

*Case Report*

Familial Aggregation of Chiari Malformation: Presentation, Pedigree, and Review of the Literature

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ABSTRACT

This article reports the largest familial aggregation of Chiari malformation in a single family to date as reported in the literature. This study is a retrospective case series of a family of whom five individuals have a confirmed case of Chiari malformation and three additional individuals have Chiari signs and symptoms. This contribution further supports the implication of genetics in the transmission of Chiari malformation. The family reported in this study also has a significant incidence of Ehlers-Danlos. Three sisters, including a set of twins, presented with confirmed cases of Chiari malformation and four of the five children of the twin sisters presented with confirmed or suspected Chiari malformation. Of note, the non-twin sister has three children who are unaffected. This report provides further evidence for a shared loci between the Chiari malformation and Ehlers-Danlos.

KEYWORDS: Chiari malformation, Genetics, Pedigrees, Primary chiari

■ INTRODUCTION

Chiari Malformation (CM) is typically considered to be the downward herniation of the cerebellar tonsils through the foramen magnum. The basic presentation of symptoms include occipital headaches, balance and coordination issues, and other associated cerebellar signs. This disease process affects both adult and pediatric patient populations, but symptoms vary by age. The presenting symptoms can be quite variable as well. Chiari malformations can be the result of a known etiology or can occur without any known causative factors. The Chiari that occurs from an unknown etiology is likely the result of a genetically determined small posterior fossa volume.

There is a growing amount of data in the literature supporting a genetic basis for the Chiari malformation. However, familial aggregation in the literature is limited to twins, triplets, and a few cases of two consecutive generations being affected. While multiple projects are underway in the United States to identify a gene that can be specifically linked to the Chiari Malformation, none has yet elucidated the gene. One of the

primary goals of the presentation of this family is to further illuminate the likely mode of genetic inheritance based on the large pedigree that is demonstrated below.

■ CASE REPORT

This study is a case report of a patient's family of whom five individuals had a confirmed case of Chiari malformations and a total of eight were symptomatic (including the 5 confirmed). The incidence of Chiari malformations confirmed by CT scans occurred in two consecutive generations. The symptomatic individuals spanned three generations. The family of this child under our care also has a very large incidence of Ehlers-Danlos syndrome.

Of the three daughters (III-7, III-8, and III-9) of the individual (II-3), all were radiographically confirmed cases of Chiari I Malformation (Figure 1). These patients lived in rural communities and thus were diagnosed with CT imaging instead of MRI, due to access and funding. However, in all of the patients the diagnosis was clear on the CT images, and was confirmed with MRI in some. Patient III-8 is the



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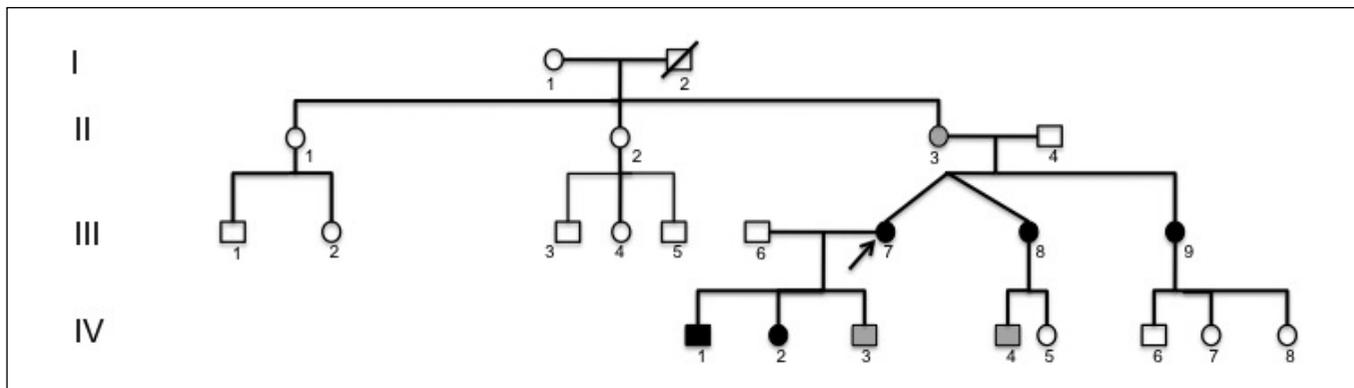


Figure 1: The proband is indicated by the arrow. The confirmed cases of Chiari are represented in black. The individuals affected by Chiari symptoms are shaded gray.

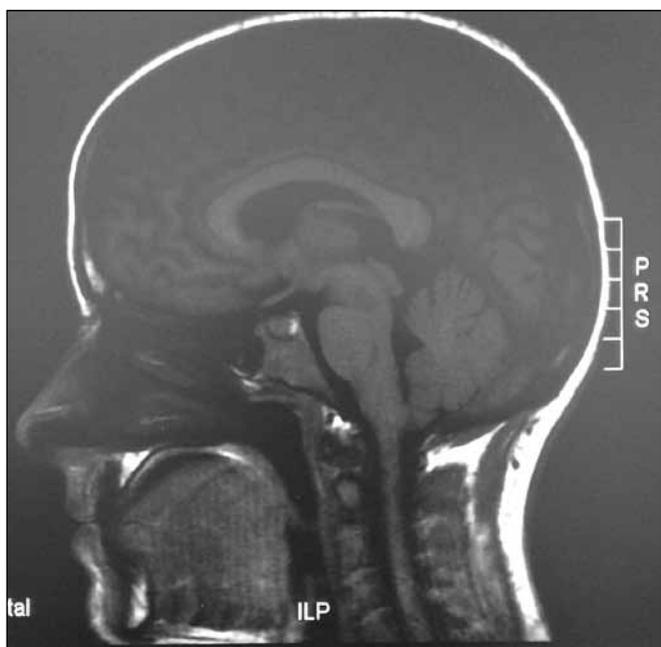


Figure 2: Patient III-8 Chiari 0 displaying a crowded posterior fossa and slight herniation of the cerebellar tonsils in the twin-sister of the proband.

only daughter of II-3 not treat for CM (Figure 2). This sister, however, does report Chiari related symptoms. The other sister with a confirmed case of Chiari I Malformation (III-9) has three children (IV-6, IV-7, IV-8) who do not have head CT scans but report frequent headaches. Patient III-7 has three children, two of which have confirmed cases of Chiari (IV-1, IV-2). The third and youngest child (IV-3) is beginning to present with Chiari-related symptoms and will likely undergo CT scan in the future. Of the five confirmed cases, four are females.

Seven patients without radiographic confirmation of a diagnosis of CM complained of persistent signs and symptoms consistent with those of Chiari malformations. To diagnose Chiari based on clinical findings, we used the presence of occipital headaches. These headaches had to be consistently present and worse with straining, coughing, or Valsalva. Other

common neurological signs were present in most (Table I). Of the seven individuals reporting signs and symptoms, four of the seven were female. Two-sets of three are siblings including one set of twins. All of these patients presented with severe headaches that occur daily or multiple times a week. Most of the individuals complained of headaches that originated in the occipital region of the head and upper neck. The patients also complain of balance and coordination deficiencies, including reported severities such as consistently stumbling into walls and doorways. They also report falling down often. Patient II-3 reports headaches for as long as she can remember. She states that these headaches “start in the back of her head and move forward to the top of her head.” Patient III-8 (Figure 1) reports a headache in the “back of her head” that never goes away,” “running into things all the time,” frequently falling down, and multiple episodes of syncope. She also reports vision difficulties and chronic pain in the back of her head and neck. Patient IV-3 reports headaches that occur multiple times a week and his parents report he has severe coordination issues. Patient IV-4 reports occipital headaches that occur every day. He has also been diagnosed with Human Growth Hormone deficiency and Ehlers-Danlos Syndrome.

Other family members have been diagnosed or have symptoms consistent with Ehlers-Danlos Syndrome. In addition to IV-4, his mother (III-8) has been diagnosed with Ehlers-Danlos Syndrome. The family reports that individuals I-2, III-1, III-2, III-3, III-4, III-5, and III-9 are all suspected of having Ehlers-Danlos Syndrome due to symptoms of hyperextensiveness.

DISCUSSION

Overcrowding of the posterior fossa or a normal amount of substance in an unusually small posterior fossa is likely the culprit of the downward displacement of the cerebellum (2, 5, 15, 22, 23, 28, 30, 31, 34, 39, 42, 45, 47). Many of the symptoms of Chiari may be the result of obstructed CSF flow (7) and the development of scar tissue of the cerebellar tonsils and the compression of the cerebellum and spinal cord (3, 7, 27).

Chiari malformation is likely the result of a small posterior fossa and thus the embryonic development of the posterior

Table I: The Various Signs and Symptoms of each Individual on the Pedigree as well as other Information

Pedigree #	Chiari	Ehlers-Danlos	Signs/Symptoms	Radiographs	Other Comments
I-1	75 yrs				
I-2	68 yrs	*Suspected	Deceased		*Due to hyperextensiveness
II-1	53 yrs		Cleft palate		
II-2	51 yrs		Thyroid issue, occipital headaches occasionally	Yes	
II-3	56 yrs		Diabetes, High blood pressure, high cholesterol, occipital headaches for as long as she can remember (start in back and move to front), numbness and tingling in left arm, C3 bulging disc	Yes	
II-4	58 yrs		High blood pressure, rare occipital headaches, sleep disorder		
III-1	21 yrs	*Suspected	Occipital Headaches		*Due to hyperextensiveness
III-2	26 yrs	*Suspected	Occipital Headaches		*Due to hyperextensiveness
III-3	29 yrs	*Suspected			*Due to hyperextensiveness
III-4	26 yrs	*Suspected			*Due to hyperextensiveness
III-5	22 yrs	*Suspected			*Due to hyperextensiveness
III-6	40 yrs				
III-7	37 yrs	Yes	Chiari Decompression surgery, sleep apnea, hypersomnia, chronic joint pain, hyperextensive, reports of syncope, food allergies	Yes	Twin of III-8
III-8	37 yrs	Yes (untreated)	Chronic pain, sleep apnea, narcolepsy, hypersomnia, Ehlers-Danlos, Severe occipital headaches, IBS, Neurological symptoms (headache back of head, neck all day never going away; runs into things all the time; falls often; passes out; chronic pain in joints all over body; difficulty focusing and finding words; vision problems; bulging disc in neck) frequent episodes of syncope	Yes	Twin of III-7
III-9	33 yrs	*Suspected	Chiari Decompression surgery, colon cancer, sleep apnea (gone after surgery), chronic pain, suspected Ehlers-Danlos	Yes	*Due to hyperextensiveness
IV-1	15 yrs	Yes (untreated)	Occipital headaches often, problems with balance and coordination, food allergies, mom had eclampsia	Yes	
IV-2	14 yrs	Yes	Chiari Decompression surgery, severe occipital headaches, balance problems, numbness, food allergies, once arm fell asleep and she didn't know who she was, born premature	Yes	
IV-3	11 yrs	Suspected	Frequent occipital headaches, food allergies, sleep apnea, missing permanent teeth, small mouth, coordination issues, memory issues	In the near future	
IV-4	13 yrs	Yes	Occipital headaches every day, coordination and balance deficits	Yes	Has Human Growth Hormone Deficiency
IV-5	11 yrs		Hyperextensive, behavioral health issues, occasional occipital headaches		
IV-6	10 yrs	Yes (untreated)	Intestinal issues, frequent occipital headaches	Yes	
IV-7	8 yrs		Frequent occipital headaches	Yes	
IV-8	5 yrs		Frequent occipital headaches	No	

fossa may be the link between genetics and phenotype (7, 24, 30, 43). Boyles reported that the volume of the posterior fossa was “highly heritable” (7). Embryologically, the Chiari malformation has been described as a mesodermal deficiency (30) and as a neuroectodermal failure (4, 26, 27). Gripp, however, proposes that displacement of the cerebellar tonsils may be due to osseous and cartilaginous abnormalities instead of being the result of embryological disturbances (19). Other authors have offered that Chiari type II, which is thought to be associated with neural tube defects, also shows the potential to have a genetic basis of inheritance (12, 16, 19, 48). It is also possible that having a small posterior fossa is the phenotype of those with a genetic predisposition to developing the Chiari malformation. This may at least be offered as an explanation of the varied phenotypic presentations of Chiari patients (24).

In the largest study of cases with familial aggregation of Chiari, Milhorat demonstrated that while still seemingly sporadic (1, 28), the Chiari malformation does seem to have the potential for genetic transmission. Milhorat’s study showed a significantly increased incidence in women (28). He demonstrated that out of 364 confirmed cases of Chiari Malformation, 275 of them were female (75%) (28). Of these reported cases, he reported that 12% self-reported a family history of Chiari (28). Milhorat reported twenty-one pedigrees that showed inheritance patterns indicative of autosomal dominant or recessive inheritance (28). The 75% incidence of females remained true in the population that reported familial aggregation (28). He concluded from his study “the demonstration of familial inheritance suggests a genetic component of transmission” (28). This large disparity of female cases to male cases has also been reported elsewhere in the literature as well (21, 30, 33).

The pedigree in this report fully supports the female predominance reported previously in the literature. Of the affected members in the family presented here, four of the five confirmed cases of Chiari were females. Also in agreement with these previously reported values is the fact that four of the seven individuals presenting with signs and symptoms of Chiari are females. These findings are also consistent with the current theory that there is a higher incidence of Ehlers-Danlos in females despite its known inheritance pattern of autosomal dominant (11, 27). No mechanism of inheritance has been discovered to explain this finding (11).

Milhorat concluded that in families with familial aggregation of Chiari, other members did seem to show an abnormal incidence of displaced cerebellar tonsils through the foramen magnum (27). Cavender points out in their study that based on “extrapolation from a study conducted by Barkovich, et al. estimates the incidence of tonsillar ectopia to be approximately 3.5%” (3, 12). This is extremely significant considering the percentage of family members afflicted with Chiari malformations in the family to be presented in this study. Specifically, 45 percent of individuals in the two generations of family members are confirmed cases and 64 percent are affected cases.

The literature shows a preponderance of reports of twins and triplets that display a familial aggregation. In 1990,

Herman reported what appears to be the first instance of Chiari malformation displayed in multiple individuals in the same family when he reported two siblings with the disease (20). This is highly unlikely to be the first case of familial aggregation, but does seem to be the first time it was reported in the literature. Atkinson et al. reported monozygotic twin sisters and the daughter of one of the sisters (1). Stovner also reported monozygotic twins and their mother as having Chiari Type I (38, 40, 41). Cavender reported a family in which monozygotic triplets all had confirmed cases of Chiari. The triplets in Cavender’s report also had syringomyelia. Cavender and Schmidt went on to conclude that because of the 100% concordance in the triplets he reported, a genetic basis for Chiari is “highly suggested” (12). Weisfeld et al. reported three sisters with Chiari malformation (49). Speer et al. reports two sets of monozygotic twins with Chiari malformations (37). Speer et al. also reported that there appears to be a higher incidence in monozygotic twins than in dizygotic twins (36). Multiple other studies showed familial aggregation of Chiari (9, 13, 14, 17, 19, 25, 29, 35, 42, 44, 46, 50-52).

In this article, the patient’s family having a large incidence of Ehlers-Danlos Syndrome also points to a correlation between the two diseases. Previous authors have proposed mechanisms for this relationship. The incidence of Ehlers-Danlos is reported to be one per 5,000 to 10,000 individuals and the incidence of CM-I is estimated at one per 1,000 to 5,000 individuals (27). The likelihood of both diseases coincidentally appearing in the same family based on the reported incidence rate in the population is one out of 10,000,000 (27). Thus it is reasonable to assume that there is a genetic linkage to these two diseases. The family pedigree shows an autosomal dominant inheritance pattern, especially when symptomatic patients without radiological confirmation are considered. This also follows the reasoning supporting the genetic linkage with Ehlers-Danlos which is also generally accepted to be autosomal dominant (27). Milhorat, et al., explored a similar association of hereditary disorders of connective tissue with CM-I by prospectively studying 2813 patients with CM-I. That study reported that 139 of 2813 patients reportedly had both a hereditary disorder of connective tissue and CM-I. Of the 139, only 44 had familial inheritance and of the 44 only 20 had greater than one relative with CM-I and even less (17) had more than one relative with a hereditary disorder of connective tissue (27). This makes this presentation of such a large pedigree significant.

The proposed mode of genetic transmission of Chiari is somewhat varied in the literature, and the large family represented by this study allows for a more substantial proposal of transmission. Mendelian transmission has been reported as autosomal dominant inheritance with decreased penetrance or autosomal recessive (6-8, 10, 18, 19, 25, 28, 32, 52). Milhorat, in the largest pedigree analysis of Chiari families, reported autosomal dominant as those with male-to-male vertical transmission and autosomal recessive as those without an affected parent (28). Petraglia also reports that the propensity of Chiari malformations to accompany other genetic diseases suggests a genetic mode of transmission (19, 24, 25, 32).

This article presents the largest-reported familial aggregation of radiograph confirmed cases of Chiari Malformation. In addition to this, a total of eight patients presented with signs and symptoms consistent with Chiari Malformations. This is the largest incidence of familial aggregation of Chiari presented to date in the literature. As larger pedigrees, like the one presented here, are presented in the literature, greater insight into the inheritance pattern and mode of transmission can be gained. A family with such a large predominance also provides an excellent candidate family for further genetic analysis – which is currently in progress. Boyles proposes Fibrillin-1 (FBN1) on chromosome 15 as a plausible candidate gene for CMI due to its known role in related genetic disorders (7). While further exploration of this gene specifically is outside the scope of this case series, the family presented in this study could potentially be an excellent source of genetic analysis. In addition to this, the family provides an excellent model for considering the potential of a genetic link between EDS and CM-I.

A primary implication of understanding the genetic basis of Chiari is that clinicians should have a significantly increased index of suspicion in patients with a family history of Chiari. Patients who are likely to have inherited a smaller posterior fossa are seemingly at a much higher risk of suffering from signs and symptoms of Chiari malformations. Even if the cerebellar tonsils are not actually herniated through the foramen magnum, the patient could be suffering from the effects of a crowded posterior fossa. It is likely the reduced size of the posterior fossa, regardless of herniation, that causes the exacerbation of symptoms with activities such as Valsalva and coughing. While, research is needed to confirm, it seems reasonable to these authors to accept that these patients would benefit from posterior fossa decompression.

■ CONCLUSION

Based on a search of the literature, no author has previously presented a family with more than three confirmed cases of Chiari. The family presented in this study contributes a significant step toward proving the genetic basis of Chiari malformations. This article provides a solid foundation for further genetic analysis of the reported family. This pedigree demonstrates a high likelihood of genetic locus homogeneity between Chiari and Ehlers-Danlos Syndrome.

The pedigree also demonstrates that clinicians treating patients with neurological signs and symptoms should have a significantly increased index of suspicion for Chiari when a family member has also been diagnosed with Chiari. This should include exploring the possibility of a crowded posterior fossa without cerebellar herniation. Further exploration is needed to identify whether or not these patients would benefit from a decompressive craniectomy.

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