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Case Report

A genetic component in Chiari I malformation: Chiari 1 malformation in all five family members ☆,☆☆

Taha F. Hassan, BS[a,*], *Ryan D. Morgan, BS*[a], *Kirie M. Psaromatis, MBA*[a], *Benedicto C. Baronia, MD*[b]

[a] *School of Medicine, Texas Tech Health Sciences Center, Lubbock, TX, USA*
[b] *Department of Surgery, Texas Tech Health Sciences Center, University Medical Hospital, Lubbock, TX, USA*

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ABSTRACT

Under certain classifications, a Chiari type I (CMI) malformation can be characterized as a herniation of the cerebellar tonsils greater than 3 mm. Patients with CMI often have a smaller posterior fossa volume, which results in a smaller amount of space for the cerebellum, leading to the herniation of the cerebellar tonsils through the foramen magnum. Although inheritable factors such as posterior fossa volume can be traced to specific genes, there has not been a gene that can be attributed to directly causing CMI. However, several cases of CMI have exhibited a familial inheritance pattern. There are mixed findings regarding the exact nature of its inheritance, with some papers arguing in favor of an autosomal dominant pattern. In this case series, we detail a mother, father, and all 3 of their children diagnosed with CMI. Previous literature has not included both a mother and father with CMI.

Introduction

Chiari type I (CMI) malformation is the herniation of the cerebellar tonsils greater than 3-5 mm below the foramen magnum and can affect any individual regardless of age [1]. Patients affected by CMI can be either asymptomatic or symptomatic. Symptomatic patients most commonly present with headaches; however, dizziness, disequilibrium, neck pain, difficulty sleeping, weakness, numbness in the upper or lower extremities, nausea, and blurred vision may also be present [2]. Cerebellar tonsillar herniation results in aberrant tonsillar pulsatile motion during the cardiac cycle, which interferes with cerebrospinal fluid (CSF) flow at the foramen magnum and causes symptoms [3,4]. Traditional treatment for symptomatic CMI involves posterior fossa decompression,

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* Corresponding author.
E-mail address: hassantaha1115@gmail.com (T.F. Hassan).
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which creates more space for the cerebellum, relieves pressure on the spinal cord, and restores normal CSF flow [5]. Additional complications such as syringomyelia, tonsillar herniation greater than 10 mm or extending down to C2, and neural compression may necessitate concomitant duraplasty [6].

Although cases that entail a familial pattern for CMI are rare, literature has shown a few instances detailing a Mendelian inheritance of CMI [7]. There are mixed results regarding the inheritance of CMI, with most of the available literature supporting an autosomal dominant inheritance pattern while others support variable inheritance patterns [8–10]. The most extensive pedigree study by Milhorat et al. [11] concluded an autosomal dominant inheritance and a greater incidence among women. Additionally, the inheritance of CMI may be related to factors such as a small posterior fossa volume [12]. CMI is also commonly linked to numerous inherited syndromes such as achondroplasia, Klippel-Feil, Goldenhar, and X-linked aqueductal stenosis [9]. Here we describe the case of symptomatic familial CMI that involves both parents, both of whom stated that they were unrelated.

Case presentation

The mother, a 40-year-old female, first visited the clinic following a referral from her ophthalmologist due to persistent headaches and inconclusive magnetic resonance imaging (MRI). She endorsed constant headaches that varied in location. Symptoms that accompanied the headaches included dizziness, nausea, blurred vision, and dysphagia. She reported these headaches to have occurred since the age of 18, with no relation to her menstrual cycle. The patient also complained about bilateral neck and shoulder pain, as well as an aching, constant lower back pain that radiates down to her legs. Associated symptoms with her leg pain included numbness, tingling, and pain worsened by bending, twisting, and lifting. She rated her lower back pain 6/10 on most days, and over-the-counter ibuprofen provided some symptomatic relief. Another MRI found a 5 mm herniation of the cerebellar tonsils through the foramen magnum (Fig. 1); she was subsequently diagnosed with a Chiari I malformation and scheduled to undergo a repeat MRI with cine flow. The MRI with cine flow revealed abnormal CSF flow at the dorsal aspect of the foramen magnum (Fig. 2). She was referred for a lumbar puncture to rule out elevated intracranial pressure (ICP) prior to decompressive surgery for CMI. A lumbar puncture revealed high ICP, and she was referred to neurology who diagnosed her with pseudotumor cerebri with secondary Chiari I malformation. She was given the option of a ventriculoperitoneal shunt (VPS) which she declined and was prescribed furosemide. She opted for VPS placement a month later and reported doing well afterward despite occasional dizziness, nausea, and headaches. She was offered decompressive surgery as she presented with persistent symptoms of Chiari, despite experiencing improvements in symptoms related to increased ICP. The patient opted for a posterior fossa decompression performed seventeen months after her VPS placement. MRI postop exhibited improvement in the CSF flow dorsally at the foramen magnum; however, flow was still diminished compared to the ventral side (Fig. 3). The patient currently shows stable findings for both CMI and the VPS, and there is no evidence of tonsillar ectopia on head CT scan (Fig. 4). She will continue to follow up annually with neurosurgery.

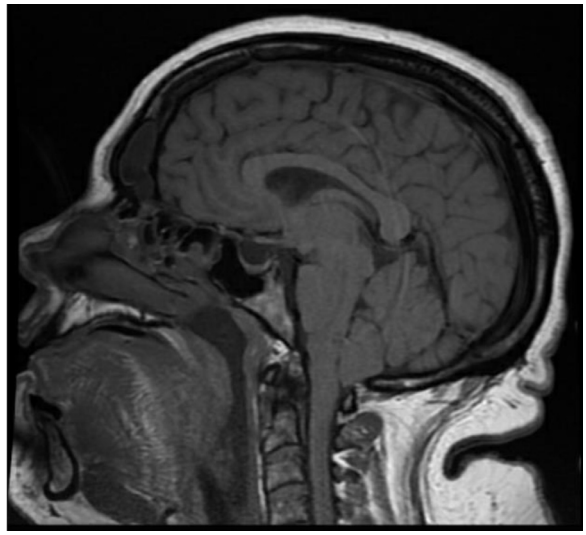

Fig. 1 – The mother's preop sagittal T1 weighted MRI showing a 5 mm herniation of the cerebellar tonsils below the foramen magnum.

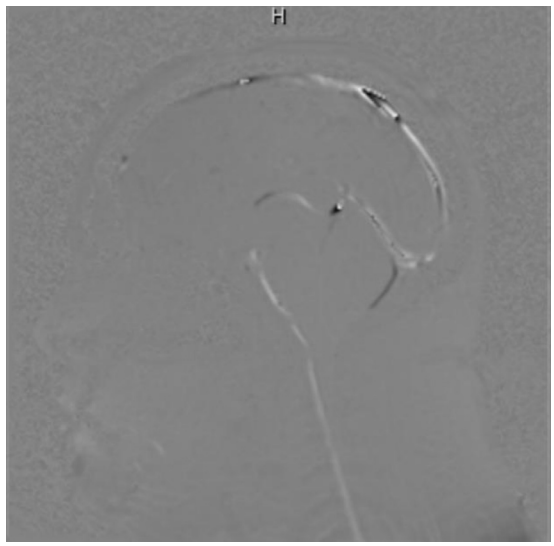

Fig. 2 – Mothers preop sagittal cine MRI demonstrating a paucity of CSF flow along the dorsal aspect of the foramen magnum with preservation of CSF ventrally.

A 42-year-old male, the family's father, presented to the emergency department complaining of chronic neck pain and shoulder discomfort that had become more pronounced over the past few weeks. MRI found a 4 mm herniation of the cerebellar tonsils through the foramen magnum (Fig. 5) accompanied by restricted flow dorsally (Fig. 6). These findings, in conjunction with the patient's presentation, were indicative of borderline CMI. He returned to the clinic 10 months later, complaining of continued neck pain, decreased range of motion

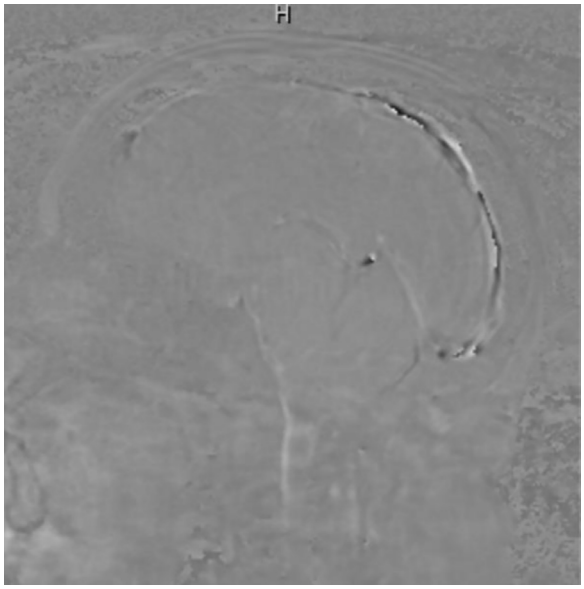

Fig. 3 – Mother's postop sagittal cine flow MRI demonstrating dorsal CSF flow improvement at the foramen magnum; however, still diminished compared to the ventral CSF flow.

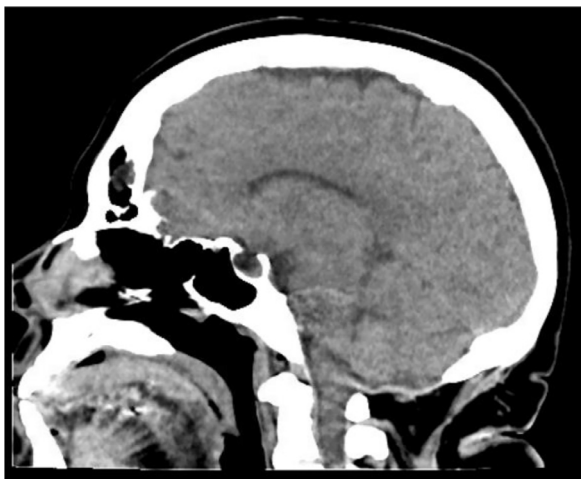

Fig. 4 – The mother's most recent head CT scan 6 years after Chiari decompression shows full resolution of tonsillar ectopia.

in the neck, and occipital headaches. The patient elected to have a Chiari decompression, which was performed 4 months later. His neck pain, stiffness, and headaches were completely resolved 2 months postoperatively; however, the patient still complained of pressure at the back of the head whenever he leaned forward, neck pain while lifting objects, and occasional lightheadedness. MRI at that point in time showed improved but still diminished CSF flow (Fig. 7). The patient's symptoms were resolved entirely by his 6-month follow-up.

A 21-year-old male, the oldest of the 3 siblings, arrived at the neurosurgery clinic complaining of what he described as an intermittent pressure-like pricking in the back of the head

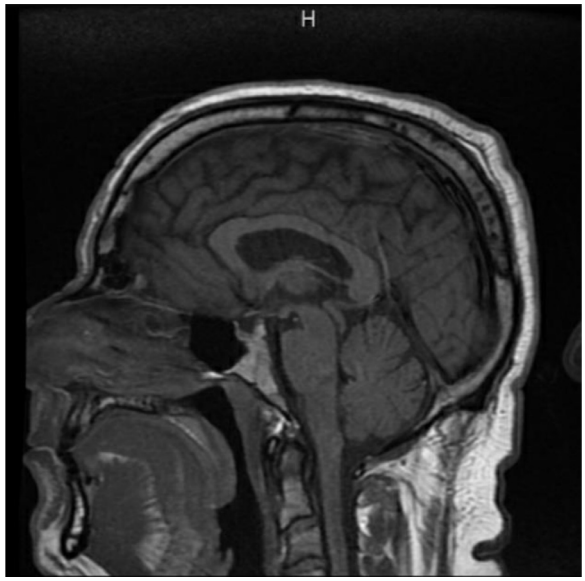

Fig. 5 – Sagittal T1 MRI findings preop for the father. There were low-lying cerebellar tonsils projecting 4 mm below the level of the foramen magnum.

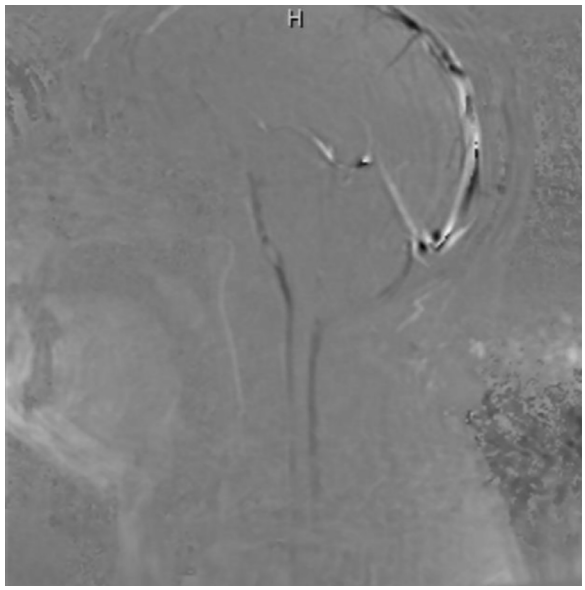

Fig. 6 – Sagittal cine flow findings for the father CSF preop. There was mild abnormal neural movement at the foramen magnum as well as diminished CSF flow at the foramen magnum dorsally.

since middle school, and discomfort of the bilateral upper and lower extremities without any associated weaknesses or numbness. This patient previously had 2 concussions which he fully recovered from both times. The patient's neck pain was aggravated by lifting heavy objects at work. MRI showed a 5 mm descent of the cerebellar tonsils (Fig. 8) and obstruction of CSF flow dorsally at the foramen magnum (Fig. 9). He was subsequently diagnosed with symptomatic Chiari I

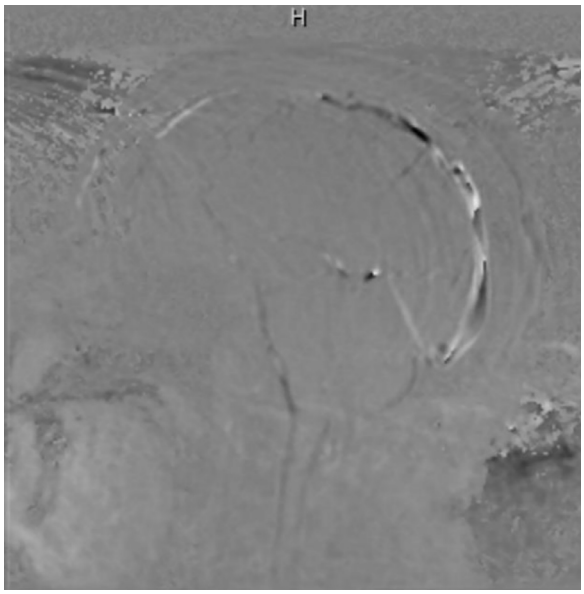

Fig. 7 – Sagittal cine flow findings for the father CSF postop. Phase contrast CSF flow demonstrates diminished flow along the dorsal aspect of the foramen magnum and at the point of maximum contact of the lower cerebral hemispheres with the dura.

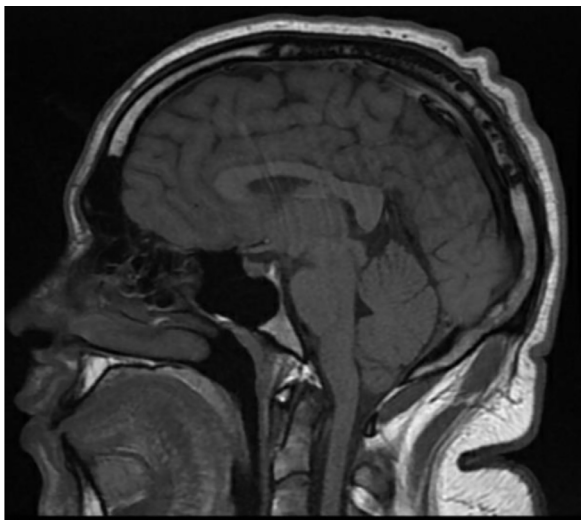

Fig. 8 – Sagittal T1 MRI findings displayed a 5 mm cerebellar tonsil herniation through the foramen magnum for the oldest brother preop.

malformation. Ophthalmology examination was negative for papilledema. The patient opted for surgical decompression initially scheduled 3 months later; however, the surgery was delayed. The patient came in with both parents 11 months after his previous visit, complaining of right arm numbness in addition to persistent neck and occipital pain. He underwent suboccipital decompressive craniectomy without complications a year after the original surgery date. The patient was asymptomatic at his 1-month postoperative follow-up

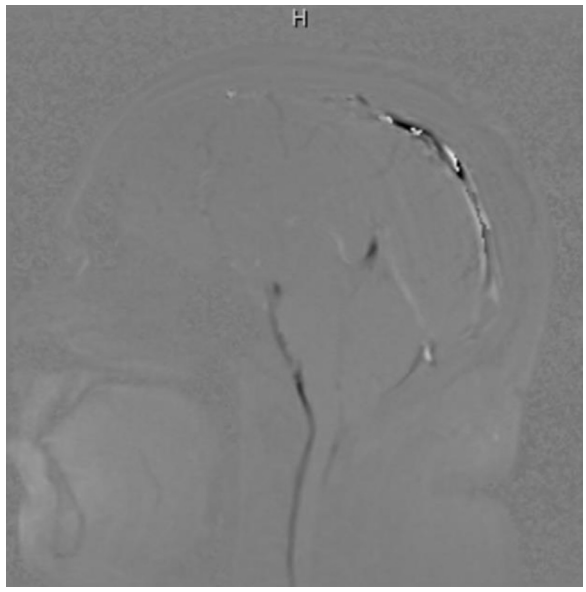

Fig. 9 – CSF flow study preop for the oldest brother demonstrated preservation of CSF flow along the ventral aspect of the foramen magnum. There was a paucity of CSF flow along the dorsal aspect of the foramen magnum. Note: there was not an MRI found postop; however, the patient had achieved resolution of symptomatic CMI.

and remained asymptomatic at his 2-year follow-up. No imaging was taken of the patient at his 1-month follow-up as he had achieved complete symptomatic resolution.

A 20-year-old male, the middle of the 3 siblings, presented to the neurosurgery clinic, complaining of neck pain and shoulder discomfort that started a year previously. The patient denied numbness and weakness in bilateral upper and lower extremities, blurred vision, and vision loss. MRI findings were significant for cerebellar tonsil herniation measuring 3 mm. He was diagnosed with CMI based on imaging and clinical presentation. MRI with cine flow 2 months later showed tonsillar descent of 6 mm with restriction of CSF flow dorsally at the level of the foramen magnum. This patient also complained of middle back pain in addition to neck pain and shoulder discomfort. The patient was diagnosed with asymptomatic CMI. A complete MRI of the spinal cord also revealed an intradural cyst located at T6. The patient returned to the clinic 14 months later, complaining of persistent neck pain affecting his daily activities. MRI revealed a 4.5 mm tonsillar descent (Fig. 10) with good dorsal and ventral flow at the cervicomedullary junction (CMJ) (Fig. 11). The patient complained about further worsening symptoms 22 months after his initial visit, with additional bilateral shoulder discomfort and occasional tingling sensations in both arms and hands. He underwent suboccipital decompressive craniectomy 2 months later without complications. Postoperative follow-up 2 months later found the patient's symptoms had resolved and he remained asymptomatic at his 5-month follow up. No imaging was taken of the patient at his 2-month follow-up as he had achieved complete symptomatic resolution.

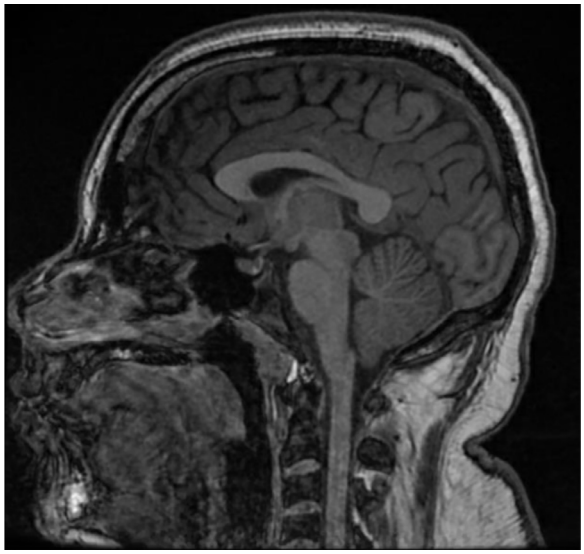

Fig. 10 – Sagittal T1 MRI findings for the second oldest brother found stable mild ectopia of cerebellar tonsils extending 4.5 mm below the level of the foramen magnum.

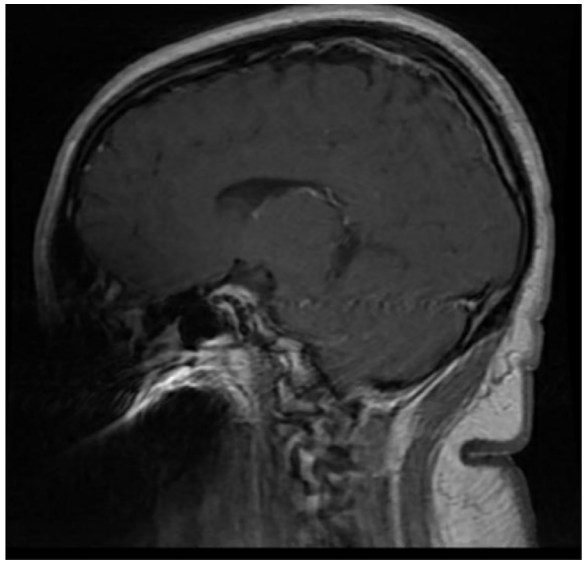

Fig. 12 – Sagittal T1 MRI findings for the youngest brother preop. The cerebellar tonsils projected approximately 12 mm below the level of the foramen magnum.

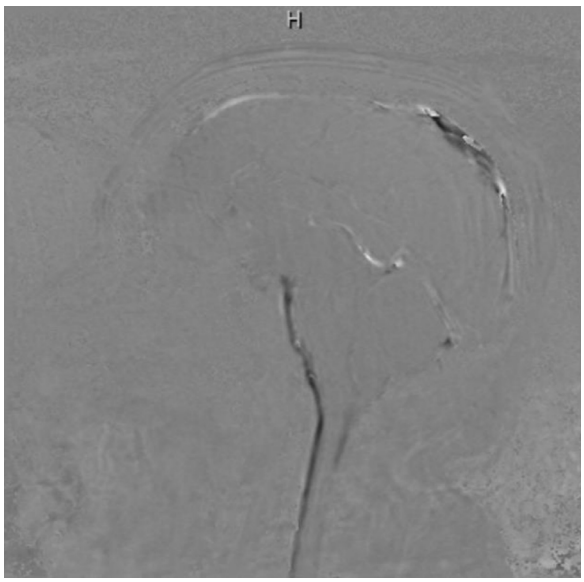

Fig. 11 – Sagittal cine flow findings for the second oldest brother preop found the preservation of CSF flow along the ventral and dorsal aspects of the foramen magnum.

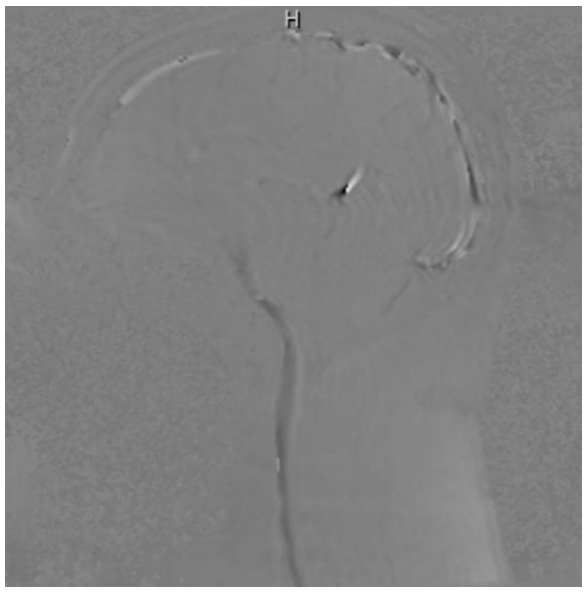

Fig. 13 – Sagittal cine flow findings for the youngest brother preop found diminished CSF flow at the foramen magnum dorsally.

The youngest son, a 15-year-old male, presented to the clinic with a chief complaint of frontal headaches. MRI revealed a 12 mm descent of the cerebellar tonsils through the foramen magnum (Fig. 12) accompanied by restricted CSF flow dorsally at the CMJ (Fig. 13). The patient was diagnosed with CMI, although he did not experience other symptoms aside from his headaches at this time. The patient limited recreational physical activity but still felt frontal headaches whenever he played sports. The patient also began experiencing neck and muscle pain in addition to the headaches, and he opted for surgical decompression 8 months later. Surgical decompression was performed 18 months after his initial visit. The patient's symptoms resolved following the operation, and he remained asymptomatic 1 year after CMI decompression. No imaging was performed postoperatively at his 2-month follow-up as he had achieved complete symptomatic resolution.

Discussion

A lack of development in the skull base leads to a smaller posterior fossa volume, limiting the amount of space that surrounds the cerebellum. This is thought to be the cause of Chiari I malformations. This reduction in volume can lead to the herniation of the cerebellar tonsils through the foramen magnum, which causes many of the symptoms seen in CMI [13]. There is also a strong correlation between CSF flow and the severity of CMI symptoms [3]. In this case series, the resolution of symptomatic CMI was associated with the restoration of CSF flow; the herniation of the cerebellar tonsils was not resolved itself.

Traditionally, CMI has been attributed to an embryological failure of the mesoderm and neuroectoderm; however, recent studies have attributed the cerebellar tonsil herniation to the inheritance of a small posterior fossa itself [12,14]. In a genetic inheritance sequencing study performed by Musolf et al., there was no phenotype found for CMI itself; however, there were genes linked to reduced posterior fossa volume. A microarray analysis by AvSar et al. [15] found that mutations in the genes OLFML2A (involved in the development of brain structures), SLC4A9 (responsible for fluid secretion and regulation of electrolyte balance in CSF), and COL4A1 (related to impaired vascular formation in the brain) may play a role in the expression of CMI. Further studies are still required to support the role of these genes in the pathogenesis of CMI outside of the 2 families studied [15]. Although there are genes directly linked to CMI, previous literature has detailed mixed results on its inheritance. The largest pedigree study conducted by Milhorat et al. [11] concluded an autosomal dominant inheritance pattern in CMI. Some of the literature is consistent with this autosomal inheritance pattern in CMI; however, other cases and studies have concluded various inheritance patterns [9,10,16]. In this case series, both parents and all 3 siblings were diagnosed with CMI. Based on this family's case series, there is not enough information present to analyze what specific type of Mendelian inheritance was seen with CMI in this family.

Although CMI has been associated with several other inheritable conditions, a direct genetic linkage has not been established between these conditions and CMI [9]. The most common associated condition with CMI is syringomyelia, as CMI has been proven to directly cause syringomyelia [17]. While genetic syndromes such as achondroplasia, Klippel-Feil, Goldenhar, X-linked aqueductal stenosis, and many others can also be found alongside CMI, none of these conditions have been genetically linked to CMI [2,7,18]. The *PAX* gene family, which are genes that encode transcription factors for embryological development through segmentation and vertebral development, have also been suggested for further gene studies to elucidate the involvement of these genes in the development of CMI [10].

Cerebellar tonsil herniation also disrupts the flow rate of cerebrospinal fluid through the CMJ. This disturbance in flow is more closely related to the severity of symptoms than the amount of herniation itself [3,14,19]. The severity of symptoms for each of the patients in this family supports this finding, as the mother and father, both of whom experienced aberrant CSF flow, experienced the most intense symptoms compared to their 3 sons. Clinical management for CMI typically opts for the most conservative treatment option available; asymptomatic patients often do not require surgery and can be treated with supportive care [20]. Chiari decompression surgery, often referred to as posterior fossa decompression or suboccipital decompressive craniectomy, removes bone in the posterior fossa to open up the foramen magnum and create more space for the cerebellum [21]. Recent studies have indicated that this procedure also resolves aberrant CSF flow at the CMJ, providing symptomatic relief and more optimal outcomes [22]. All patients in this family elected for decompressive Chiari surgery and achieved resolution of their symptomatic CMIs.

Though CMI is relatively common within the general population, there is still little known regarding its inheritance pattern. Multiple genes and inheritance patterns have been suggested; however, conclusive evidence is lacking. Here we present the case of familial CMI in which all 5 family members, including both parents, had CMI characterized by tonsillar ectopia and restricted CSF flow. This has not previously been described in the literature and may offer new insights into the inheritance of this malformation. More research is needed to clearly elucidate the genetic component and inheritance of CMI. A genetic study for this case study was proposed and the process to begin it was initiated; however, a lack of funding as well as difficulty with following up with the family after their surgeries made it difficult to perform 1 for this family.

Author contributions

Taha Hassan contributed to the conception and writing of the original draft and critical revisions. Ryan D. Morgan contributed to the writing, review, and critical revision of the manuscript. Kirie Psaromatis contributed to the revision of the original draft. Benedicto Baronia contributed to the conception, supervision, review, and critical revision of the manuscript. All authors approved the final version of the manuscript.

Data availability statement

The data that support the findings of this study are not publicly available due to policies related to patient confidentiality by the Texas Tech Health Sciences Center but are available from T.H. upon reasonable request.

Statement of ethics

Ethical approval is not required for this study in accordance with local guidelines.

Patient consent

Written informed consent was obtained from the individuals involved and legal guardians for publication of the details of their medical case and any accompanying images.

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