosis and CM patients with preoperative CT venography to identify any transosseous venous channels. Furthermore, opening the dura for CM decompression in these cases may increase the risk of hemorrhage due to abnormal venous sinuses. In our experience, opening the dura has not been necessary for the treatment of CM in these patients. In some cases, preoperative detection of major venous collaterals at the site of a proposed CM decompression may suggest that even bone removal at the foramen magnum is not safe and should not be performed.[1,37]

In general, most surgeons agree that CM should not be treated unless it is symptomatic or, in some cases, associated with a spinal syrinx. It is possible that the indications for surgical treatment of CM may be different for individuals with associated craniosynostosis. In some cases, CM decompression can be done simply at the time of a planned craniosynostosis repair. In this retrospective analysis, it is impossible to accurately describe all of the factors that went into each surgical decision. In general, we approach patients with both lambdoid synostosis and CM with an eye to expanding the posterior vault with over-correction. When a significant CM is seen on preoperative imaging, we often will include a posterior fossa decompression in the operation to repair the craniosynostosis. To the limits of this retrospective analysis, we do not believe that CSF flow was ever used as an important criterion for performing a posterior fossa decompression. Several groups recommend posterior fossa expansion surgery as the treatment of choice for all cases of CM identified prior to craniosynostosis correction, even in the absence of symptoms.[5,38,44] It is possible that, in many instances, the CM will resolve or improve following craniosynostosis repair (Table 3). Di Rocco and Velardi[6] reported on a single case in which a supratentorial cranial expansion resulted in resolution of an acquired CM. Given the very young age of patients undergoing craniosynostosis repair, it is important to consider that any bony decompression may be less durable compared with CM decompression performed later.[35] For this reason, Fearon and Rhodes[7] have advocated delaying posterior remodeling procedures in patients with Pfeiffer syndrome until at least 13 months of age. For patients with CM diagnosed before craniosynostosis repair, we reserve CM decompression for patients who exhibit symptoms of CM or a spinal cord syrinx af-

ter an extended interval following surgical correction of the skull deformity. Exceptions may be made if the CM is symptomatic or associated with a spinal syrinx. The presence of posterior fossa transosseous venous collaterals, however, would lead us to reconsider any posterior fossa decompression.

In cases associated with hydrocephalus or intracranial hypertension, it may be necessary to treat the hydrocephalus or relieve the ICP to treat the CM. Pouratian et al.[25] have reported on 2 cases of acquired CM associated with craniosynostosis and hydrocephalus that were initially treated with CSF diversion. Others have also reported on CM development after treatment of hydrocephalus.[9,28] The role of endoscopic third ventriculostomy is not clear. Fearon et al.[8] reported on a small series of patients with craniofacial dysostosis, CM, and hydrocephalus; patients who did not require surgical management of the CM underwent endoscopic third ventriculostomy, in contrast to those treated with a VP shunt for their hydrocephalus. In most cases, we prefer to treat the hydrocephalus with a shunt procedure prior to treating CM.

There are several limitations to our study. In this retrospective analysis, the treating physicians may have recommended a different treatment for patients depending on the perceived severity of the craniosynostosis or the CM. Patients with symptoms, a spinal syrinx, or a greater degree of tonsillar cerebellar descent were more likely to be surgically treated. Therefore, any attempt to compare outcomes of patients by treatment pattern will reflect this selection bias. Furthermore, MR imaging was not performed in all patients presenting with craniosynostosis. Our selective use of MR imaging in patients with craniosynostosis has resulted in a sampling bias that must be considered in any analysis of these results. Sampling bias also needs to be considered when pondering the role of hydrocephalus in these patients, because individuals with hydrocephalus were more likely to undergo repeated imaging. Although we reported on a large number of patients with craniosynostosis, CM presentations and treatments were diverse in this group of patients. This diversity resulted in relatively small sample sizes for the analysis of individual treatment strategies. Finally, none of the patients in this series were treated using minimally invasive strip craniectomy techniques that are increasingly used for treatment of craniosynostosis.[15,16,19] It is possible that these techniques will result in different rates of occurrence and different treatment outcomes for CM.

Conclusions

Chiari malformation is seen frequently in patients with syndromic, multisuture and single-suture synostosis of the lambdoid suture. In some cases, the CM and craniosynostosis present concurrently. In other patients, we have noted the development of CM after the surgical treatment of the craniosynostosis. In patients presenting with both CM and craniosynostosis, we recommend treating the craniosynostosis first, with simultaneous posterior fossa expansion only if there are neurological symptoms or spinal syringes. When CM decompression is not carried out at the time of craniosynostosis repair, it should be considered if neurological symptoms or a spinal syrinx persist after the initial surgery. Neurosurgical follow-up is particularly necessary for patients with multisuture, syndromic, or lambdoid craniosynostosis, as well as for those patients requiring treatment of hydrocephalus.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Maher, Muraszko. Acquisition of data: Strahle, Maher, Kapurch. Analysis and interpretation of data: all authors. Drafting the article: Maher, Strahle. Critically revising the article: Maher, Muraszko, Buchman, Garton. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Maher. Statistical analysis: Maher. Study supervision: Maher, Muraszko, Garton, Buchman.

Acknowledgment

The authors thank Holly Wagner for providing editorial assistance.

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Manuscript submitted May 15, 2011.
Accepted June 8, 2011.

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Neurosurg Focus 31 (3):E3, 2011

Associated disorders of Chiari Type I malformations: a review

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A single pathophysiological mechanism of Chiari Type I malformations (CM-I) has been a topic of debate. To help better understand CM-I, the authors review disorders known to be associated with CM-I. The primary methodology found among most of them is deformation of the posterior cranial fossa, usually with subsequent decrease in volume. Other mechanisms exist as well, which can be categorized as either congenital or acquired. In understanding the relationship of such disorders with CM-I, we may gain further insight into the process by which cerebellar tonsillar herniation occurs. Some of these pathologies appear to be true associations, but many appear to be spurious. *(DOI: 10.3171/2011.6.FOCUS11112)*

Key Words • **hindbrain** • **herniation** • **tonsillar ectopia** • **Chiari malformation**

In the late 19th century, Hans Chiari[7] discovered and classified 3 types of rhombencephalic congenital anomalies that would later be termed Chiari malformation Types I, II, and III. Dr. Chiari postulated that the cerebellar herniation might have been due to hydrocephalus with the 3 different types representing various degrees of disease progression.[31] In the ensuing years, Chiari's mechanism of pathogenesis would be disproven as the primary cause of CM-I. Among the classifications, however, no current consensus exists for the exact pathogenesis or treatment regimen for all.[67] Many have formed theories such as the hindbrain dysgenesis and developmental arrest theory, caudal traction theory, small posterior fossa/hindbrain overgrowth theory, hydrocephalus and hydrodynamic theory of Gardner, and the lack of embryological ventricular distention theory, yet no single theory has been able to prove a single pathway in the pathogenesis of CM-I.[3,12,15,30,34,36,40,42,43,47,55,70,75] This article, however, will not review each of those theories. Instead, it intends to document the conditions associated with CM-I to potentially provide insight into how the pathophysiological mechanism of one condition, no matter how remote, might lead to the development of CM-I. Many of these associations are summarized in Table 1. It should also be noted that many of these associations may be incidental; an asymptomatic hindbrain hernia has been identified due to testing for other pathological entities (such as endocrinopathies).

Abbreviations used in this paper: CHERI = CM-I with or without cleft palate, deviant electroencephalography or epilepsy, and retarded intelligence with delayed language development; CM-I = Chiari malformation Type I.

Pathophysiology

Morphometric studies by Schady et al.[59] and Milhorat et al.[36] have provided evidence that the volume of the posterior cranial fossa in patients with CM-I was 23% less than controls. Furthermore, Badie and colleagues[3] discovered the ratio of posterior fossa volume to supratentorial space was significantly lower in symptomatic CM-I patients compared with control patients. Marin-Padilla and Marin-Padilla[32] added to the understanding of this anatomical pathology by inducing underdevelopment of the basiocciput and posterior fossa in hamsters through high doses of vitamin A. In doing so, these authors demonstrated how impairing posterior fossa development could induce caudal displacement of the cerebellum. Others, however, have challenged this proposition with studies showing no difference in posterior fossa volume.[79] Additional morphological findings in CM-I may include an underdeveloped supraocciput and exocciput, large foramen magnum, short clivus, and longer anterior cranial fossa.[44,62,80] Therefore, while it may be a common school of thought, a smaller posterior fossa does not necessarily lead to CM-I.

TABLE 1: Disorders associated with CM-I

craniosynostosis
Antley-Bixler syndrome
Apert syndrome
Crouzon syndrome
Jackson-Weiss syndrome
Kleeblattschädel syndrome
Loeys-Dietz syndrome Type I
Seckel syndrome
Shprintzen-Goldberg syndrome
endocrinology
achondroplasia
acromegaly
growth hormone deficiency
hyperostosis
craniometaphyseal dysplasia
erythroid hyperplasia
osteopetrosis
Paget disease
bone mineral deficiency
familial vitamin D–resistant rickets
cutaneous disorders
acanthosis nigricans
blue rubber bleb nevus syndrome
giant congenital melanocytic nevi
LEOPARD syndrome
macrocephaly-cutis marmorata telangiectatica congenita
neurofibromatosis Type I
phacomatosis pigmentovascularis Type II
Waardenburg syndrome
spinal defects
atlantoaxial assimilation
basilar impression
caudal regression syndrome
Klippel-Feil syndrome
lipomeningomyelocele
odontoid retroflexion
spondyloepiphyseal dysplasia
space-occupying lesions
other
Beckwith-Wiedemann syndrome
CHERI
cloacal exstrophy
Costello syndrome
cystic fibrosis
Ehlers-Danlos syndrome
Fabry disease
Kabuki syndrome
Pierre-Robin syndrome
situs inversus
Williams-Beuren syndrome

Hydrocephalus

Hans Chiari's aforementioned original theory regarding the causative association between hydrocephalus and hindbrain herniation has not allowed for an all-encompassing explanation into the pathophysiology of CM-I. Nonetheless, hydrocephalus is noted in approximately 4%–18% of patients with CM-I.[3,70] Tubbs et al.,[65] in a review of 500 patients with CM-I treated between 1989 and 2010, demonstrated that 9.8% of patients had concomitant hydrocephalus. These patients all required CSF diversion in addition to an operative posterior fossa decompression. This association is likely secondary to fourth ventricular outflow tract obstruction or concurrent aqueductal stenosis. As a result, endoscopic third ventriculostomy has been used with success in this patient population.

Craniosynostosis

Craniosynostosis and CM-I is a well-documented association first noted by Saldino et al.,[58] in which certain patients will have abnormalities in the skull base with subsequent decreased posterior fossa volume and tonsillar herniation. More specifically, this most often occurs when the lambdoid sutures fuse too early in skull development, which is representative of 1% of all types of craniosynostosis.[21] Synostosis can exist solitarily or as part of a syndrome such as Crouzon (72.7%), Apert (1.9%), Pfeiffer (50%), and Kleeblattschädel syndromes (100%).[8,9] Additional studies estimated the Crouzon syndrome association to be as high as 70%.[63] Moreover, CM-I is now believed to be associated with Pfeiffer Type II,[50] Jackson-Weiss,[46] Seckel,[22] Antley-Bixler,[6] and Shprintzen-Goldberg syndromes[17] as well. In each of these associated syndromes, CM-I is not present at birth because the lambdoid suture has not yet fused. The incidence and severity, however, has been correlated to the time of closure.[24,54] Therefore, the higher incidence of CM-I in patients with Crouzon syndrome can be explained by the timing of fusion of involved sutures as compared with Apert syndrome.[8] Normally, the skull continues to expand along with brain growth until the age of 16 years.[37]

Although lambdoid synostosis is the most common type of craniosynostosis to be associated with CM-I, evidence of additional premature suture closures leading to CM-I is growing. In utero synostosis of the sagittal and coronal sutures, for example, can force neural growth posteriorly and inferiorly as is present in the association with Loeys-Dietz syndrome.[57] As a result, the attachment of the tentorium cerebelli is displaced toward the foramen magnum with subsequent reduction in posterior fossa size and development of CM-I.[9] Additionally, Tubbs et al.[66] reported a 30% incidence of CM-I associated with simple metopic ridging without signs of trigonocephaly; Tubbs et al.[65] hypothesized that this was the result of a decrease in anterior cranial fossa volume.

Endocrinopathy

Reduced posterior fossa volume is also observed in other medical conditions, including those involved in cell signaling. For example, growth hormone deficiency has been linked to CM-I in 5%–20% of patients with growth hormone deficiency.[20,77] This endocrine deficiency in children is believed to be a physiological mechanism for insufficient development of the posterior fossa with resultant tonsillar herniation.[78] While the posterior fossa volume of patients with growth hormone deficiency has

not been found to be significantly smaller, research has shown certain bone structures to be underdeveloped, similar to those commonly noted in patients with CM-I.[78] Additionally, somatotropin replacement therapy in patients with growth hormone deficiency and CM-I has resulted in improvement of tonsillar herniation with stabilization in syrinx size in some patients.[80] Conclusive evidence, however, of the pathophysiological mechanism and possible treatments has yet to be determined.

Acromegaly has also been implicated as an endocrine-related disorder causing CM-I, which also fits in the category of hyperostosis (excessive bone growth). In this scenario, an excessive amount of growth hormone is believed to thicken the bones of the posterior fossa, resulting in CM-I. Chiari Type I malformation has also been observed in patients with achondroplasia because of the small, shallow posterior cranial fossa present in these patients.[38]

Hyperostosis

When hyperostosis affects the posterior fossa, it can often lead to CM-I. Paget disease of the skull is one example in which exaggerated bone turnover leads to thickening and deformation of bones. When this process takes place in the skull, it can compromise the posterior fossa and in a few cases has been reported to result in CM-I. Both Iglesias-Osma et al.[23] and Richards et al.[53] have described cases of this association but few others have been reported.

Cases of CM-I relating to craniometaphyseal dysplasia are also exceedingly rare, but have nonetheless been noted in the past. Craniometaphyseal dysplasia, similar to the other types of hyperostosis, can manifest with CM-I due to abnormal bone formation and progressive thickening. Of the few cases, Sewell and colleagues[61] documented cervicomedullary compression as well. Chiari Type I malformation secondary to osteopetrosis[26] and erythroid hyperplasia[51] have been documented but are also considered to be exceptionally rare.

Bone Mineral Deficiency

In regard to bone mineral deficiencies, patients with familial vitamin D–resistant rickets have a higher incidence of CM-I,[5] believed to be due to overcrowding of the posterior fossa. In this condition, bone overgrowths and calvarial thickening as a result of low serum phosphate has been proposed to be the attributing factor. Further studies, however, have not found a difference in rachitic patients' posterior fossa volumes, and thus the pathophysiological mechanism remains unknown.[74] Kuether and Piatt[25] suggested in a case study that CM-I development from rickets is due to foramen magnum stenosis. Interestingly, Renier et al.[52] discovered that among 129 patients with oxycephaly, 15% suffered from rickets.

Cutaneous Disorders

Although it may not be considered a traditional association, cutaneous disorders are frequently reported to occur in conjunction with CM-I. One such disorder is neurofibromatosis Type I, in which a relationship as high as 8% has been reported.[71] Some investigators have hypothesized that mesodermal deficiency arrests posterior cranial fossa development, which is also proposed to occur in cutaneous disorders such as neurofibromatosis Type I.[36]

Equally mysterious is the association of CM-I with macrocephaly-cutis marmorata telangiectatica congenita,[73] which is characterized by benign spider nevuslike telangiectasias and superficial ulcerations, but little is known about the pathology. Hence, no mechanism has been suggested for the association.

Several other cutaneous disorders have been suggested as having an association with CM-I, including LEOPARD syndrome,[1] blue rubber bleb nevus syndrome,[27] giant congenital melanocytic nevi,[14] phacomatosis pigmentovascularis Type II,[11] acanthosis nigricans,[33] and Waardenburg syndrome variants.[41] These associations are all based on rare case reports and thus may have occurred coincidentally with CM-I.

Spinal Defects

Not all causes of CM-I have been shown to be directly related to the posterior fossa and skull base. A few disorders, such as spondyloepiphyseal dysplasia,[18] caudal regression syndrome,[68,69] Klippel-Feil syndrome, atlantoaxial assimilation, basilar impression, and odontoid retroflexion (in which the vertebral column is the site of deformation) are also associated with CM-I. Little is known about the pathophysiology of these spinal deformities, but it is believed that difficulty in equilibrating the dynamic CSF pulse pressure induced by the Valsalva maneuver is responsible for the CM-I presentation.

Lipomeningomyelocele has also proven to be coupled with CM-I in as many as 3%–6% of patients.[2,4] It has been postulated that a decrease in intracranial nervous tissue and CSF due to the lipomeningomyelocele removes the expansile pressure of the brain on the skull, thus causing the posterior fossa to be smaller and less developed.[76]

Space-Occupying Lesions

To this point, all disorders mentioned in association with CM-I have been congenital, but acquired methods of CM-I manifestation exist as well. This category includes both space-occupying lesions and CSF leaks. Space-occupying lesions within the posterior cranial fossa can be caused by a variety of disorders, ranging from brain tumors to hematomas. These can include supratentorial[45] and infratentorial[64] lesions. The multitude of potential space-occupying lesions is vast and thus beyond the scope of this review.

Not Otherwise Specified

A case of Beckwith-Wiedemann syndrome in association with CM-I has been reported. Tubbs and Oakes[68] hypothesized that the pathological mechanism responsible for the CM-I was hemihypertrophy involvement of the skull. Beckwith-Wiedemann in combination with CM-I,

however, is exceedingly rare as no other case reports could be found. Costello syndrome has also been recognized as presenting with concomitant CM-I, although it, too, is described as having a low frequency association.[64] Both hemihypertrophy[56] and growth hormone deficiency[29] have been reported in patients with Costello syndrome and CM-I; therefore, there may be a common pathogenesis. Furthermore, an association of Marfan syndrome with CM-I is commonly recognized due to intracranial hypotension.[49] Additionally, associations with Williams-Beuren syndrome have been found with morphometric analyses suggesting a diminished posterior fossa leading to CM-I.[13,48] Finally, associations with disorders such as cystic fibrosis,[39] Pierre-Robin syndrome,[28] Ehlers-Danlos syndrome,[35] Fabry disease,[16] Kabuki syndrome,[10] situs inversus,[60] CHERI,[19] and cloacal exstrophy[72] have been made with no clear pathophysiological mechanism yet identified.

Conclusions

There exists a plethora of diseases affiliated with CM-I, many of which have been mentioned in this article and certainly more to be discovered in the future. While the final outcome of CM-I may be the same, the strength of the correlation and pathophysiological mechanisms of each differs greatly and some may be spurious associations. Thus, the need for additional genetic research and investigation of CM-I continues.

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: Tubbs, Oakes. Acquisition of data: Tubbs, Loukas, Shayota, Oelhafen. Analysis and interpretation of data: Tubbs, Miller, Oakes. Drafting the article: Tubbs, Loukas, Miller. Critically revising the article: Tubbs, Shayota, Oelhafen, Chern. Reviewed submitted version of manuscript: Tubbs, Loukas, Chern, Miller, Oakes. Approved the final version of the manuscript on behalf of all authors: Tubbs.

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Manuscript submitted May 20, 2011.
Accepted June 17, 2011.
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Neurosurg Focus 31 (3):E4, 2011

Volumetric analysis of syringomyelia following hindbrain decompression for Chiari malformation Type I: syringomyelia resolution follows exponential kinetics

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Object. Resolution of syringomyelia is common following hindbrain decompression for Chiari malformation, yet little is known about the kinetics governing this process. The authors sought to establish the volumetric rate of syringomyelia resolution.

Methods. A retrospective cohort of patients undergoing hindbrain decompression for a Chiari malformation Type I with preoperative cervical or thoracic syringomyelia was identified. Patients were included in the study if they had at least 3 neuroimaging studies that detailed the entirety of their preoperative syringomyelia over a minimum of 6 months postoperatively. The authors reconstructed the MR images in 3 dimensions and calculated the volume of the syringomyelia. They plotted the syringomyelia volume over time and constructed regression models using the method of least squares. The Akaike information criterion and Bayesian information criterion were used to calculate the relative goodness of fit. The coefficients of determination R^2 (unadjusted and adjusted) were calculated to describe the proportion of variability in each individual data set accounted for by the statistical model.

Results. Two patients were identified as meeting inclusion criteria. Plots of the least-squares best fit were identified as $4.01459e^{-0.0180804x}$ and $13.2556e^{-0.00615859x}$. Decay of the syringomyelia followed an exponential model in both patients ($R^2 = 0.989582$ and 0.948864).

Conclusions. Three-dimensional analysis of syringomyelia resolution over time enables the kinetics to be estimated. This technique is yet to be validated in a large cohort. Because syringomyelia is the final common pathway for a number of different pathological processes, it is possible that this exponential only applies to syringomyelia related to treatment of Chiari malformation Type I. *(DOI: 10.3171/2011.6.FOCUS11106)*

Key Words • **Chiari malformation** • **syringomyelia** • **syrinx** • **MR imaging** • **volumetrics**

Chiari malformation Type I is defined as caudal displacement of the cerebellar tonsils below the level of the foramen magnum, causing compression of the brainstem and upper cervical cord. The diagnostic criteria have been debated because the absolute degree of descent below the level of the foramen magnum may be less important than the degree of compression of the cervicomedullary junction. Individuals can remain asymptomatic despite a significant descent of the tonsils, and conversely, patients can be symptomatic with little to no caudal displacement of the tonsils.[10]

Compression of the spinal cord, whether caused by CM-I, by a disc herniation, or by a mass lesion, has been associated with syringomyelia. The mechanism of syringomyelia formation is poorly understood, and several hypotheses have been proposed.[6,8,9,11] Some have postulated that the drainage of CSF produced by the ependymal cells of the central canal is blocked, leading to a caudal accumulation of fluid. Others have argued that, in the case of CM-I, occlusion of the foramen magnum causes the intracranial CSF pulsations to be driven into the central canal or into the spinal Virchow-Robin spaces instead of its normal egress via the spinal subarachnoid space.[8] Although the theory postulated by Oldfield et al. may be the most accurate,[7,14] the pathogenesis may be an amalgamation of many theories, including those by Gardner,[5] Williams,[22] Ball and Dayan,[4] Aboulker,[1,2] and Greitz.[6]

Regardless of mechanism, it has long been recognized that restoration of CSF flow around the spinal cord is associated with a resolution of syringomyelia.[21] The kinetics governing resolution of syringomyelia following decompression of the spinal cord remains to be elucidated. In this study, we performed a volumetric analysis of syringomyelia after CM-I decompression and examined the pattern of decay.

Abbreviation used in this paper: CM-I = Chiari malformation Type I.

Methods

We identified patients with CM-I and syringomyelia who underwent hindbrain decompression. Patients were included for analysis if there were at least 3 postoperative MR images detailing the entire extent of their preoperative syringomyelia, allowing a curve to be plotted. The volume at each time point was calculated by importing DICOM data into OsiriX open-source software (Pixmeo) and identifying the syringomyelia as the region of interest (Fig. 1). Axial coherent oscillatory state acquisition for the manipulation of image contrast (COSMIC) sequences were used for this, allowing for optimal differentiation between the CSF and spinal cord.[20] The 3D volume was rendered and calculated (Fig. 2).[16] We then plotted the syringomyelia volume over time and constructed regression models using the method of least squares.[12] The Akaike information criterion[3] and Bayesian information criterion[17] were used to calculate the relative goodness of fit. The coefficients of determination R^2 (unadjusted and adjusted) were calculated to describe the proportion of variability for each individual data set accounted for by the statistical model. An independent biostatistician validated the study methodology and data analysis.

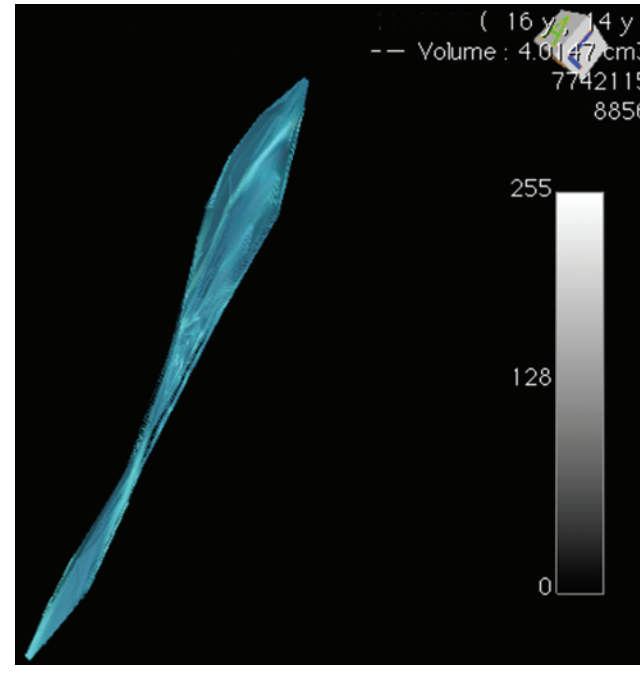

Fig. 2. Three-dimensional reconstruction. Using consecutive regions of interest, a 3D volume was rendered and quantitatively calculated.

Results

Two patients were identified as meeting inclusion criteria. Plots of the least-squares best fit were identified as $4.01459e^{-0.0180804x}$ for the patient in Case 1 and $13.2556e^{-0.00615859x}$ for the patient in Case 2 (Fig. 3). Decay of the syringomyelia followed an exponential model closely in both patients as evidenced by Akaike information criterion, Bayesian information criterion, R^2, and R^2-adjusted in Case 1 of 4.77068, 2.92957, 0.989582, and 0.979164, respectively. Case 2 had comparable values of 18.4951, 16.654, 0.948864, and 0.897728, respectively.

Discussion

It is unclear why syringomyelia only develops in a subset of individuals with CM-I. The condition may be related to the degree of compression rather than to the absolute caudal migration of the cerebellar tonsils or to unidentified factors. Other compressive lesions at the cervicomedullary junction can cause syringomyelia.[19] The resolution of syringomyelia after CM-I decompression, however, is well characterized and occurs in the majority of cases.[21] Instances in which syringomyelia fails to resolve postoperatively can be due to arachnoid webbing, extra- or intradural adhesions or scarring, or failure to adequately decompress the craniocervical junction.[7,18] Interestingly, syringomyelia can also resolve spontaneously on rare occasions.[9] Wetjen and coauthors[21] have estimated the rate of syringomyelia resolution by examining the postoperative images in patients after CM-I decompression. Based on the largest anteroposterior diameter of the syringomyelia, the authors concluded that the median time to greater than 50% narrowing of the syringomyelia was 3.6 months postoperatively, whereas the

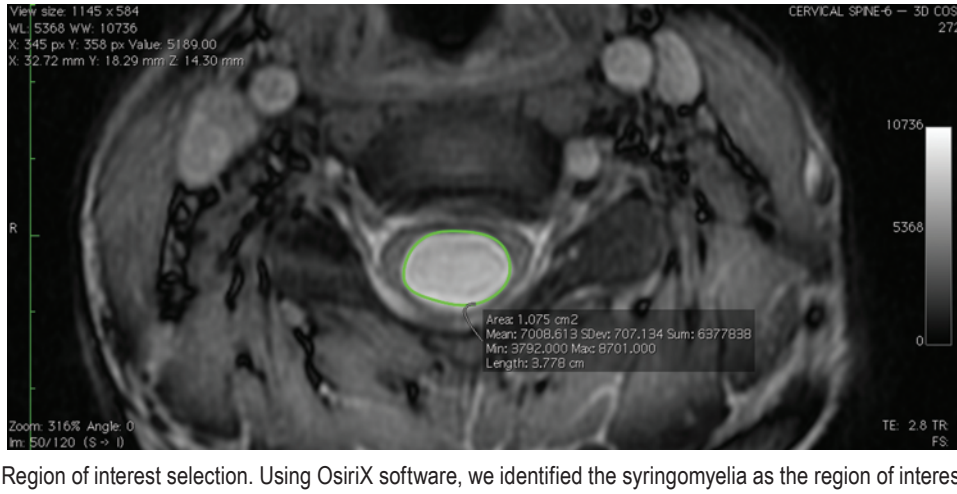

Fig. 1. Region of interest selection. Using OsiriX software, we identified the syringomyelia as the region of interest.

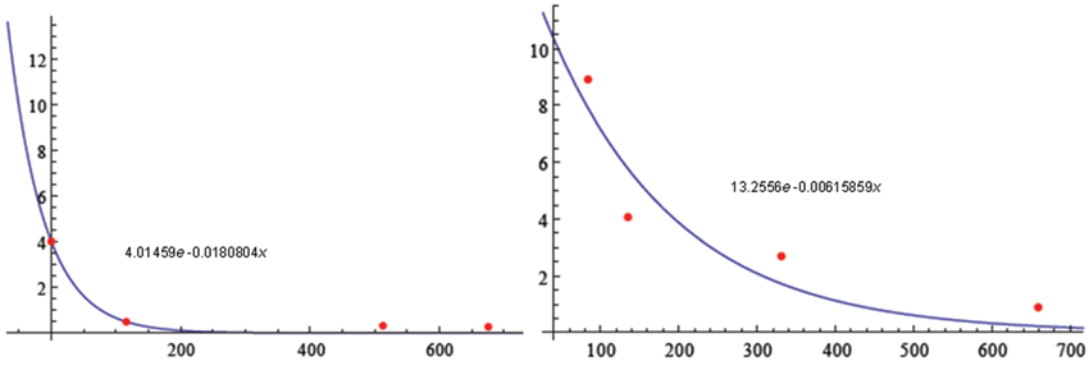

Fig. 3. Rate of syringomyelia decay. Plots of the least-squares best fit in Cases 1 **(left)** and 2 **(right)**. x axis = number of days following surgery; y axis = syringomyelia volume (cm^3). **Left:** Wolfram Alpha LLC. 2011. Wolfram|Alpha. http://www.wolframalpha.com/input/?i=exponential+fit+{0%2C+4.0147}%2C+{116%2C+0.4918}%2C+{513%2C0.3165}%2C+{676%2C0.2689} (Accessed July 14, 2011). **Right:** Wolfram Alpha LLC. 2011. Wolfram|Alpha. http://www.wolframalpha.com/input/?i=exponential+fit+{84%2C8.916}%2C+{135%2C+4.0665}%2C+{331%2C2.6985}%2C+{659%2C+0.8934} (Accessed July 14, 2011).

mean time was 6.5 months. To our knowledge, these are the best data available on the rate of syringomyelia resolution after CM-I decompression, although volumetric analysis related to Chiari malformation and interval changes over time go back as far as Nyland and Krogness.[13]

Most authors describe a syringomyelia by its width or by its cranial to caudal extent. Although measuring its diameter on axial imaging or its longitudinal extent over time allows one to estimate the size of a syringomyelia, it is not a direct measurement of volume. Because a syrinx is an irregular 3D structure, MR imaging–based volume measurement as suggested in this study may be a more precise measurement than linear dimension estimates. In this study, we plotted the volume of a syringomyelia over time and found that its resolution follows exponential decay. Potential implications of this technique are that, if validated, volumetric resolution of a syrinx may be correlated with the adequacy of hindbrain decompression.

The factors governing the rate of syringomyelia resolution may be complex and depend on the viscosity of the syringomyelia fluid, the shape of the cavity, the elasticity of the spinal cord, and the transmural pressure. Although flow in elastic tubes such as blood vessels has been modeled,[15] little is known about the kinetics of syringomyelia. It is likely that the kinetics are more complex than the simple emptying of a container or balloon (Fig. 3). Syringomyelia can take months to empty after surgery, suggesting that complex factors affect this process. Ultimately, the volume of a syringomyelia represents the net difference between factors governing its accumulation and those affecting its drainage, and volumetric measurements over time as in the current study do not allow one to characterize these opposing forces. It appears that emptying of the syringomyelia is not limited by the outflow rostrally through the central canal. If this were the case (simply losing fluid volume through a very narrow central canal), one would expect the bottleneck at the rostral aspect to be the limiting factor and one would see a linear decline in volume over time. In this instance, the exponential decay suggests that the rate of loss is dependent on the residual volume: the greater the residual volume, the greater the rate of egress.

Conclusions

Three-dimensional analysis of syringomyelia resolution following surgery over time enables the kinetics to be estimated and can be described as exponential decay. This analysis should be interpreted as an unvalidated metric that will need to be assessed in a larger group to establish a generalizable mechanism of syrinx resolution. Because syringomyelia is the final common pathway for a number of different pathological processes, it is possible that this exponential decay only applies to syringomyelia related to treatment of CM-I.

Disclosure

This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Institutes of Health Award No. UL1 RR 025758 and financial contributions from Harvard University and its affiliated academic health care centers). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, the National Center for Research Resources, or the National Institutes of Health. The authors used the open-source software OsiriX Imaging Software for volumetric analysis. This open-source version does not have FDA 510(k) clearance for clinical use in the US.

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

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Manuscript submitted May 15, 2011.
Accepted June 23, 2011.

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Neurosurg Focus 31 (3):E5, 2011

Standard and cardiac-gated phase-contrast magnetic resonance imaging in the clinical course of patients with Chiari malformation Type I

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Object. The causal treatment of Chiari malformation Type I (CM-I) consists of removing the obstruction of CSF flow at the level of the foramen magnum. Cerebrospinal fluid flow can be visualized using dynamic phase-contrast MR imaging. Because there is only a paucity of studies evaluating CSF dynamics in the region of the spinal canal on the basis of preoperative and postoperative measurements, the authors investigated the clinical usefulness of cardiac-gated phase-contrast MR imaging in patients with CM-I.

Methods. Ninety patients with CM-I underwent preoperative MR imaging of CSF pulsation. Syringomyelia was present in 59 patients and absent in 31 patients. Phase-contrast MR imaging of the entire CNS was used to investigate 22 patients with CM-I before surgery and after a mean postoperative period of 12 months (median 12 months, range 3–33 months). In addition to the dynamic studies, absolute flow velocities, the extension of the syrinx, and tonsillar descent were also measured.

Results. The changes in pulsation were highly significant in the region of the (enlarged) cistern ($p = 0.0005$). Maximum and minimum velocities (the pulsation amplitude) increased considerably in the region where the syrinx was largest in diameter. The changes of pulsation in these patients were significant in the subarachnoid space in all spinal segments but not in the syrinx itself and in the central canal.

Conclusions. The demonstration of CSF flow pulsation can contribute to assessments of surgical outcomes. The results presented here, however, raise doubts about current theories on the pathogenesis of syringomyelia. *(DOI: 10.3171/2011.7.FOCUS11105)*

Key Words • Chiari malformation Type I • syringomyelia • phase-contrast magnetic resonance imaging • cerebrospinal fluid pulsation

For decades it was assumed in the literature that patients with CM-I were a homogenous group. Milhorat,[21] however, defined 5 subtypes of CM-I associated with different causative factors: 1) constriction of the posterior cranial fossa occurring with classic CM-I; 2) downward traction of the spinal cord occurring with tethered cord syndrome and occult tethered cord syndrome; 3) hypermobility of the atlantooccipital and atlantoaxial joints; 4) increased intracranial pressure; and 5) intraspinal hypotension. Yet there is general agreement that the most common cause of CM-I is a smaller than normal posterior fossa volume.[1]

Abbreviation used in this paper: CM-I = Chiari malformation Type I.

Because impaired CSF pulsations are an essential precondition for the development of syringomyelia, their visualization and quantification play a crucial role in the understanding of individual cases and the planning of causal treatment. In the past, a number of different MR imaging techniques have been developed and described that allow CSF movement to be assessed in terms of velocity and direction.[2,8,15,17,29,31,32] At present, the most commonly used technique is cardiac-gated phase-contrast MR imaging. In the 1990s, this method was introduced and established primarily for investigations of the brain by Quencer et al.,[27] Levy et al.,[17,18] and Nitz and colleagues[23]—as well as by Schroth and Klose[32] in Germany—and has been verified in several studies.[3,5,18] This method allows MR images of CSF flow to be displayed in a cine mode throughout the cardiac cycle.

Although the international literature reports that dynamic phase-contrast MR imaging is the standard method for diagnosing patients with CM-I,[16] it is a technique that is not routinely used in clinical practice. The visualization of CSF flow in the region of the cerebrum has been studied extensively and analyzed in a structured manner.[13–15] There is, however, a paucity of structured studies evaluating CSF dynamics in the region of the spinal canal in a reasonable number of patients. For this reason, we investigated the clinical usefulness of cardiac-gated phase-contrast MR imaging for the visualization of CSF flow in the spinal canal of patients with CM-I and assessed absolute CSF flow velocities, in particular postoperative changes.

Methods

Study Population

The study included all patients with CM-I who underwent MR imaging at the Departments of Neurosurgery and Radiology, German Armed Forces Hospital of Ulm, from January 1, 2003, to September 31, 2007. Apart from standard projections, we extensively studied CSF motion using phase-contrast MR imaging of the craniocervical junction, the cervical spine, the thoracic spine, and the lumbar spine in the median sagittal plane for the visualization of craniocaudal CSF flow.

Assessments and Outcome Variables

We determined the position of the cerebellar tonsils in relation to the foramen magnum. Because the dorsal border of the foramen magnum was not clearly defined after surgery, the location of the cerebellar tonsils was determined in the following manner. A straight line was drawn at the level of the endplate of C-2, and the length of the perpendicular line from the tip of the cerebellar tonsils to the aforementioned straight line was measured. The extension of the syrinx was expressed by the vertebral levels, along which the syrinx extended in the craniocaudal direction (for example, C4–T2). The size of the syrinx in the axial plane was measured at the site where the syrinx was largest in diameter. Apart from absolute values, we determined relative values on the basis of the overall anterior-posterior diameter of the spinal canal (anterior-posterior diameter ratio).

Phase-contrast MR imaging studies can be analyzed qualitatively and quantitatively. A qualitative analysis consists of evaluating the homogeneity of CSF flow and allows examiners to detect CSF flow obstructions. In addition, the direction of CSF flow can be determined in the various compartments, such as the subarachnoid space or the syrinx cavity. In a quantitative analysis, absolute CSF velocities can be measured on the basis of the direction vector. Cranial flow is displayed in black (negative sign) on the MR image and caudal flow in white (positive sign).

For every measuring site, we also assessed maximum velocities (maximum velocities [+], CSF flow in the cranial direction), minimum velocities (maximum velocities [–], CSF flow in the caudal direction), mean velocities, and median velocities.

Results

Syringomyelia Groups

In the aforementioned period, 90 patients with CM-I (61 women, 29 men, mean age 39 years, median age 40 years, range 3–80 years) were examined and treated at our institution in accordance with the protocol described above. Fifty-nine of these patients had syringomyelia (41 women, 18 men, mean age 44 years, median age 47 years, range 6–80 years) and 31 did not have syringomyelia (20 women, 11 men, mean age 28 years, median age 29 years, range 3–65 years). Two patients were included in both groups because they developed syringomyelia over a period of 4 years. For this reason, their earlier data pertained to the group of patients without syringomyelia and their later data to the group of patients with syringomyelia. Particularly noteworthy is that the mean age of patients without syringomyelia was significantly lower ($p < 0.0005$) than that of patients with syringomyelia.

Patients without syringomyelia mainly reported general disease symptoms. For example, there was a significant difference in the frequency of headaches between patients with and without syringomyelia ($p < 0.05$). The difference in neurological deficits and other symptoms involving the extremities was similarly significant. It was interesting to note that a loss of temperature sensation, which is a typical symptom of syringomyelia, was reported by only 6 (15%) of 40 patients with this data available.

No more than 2 patients with syringomyelia and 4 patients without syringomyelia had been treated with ventriculoperitoneal shunting. Conservative treatment was indicated in only 3 patients with syringomyelia and in 20 patients without syringomyelia.

Surgical History and Reoperation

In the group of patients with syringomyelia, 38 had undergone initial surgery at our institution. Six patients had undergone initial surgery at another institution and underwent revision surgery at our hospital. Three patients had undergone surgery only at another institution. In the group of patients without syringomyelia, 6 patients had undergone initial surgery at our institution. No patient who had undergone initial surgery at another institution required revision surgery. Two patients had undergone surgery only at another institution. We recommended surgery for a total of 10 patients who declined to undergo surgical treatment at that time.

Of the 44 patients who underwent surgery for CM-I, 3 (7%) required reoperation at the craniocervical junction. In the first case, the patient presented with a new cyst in the region of the foramen of Magendie and syringobulbia after 2 years. In the second case, decompression had not been wide enough. In the third case, an enlarged obex membrane had gone unnoticed during initial surgery. In all 3 patients, syringomyelia symptoms and imaging findings improved after revision surgery.

Anatomical Differences

The cerebellar tonsils were located an average of 13 mm (median 11 mm, range 5–38 mm) below the level of

the foramen magnum in patients with syringomyelia and an average of 16 mm (median 13 mm, range 5–67 mm) below the foramen magnum in patients without syringomyelia. This difference between the 2 groups of patients was not significant ($p = 0.19$).

The C-6 level was the spinal segment most commonly affected by syringomyelia (35 patients), followed by the C-5 and C-7 levels (34 patients each). In 16 patients, the syrinx extended over more than 15 vertebral levels. The C-6 level was also the region where the syrinx was largest in diameter in the majority of cases (8 patients).

Neuroimaging

A complete series of MR images that were obtained before surgery and after a mean postoperative period of 1 year (median 12 months, range 3–33 months) were available for 22 patients. In these cases, the craniocaudal extension of the syrinx had decreased by an average of 2.5 vertebral levels (median 1.5 levels, range 0–11 levels). There were no changes in the craniocaudal extension of the syrinx in 8 patients. By contrast, a considerable decrease in the anterior-posterior extension of the syrinx was noted in all patients. The mean anterior-posterior diameter ratio decreased from 0.67 (median 0.69, range 0.17–1.00) to 0.2 (median 0.17, range 0.00–0.57). The mean decrease was thus 0.47 (median 0.46, range 0.00–0.92), which was highly significant ($p < 0.00005$).

In these 22 patients, the mean distance from the cerebellar tonsils to the C-2 level was 1.7 cm before surgery (median 2.0 cm, range −0.4 to 3.2 cm) and 2.4 cm after surgery (median 2.4 cm, range 0.7–4.0 cm). Mean postoperative tonsillar ascent was thus 0.7 cm (median 0.7 cm, range −0.1 to 2.0 cm). This difference, too, was highly significant ($p < 0.00005$).

Phase-Contrast Imaging

Phase-contrast imaging demonstrated partial or complete obstruction of the pulsatile CSF flow at the craniocervical junction in all patients with CM-I. All but 4 patients also showed partial or complete blockage of CSF flow in the ventral subarachnoid space of the foramen magnum. Particularly noteworthy was a phase shift between the pulsations in the aqueduct and at the craniocervical junction (Fig. 1) and between the pulsations in the cervical subarachnoid space and the syrinx cavity (Fig. 2).

In 3 patients, phase-contrast MR imaging demonstrated CSF flow obstruction not only at the craniocervical junction but also in the spinal canal. Two of the 3 patients required surgery for persistent syringomyelia at these additional sites of obstruction. In both cases, the size of the syrinx was considerably reduced after surgery.

Flow Velocities

The highest flow velocities were measured in the ventral subarachnoid space of the cervical spine and in the prepontine subarachnoid space. When the sites of maximum pulsations were determined for each patient, maximum (caudal and cranial) pulsations at the craniocervical junction were detected most often in the prepontine subarachnoid space in patients both with and without syringomyelia (Table 1).

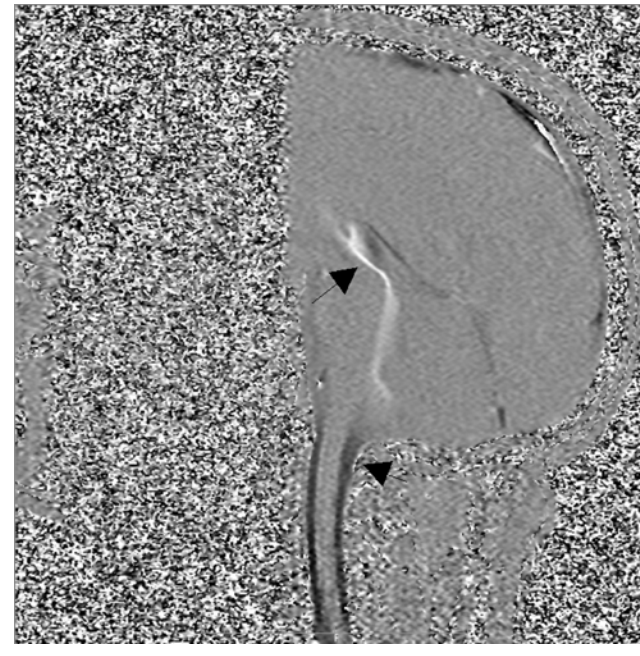

Fig. 1. Cardiac-gated phase-contrast MR image showing phase shift between pulsations in the aqueduct and the cerebellomedullary cistern in a patient with CM-I. The *upper arrow* points to the aqueduct, where CSF flows in the cranial direction *(white)*. The *lower arrow* points to the subarachnoid space of the upper cervical canal, where CSF flows in the caudal direction *(black)*. The image thus shows inhomogeneity and different directions of CSF flow in the region of obstruction at the level of the foramen magnum.

In the region of the cervical spine, more than half of the patients with syringomyelia showed maximum flow velocities (27 of 40 patients, 68%) and minimum velocities (24 of 40 patients, 60%) in the ventral subarachnoid space. In the region of the thoracic spine, the distribution of flow velocities was similar to that in the region of maximum extension of the syrinx because these 2 regions are often close to each other. In the region of maximum extension, each of the 3 measurement sites exhibited approximately one-third of the maximum pulsations. In the group of patients without syringomyelia, only 1 patient showed maximum pulsations and only 1 patient showed minimum pulsations in the region of the central canal.

An analysis of how flow velocities changed after surgical decompression revealed very interesting results. The difference between maximum and minimal velocities or, in other words, the velocity amplitude (Δ), considerably increased in the subarachnoid space with the exception of the region dorsal to the thoracic spinal cord (Table 2). In some cases, these changes were highly significant.

After decompression, an improvement in CSF flow was demonstrated in the region of the newly created cerebellomedullary cistern in all patients. Cerebrospinal fluid flow also improved in the ventral subarachnoid space.

The changes in pulsation were highly significant in the surgically enlarged cerebellomedullary cistern ($p = 0.0005$). Also noteworthy was the change in the amplitude in the region where the syrinx was largest in diameter,

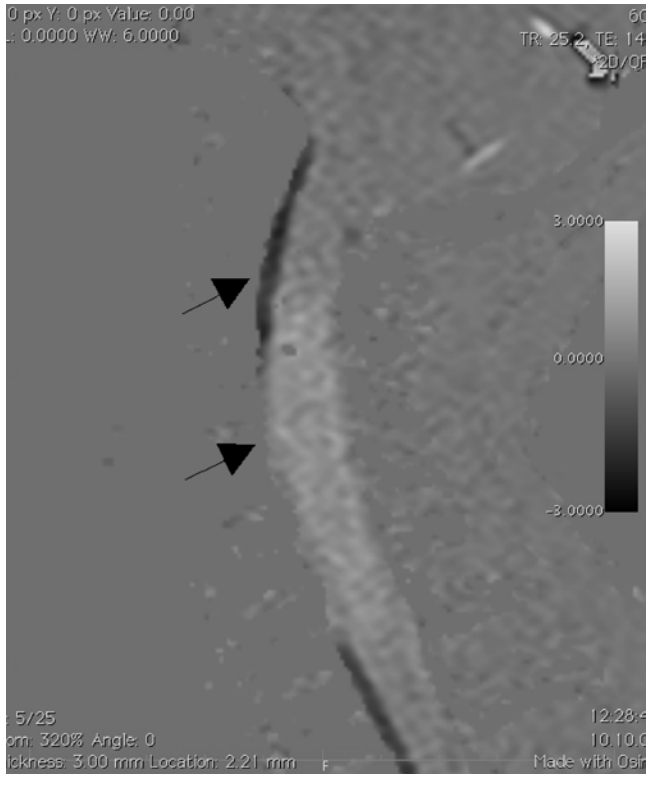

Fig. 2. Cardiac-gated phase-contrast MR image showing phase shift between pulsations in the subarachnoid space and the syrinx cavity in a patient with CM-I. The *upper arrow* points to ventral pulsations in the subarachnoid space of the upper cervical cord. The image shows complete compression of the subarachnoid space by the syrinx and ventral pulsations in the caudal direction. The *lower arrow* points to the area where the syrinx is largest in diameter. No pulsation can be detected in the subarachnoid space. Pulsations can only be observed in the syrinx cavity, where CSF flows in the cranial direction *(white)*. The image thus reveals pulsations in opposite directions.

that is, in a region where the subarachnoid space was considerably wider after surgery. Maximum and minimum velocities increased considerably in this region. Tonsillar pulsations decreased, but not significantly. Interestingly, patients with a highly significant change in postoperative syrinx width ($p < 0.00005$) showed changes in pulsations that were significant in the subarachnoid space in all spinal segments but were not significant in the syrinx itself and in the spinal canal.

Analogous comparisons between patients with and without syringomyelia revealed highly significant differences in flow velocity amplitudes only in the ventral cervical subarachnoid space ($p < 0.005$) and less significant differences in the region of the thoracic central canal ($p < 0.05$).

Discussion

In large series of patients, the mean age of onset of CM-I is reported to be 25 years, and women account for 75% of patients.[22] In our study, a similarly high percentage of the patients were female (68%). The mean age of onset, however, was considerably higher (almost 40 years). In our patient population, there was a clear relationship

TABLE 1: Mean minimum and maximum flow velocities in patients with CM-I

Location	Velocity (cm/sec)*		
	Minimum	Maximum	Δ
aqueduct			
CM-I w/ syringomyelia	–1.16	1.07	2.20
CM-I w/o syringomyelia	–0.74	1.13	1.88
CM-I after surgery	–1.65	1.95	3.40
4th ventricle			
CM-I w/ syringomyelia	–0.60	0.70	1.46
CM-I w/o syringomyelia	–0.66	0.69	1.35
CM-I after surgery	–1.29	1.11	2.36
prepontine subarachnoid space			
CM-I w/ syringomyelia	–2.08	1.70	3.46
CM-I w/o syringomyelia	–2.33	1.87	4.20
CM-I after surgery	–2.77	2.47	4.94
pons			
CM-I w/ syringomyelia	–0.40	0.53	1.16
CM-I w/o syringomyelia	–0.39	0.55	0.94
CM-I after surgery	–0.44	0.52	1.02
cerebellomedullary cistern			
CM-I w/ syringomyelia	–0.78	0.88	1.66
CM-I w/o syringomyelia	–1.16	0.85	2.01
CM-I after surgery	–1.33	0.97	2.31
tonsil			
CM-I w/ syringomyelia	–0.51	0.52	1.26
CM-I w/o syringomyelia	–0.54	0.56	1.10
CM-I after surgery	–0.53	0.65	1.19
ventral subarachnoid space†			
CM-I w/ syringomyelia	–2.27	1.57	3.71
CM-I w/o syringomyelia	–3.33	2.03	5.36
CM-I after surgery	–3.65	2.79	6.37
central canal†			
CM-I w/ syringomyelia	–0.80	0.87	1.85
CM-I w/o syringomyelia	–0.52	0.72	1.21
CM-I after surgery	–0.88	1.06	1.94
dorsal subarachnoid space†			
CM-I w/ syringomyelia	–1.68	1.24	2.81
CM-I w/o syringomyelia	–1.17	1.40	2.58
CM-I after surgery	–1.06	1.13	2.16
ventral subarachnoid space‡			
CM-I w/ syringomyelia	–1.97	1.51	3.26
CM-I w/o syringomyelia	–1.65	1.56	3.22
CM-I after surgery	–3.30	2.29	5.40
central canal‡			
CM-I w/ syringomyelia	–1.23	1.07	2.39
CM-I w/o syringomyelia	–0.53	0.62	1.16
CM-I after surgery	–0.77	0.93	1.71

(continued)

TABLE 1: Mean minimum and maximum flow velocities in patients with CM-I *(continued)*

Location	Velocity (cm/sec)*		
	Minimum	Maximum	Δ
dorsal subarachnoid space‡			
CM-I w/ syringomyelia	–1.81	1.47	3.17
CM-I w/o syringomyelia	–2.32	1.76	4.09
CM-I after surgery	–2.64	1.94	4.41
ventral subarachnoid space§			
CM-I w/ syringomyelia	–1.48	1.57	3.18
CM-I after surgery	–3.78	2.63	6.19
syrinx			
CM-I w/ syringomyelia	–1.48	1.23	2.77
CM-I after surgery	–1.15	1.25	2.43
dorsal subarachnoid space§			
CM-I w/ syringomyelia	–1.55	1.47	3.05
CM-I after surgery	–2.07	2.04	4.04

* The velocity in the table was rounded to 2 decimal points, whereas the Δ value was calculated using the total amount of the velocity.
† Cervical spine.
‡ Thoracic spine.
§ Syrinx.

between patient age and the occurrence of syringomyelia. The development of syringomyelia in patients with CM-I appears to be only a matter of time.

Clinical manifestations of CM-I can be attributable to 3 causes: direct compression of the brainstem, an impairment of CSF drainage and hydrocephalus, and syringomyelia. Dissociated sensory loss, which is the classic clinical feature, was reported less frequently than expected. Milhorat et al.[22] studied a large series of patients and found that dizziness, pressure in the ears, and tinnitus were the most common symptoms irrespective of the presence or absence of syringomyelia. The presence of headache, and especially headache linked to coughing, was found to be associated with a temporary increase in intracranial pressure.[28] It was interesting to note the high incidence of headaches in patients without syringomyelia.

In the literature, the mean extent of tonsillar herniation is reported to be 11 mm.[19] This is similar to our findings (13 mm). Mikulis et al.[20] found a strong correlation between tonsillar descent and age and suggested that age must be considered in the definition of CM-I. Heiss et al.[12] reported that patients who underwent surgery for CM-I showed a decrease in tonsillar herniation from a mean of 11 mm to a mean of 5.5 mm as early as 6 months after surgery. This finding is confirmed by our study, in which the mean postoperative tonsillar ascent was 7 mm. These results suggest that cerebellar tonsil herniation is acquired and not congenital.

The literature provides only a paucity of studies attempting to explain why some patients with CM-I have syringomyelia and why others do not (or not yet). Stovner and Rinck[33] reported that syringomyelia was found significantly more frequently in patients with tonsillar herniation of 9–14 mm than in patients with a smaller or larger degree of herniation ($p < 0.001$). These results, however, appear to be somewhat arbitrary and implausible and are not supported by our own experience.

TABLE 2: Comparison of preoperative and postoperative CSF flow velocities in 22 patients*

Location	Velocity (cm/sec)						p Value
	Preop Min	Preop Max	Preop Δ	Postop Min	Postop Max	Postop Δ	
aqueduct	–1.64	1.41	3.05	–1.65	2.14	3.91	1.0
4th ventricle	–0.81	0.69	1.50	–1.26	0.92	2.18	0.27
prepontine subarachnoid space	–3.03	2.00	5.03	–2.79	2.47	5.26	0.68
pons	–0.62	0.41	1.05	–0.44	0.56	1.00	0.59
cerebellomedullary cistern	–0.57	0.56	1.12§	–1.42	0.99	2.40§	**0.0005**
tonsil	–1.06	0.62	1.68	–0.53	0.70	1.22	0.09
ventral subarachnoid space†	–2.52	1.50	4.03§	–3.69	2.72	6.41§	**0.005**
central canal†	–1.24	0.93	2.16	–0.88	1.15	2.04	0.93
dorsal subarachnoid space†	–1.94	1.07	3.00	–1.04	1.24	2.28	0.07
ventral subarachnoid space‡	–1.79	1.44	3.24§	–1.79	2.29	5.67§	**0.003**
central canal‡	–0.83	1.21	2.04	–0.65	0.87	1.54	0.58
dorsal subarachnoid space‡	–2.21	1.73	3.93	–2.63	1.94	4.57	0.37
ventral subarachnoid space§	–1.24	1.30	2.60§	–3.93	2.69	6.76§	**0.00009**
syrinx	–1.61	1.32	3.04§	–0.97	1.02	1.98§	0.06
dorsal subarachnoid space§	–1.04	1.10	2.05§	–2.12	2.05	4.17§	**0.001**

* Boldface p values indicate a statistically significant difference. The velocity in the table was rounded to 2 decimal points, whereas the Δ value was calculated using the total amount of the velocity.
† Cervical spine.
‡ Thoracic spine.
§ Syrinx.

It is still unclear whether systolic CSF flow is more impaired than diastolic CSF flow in patients with CM-I[4] or whether the opposite is true.[14] Our results suggest that CSF flow is impaired in both directions. Whereas systolic CSF flow velocity is reduced or absent at the dorsal and ventral margins of the foramen magnum,[25] velocity is elevated in the prepontine cistern.[4] Milhorat et al.[22] reported that dorsal flow was impaired 3 times more often than ventral flow. However, it is difficult to compare available studies in this respect because there are no standardized measuring sites.

Our study did not confirm that surgical decompression can lead to a reversal of flow velocity abnormalities or a normalization of flow velocities.[4] Some studies suggest that the duration of systolic caudal pulsations appears to be considerably longer in patients with CM-I than in patients without this condition and in patients who underwent surgical treatment.[25] Phase-contrast MR imaging can visualize tonsillar pulsations but did not reveal differences between CM-I patients with or without syringomyelia.[26]

Successful surgical decompression should improve not only dorsal but also ventral CSF flow.[24] Brugières et al.[6] were able to show that effective decompression in patients with CM-I is associated with a postoperative decrease in CSF flow velocities in the syrinx. Whereas our results confirm this finding at a low level of significance, the velocity increase in the subarachnoid space was highly significant in the region where the syrinx was largest in diameter. One possible explanation is the marked postoperative increase in spinal cord volume in association with an increase in the contribution of the spinal cord to CSF pulsations. In addition, the CSF volume that had been shifted in the region of the syrinx was postoperatively shifted in the subarachnoid space. In contrast to our clear results, Iskandar and his working group[7,11] reported a postoperative decrease in flow velocity. It should be noted, however, that their studies involved only 4 patients with syringomyelia and 4 patients without syringomyelia.

Normal preoperative CSF flow in the region of the craniocervical junction in spite of tonsillar descent of more than 5 mm appears to predict an unsatisfactory surgical outcome.[19] This was to be expected considering the theories presented here. A seemingly trivial result, which, however, confirms the findings from phase-contrast MR imaging, is that syrinx size was significantly reduced in all patients with preoperative CSF flow obstruction at the craniocervical junction and postoperative reversal or improvement of CSF obstruction.

The indications for surgery in patients with CM-I remain controversial. A worldwide survey on the management of CM-I[30] showed consensus among pediatric neurosurgeons that no operation should be performed in asymptomatic patients with CM-I unless there is associated syringomyelia and that surgery should be performed in patients with CM-I when scoliosis and syringomyelia are present. There was no consensus about the management of patients without scoliosis. Haroun et al.,[10] who surveyed members of the Pediatric Section of the AANS, reported similar results. In this context, phase-contrast MR imaging can be useful. It demonstrates CSF flow obstruction at the craniocervical junction, especially in patients with borderline tonsillar herniation. This finding can contribute to a clinical decision for or against surgery. If surgery does not lead to a rapid decrease in syrinx size, phase-contrast MR imaging may nevertheless demonstrate an improvement in CSF flow and may thus show that a reduction in syrinx size can still be expected. Cerebrospinal fluid pulsation studies can provide evidence of additional causes of syringomyelia in the region of the vertebral column. Our research thus shows that a qualitative analysis of phase-contrast MR imaging can provide additional information and can thus help clinicians make a decision for or against surgery, and that a quantitative analysis is more of scientific than of clinical interest.

To our knowledge, there is no study reporting that a decrease in syrinx diameter is associated with a direct significant increase in flow velocity in the region where the syrinx was largest in diameter. This completely contradicts a current theory proposed by Greitz,[9] who believes that syringomyelia develops passively as a result of the Venturi effect, which implies an increase in CSF velocity in narrow regions of the CSF pathways.

Conclusions

Cardiac-gated phase-contrast MR imaging can contribute to assessments of surgical outcomes in patients who underwent decompression for CM-I and can be a useful tool for identifying the cause of surgical failure. The results presented here raise doubts about current theories on the pathogenesis of syringomyelia.

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: Mauer. Acquisition of data: Mauer, Gottschalk, Mueller, Weselek. Analysis and interpretation of data: Mauer, Gottschalk, Mueller, Weselek. Drafting the article: Mauer, Mueller, Weselek. Critically revising the article: Gottschalk, Schulz. Reviewed submitted version of manuscript: Kunz. Approved the final version of the manuscript on behalf of all authors: Mauer. Statistical analysis: Mauer, Mueller, Weselek, Schulz. Administrative/technical/material support: Gottschalk, Kunz, Schulz. Study supervision: Kunz.

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Manuscript submitted May 13, 2011.
Accepted July 14, 2011.

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