Malignant Infantile Osteopetrosis

Otolaryngological Complications and Management

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Objectives: To inform otolaryngologists about upper airway obstruction requiring tracheotomy and other otolaryngological manifestations of malignant infantile osteopetrosis (MIOP) and to discuss pathophysiological features, management, and new treatment strategies in MIOP.

Design: Ongoing case series combined with a retrospective chart review.

Setting: International tertiary pediatric hospital.

Interventions: Patients with MIOP were initially referred for treatment and routine follow-up. Tracheotomy was performed to manage obstructive sleep apnea. Audiograms were also performed at regular intervals.

Results: The records of 9 patients were examined. The otolaryngological findings of hearing loss, obstructive sleep apnea (sometimes requiring tracheotomy), otitis media, and chronic osteomyelitis with facial fistulas were identified.

Conclusions: Osteopetrosis is a rare condition caused by a failure of the osteoclast to resorb bone. This results in thickened dense, deformed, and easily fractured bone. As a result, growth failure, anemia, hypoplastic dentition, chronic infections, facial fistulas, blindness, hearing loss, nasal congestion, and upper airway obstruction may occur. The management of otolaryngological problems in a child with osteopetrosis is an important component in comprehensive care. To our knowledge, this study represents the largest case series of MIOP in the otolaryngology literature.


OSTEOPETROSIS is a rare inherited disease that affects all bones in humans and various mammals.1 It is the result of a defect in the osteoclast's ability to resorb bone and mineralized cartilage.1 The “malignant infantile” form of osteopetrosis (MIOP) is the most severe variant of the disease; it affects infants and is usually fatal before the second decade of life.1,2 The clinical manifestations that are of concern to otolaryngologists include nasal obstruction, deafness, and stenosis of the neural foramina, which can lead to optic atrophy and oculomotor and facial palsies.3 One of the most striking problems associated with MIOP is the need for a tracheotomy to treat obstructive sleep apnea (OSA). We describe complications in 9 cases of MIOP, with an otolaryngological emphasis. We also discuss the various treatment strategies that have evolved over the past 15 years.

CASE 1

This case has been previously described, in part, in another journal. A 2-month-old boy was diagnosed as having MIOP after presenting with severe somnolence, hepatosplenomegaly, narrow external auditory canals, and nasal congestion. When he was 5 years old, the results of his sleep study were abnormal, and a tracheotomy, tonsillectomy, and adenoidectomy were performed. The results of a second sleep study, performed when he was 5 years 11 months old, with a plugged tracheotomy tube, were normal, resulting in the removal of the tracheotomy tube. Subsequently, increased daytime somnolence was noticed at 9 years of age, and the tracheotomy tube was reintroduced. The patient’s hearing was normal at 4 years of age, but a progressive mixed hearing loss was documented by the age of 6 years. Bi-
PATIENTS AND METHODS

We performed a retrospective chart review of 9 patients (5 boys and 4 girls), including 3 children with active MIOP who are presently under our care. The children were treated at St Jude Children’s Research Hospital (SJCRH), Memphis, Tenn, between 1980 and 1997. The average age at diagnosis was 12.2 weeks in 8 patients, and 1 case was identified in utero (Table). The diagnosis was usually made with a radiograph or after the onset of blindness or seizures.

Five patients (56%) were diagnosed as having OSA during the course of their illness (Table); OSA was even noted at birth in 1 patient but resolved at the age of 3 months. The diagnosis was made by sleep studies in 3 cases; the other 2 cases were diagnosed by clinical findings before sleep studies were used in children. Three patients required tracheotomies for OSA and because of failure to thrive. All 9 patients with MIOP had nasal congestion. Four patients had periodontal and mandibular abscesses or necrosis, and 3 developed persistent fistulas (2 mandibular and 1 nasal-antral-cutaneous). One patient was noted to have bilateral facial paresis. Five patients had fractures documented on x-ray films.

Treatment included monocyte-macrophage colony-stimulating factor, which was administered to 8 patients (Table). A combination regimen consisting of interferon gamma, calcitriol, and a low calcium diet was administered to 3 patients. One patient received a bone marrow transplant (BMT) from a matched unrelated donor. Only the BMT had substantial prolonged benefit.

A 5-month-old boy presented with blindness and was diagnosed as having MIOP after radiographic evaluation. He also had nasal congestion due to the narrowed nasal cavity noted at birth. The patient has had normal results on repeated hearing tests, with persistent type B tympanograms at 8 and 12 years of age.

CASE 3

A 6-week-old boy was diagnosed as having MIOP after having seizures. He was referred to SJCRH at 16 years of age and was noted to have nasal congestion, ossified turbinates, and narrow slits for nasal passages. He had increased daytime somnolence, and the results of a sleep study were abnormal. The patient died of OSA at home at 17 years of age. He had bilateral hearing aids for a mixed hearing loss. He also had a nasal-antral-cutaneous fistula. Surgical debridement and antibiotic treatment were used, but the fistula never healed.

Case 4

A 3-month-old girl was diagnosed as having MIOP and was reported to have had nasal congestion and OSA since birth. The apneic episodes ceased at 3 months of age. Initially, the patient had normal hearing, but at 6 years of age a bilateral conductive hearing loss was noticed, and repeated tympanograms were type B.

CASE 5

A 3-month-old boy was diagnosed as having MIOP after radiographic evaluation. He was noted to have nasal congestion on his first visit to SJCRH at 4 years of age. At 7 years of age, he had abnormal results on his sleep study, and a tracheotomy was performed. His audiograms showed no abnormalities, and repeated tympanograms were flat. Subsequently, he developed a draining fistula through a previously well-healed mandibular fracture.

CASE 6

A 3 1/2-month-old girl was diagnosed as having nasal congestion, OSA, and unilateral optic atrophy. Obstructive sleep apnea syndrome and failure to thrive were the contributing factors leading to a tracheotomy at 7 months of age. She has normal hearing with type B tympanograms at 2 years of age. She received a 5 of 6 antigen-matched donor BMT. Since the BMT, she has demonstrated noticeable weight gain and growth (Figure 1 and Figure 2).

CASE 7

A 3-month-old girl was diagnosed as having MIOP after radiographic evaluation. She was noted to have nasal congestion at 2 years of age. Moderate bilateral hearing loss was noted on audiograms at 1 and 2 years of age. Tympanograms were not performed.

CASE 8

This was the only case of MIOP diagnosed in utero (at 8 months’ gestation). The patient was noted to have chronic, severe nasal congestion, OSA, and failure to thrive at 2 years of age. A tracheotomy or uvulopharyngopalatoplasty was recommended but was not performed because of the patient’s severe developmental delay. The patient died at 4 years of age.

CASE 9

A 4-month-old girl was diagnosed as having MIOP after radiographic evaluation. Nasal congestion had begun shortly after birth. The patient had 3 or 4 episodes of acute otitis media before 9 months of age.

The reported incidence of osteopetrosis ranges between 1:100 000 and 1:500 000, although a single county in Denmark has recorded an incidence of 5.5:100 000.4 Sex or...
ethnicity is not a factor.4 Typical clinical findings are frag-
ile bones, failure to thrive, hepatosplenomegaly, throm-
bocytopenia, leukoerythroblastosis, and increased sus-
ceptibility to infection.3 The disease is usually fatal during
infancy, but the life expectancy has increased as a result
of better medical care.5

The characteristic pathophysiological features of
MIOP are the result of the lack of osteoclastic function.
The most severe form is transmitted as an autosomal re-
cessive trait and is characterized by an excess accumu-
lation of bone throughout the body. The osteoclast is a
large multinucleated cell whose function is to absorb and
remove osseous tissue. When the osteoclast’s activity de-
creases, “marbling” of the bone occurs and is charac-
terized by sclerosis, brittleness, and radiopacity, with asso-
ciated hematologic and neurological abnormalities
(Figure 3).6 This bone formation leads to the encroach-
ment of the marrow spaces, which directly results in ane-
mia and thrombocytopenia.6

In 1988, Carter et al3 described the first case of OSA
occurring with MIOP. Subsequently, we have noted 4
other cases with this association. The age at onset of the
apneic episodes is variable, ranging from birth to 7 years.
The proposed etiology of OSA is due to contributing fac-

### Summary of Patient Data*

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age at Diagnosis, mo</th>
<th>Nasal Congestion</th>
<th>Sleep Apnea</th>
<th>Tracheotomy</th>
<th>Facial Fistula</th>
<th>Audiogram</th>
<th>Tympanometry</th>
<th>Tympanostomy Tube</th>
<th>Treatment</th>
<th>Other Associated Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/2</td>
<td>+</td>
<td>+</td>
<td>+ (×2)</td>
<td></td>
<td></td>
<td>Type B</td>
<td>+</td>
<td>M-CSF INF</td>
<td>Optic atrophy, chronic osteomyelitis, periodontal abscess, fractures, mandibular abscess</td>
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<tr>
<td>2/M/5</td>
<td>+</td>
<td>. . .</td>
<td>-</td>
<td></td>
<td></td>
<td>Type B</td>
<td>-</td>
<td>M-CSF INF</td>
<td>Optic atrophy, hydrocephalus</td>
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<tr>
<td>3/M/1.5</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
<td></td>
<td>Bilateral hearing aids</td>
<td>ND</td>
<td>M-CSF</td>
<td>Fractures, optic atrophy, bilateral facial paresis</td>
</tr>
<tr>
<td>4/F/3</td>
<td>+</td>
<td>+†</td>
<td>-</td>
<td></td>
<td></td>
<td>Conductive hearing loss</td>
<td>Type B</td>
<td>M-CSF</td>
<td>Optic atrophy</td>
</tr>
<tr>
<td>5/M/3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ NL</td>
<td></td>
<td>Bilateral hearing loss</td>
<td>ND</td>
<td>M-CSF</td>
<td>Hydrocephalus, fractures</td>
</tr>
<tr>
<td>6/F/3.5</td>
<td>. . .</td>
<td>+</td>
<td>+</td>
<td>+ NL</td>
<td></td>
<td>ND</td>
<td>Type B</td>
<td>M-CSF INF</td>
<td>Optic atrophy</td>
</tr>
<tr>
<td>7/M/3</td>
<td>. . .</td>
<td>+</td>
<td>-</td>
<td>- Moderate hearing loss</td>
<td>ND</td>
<td>Type B</td>
<td>M-CSF INF</td>
<td>Optic atrophy, chronic otitis media</td>
<td></td>
</tr>
<tr>
<td>8/M/6 in utero</td>
<td>+</td>
<td>+</td>
<td>-‡</td>
<td>- ND</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>M-CSF INF</td>
<td>Developmental delay, failure to thrive, optic atrophy</td>
</tr>
<tr>
<td>9/F/4</td>
<td>+</td>
<td>. . .</td>
<td>-</td>
<td>- ND</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>M-CSF INF</td>
<td>Optic atrophy, seizures, chronic otitis media</td>
</tr>
</tbody>
</table>

*Plus sign indicates present; ellipses, not detected on history; minus sign, absent; NL, normal; ND, not done; M-CSF, monocyte-macrophage colony-stimulating factor; INF, interferon gamma; and BMT, bone marrow transplant.
†Noted at birth but disappeared at 3 months of age.
‡Tracheotomy and uvulopalatopharyngoplasty considered but not performed because of profound developmental delay.
tors such as hypognathism, caused by disordered growth of the mandible, and narrowing of the nasal passages, including the turbinates and septum. The nasal congestion is due to the abnormal bone growth in the septum, turbinates, and nasal bones, which can then cause an impingement on the nasal airway and may play a role in OSA. The anatomical narrowing of the area between the base of the tongue and the posterior pharyngeal wall is also a contributing factor. Medical management, such as frequent nasal suctioning, instillation of intranasal steroids, and saline drops, has not been successful. Surgical removal of the tonsils, adenoids, and the posterior portion of the palate has relieved the obstruction only temporarily. Only the insertion of a tracheotomy tube has eliminated the OSA.

Stenosis of neural foramina does occur in this patient population. Optic atrophy occurs most frequently, followed by facial nerve paralysis. If the jugular foramen is stenotic, then the vagus nerve will be compressed, causing vocal cord impairment. In our series, all patients had a normal voice or normal results on their laryngeal examination. Stenosis is a possible cause of OSA.

Many syndromes are associated with OSA. Recent reports have demonstrated the correlation between craniofacial anomalies, such as Pierre-Robin and Treacher-Collins syndromes and Crouzon disease, and OSA. Hurler and Hunter syndromes are 2 forms of mucopolysaccharidosis that are also associated with OSA. In children diagnosed as having these syndromes, as well as those who have MIOP, OSA is a major management problem that requires otolaryngological consultation.

Patients who have MIOP need to be watched carefully for the development of OSA. Sleep apnea, which developed in more than 50% of our patients, generally occurs between the ages of 7 months and 16 years (mean age, 6 years). The symptoms, which include snoring, daytime somnolence, failure to thrive, and apneic episodes, may be temporarily relieved by surgery; however, sleep apnea can recur. One of our patients died as a result of complications of OSA. A periodic sleep study is recommended, even if the disorder is not suspected.

Osteomyelitis of the mandible is a clinical manifestation that is of concern to otolaryngologists. An increased incidence of osteomyelitis in MIOP has been well established. The development of osteomyelitis of the jaw may appear concurrently with the eruption of teeth, which are generally abnormally shaped and hypoplastic. Gingivitis and periodontitis usually develop in such cases. The inflamed gingiva adjacent to the compromised, often necrotic underlying bone has diminished resistance to infection, which can then result in osteomyelitis. In several cases of osteopetrosis, osteomyelitis has developed after a dental extraction. Intraoral osteomyelitis in patients with osteopetrosis is associated with poor hygiene and crowding of deciduous teeth. Sinus tracts, deep caries, retarded eruption of teeth, and deformed crown formation lead to exposed bone (Figure 4). The facial findings that may result from osteomyelitis are overgrowth of facial bones, a characteristic square jaw appearance, painless swelling, skin redness, sinus discharge below the tip of the chin, and multiple persistent draining fistulas (Figure 5). Panoramic radiographic examination reveals many classic findings, such as the roots of the teeth and the mandibular canal fused with cortical plates and dense sclerotic bone in molar regions of the mandible. There is often evidence of old fractures and extensive areas of mandibular and maxillary bone necrosis. Patients presenting with osteomyelitis should be treated with antibiotics and other conservative therapies. In our experience, surgery should be avoided because of poor wound healing due to the unchanged, underlying clinical pathology. Conductive and sensorineural hearing loss are also associated with MIOP. There are a number of reasons for the conductive hearing loss in patients with MIOP. A partial bony atresia of the left and right external auditory meatus has been demonstrated in a number of patients. The anterior suspensory ligament of the malleus was ossified in 1 child. An abnormal primitive cartilaginous matrix with poor intrachondral bone formation of the malleus and a thickened fibrous layer associated with the tympanic membrane were demonstrated in another. In our series, the tympanogram in every patient in whom one
was obtained was found to be flat, probably as a result of the thickened fibrous layer. In 14 patients, the mastoid air cells were entirely absent owing to the buildup of the osteopetrotic sclerotic bone formation; a deformity of the stapes has also been reported. In 1 case, there were defective bony development and remodeling and excessive bone formation, which resulted in recurrent otitis media. In most cases, sensorineural hearing loss is theorized to be due to auditory nerve compression by the abnormal bony growth in the internal auditory canal.

There are several therapeutic options for patients with MIOP. At present, BMT is the treatment of choice. Recently, recombinant human interferon gamma and monocyte-macrophage colony-stimulating factor have been used, with varied success.

At SJCRH, 1 patient (No. 6) has been treated successfully with a 5 of 6 antigen-matched donor transplant. Since the BMT, there have been noticeable weight gain, growth, and resolution of an abnormal facial appearance (Figure 4 and Figure 5). The diameter of the internal optic foramina has also increased. The usual fatal course of MIOP has been reversed by successful BMT from HLA-identical or, more recently, matched unrelated donors. In 5 patients, after an average of 11 months post-BMT, the symptoms of MIOP were completely resolved. Hematologic, radiologic, and biochemical tests have demonstrated the corrective effects of BMT and the deforming features of MIOP. Also, osteoclast activity has been increased, resulting in the reduction of sclerotic dense bone. These cases have demonstrated the effectiveness of BMT as the preferred therapy for reversing the features of MIOP.

In 1992, Key et al reported that interferon gamma therapy was partially effective in patients with osteopetrosis. They noted increased bone resorption, increased superoxide formation in leukocytes, and an improvement in conductive hearing loss. Importantly, computed tomography disclosed an increase in the cross-sectional areas of the auditory canal and the optic foramina. During therapy, the enzymatically active brush border of osteoclastic cells became ruffled. Thus, although the number of osteoclasts did not change, the function of individual osteoclast cells increased. Bone biopsy specimens demonstrated a decrease in the area of trabecular bone. Also, a significant lowering of the frequency of infections was correlated with therapy. Side effects associated with interferon therapy were hyperpyrexia and diarrhea, which disappeared after the dosage was decreased. Although these studies suggest that treatment with interferon gamma is a reasonable therapeutic option for patients with osteopetrosis, others have not found substantial benefit in a number of patients.

Monocyte-macrophage colony-stimulating factor has been effective in an animal model in stimulating the production of superoxide and activation and differentiation of macrophages. After monocyte-macrophage colony-stimulating factor was administered, the cell population of osteoclasts increased considerably. As a result, the number of monocytes and white blood cells in the peripheral blood of the animals increased to normal levels. However, although the animal model suggests that there are beneficial effects to the use of macrophage colony-stimulating factor, the clinical studies of patients with osteopetrosis at SJCRH were not able to demonstrate significant clinical improvement.

CONCLUSIONS

This article documents the risk of OSA developing in patients with MIOP and describes the otolaryngological manifestations of MIOP, including osteomyelitis and hearing loss. In our series, a tracheotomy was required to alleviate OSA in 3 of 9 children. Symptoms associated with osteomyelitis, including chronic draining fistulas, sinus discharge, and painless soft tissue swelling, were treated with limited success in a conservative manner. Conductive and mixed hearing loss are also associated with MIOP. Factors that account for the hearing loss include excessive bone formation, a malformed stapes, a thickened fibrous layer of the tympanic membrane, recurrent otitis media, and narrowing of the internal auditory meatus.

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