Patients with autosomal-recessive osteopetrosis presenting with hydrocephalus and hindbrain posterior fossa crowding

Report of 3 cases


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Osteopetrosis is a heterogeneous group of disorders characterized by abnormal bone sclerosis. As a result, patients often require input regarding various neurological complications. Although autosomal-recessive osteopetrosis has been associated with hydrocephalus, it has not been linked to hindbrain abnormalities. The authors present 3 cases of autosomal-recessive osteopetrosis in patients who presented with hydrocephalus. In each of these patients, cerebrospinal fluid diversion procedures were required and hindbrain compression developed. To date, only 1 patient has needed craniocervical decompression due to symptomatic brainstem compression. (DOI: 10.3171/PED-08/01/103)

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Osteopetrosis is a heterogeneous group of disorders characterized by abnormal bone sclerosis. The disorder is thought to be almost exclusively caused by a defect in osteoclast function, which results in increased skeletal mass and contributes to the brittleness of bone. Traditionally, osteopetrosis has been characterized by its clinical manifestations. These categories include infantile, or “malignant,” osteopetrosis and intermediate osteopetrosis. Both are inherited in an autosomal-recessive pattern and are associated with a more severe clinical course. In infantile osteopetrosis, the disease is most often diagnosed within the 1st year of a child’s life with only 30% survival up to 6 years of age. There are a wide variety of clinical features including aplastic anemia, hepatosplenomegaly, osteomyelitis, and failure to thrive.

More recent studies have revealed 3 genotypes responsible for most cases of autosomal-recessive disease. Fifty to 60% of children with severe osteopetrosis have been shown to carry a mutation in the gene responsible for the osteoclast proton pump. One of the earlier defects identified in humans is a deficiency in the enzyme carbonic anhydrase II. Although seen in <5% of patients, this defect is often associated with renal tubular acidosis as well as other features of severe autosomal-recessive osteopetrosis. A third recognized defect that often results in intermediate osteopetrosis is a chloride channel coupled to the osteoclast proton pump.

Osteosclerosis can result in foraminal narrowing in the skull with neurological consequences, including cranial nerve palsies, progressive blindness from optic nerve compromise, and brainstem compression from foramen magnum narrowing. Hydrocephalus has been observed in several cases but its exact cause has yet to be elucidated. Similarly, the association between osteopetrosis and hindbrain abnormalities has been poorly demonstrated.

We describe the cases of 3 children, all of whom had symptomatic hydrocephalus and hindbrain compression at the level of the foramen magnum. A literature review of this subject is also included.

Case Reports

Case 1

This 7-year-old girl presented with headaches, sudden deterioration in vision, and papilledema. She was of Asian origin and unrelated parentage. Her history included a diagnosis of autosomal-recessive osteopetrosis at the age of 14 months. The diagnosis was made following evaluations for developmental delay, multiple fractures, and concerns about her vision. She had undergone bilateral optic nerve decompression at 2 years of age.

Magnetic resonance imaging on this occasion revealed triventricular hydrocephalus (Fig. 1A and B), which was

Abbreviations used in this paper: CM = Chiari malformation; CSF = cerebrospinal fluid; CT = computed tomography; ETV = endoscopic third ventriculostomy; HLA = human leukocyte antigen; ICP = intracranial pressure; MR = magnetic resonance.
successfully treated with ETV (Fig. 1C and D). The patient’s symptoms resolved, and her visual acuity improved. Clinically and radiologically her condition remained stable for 4 years. More recently, she has experienced intermittent neck pain. A recent MR image demonstrated crowding of the posterior fossa with a degree of hindbrain herniation (Fig. 2A). There was no evidence of hydrocephalus.

Case 2

This younger sister of the girl in Case 1 presented to us at the age of 5 years with headaches, nausea, and vomiting. Autosomal-recessive osteopetrosis had also been diagnosed in this girl based on her family history, neonatal hypocalcemia, and feeding difficulties. Nystagmus was noted at the time, and optic nerve compression was confirmed by prolonged visual evoked responses and imaging. At the age of 11 months she underwent bilateral optic nerve decompression, resulting in stable vision.

Clinical examination on her presentation to us revealed signs of elevated ICP, and a cranial CT scan showed hydrocephalus (Fig. 3A and B). The hydrocephalus was successfully treated with ETV (Fig. 3C and D). Subsequent imaging showed evidence of early cerebellar tonsillar descent through the foramen magnum. Recently, her parents noted that she too has been experiencing intermittent neck pain, and a recent MR image demonstrated persistent crowding at the level of the foramen magnum from hindbrain herniation (Fig. 2B).

Case 3

This boy, also of Asian descent, originally presented at the age of 8 weeks with neonatal jaundice, polyuria, and failure to thrive. A carbonic anhydrase II deficiency was subsequently diagnosed and resulted in severe autosomal-recessive osteopetrosis. Associated problems included renal tubular acidosis, megaloblastic anemia, and thrombocytopenia. At the age of 7 months the boy presented with a roving nystagmus.

On examination of the boy at 13 months of age, he demonstrated difficulty in fixing his gaze and a roving nystagmus. Further imaging revealed severe hydrocephalus with features of a CM. He underwent insertion of a ventriculoperitoneal shunt. Despite radiologically demonstrated improvement of the hydrocephalus, ophthalmological assessment revealed reduced visual evoked responses and right-sided optic nerve compression; therefore, he underwent right optic nerve decompression. Six months later, he re-presented with worsening bulbar function, and repeated MR imaging confirmed a worsening CM and brainstem compression due to foramen magnum narrowing (Fig. 2C). Because of the decision to offer bone marrow transplantation, he underwent posterior fossa decompression. He subsequently underwent
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Bone marrow transplantation but unfortunately died due to sepsis 3 months later.

Discussion

Of the 3 described cases of autosomal-recessive osteopetrosis with associated hydrocephalus, all required CSF diversion procedures and all had a hindbrain abnormality, although to date only 1 has required craniocervical decompression. There was an ethical issue in Case 3 with regard to the decision to perform decompression in a child with such severe disease; however, this decision was made after multidisciplinary discussions as the child had already been accepted for bone marrow transplantation. Osteopetrosis of this type is associated with a poor prognosis. Bone marrow transplantation is the only intervention that has been shown to significantly alter the disease course and improve long-term prognosis; however, its success has been shown to be dependent on the suitability of the HLA match. In a series of patients with autosomal-recessive osteopetrosis treated with bone marrow transplantation, a 79% 5-year disease-free survival rate was noted with HLA-identical donors. Compare this rate with the 13% 5-year disease-free survival rate in patients receiving marrow from an HLA haplotype-mismatched related donor.

Because of the propensity for osteopetrosis to be associated with abnormal bone sclerosis, patients often require neurosurgical input for various neurological complications. Osteopetrosis can cause narrowing of any osseous foramina and so can theoretically affect any cranial nerve in contact with bone at this point. The most recognized and well-established compression occurs in the optic canal, resulting in visual failure. Defects in the lower cranial nerves involved in bulbar function have not been reported, which may be due to the inherent poor prognosis associated with poor airway and swallowing control. Other commonly affected cranial nerves include the facial and trigeminal nerves, which can be affected by spasm, neuralgia, or paralysis. Hearing can be compromised at an early stage in infancy due to bone mass encroachment onto the middle ear cavity and auditory nerve canal.

Studies from as early as the 1920s revealed an association between postmortem ventriculomegaly and osteopetrosis (then termed “Albers–Schönberg disease”). Subsequent studies and case reports showed an association with elevated spinal fluid pressure (CSF). This manifestation was thought to be caused by coexisting intracranial hemorrhage. It was not until the 1960s that the first documented shunting procedure for hydrocephalus was performed in a patient with osteopetrosis. A further report of high CSF pressure on ventriculography with a small ventricle size presented the possibility of a pseudotumor-like syndrome leading to increased ICP. The origin of the hydrocephalus was unclear until a report on twins with osteopetrosis and associated hydrocephalus, which was thought to be caused by outflow obstruction in the posterior fossa.

Other reports focused on osteopetrosis and hydrocephalus have included the case of a malignant recessive form of osteopetrosis demonstrating hydrocephalus with an associated Dandy–Walker syndrome and agenesis of the corpus callosum. Severe medullary insufficiency and pulmonary infection developed in this patient, who died at the age of 2 months. Recently, there has been an unusual report of ventriculoperitoneal shunt blockage due to osseous overgrowth at the proximal shunt margin in a patient with osteopetrosis. The patient had not originally received a shunt for hydrocephalus per se but rather for gradual visual deterioration caused by increased ICP and for obliteration of the optic nerve foramina caused by a cranial mass.

There have been 2 reports of lethal autosomal-recessive osteopetrosis with associated hydrocephalus diagnosed while the patient was in utero. In 1 case this disorder was thought to be caused by cortical distortion and in the other, by excessive fetal bone growth and CSF obstruction. It has been postulated that hydrocephalus accounts for, or contributes to, the cognitive deficits associated with osteopetrosis.

This association has been difficult to validate given that many children born with recessive-type malignant osteopetrosis have multiple problems with coexisting genetic disorders. Another consequence of hydrocephalus and elevated ICP has been thought to be optic atrophy and blindness. Alternatively, constriction at the skull base may result in venous outflow obstruction and raised venous pressure causing papilledema. However, the traditional view is that the optic nerve injury is caused by direct compression within the optic canal.

The association between osteopetrosis and hindbrain abnormalities has not been previously clarified. However, there have been 3 case reports of osteopetrosis in association with a syringomyelia, with brainstem compression, or with cervical myelopathy. Syringomyelia was reported in a
case of autosomal-dominant osteopetrosis and was thought to be caused by subarachnoid space narrowing due to sclerotic and thickened bone. Brainstem compression has been reported in a 1-year-old girl with severe infantile osteopetrosis and hydrocephalus probably caused by impingement at the foramen magnum. Cervical myelopathy was reported in association with hydrocephalus and was thought to be caused by thickening of the vertebral elements.

In contrast, there have been several reports of cranio-metaphyseal dysplasia associated with hydrocephalus and CMs. Cranio-metaphyseal dysplasia is a rare cranio-tubular sclerosing bone disorder belonging to the osteopetroses group. However, it is distinct from osteopetrosis in that it has minimal cranial involvement and is not purely a disorder of endochondral bone formation. In these cases, the hydrocephalus was postulated to be caused by either venous outlet obstruction or reduced buffering capacity due to overgrowth of the cranial vault. In 1 case, posterior fossa compression and a CM occurred due to foramen magnum stenosis and hyperostosis of the occipital bone and were associated with a syringomyelia.

In this paper, Case 3 represents a more severe form of the disease, as evidenced by the patient’s earlier presentation, symptomatic CM, and generally poor neurological state. His need for bone marrow transplantation and his subsequent demise sets this form of the disease apart from the type in the other 2 cases. The fact that ETV successfully controlled the hydrocephalus in the patients in Cases 1 and 2 indirectly implies that fourth ventricle outflow obstruction is a significant contributing factor to the development of hydrocephalus in osteopetrosis. Although venous hypertension may have a role in the development of increased ICP, its role in the evolution of hydrocephalus is far from clear. As in achondroplasia (which is associated with ventriculomegaly and macrocephaly), one could postulate that in osteopetrosis, early venous obstruction (prior to suture closure) results in hydrocephalus; however, later-onset hydrocephalus may be caused by fourth ventricle outflow problems associated with acquired foramen magnum compression.

Conclusions

Autosomal-recessive osteopetrosis, to our knowledge, has not been associated with hindbrain abnormalities. In contrast, hydrocephalus has been repeatedly linked to autosomal-recessive osteopetrosis and may be a result of fourth ventricle or venous outflow obstruction, depending on patient age at disease onset.

References


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