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 Chiari7 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.57 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.5,3,12,15,30,34,36,40,42,43,47,55,70,75 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.

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.

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).

Pathophysiology

Morphometric studies by Schady et al.39 and Milhorat et al.46 have provided evidence that the volume of the posterior cranial fossa in patients with CM-I was 23% less than controls. Furthermore, Badie and colleagues3 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-Padilla52 added to the understanding of this anatomical pathology by inducing underdevelopment of the basiocipit 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.
theless, hydrocephalus is noted in approximately 4%–18% of patients with CM-I. Tubbs et al., 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., 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. Synostosis can exist solitarily or as part of a syndrome such as Crouzon (72.7%), Apert (1.9%), Pfeiffer (50%), and Kleeblattschädel syndromes (100%). Additional studies estimated the Crouzon syndrome association to be as high as 70%.

CM-I is now believed to be associated with Pfeiffer Type II, Jackson-Weiss, Seckel, Antley-Bixler, and Shprintzen-Goldberg syndromes 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. 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. Normally, the skull continues to expand along with brain growth until the age of 16 years.

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 Loeps-Dietz syndrome. 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. Additionnally, Tubbs et al. reported a 30% incidence of CM-I associated with simple metopic ridging without signs of trigonocephaly; Tubbs et al. 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. This endocrine deficiency in children is believed to be a physiological mechanism for insufficient development of the posterior fossa with resultant tonsillar herniation. While the posterior fossa volume of patients with growth hormone deficiency has

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**TABLE 1: Disorders associated with CM-I**

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<tr>
<th>Disorder</th>
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<tr>
<td>craniosynostosis</td>
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<td>Antley-Bixler syndrome</td>
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<td>Apert syndrome</td>
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<td>Crouzon syndrome</td>
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<td>Jackson-Weiss syndrome</td>
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<td>Kleeblattschädel syndrome</td>
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<td>Loeps-Dietz syndrome Type I</td>
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<td>Seckel syndrome</td>
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<td>Shprintzen-Goldberg syndrome</td>
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<td>endocrinology</td>
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<td>achondroplasia</td>
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<td>acromegaly</td>
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<td>growth hormone deficiency</td>
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<td>hyperostosis</td>
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<td>Paget disease</td>
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<tr>
<td>bone mineral deficiency</td>
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<tr>
<td>familial vitamin D–resistant rickets</td>
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<td>cutaneous disorders</td>
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<td>acanthosis nigricans</td>
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<td>blue rubber bleb nevis syndrome</td>
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<tr>
<td>giant congenital melanocytic nevi</td>
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<td>LEOPARD syndrome</td>
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<tr>
<td>macrocephaly-cuts marmorata telangiectatica congenita</td>
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<tr>
<td>neurofibromatosis Type I</td>
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<td>phacomatosi pigmenotvascularis Type II</td>
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<td>Waardenburg syndrome</td>
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<td>spinal defects</td>
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<td>basilar impression</td>
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<td>caudal regression syndrome</td>
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<td>Klippel-Feil syndrome</td>
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<td>Beckwith-Wiedemann syndrome</td>
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<tr>
<td>CHERI</td>
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<td>cloacal exotrophy</td>
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<td>Pierre-Robin syndrome</td>
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<td>situs inversus</td>
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<td>Williams-Beuren syndrome</td>
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**Hydrocephalus**

Hans Chiari’s aforementioned original theory regarding the causative association between hydrocephalus and hind brain herniation has not allowed for an all-encompassing explanation into the pathophysiology of CM-I. Nonetheless, hydrocephalus is noted in approximately 4%–18%
Associated disorders of Chiari Type I malformations

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. 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. 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.

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. and Richards et al. 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. Craniofacial 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 documented cervicomедullary compression as well. Chiari Type I malformation secondary to osteopetrosis and erythroid hyperplasia 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, 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. Kuether and Piatti suggested in a case study that CM-I development from rickets is due to foramen magnum stenosis. Interestingly, Renier et al. 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. 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.

Equally mysterious is the association of CM-I with macrocephaly-cutis marmorata telangiectatica congenita, 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, blue rubber bleb nevus syndrome, giant congenital melanocytic nevi, phacomatoses pigmentovascularis Type II, acanthosis nigricans, and Waardenburg syndrome variants. 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 spondylolyphisyseal dysplasia, caudal regression syndrome, Klippel-Feil syndrome, and atlantoaxial assimilation, cause deformities and odontoid retroflexion in which the vertebral column is the site of deformation. These disorders 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 also has proven to be coupled with CM-I in as many as 3%-6% of patients. 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.

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 and infratentorial 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 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. Both hemihypertrophy and growth hormone deficiency 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. Additionally, associations with Williams-Beuren syndrome have been found with morphometric analyses suggesting a diminished posterior fossa leading to CM-I. Finally, associations with disorders such as cystic fibrosis, Pierre-Robin syndrome, Ehlers-Danlos syndrome, Fabry disease, Kabuki syndrome, situs inversus, CHERRI and cloacal extrophy 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, Chern. 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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