

Chiari in the Family: Inheritance of the Chiari I Malformation

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This report presents three families with Chiari malformation type I that became symptomatic during childhood: a mother and son; a set of monozygotic twins; and two half-siblings and their two maternal cousins. These children presented with various symptoms, including headache, stiff neck, and swallowing difficulty. A review of the relevant literature is presented, with an emphasis on familial examples and proposed inheritance. Less common presentations of Chiari malformation type I are discussed, as well as the possible pathogenesis of Chiari malformation type I and associated syringomyelia. © 2006 by Elsevier Inc. All rights reserved.

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Introduction

Chiari malformation type I is the congenital or acquired protrusion of the cerebellar tonsils through the foramen magnum, which can result in obstructive hydrocephalus. It is typically defined radiologically as tonsillar descent greater than 5 mm below the foramen magnum. It may be asymptomatic or cause increased intracranial pressure manifested by chronic headaches, progressive cerebellar ataxia, progressive spastic quadriparesis, or down-beating

nystagmus, as well as many other symptoms. There may also be associated syringomyelia, a cavitation of the central areas of the spinal cord and unconnected to the central canal, presenting as pain, numbness, or weakness in the upper or lower extremities. Historically, nonsyndromic cases of Chiari malformation type I were considered to be sporadic and without genetic etiology [1], but recent reports of familial clustering of this disorder [2-14] have suggested an inherited component. This report describes three families with at least two cases of symptomatic Chiari malformation type I and discusses its inheritance and pathogenesis. The work was conducted at the Riley Hospital for Children, Indianapolis, Indiana.

Case Report

Family 1

The proband (1-1) was a 19-month-old male who presented to the child neurology outpatient clinic for evaluation of possible cerebral palsy. He was born at term to a 28 year-old gravida 2, para 1-2 woman after pregnancy complicated only by cesarean section for cephalopelvic disproportion. Birth weight and head circumference were unavailable. He was hospitalized for 1 week after birth for pneumonia. He sat unsupported at 6 months, but his mother observed that he was "hunched over with his legs spread out." He walked "late," with his feet turned out. He had no regression.

His examination revealed head circumference of 52.7 cm (>98th percentile); height was 87 cm (~80th percentile), and weight was 13.7 kg (~98th percentile). His face was remarkable for prominent forehead, wide-set eyes, and a small, pointed chin. Cardiac, pulmonary, abdominal, and skin examinations were unremarkable. On neurologic examination he was alert and cooperative. He said only "bye-bye," as he was leaving. He was able to build a tower of six blocks. Cranial nerve examination was normal. He had increased tone in the right arm and leg. Otherwise, he moved all four extremities well and demonstrated bilateral pincer grasp. Reflexes were 2 to 3+ bilaterally at the biceps, 2 to 3+ knee jerks. Babinski reflex was present bilaterally. He had a wide-based slightly spastic gait with less movement of the right leg.

The family history was remarkable for "cerebral palsy" in his mother (2-1); she reported that she had a mild left hemiparesis as a child and had been treated for cerebral palsy at an outside hospital. She did not walk until 2 years of age. She reported also a 2-year history of chronic headaches and low back pain, both beginning soon after giving birth to her son. Her headaches were characterized by sharp frontal pain with associated photophobia and phonophobia and lasted several hours. Her low back pain radiated down the side of her left leg. She stated that her late father also had a large head with wide-set blue eyes, and had suffered from severe headaches for most of his life (Fig 1).

The mother's head circumference was 60 cm (>98th percentile), and she resembled both her son and father, including wide-set blue eyes. Her cranial nerve examination was normal. Motor examination was normal

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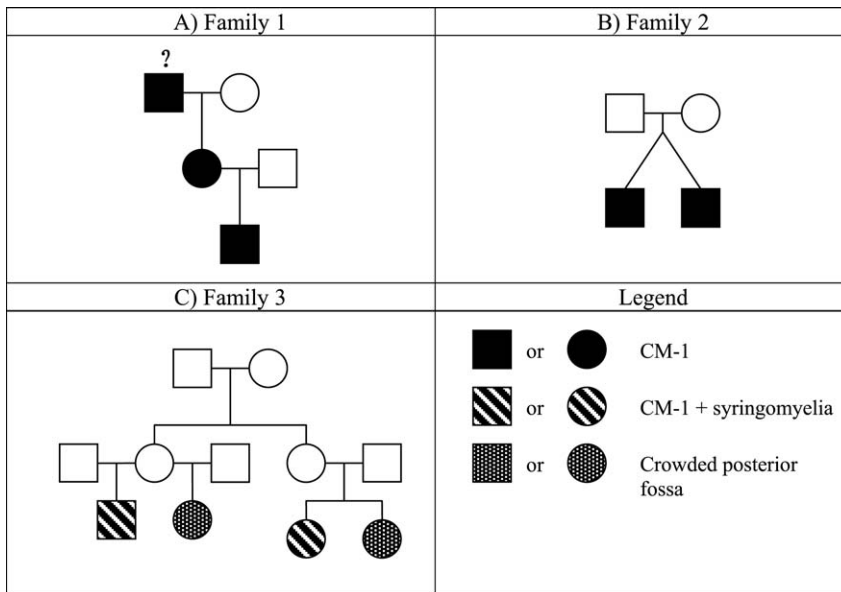


Figure 1. Pedigree of families. (A) Family 1 includes mother and son with Chiari malformation type I and other phenotypic similarities. There is a history of similar features as well as frequent headaches in the maternal grandfather. The phenotypic features with Chiari malformation type I may represent a familial syndrome. (B) Family 2 exhibits monozygotic twins with reflux and poor swallowing skills, both with Chiari malformation type I on magnetic resonance imaging. (C) Family 3; four family members are symptomatic with confirmed Chiari malformation type I or crowded posterior fossa. There is a half-brother and sister as well as their two female first cousins affected.

except for 4+/5 strength bilaterally in her hip flexors. She had difficulty walking on her toes. She could not tandem walk and was unable to stand on either foot for more than 2 to 3 seconds, but sensory and cerebellar examinations were otherwise normal. Reflexes were 3+ at the ankles, but were otherwise normal.

Magnetic resonance imaging of the son's brain revealed Chiari malformation type I extending nearly to the caudal edge of the C2 vertebral body with normal ventricular size and shape and no intracranial masses. His mother's brain magnetic resonance imaging revealed Chiari malformation type I extending approximately 9 mm caudal to the foramen magnum with crowding at the craniocervical junction but otherwise was normal. Spine magnetic resonance imaging revealed degenerative disc disease at T₁₂-L₁ and L₅-S₁.

The mother refused neurosurgical consultation for either herself or her son. She returned with her son when he was 23 months old. He now was more talkative and more interactive with the examiner. He continued to demonstrate increased tone in his right leg and had a slightly spastic gait. After this visit, further attempts to contact the family failed.

Family 2

The monozygotic twin probands were born at 32 weeks of age by emergency cesarean section for fetal distress. The pregnancy was complicated by preeclampsia and possible HELLP syndrome which is characterized by hemolytic anemia, elevated liver function enzymes, and decreased platelets.

Twin A (1-1) presented to the clinic at 15 months of age with poor swallowing, severe gastroesophageal reflux disease, and failure to thrive. A swallowing study indicated abnormal tongue coordination and decreased laryngeal elevation during swallowing. He aspirated both liquids and solids, and required laparoscopic Nissen fundoplication and G-tube. He had an otherwise normal developmental history except for language limited to 3-4 words and babbling. Medical history was significant for asthma and respiratory distress secondary to aspiration and gastroesophageal reflux.

On physical examination, his weight was 9.8 kg (10-25th percentile); height was 77.5 cm (25th percentile), and head circumference was 46.5 cm (25th percentile). Cardiovascular, pulmonary, abdominal, and extremity examinations were normal. Cognition was appropriate for his age. Cranial nerve examination was normal, with gag reflex intact bilaterally and tongue midline to protrusion. There was no asymmetry or facial weakness. He manifested mild axial hypotonia, but appendicular muscle bulk and tone were normal. Cerebellar, function, muscle stretch reflexes, and sensation were normal. His gait was appropriate for his age.

His brain magnetic resonance imaging indicated low-lying cerebellar tonsils, 7 mm below the level of the foramen magnum, with no malformation of the medulla (Fig 2). The study otherwise was normal, including specifically the perisylvian regions.

Two weeks after his initial visit, Twin A presented with worsening swallowing problems and problems breathing, prompting urgent neurosurgical evaluation. The patient underwent posterior decompression 11 days later owing to his worsening symptoms, with no complications. At his follow-up visit 4 months later, his breathing and feeding dysfunction had improved significantly. His motor skills also improved, although he retained mild clumsiness.

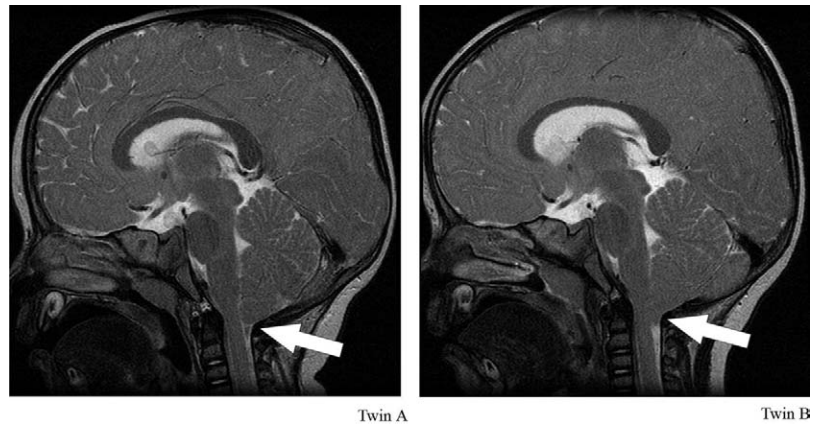
Twin B (1-2) also manifested significant swallowing difficulties and gastroesophageal reflux, but less severe than his brother's. His magnetic resonance imaging disclosed low-lying cerebellar tonsils, 11 mm below the level of the foramen magnum, as well as mild diffuse white matter volume loss within the cerebral hemispheres and a small area of gliosis within periventricular white matter (Fig 2).

Because of the success of his twin brother's procedure, Twin B underwent posterior fossa decompression. Tissue was not taken for neuropathologic examination during either operation. Two months post-operation, he no longer choked or aspirated, and his breathing had improved remarkably. His previous balance problems also improved after subsequent therapy.

Family 3

The proband (1-1) presented at 11 years of age complaining of decline in his athletic ability, bladder urgency and difficulty emptying, as well as vague left hand numbness. He had a psychiatric history of behavior problems and was being treated for bipolar disorder and obsessive-compulsive disorder. Physical examination was unremarkable except for a head circumference of 58 cm (>98th percentile). No neurologic abnormalities were recorded in the documentation. A spine magnetic resonance imaging scan revealed a thoracic syrinx, so the patient was referred to the pediatric neurosurgery clinic. Initial magnetic resonance imaging did not disclose any cerebellar tonsillar heterotopia. After normal urologic studies, he was monitored clinically with deferral of surgery. A year later the patient experienced worse thoracic back pain as well as tingling of his hands and feet bilaterally. Brain and spine magnetic resonance imaging performed at that time documented enlargement of his syrinx from his scan taken 5 months earlier, as well as a new small syrinx from C₁-C₂. In addition, his cerebellar tonsils now descended caudal to C₁, consistent with Chiari malformation type I. Due to the severity of his symptoms and progressive enlarging syrinx, he

Figure 2. Sagittal magnetic resonance imaging scans (TR/TE: 4350/96, TR/TE: 3716/95 ms) demonstrating Chiari malformation type I in Twin A (left) and Twin B (right). The arrow in Twin A identifies a 7-mm protrusion; Twin B manifests an 11-mm protrusion. Both twins manifested lower cranial nerve dysfunction; Twin A had more severe symptoms.



underwent posterior fossa decompression. Surgical findings included an arachnoid cyst–like fluid collection in the posterior fossa at the level of the cerebellar tonsils. Immediately after the decompression, the patient experienced complete remission from his symptoms, but has experienced a number of exacerbations since then. These exacerbations have been treated with some success using steroids.

The patient's maternal half-sister (1-2) presented at 9 years of age for right frontal headaches with blurred vision occurring once or twice per week. She also complained of posterior neck pain and stiffness, numbness in legs on one occasion, and chronic constipation. Initial neurologic examination was unremarkable. Head circumference was 54 cm (75th percentile). Magnetic resonance imaging at this time revealed mild foraminal crowding and no significant tonsillar descent. She did not improve with conservative measures and began to have severe shoulder pain that was significantly affecting her quality of life. Her parents opted for an elective Chiari decompression procedure, because of the success with her half-brother. Her surgical findings were also significant for arachnoid cysts or pockets of fluid contributing to the compression of the posterior fossa. At follow-up 6 weeks later, she manifested considerable symptomatic improvement.

This sibships' maternal first cousin (1-3) also underwent neurologic evaluation, 7 years of age, for head tremor, nystagmus, and pain in the back of the head and neck, occasionally with nausea. Details of the neurologic evaluation are limited in the documentation. Brain and spine magnetic resonance imaging at that time demonstrated a mild Chiari malformation type I, with no syrinx present. It was decided to follow up in 4 months with repeat magnetic resonance imaging. In the interim she developed choking episodes and more frequent occipital headaches, as well as tingling in her hands. Magnetic resonance imaging at that time revealed a new small syrinx at T₃-T₄ level. She underwent posterior fossa decompression and within 2 months had complete resolution of her symptoms.

Patient 1-3's full sister (1-4) presented to neurosurgery at 12 years of age with a protracted history of shoulder pain and scoliosis, as well as headaches at least once per week that were becoming more frequent. Neurologic examination was grossly normal at this time. Because of her strong family history of Chiari malformation type I, magnetic resonance imaging was performed, revealing mild cerebellar heterotopia extending to just rostral of the C₁ vertebral body. A year and a half after initial presentation, she had not yet had surgical intervention, but had continued head and neck pain and some new vision problems. She seems to "choke on spit" at least once a day, but does not choke while eating. She continues to be managed conservatively.

Discussion

Evidence for familial Chiari malformation type I has accumulated for the past 15 years. There now are a number of reports of monozygotic twins and triplets with Chiari

malformation type I [2,3,6,13,15] as well as siblings and cousins (Table 1). These reports suggest a strong genetic basis for Chiari malformation type I and also suggest a possible inheritance pattern for familial cases. Familial syringomyelia has been described numerous times in the literature [14,16,17], but Zakeri et al. describe familial syringomyelia in which both affected patients also have Chiari malformation type I [14]. Upon closer examination of familial syringomyelia, these cases actually may represent familial Chiari malformation type I as well or more subtle posterior fossa insufficiency.

In the first family, there were two, and possibly three generations of symptomatic Chiari malformation type I. There was also a question of whether or not there were some syndromic elements to its inheritance because of the common traits of a large head circumference and wide-set blue eyes. There are a number of inheritable syndromes that typically are associated with Chiari malformation type I such as Klippel-Feil syndrome, hypophosphatemic rickets, achondroplasia, spondyloepiphyseal dysplasia tarda, primary basilar impression, and renal-coloboma syndrome, among many others [10]. It is possible that this family represents a rare previously described syndrome or even their own autosomal dominant syndrome. Interestingly, selecting for coat color appears to have influenced the development of occipital hypoplasia and Chiari malformation type I in Cavalier King Charles spaniels [18]; it is not known what, if any, traits are linked to Chiari malformation type I in humans.

The monozygotic twins in Family 2 could indicate genetic transmission of Chiari malformation type I. Although environmental factors cannot be ruled out, their case can represent either vertical transmission from one or both of their parents or a sporadic germ line dominant mutation. The third family presented a familial clustering with half-siblings and first cousins affected with seemingly normal mothers. In the absence of vertical transmission and without proof of multiple affected generations, oligogenic, polygenic, or most likely, a multifactorial inheritance of a major gene effect such as lesser posterior fossa volume all are possible mechanisms of inheritance.

Table 1. Recent studies describing familial incidence of Chiari I malformation

Study [Ref.]	# of Families	Affected Members	Proposed Inheritance
Coria et al. (1983) 4	1	3 generations with occipital dysplasia	AD
Herman et al. (1990) 7	1	Siblings	N/A
Stovner et al. (1992) 15	1	Twins, first degree relatives	N/A
Stovner and Sjaastad O. (1995) 12	1	Siblings	N/A
Cavender and Schmidt (1995) 3	1	Monozygotic triplets	N/A
Zakeri et al. (1995) 14	1	Siblings	N/A
Gripp et al. (1997) 6	1	Twins, father	N/A
Atkinson et al. (1998) 2	2	Monozygotic twin sisters and daughter	N/A
Milhorat et al. (1999) 9	21	Parent-child, sibling, avuncular pairs, cousins	AD with reduced penetrance or AR
Speer et al. (2000) 10	31	Parent-child, sibling, avuncular pairs, cousins	Homeobox genes
Tubbs et al. (2004) 13	1	Dizygotic twins	N/A
George and Page (2005) 5	1	Siblings	N/A
Mavinkurve et al. (2005) 8	1	Siblings	N/A
Szewka, et al. (2005) [This study]	3	Parent-child, monozygotic twins, avuncular pairs and cousins	Multifactorial inheritance

Abbreviations:
AD = Autosomal dominant inheritance pattern
AR = Autosomal recessive inheritance pattern
N/A = Inheritance pattern not mentioned in article

It is not clear if the Chiari malformation type I phenotype represents a primary malformation or the result of an abnormal developmental sequence. It is interesting to note that some inheritable syndromes associated with Chiari malformation type I, particularly primary basilar impression and Klippel-Feil syndrome, often result in decreased posterior fossa volumes. Nishikawa et al. suggested that a mesodermal deficiency causes decreased posterior cranial fossa volume which secondarily induces brain protrusion. Perhaps what is inherited is a small posterior cranial fossa causing an anatomical predisposition to protrusion, which in more severe cases occurs early on in life or during intrauterine development. Milder cases fail to herniate, or become symptomatic only when trauma or other environmental triggers supervene [19]. Milhorat et al. found in their study of 364 patients with Chiari malformation type I that there was a statistically significant decrease in mean total volume of the posterior cranial fossa. All of those patients studied manifested compression of cerebrospinal fluid spaces around the cerebellum on magnetic resonance imaging. Twenty-five percent of symptomatic adults could correlate onset of symptoms with a trauma [9]. In our third family, the half-siblings were found to have arachnoid cysts in their posterior fossa which we suggest combined with a familial decrease in posterior fossa volume to cause the tonsillar protrusion. Additionally, the magnetic resonance imaging of Patient 1 in that family did not originally demonstrate Chiari malformation type I, but developed later on in the course of his illness.

Syringomyelia is known to be associated with Chiari malformation type I, occurring in anywhere from 30% to 85% of patients with Chiari malformation type I in the general population [20]. No studies regarding prevalence

of syringomyelia in children with Chiari malformation type I were found. It is possible that some cases of syringomyelia associated with Chiari malformation type I are merely another manifestation of a single sequence involving posterior fossa size. Gardner's dysembryogenetic theory proposes that the pulsatile systolic wave in the spinal subarachnoid space combined with a foramen magnum obstruction causes forceful projection of cerebral spinal fluid through the central canal and resultant syrinx formation [21]. Most recently, Levine proposed that because the composition of the fluid within the syrinx differs from that of cerebral spinal fluid, it may be that trauma on the cord from above causes mechanical stress to the cord, causing injury to the tissue and extravasation of plasma infiltrate into the syrinx [22]. Regardless of the mechanism, syringomyelia can have serious and permanent effects on a patient. The presence of Chiari malformation type I should raise suspicion of an associated syrinx and afford early diagnosis and possible intervention.

The cases presented here also manifested marked interfamilial but less intrafamilial variability in findings. In Family 1, the mother's original diagnosis was "cerebral palsy"—she did not receive any diagnostic imaging until she came to our clinic. From his original examination, her son was also believed to have cerebral palsy. In the second family, monozygotic twins were present, both with significant Chiari malformation type I causing similar symptoms of lower cranial nerve dysfunction. The children in Family 3 presented with a wide variety of symptoms, which included headache, neck pain, and weakness. This interfamilial phenotypic heterogeneity further supports a polygenic or multifactorial inheritance pattern, possibly

with the separate genes or environmental factors involved causing similar symptom sets within families.

Dyste and Menezes reported that 13 of 16 pediatric patients with symptomatic Chiari malformation type I had motor deficit on physical examination and 8 of 16 had hyperreflexia [23]. Up to 20% may have lower cranial nerve symptoms and 30% may have progressive scoliosis [24]. Other studies suggest a role for Chiari malformation type I in the etiology of some cases of sleep apnea, seizures, and developmental disabilities [25]. Chiari malformation type I should be included in the differential diagnosis of chronic headaches, cranial nerve dysfunction, weakness, sensory loss, and scoliosis [24]. It has in fact been suggested that familial idiopathic scoliosis may be included in a spectrum of disorders that includes Chiari malformation type I and syringomyelia [26-30]. Decompression of the posterior fossa may lead to recovery or improvement of symptoms.

Conclusion

Increasing evidence suggests that in some families, there are strong genetic contributors to the development of Chiari malformation type I. While many cases never become symptomatic, those that do can be devastating to the patient and the family. We suggest that clinicians have an increased index of suspicion for Chiari malformation type I in children with nonspecific neurologic symptoms who have family members with Chiari malformation type I or syringomyelia. We also recommend that, when faced with children with symptoms consistent with Chiari malformation type I as well as other disorders, clinicians consider Chiari malformation type I early in the diagnostic evaluation.

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