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.2 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.

REPORT OF CASES

CASE 1

This case has been previously described, in part, in another journal.2 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-
lateral tympanostomy tubes were placed at 7 years of age, and mucoid discharge was found. At 17 years of age, a bilateral moderate to severe mixed hearing loss with flat tympanograms was noted.

CASE 2

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 turbinate, 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 age 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 3½-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 uvulopharyngopalato-plasty 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.

COMMENT

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 5.5:100,000.² Sex or
ethnicity is not a factor. Typical clinical findings are fragile bones, failure to thrive, hepatosplenomegaly, thrombocytopenia, leukoerythroblastosis, and increased susceptibility to infection. The disease is usually fatal during infancy, but the life expectancy has increased as a result of better medical care.

The characteristic pathophysiological features of MIOP are the result of the lack of osteoclastic function. The most severe form is transmitted as an autosomal recessive trait and is characterized by an excess accumulation 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 decreases, “marbling” of the bone occurs and is characterized by sclerosis, brittleness, and radiopacity, with associated hematologic and neurological abnormalities (Figure 3). This bone formation leads to the encroachment of the marrow spaces, which directly results in anemia and thrombocytopenia.

In 1988, Carter et al 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-

<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>Tympanostomy Tube</th>
<th>Treatment</th>
<th>Other Associated Symptoms</th>
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<tr>
<td>1/M/2</td>
<td>+</td>
<td>+</td>
<td>+ (×2)</td>
<td>+</td>
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<td>+</td>
<td>M-CSF INF</td>
<td>Optic atrophy, chronic osteomyelitis, periodontal abscesses, fractures, mandibular abscesses</td>
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<td>. . .</td>
<td>−</td>
<td>−</td>
<td>NL</td>
<td>Type B</td>
<td>M-CSF INF</td>
<td>Optic atrophy, hydrocephalus</td>
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<tr>
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<td>+</td>
<td>−</td>
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<td>ND</td>
<td>M-CSF</td>
<td>Fractures, optic atrophy, bilateral facial paresis</td>
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<tr>
<td>4/F/3</td>
<td>+</td>
<td>+ †</td>
<td>−</td>
<td>−</td>
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<td>Type B</td>
<td>M-CSF</td>
<td>Optic atrophy</td>
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<tr>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>ND</td>
<td>M-CSF</td>
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<tr>
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<td>+</td>
<td>. . .</td>
<td>+</td>
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<td>ND</td>
<td>M-CSF</td>
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<td>+</td>
<td>− ‡</td>
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<td>ND</td>
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<tr>
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<td>. . .</td>
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<td>−</td>
<td>ND</td>
<td>ND</td>
<td>M-CSF</td>
<td>Optic atrophy, seizures, chronic otitis media</td>
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*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.

Figure 1. A 7-month-old girl with malignant infantile osteopetrosis.

Figure 2. Same patient seen in Figure 1, now 2 years of age and 1 year after a successful bone marrow transplantation. Note the facial changes.
Compensatory growth of the midface is the hallmark of MIOP.14,15 Involvement of the nasopharynx, however, is of great concern to otolaryngologists. An increased incidence of osteomyelitis in MIOP has been well established.2,11-13 The development of osteomyelitis of the jaw may manifest concurrently with the eruption of teeth, which are generally abnormally shaped and hypoplastic. Gingivitis and periodontitis usually develop in such cases.11 The inflamed gingiva adjacent to the compromised, often necrotic underlying bone has diminished resistance to infection, which can then result in osteomyelitis.11 In several cases of osteopetrosis, osteomyelitis has developed after a dental extraction.13 Intraoral osteomyelitis in patients with osteopetrosis is associated with poor hygiene and crowding of deciduous teeth.2,12,13 Sinus tracts, deep caries, retarded eruption of teeth, and deformed crown formation lead to exposed bone (Figure 4).2,12,13 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).11-13 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.2,11-13 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.14,15 There are a number of reasons for the conductive hearing loss in patients with MIOP.13 A partial bony atresia of the left and right external auditory meatus has been demonstrated in a number of patients.5,16 The anterior suspensory ligament of the malleus was ossified in 1 child.15 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.17 In our series, the tympanogram in every patient in whom one

Figure 3. Lateral head radiograph demonstrating the typical radiologic appearance of osteopetrosis. Note the marbling of the bone and the dense bone formation.

Figure 4. Intraoral view showing the lower lip (arrowhead) and the anterior floor of the mouth (arrow), which reveals crowding of teeth, caries, exposed bone, and osteomyelitis.
rent 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. \(^1\)

In 1992, Key et al\(^{19}\) 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. \(^19,20\) Importantly, computed tomography disclosed an increase in the cross-sectional areas of the auditory canal and the optic foramina. \(^19,20\) During therapy, the enzymatically active brush border of osteoclastic cells became ruffled. \(^19\) Thus, although the number of osteoclasts did not change, the function of individual osteoclast cells increased. \(^20\) Bone biopsy specimens demonstrated a decrease in the area of trabecular bone. \(^19\) Also, a significant lowering of the frequency of infections was correlated with therapy. \(^19,20\)

Side effects associated with interferon therapy were hyperpyrexia and diarrhea, which disappeared after the dosage was decreased. \(^19,20\) 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. \(^21\)

Monocyte-macrophage colony-stimulating factor has been effective in an animal model in stimulating the production of superoxide and activation and differentiation of macrophages. \(^22,23\) After monocyte-macrophage colony-stimulating factor was administered, the cell population of osteoclasts increased considerably. \(^23\) As a result, the number of monocytes and white blood cells in the peripheral blood of the animals increased to normal levels. \(^24\) 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.

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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**Figure 5.** The typical facial findings of osteomyelitis include the square jaw, asymmetry of the facial bones, and persistent draining fistulas, which are covered with gauze (arrows). The arrowheads point out the healed fistulas.
REFERENCES