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.FOCUS111104)

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. 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. Estimates suggest that approximately 215,000 Americans may be affected with CM, with or without syringomyelia. 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. An estimated 65%–80% of patients with CM present with syringomyelia. 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. A recent large retrospective series of 500 cases spanning the past 2 decades found the prevalence of familial CM to be about 3%. A past study of 364 patients with CM found that 12% of patients had a close relative with CM and/or syringomyelia. We report on a series of 3 family pairs in whom a CM was present (Table 1).
TABLE 1: Cases of familial Chiari malformation*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs) at Presentation</th>
<th>Major Preop Symptoms</th>
<th>Cerebellar Tonsilar Descent (mm)</th>
<th>Postop Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>20</td>
<td>HA (tussive &amp; exertional), paresthesias, hyperreflexia</td>
<td>no</td>
<td>9</td>
</tr>
<tr>
<td>1b</td>
<td>57</td>
<td>HA (tussive &amp; exertional), paresthesias, oculomotor symptoms, LE dysesthesia</td>
<td>no</td>
<td>7</td>
</tr>
<tr>
<td>2a</td>
<td>23</td>
<td>blurry vision, clonus, LE hypertonia, hyperreflexia, gait difficulty</td>
<td>no</td>
<td>17</td>
</tr>
<tr>
<td>2b</td>
<td>62</td>
<td>asymptomatic</td>
<td>no</td>
<td>6</td>
</tr>
<tr>
<td>3a</td>
<td>24</td>
<td>HA (tussive &amp; exertional), UE paresthesias, hearing changes</td>
<td>no</td>
<td>8</td>
</tr>
<tr>
<td>3b</td>
<td>44</td>
<td>paresthesias, HA, nystagmus, diplopia, balance &amp; coordination problems</td>
<td>yes</td>
<td>8</td>
</tr>
</tbody>
</table>

* 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 descending 7 mm below the level of the foramen magnum. The patient underwent a suboccipital craniectomy, 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 paraplastic errors while typing. Examination revealed decreased 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 spondylisis. The patient experienced significant relief of symptoms with nonsurgical management of her spondylisis; 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. Two-thirds of patients with CM have posterior occipital bone anomalies with volumetric reduction. Chiari malformation has been thought to be related to the underdevelopment of the occipital somites that originate from the paraxial mesoderm during nervous system development. 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, 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 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. In all but one of these case reports, the twins or triplets were monozygous, and in the outlier zygosity was undetermined. 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. A twin study by Speer et al. 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 (pseudoahypparathyroidism), X-linked aqueductal stenosis, Goldenhar syndrome, Williams syndrome, Shprintzen-Goldberg syndrome, achondroplasia, familial osteosclerosis, spondyloepiphyses dysplasia tarda, velocardiofacial syndrome, primary basilar impression, and renal-coboloma syndrome, among many others. 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. 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.\textsuperscript{27,26} 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. \textit{PAX1}, a highly conserved gene mapped to chromosome 20p11.2, involved in segmentation and vertebral development during embryogenesis, has been suggested for future study.\textsuperscript{35} It plays an important role in the segmentation of somites and the differentiation of sclerotomal cells,\textsuperscript{4} and the gene is regulated by a complex balance of signaling factors during development.\textsuperscript{24} \textit{PAX1} mutations have been implicated in Klippel-Feil syndrome,\textsuperscript{34} 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.\textsuperscript{16} The \textit{PAX} family of genes encodes for transcription factors that play a role in pattern formation during embryogenesis in vertebrates. Other studies have implicated \textit{PAX2} mutations and \textit{FGF2} mutations as potential culprit genes in the formation of Chiari malformations.\textsuperscript{12,32} \textit{PAX3} and \textit{PAX6} have also been implicated in various developmental abnormalities,\textsuperscript{20} and although studies in direct relevance to Chiari malformations are limited, these are also candidate genes.

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

Familial CM has been recently described in conjunction with craniofrontonasal dysplasia,\textsuperscript{19} a rare X-linked syndrome linked to the \textit{EFNB1} gene mapped on chromosome Xq12, which encodes ephrin B1.\textsuperscript{46,47,50} The \textit{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, Mahone et al.\textsuperscript{39} 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.\textsuperscript{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 \textit{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.\textsuperscript{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.\textsuperscript{42} Cases of familial syringomyelia have also been reported as well,\textsuperscript{8,22,51,52} and although some believe that familial syringomyelia should be more accurately classified as familial CM with associated syringomyelia,\textsuperscript{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 syringomyelia.\textsuperscript{23} 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-
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Cerebellar 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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