Osteopetrosis with Chiari I malformation: presentation and surgical management

Case report

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Osteopetrosis is a heterogeneous group of rare, inherited disorders of the skeleton due to restriction of growth of cranial foramina and calvarial thickening. A 25-year-old woman with a history of autosomal dominant osteopetrosis presented to the authors' institution with headache worsened by exertion and radiating from the occipital region forward with episodes of choking/coughing when eating and a loss of gag reflex on physical examination. On MR imaging, she was found to have severe posterior fossa calvarial thickening resulting in a small posterior fossa and tonsillar ectopia of 9 mm and compression and deformation of the brainstem. She underwent posterior fossa craniectomy, foramen magnum decompression, and partial C-1 laminectomy with external durotomy. The patient did well postoperatively with resolution of symptoms. This case describes a new neurological manifestation of autosomal dominant osteopetrosis. To the authors' knowledge, this report represents the first described case of extreme posterior fossa calvarial thickening from autosomal dominant osteopetrosis with associated Chiari I malformation (CM-I) requiring posterior fossa decompression and extradural decompression. Given previously published MR imaging data that demonstrate the association of osteopetrosis and CM may be more common than in this case alone, the authors discuss the need for further investigation of the incidence of CM-I in patients with autosomal dominant osteopetrosis. Additionally, they review osteopetrosis and other diagnoses of calvarial hyperostosis presenting as CM-I. (DOI: 10.3171/2011.1.PEDS10353)

Key Words • osteopetrosis • Chiari I malformation • hyperostosis • posterior fossa decompression • suboccipital craniectomy

Abbreviations used in this paper: ADOI = autosomal dominant osteopetrosis Type II; CM-I = Chiari I malformation.

This article contains some figures that are displayed in color online but in black and white in the print edition.
Reports show that patients with CM-I usually have a congenitally hypoplastic posterior fossa that is associated with underdevelopment of the occipital bone, low-lying tentorium, or thickened or elevated occipital bone. Some reports demonstrate a positive correlation between posterior fossa size and the degree of cerebellar ectopia. Here we present a case of CM-I due to severe posterior fossa calvarial thickening from osteopetrosis and the respective surgical management. We discuss osteopetrosis and other hyperostoctic conditions that have been associated with CM-I. We also discuss the possibility that CM-I is more prevalent in osteopetrosis than previously denoted in the literature. We advocate for close observation of neurological manifestations of CM-I in patients with osteopetrotic conditions.

**Case Report**

*History and Examination.* This 25-year-old woman with a history of osteopetrosis presented with a long history of exertional headaches beginning in the occipital region and extending forward. She described her headaches as occasionally disabling that exacerbated with lifting. The headaches were dull or rolling in nature and intermittent; they sometimes lasted for 10 consecutive days and occasionally were absent for a week. Cervical flexion and extension caused a sharp pain. She described difficulty in swallowing liquids, which resulted in coughing and choking episodes. She denied tinnitus but stated hearing a static-like noise when talking loudly, which was usually associated with headache. She felt dizzy and light-headed at times as well.

The patient has a family history of known autosomal dominant osteopetrosis, and she was originally diagnosed with osteopetrosis 9 years earlier after a head CT revealed calvarial thickening.

On neurological examination, the patient had normal cranial nerve function except for decreased sensation to touch and pinprick in the infraorbital nerve distribution on the left. Funduscopic examination findings were normal without papilledema. The patient had an absent gag response bilaterally. The strength in her upper and lower extremities was normal. She had normal sensation throughout, and her deep tendon reflexes were normal. Her balance and gait were normal. She had a long face and large mandible.

An MR imaging study of the brain demonstrated a markedly thickened calvaria and thickened skull base (Fig. 1A). The MR imaging study revealed hindbrain herniation with tonsillar ectopia and impaction at the foramen magnum (Fig. 1B) with compression and deformation of the brainstem (Fig. 1C). A head CT scan confirmed marked thickening of the calvaria and skull base (Fig. 1D and E).

Evaluation included a swallow examination, complete bone survey (Fig. 2), and renal, liver, hematological, and endocrinological evaluations prior to further neurosurgical management of the patient’s CM-I. The bone survey (Fig. 2) demonstrated the extent of the disease and was used in genetic analysis, confirming the diagnosis and type and mode of inheritance of osteopetrosis, excluding other sclerosing bone disorders. After workup, it was deemed that the patient would benefit from a posterior fossa decompression, and the patient elected to undergo surgical management.

*Operation.* A posterior fossa craniectomy encompassed removal of the posterior rim of foramen magnum and ascended upward approximately 0.5 cm below the external occipital protuberance and progressed laterally for about 2 cm to either side of the midline. The bone at the inferior nuchal line was grossly abnormal and had a large overhang inferriorly and laterally, which had the appearance of a staghorn. Given the large amount of bone removal required, this took approximately 160 minutes with numerous drill bits. The final removal of the inner table of bone was made using Kerrison rongeurs and curettes (Fig. 3 left). At the end of this portion of the craniectomy, the calvarial bone was sloped so that it was not an abrupt bone resection. The thickness of calvarial bone at this location, between the superior and the inferior nuchal line, was 44 mm on direct measurement (Fig. 3 right).

The superior half of the bifid posterior arch of C-1 was removed using the diamond drill bit. The wide constrictive epidural band that was present between foramen magnum and C-1 was excised (Fig. 3 right). An external durotomy was made starting at the midportion of the atlas arch and extended 2 cm above the foramen magnum. An intraoperative ultrasonography study showed that there was no compressive area in the posterior fossa or at the cervicomедullary junction. The cerebellar tonsillar tips pulsed normally and had normal motion. Closure ensued with paraspinal muscle approximation in multiple layers followed by tight fascial closure and skin closure.

*Postoperative Course.* The patient’s symptoms and signs regressed in the 1st week postoperatively. Although the patient did not return as an outpatient, she underwent follow-up for suture removal, and at her regularly scheduled 6-week appointment, she stated she was doing well with no recurrence of symptoms.

**Discussion**

Osteopetrosis is a rare disease with relatively few large studies investigating and clearly elucidating the neurological manifestations of the disease. This case describes CM-I as a new neurological manifestation of autosomal dominant osteopetrosis. To our knowledge, this report represents the first described case of extreme posterior fossa calvarial thickening caused by autosomal dominant osteopetrosis with associated CM-I requiring posterior fossa decompression and extradural decompression. In the literature, there are 5 pediatric cases of autosomal recessive osteopetrosis associated with hindbrain herniation (Table 1). The causative role of osteopetrosis with CM-I is unclear. Hypotheses include mass effect from the significant calvarial thickening and subsequent downward tonsillar herniation. Additionally, the relationship of the skull base to calvarial thickening may have
resulted in a smaller posterior fossa. Furthermore, stenosis at the foramen magnum or underdeveloped occipital bones due to lack of remodeling from osteoclast activity may also lead to a smaller posterior fossa.

In our patient, severe posterior fossa calvarial thickening was noted to decrease the size of the posterior fossa, the likely cause of tonsillar ectopia in this patient. Although there are many reports implicating a small pos-

Fig. 1. Significant cranial hyperostosis and sclerosis leading to a decrease in size of the cranial vault and posterior fossa, causing hindbrain herniation and brainstem compression. A–C: Sagittal T1-weighted MR images of the brain (A and B) demonstrating the significant cranial hyperostosis and sclerosis and compression on the supratentorial and infratentorial compartment leading to tonsillar ectopia of 9 mm and CM-I. There is notable brainstem compression and deformation by tonsillar herniation on the axial T2-weighted image (C). D: Sagittal CT scan of the head demonstrating the significant cranial hyperostosis and sclerosis. E: Axial CT of the head demonstrating the significant cranial hyperostosis and sclerosis surrounding the cerebellum and brainstem. Bar = 10 mm.

Fig. 2. A complete skeletal survey was conducted with increased bone density and thickening throughout the axial and appendicular skeleton. A: Lateral skull radiograph demonstrating increased bone density and thickening of the mandible and calvaria. B: Anteroposterior skull radiograph demonstrating increased bone density and thickening of the thoracic spine. C: Anteroposterior skull radiograph demonstrating increased bone density and thickening of the lumbar spine.
terior fossa in development of CM-I rather than a primary malformation of brain development, other reports have described normal posterior fossa geometry and size in patients with CM-I. A small posterior fossa size may be sufficient but not required for CM-I, suggesting additional factors involved in its pathogenesis.

Although there is a spectrum of severity to the disease, there are distinct clinical differences between autosomal dominant osteopetrosis, autosomal recessive, and X-linked osteopetrosis. Patients with autosomal recessive and X-linked osteopetroses have a much more severe phenotype, succumb to the disease, and do not proceed to adulthood. However, many patients with autosomal dominant osteopetrosis are only slightly symptomatic and will proceed to adulthood and have a normal life expectancy. They may experience headaches and cranial nerve palsies often from cranial nerve foraminal narrowing. However, these same symptoms occur in cases of CM. Making further study even more important and why it may not have been investigated previously is the commonality of the neurological symptoms of patients with autosomal dominant osteopetrosis with cranial nerve foraminal narrowing and CM.

Although there are relatively few papers discussing the cranial MR imaging findings in patients with osteopetrosis, one study found that 3 of 6 patients with autosomal dominant osteopetrosis exhibited tonsillar herniation on imaging—a report that demonstrates that the association of osteopetrosis and CM may be more common than this case alone. Further evidence supporting the association of osteopetrosis and CM, cranial MR imaging findings showed that 18 of 34 patients with autosomal recessive osteopetrosis had tonsillar herniation. Whether patients with osteopetrosis are symptomatic from this tonsillar herniation is unknown. We believe that CM should be in the differential diagnosis in patients with autosomal dominant osteopetrosis, especially if they present with headache and cranial nerve palsies. Further study of patients with autosomal dominant osteopetrosis is needed to determine the incidence of tonsillar herniation and CM.

### Osteopetrosis

Osteopetrosis is caused by failure of osteoclast development or function, and mutations in at least 10 genes have been identified as causative in humans. Diagnosis is largely based on clinical and radiographic evaluation. Osteopetrotic conditions vary greatly in their presentation and severity. These conditions can be inherited as autosomal recessive, autosomal dominant, or X-linked with the most severe forms being autosomal recessive and X-linked. Treatment of osteopetrotic conditions is largely symptomatic.

The patient in this report had clinical findings and family history consistent with either the autosomal dominant osteopetrosis Type II (ADOII or Albers-Schoenber disease) or the intermediate autosomal dominant osteopetrosis. Mutations in the CLCN7 gene are responsible for both types of osteopetrosis.

Onset of ADOII is typically during late childhood or adolescence. The condition is variable and can include fractures in the long bones and/or the posterior arch of the skull. The patient in case 1 presented with symptoms consistent with CM-I, and further investigation revealed the presence of CM.

### TABLE 1: Reported cases of osteopetrosis and Chiari malformation*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Mode of Inheritance</th>
<th>MRI Finding</th>
<th>Presentation</th>
<th>Treatment</th>
<th>Outcome Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>present case</td>
<td>25, F</td>
<td>AD</td>
<td>CM-I, brainstem compression from tonsillar herniation</td>
<td>HA, swallowing difficulty</td>
<td>pst fossa decompression</td>
<td>symptoms resolved</td>
</tr>
<tr>
<td>Kulkarni et al., 2007</td>
<td>15, M</td>
<td>unknown</td>
<td>CM-I, cervical syrinx</td>
<td>HA, hoarseness</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Jamjoom et al., 2009</td>
<td>4, M</td>
<td>AR</td>
<td>CM-I, oxycephaly, persistent open fontanel</td>
<td>signs &amp; symptoms of increased ICP</td>
<td>bifrontal craniotomy, resection of hypertrophied bone</td>
<td>intraop cardiac arrest</td>
</tr>
<tr>
<td>Al-Tamimi et al., 2008</td>
<td>11, F</td>
<td>AR</td>
<td>crowding of pst fossa, hindbrain herniation</td>
<td>intermittent neck pain</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1.5, M</td>
<td>AR</td>
<td>CM-I</td>
<td>crowding of pst fossa, hindbrain herniation</td>
<td>intermittent neck pain</td>
<td>pst fossa decompression</td>
<td>died of sepsis 3 mos postop</td>
</tr>
</tbody>
</table>

* AD = autosomal dominant; AR = autosomal recessive; HA = headache; ICP = intracranial pressure; NR = not reported; pst = posterior.
Osteopetrosis with Chiari I malformation

a vertebral body), scoliosis, and osteoarthritis in the hip or elsewhere. Osteomyelitis of the mandible is often seen with dental abscess or caries. Osteosclerosis of the spine is a prominent feature with a sandwich vertebra appearance. Most affected individuals have a bone-within-bone appearance, particularly in the iliac wings but in other bones as well. Cranial nerve compression is uncommon with this form but is occasionally seen. Sometimes ADOII is called the “benign osteopetrosis,” but 60%–80% of individuals with radiological signs of ADOII have clinical problems as described above. Life expectancy is normal with ADOII.

Onset of the intermediate form of osteopetrosis is during childhood, and findings may include fractures after minor trauma and characteristic skeletal changes found incidentally on radiography (calvarial thickening, dense bones, or bone within bone). Mild to absent anemia, occasional optic nerve compression, and visual impairment may occur. Intermediate autosomal dominant osteopetrosis can be inherited in either an autosomal dominant or recessive manner. Life expectancy is usually normal with this form of osteopetrosis.

Onset of autosomal recessive osteopetrosis occurs in infancy; findings may include fractures, poor growth, sclerosis of the skull base (with or without choanal stenosis or hydrocephalus) resulting in optic nerve compression, facial palsy, hearing loss, absence of the bone marrow cavity resulting in severe anemia and thrombocytopenia, dental abnormalities, odontomas, risk for mandibular osteomyelitis, and hypocalcemia with tetanic seizures and secondary hyperparathyroidism. Without treatment, the maximal life span in patients with autosomal recessive osteopetrosis is very limited.

Hyperostotic Conditions and CM-I

Just as in this report, differentiating osteopetrosis from other inheritable sclerosing bone disorders is important as they can also affect the calvaria and are also associated with CM-I. Craniofacial dysplasia is a rare, genetic craniotubular bone remodeling disorder characterized by early progressive hyperostosis and sclerosis of the craniofacial bones and abnormal remodeling of the metaphyses of the tubular bones. One case of autosomal recessive and a second case of autosomal dominant craniofacial dysplasia have been associated with CM-I.

Posterior fossa decompressions were performed in both cases. Other hyperostotic disorders have been associated with CM-I and include Camurati-Engelmann disease (progressive diaphyseal dysplasia), Worth-type endosteal hyperostosis (autosomal dominant osteosclerosis), and osteosclerosis. There are some patients with hyperostosis that are unable to be classified or receive a specific diagnosis who have acquired CM-I.

Surgical Management of CM-I

All patients with CM-I are treated on an individual basis. If a patient presents with tonsillar herniation and signs/symptoms consistent with CM-I, a posterior fossa decompression is performed, usually with a partial C-1 laminectomy and extradural durotomy. In cases presenting with syringomyelia, it is the senior author’s practice to perform an intradural exploration to identify an arachnoid web or veil impairing CSF flow through the foramen of Magendie and to ensure that the tonsils are decreased in size. A cervical fascia duraplasty is performed.

If the patient does not present with syringomyelia, after satisfactory posterior fossa and extradural decompression is performed, an intraoperative ultrasonography study is done to determine if there is good pulsatile CSF flow through the foramen magnum. If the flow is not deemed adequate, intradural exploration is performed.

Patients with irreducible ventral compression undergo transoral-transpalatopharyngeal decompression and occipitocervical fusion. Other patients with either congenital malformations of the occipitocervical junction or occipitocervical instability also undergo occipitocervical fusion. The senior author has had excellent fusion rates up to 97% in published series.

Conclusions

Although it has been long known that patients with osteopetrosis are susceptible to cranial neuropathies, CM-I has rarely been reported in this population. This case describes a new neurological manifestation of autosomal dominant osteopetrosis. To our knowledge, this report represents the first described case of extreme posterior fossa calvarial thickening from autosomal dominant osteopetrosis with associated CM-I requiring posterior fossa decompression and extradural decompression. However, it is possible that CM-I may be more prevalent than previously reported given published cranial MRI imaging data. Further study is needed. Even with severe calvarial thickening, a posterior fossa decompression is feasible without complication and results in a good outcome with meticulous drilling and thinning of the posterior fossa bone.

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: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: Dlouhy. Critically revising the article: both authors. Reviewed final version of the manuscript and approved it for submission: both authors. Administrative/technical/material support: both authors. Study supervision: Menezes.

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