Case Report

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Genetic testing confirmed osteopetrosis with initial presentation of nystagmus

Kai-Yen Chiu[1], Yu-Yang Lin[1], Yao-Lin Liu[1], Ni-Chung Lee[2], Tzu-Hsun Tsai[1]*

Abstract:

Osteopetrosis (OS) is a rare heritable disorder characterized by osteoclast dysfunction and increased bone density on radiography. Optic nerve osseous compression is the most frequent ocular complication of OS, with nystagmus, strabismus, ptosis, proptosis, and lagophthalmos occurring less frequently. However, it is uncommon for patients to have neurological or ocular symptoms at initial presentation. Herein, we present the case of a 3-year-old girl with the initial presentation of ocular symptoms who was confirmed to have OS through genetic testing. She was born full-term and found to have nystagmus since the age of 1 year. Her best-corrected visual acuity was 1.2/60 for both eyes. Exotropia of the left eye and bilateral small-amplitude pendular nystagmus were also noted. Color fundoscopy revealed a tessellated fundus and pale discs with cup-to-disc ratios of 0.5–0.6. Magnetic resonance imaging revealed bilateral optic canal stenosis and optic nerve atrophy. Whole-exome sequencing revealed a biallelic chloride voltage-gated channel 7 mutation, c.2297T > C (p.Leu766Pro) and c.1577G > A (p.Arg526Gln), and autosomal recessive OS was diagnosed. The patient is currently being evaluated for possible hematopoietic stem cell transplantation. We suggest that OS should be considered a differential diagnosis for unexplained nystagmus and optic nerve atrophy.

Keywords:

Nystagmus, optic nerve atrophy, osteopetrosis

Introduction

Osteopetrosis (OS), or marble bone disease, is a group of rare heritable disorders with an incidence of one in 250,000 births for the autosomal recessive form and one in 20,000 births for the autosomal dominant form.[1] OS is characterized by increased bone density and "bone within the bone" signs observed on radiography.[2] Overly dense bones do not strengthen structural stability. In contrast, OS results in brittle bones that are susceptible to fracture, skeletal deformity, dental abnormalities, and bone marrow insufficiency.[3] Optic nerve atrophy is a common complication caused by osseous compression or, sometimes, primary neural degeneration.[4-6] Several independent pathogenic genes have been identified.[6,7] Although they all lead to defective osteoclast differentiation or function, different genetic mechanisms result in heterogeneous phenotypes.[6,7] The initial clinical manifestations of OS mostly include bone marrow insufficiency, sepsis, osteomyelitis, and repeated fractures.[8] Herein, we present the case of a 3-year-old female patient diagnosed with OS who presented with ocular symptoms as the initial manifestation. Relevant studies were reviewed, and the clinical insights gained from this rare case are discussed.

Case Report

A 3-year-old girl born full-term without significant developmental abnormalities presented with bilateral amblyopia and nystagmus that was observed at the age of

[1]*Department of Ophthalmology, College of Medicine, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan,* [2]*Department of Pediatrics and Medical Genetics, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan*

***Address for correspondence:**
Dr. Tzu-Hsun Tsai, 12F, No. 7, Zhongshan S. Road, Zhongzheng, Taipei City 10002, Taiwan.
E-mail: tsaith@ntuh.gov.tw

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1 year. She was referred to our outpatient department for optic nerve atrophy of unknown cause despite multiple blood tests and imaging surveys. During her visit, physical examination revealed a mild right head tilt with a face turn to the left, delayed dental eruption (only five teeth at the age of three), and mild dolichocephaly. The best-corrected visual acuity was 1.2/60 for both eyes. Exotropia of the left eye and bilateral small-amplitude pendular nystagmus were also noted. Color fundoscopy revealed a tessellated fundus and pale discs with cup-to-disc ratios of 0.5–0.6 [Figure 1]. Optic coherence tomography revealed a relatively flat bilateral fovea. Visual-evoked potential testing showed responses with reduced amplitude and delayed latency in both eyes. Magnetic resonance imaging (MRI) demonstrated bilateral optic canal stenosis and optic nerve atrophy [Figure 2], along with thickened basal skull, mildly thin gene and body of corpus callosum, and narrowing of the internal auditory canals and thin chiasm. Whole-exome sequencing revealed a biallelic chloride voltage-gated channel 7 (*CLCN7*) mutation (c.2297T>C [p.Leu766Pro] and c.1577G>A [p.Arg526Gln]), and autosomal recessive OS (ARO) was diagnosed. *CLCN7* sequencing of the parents revealed that the former mutation was inherited from her mother, and the latter was inherited from her father. The follow-up X-ray revealed vertebral "bone within bone'' and "sandwich" appearance and a diffuse increase in bone density [Figure 3]. The complete blood count results and serum calcium concentration were normal. The patient is currently undergoing comprehensive evaluation and preparation for hematopoietic stem cell transplantation (HSCT).

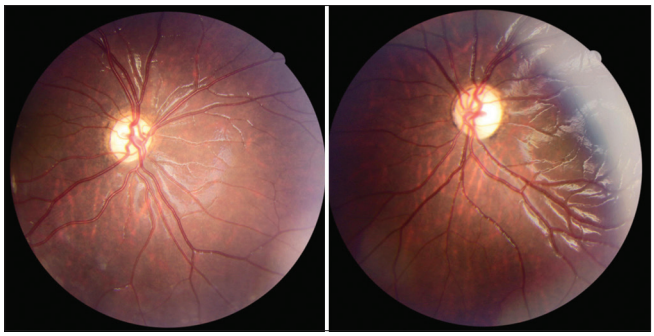

Figure 1: Fundoscopy examination revealed tessellated fundus and pale discs with cup to disc ratios of 0.5–6 without papilledema

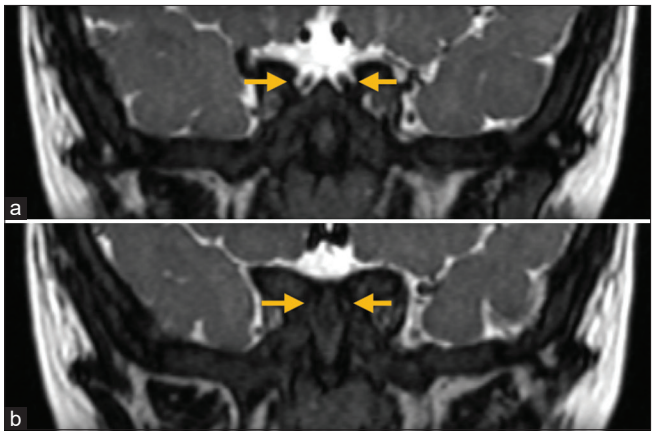

Figure 2: Coronal view of cube magnetic resonance imaging, T2 3-D reconstruction, (a) Bilateral optic canal stenosis (arrows), more severe at the right side, (b) bilateral optic nerve atrophy (arrows), where the diameter of optic nerves are extremely small

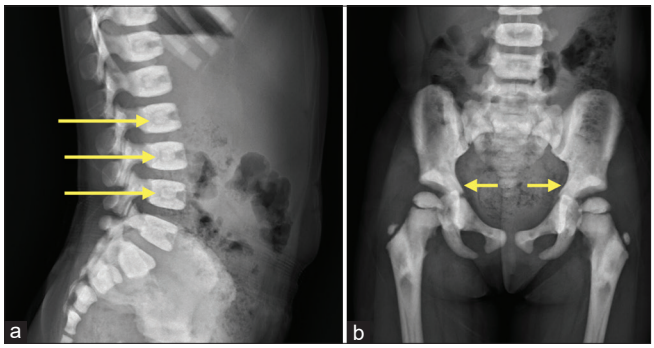

Figure 3: Figure 3: X ray of pelvis and vertebrae in the case (a) vertebral "bone within bone" (arrows), (b) diffusely increased density on the both sides of the pelvic girdles (arrows)

Discussion

In this report, we present a case of OS, which is a group of bone disorders characterized by sclerosis of the bone due to dysfunctional bone absorption by osteoclasts. Abnormal bone modeling and remodeling result in increased bone density, structural brittleness, dental developmental abnormalities, and hematologic impairment.[9] In addition to the impairment of the bone structure and marrow, cranial nerves can be affected by compressive cranial neuropathies, increased intracranial pressure, or primary neurodegeneration.[7,10] This disease is clinically and genetically heterogeneous. Based on clinical manifestations and a genetic basis, OS is classified into three major forms: severe (early onset), intermediate, and mild (late onset).[9] The severe type is inherited in an autosomal recessive pattern and presents at birth or during the few early months with recurrent fractures, optic nerve injury caused by osseous compression, bone marrow failure, severe infection, and early mortality. Without treatment, the duration of survival of infants is rarely longer than 2 years.[9] Other than HSCT, frequent blood transfusion for severe anemia or thrombocytopenia and surgical intervention for fracture, dental procedure, or cranial decompression may be required depending on the heterogeneous phenotype of each case.[10] In contrast, the mild type, also known as the benign adult type, is inherited in an autosomal dominant pattern, and the clinical presentations are variable, ranging from asymptomatic to severe.[11,12] Due to the more benign course and considering the potential adverse complications of HSCT, autosomal dominant OS is usually not treated with HSCT.[6]

Regarding the intermediate type, the inheritance pattern can be autosomal dominant or recessive, and the progression, severity, and clinical manifestations are also heterogeneous.[9] However, blood transfusions are not necessary for the intermediate type because hematologic impairment is usually mild.[9] Based on the definition above, the patient had manifestations of the intermediate-type ARO; her age was 3 years, and she had no apparent hematologic impairment. Nevertheless, the initial clinical manifestations of severe and intermediate types are commonly bone marrow insufficiency, sepsis, osteomyelitis, and repeated fractures.[8] In this case, neurological symptoms were the initial presentations, which have rarely been reported in the existing literature.

Ocular complications are prevalent in OS, particularly severe cases. Optic nerve atrophy, which is caused by osseous compression of the stenotic optic foramen, is the most common ocular sign. Nevertheless, retinal degeneration, impaired optic nerve myelination, and primary neurodegeneration can also lead to vision deterioration.[5-7,13] In addition to vision loss, nystagmus, strabismus, ptosis, proptosis, and lagophthalmos are sometimes present.[10] In addition to physical examination, several ophthalmologic and neurological evaluations are recommended. Fundoscopy is used to evaluate possible optic atrophy or papilledema due to elevated intracranial pressure or retinal venous compression.[1,5,8,10] Visual-evoked potential testing facilitates the early detection of visual impairment, timely diagnosis, and early intervention.[5,10] Computed topography (CT) facilitates the visualization of the optic canal to confirm or rule out optic nerve compression. However, owing to radiation protection and better image quality of soft tissue, MRI is more recommended than CT.[9,14] MRI may reveal stenosis in all cranial foramina and narrowing of central nerve channels. Hydrocephalus resulting from increased intracranial pressure and neurodegenerative changes such as cerebral atrophy and corpus callosum agenesis can also be presented.[4] Electroencephalography (EEG) can detect primary neurodegeneration during the early stages of the disease.[5,9,10]

In addition to clinical manifestations, OS can be diagnosed based on imaging and genetic testing. Radiography is sometimes sufficient to make a diagnosis because of the unique radiographic features characterizing the disease. Dense bones have a bone-within-bone appearance, especially in the pelvis, phalanges, long bones, and vertebrae. "Sandwich vertebrae" is used to describe the vertebral midbody sandwiched between the inferior and superior dense bands.[15] Sometimes multiple fractures at different stages (new, healing, and old) could be seen.[10] With the advancement of knowledge of pathogenic genes associated with OS, which account for distinct phenotypic characteristics and necessitate different treatment strategies, genetic testing should be performed for suspected cases or when a diagnosis is established.[7,9]

CLCN7, the culprit gene in this case, encodes an H^+/Cl^- exchange transporter that is an antiporter expressed on the ruffled border of osteoclasts and the membranes of late endosomes and lysosomes, which are important for the regulation of luminal Cl – concentration in the central nervous system (CNS).[16] Therefore, the defect of the transporter not only damages osteoclastic resorption but compromises central nervous function.[17] The *CLCN7* mutation is the second most frequent form, accounting for 17% of all ARO.[7] However, the severity of growth retardation, hematological impairment, visual loss, and CNS symptoms are heterogeneous and widely variable.[6] Severe hypocalcemia is usually observed in patients with ARO *CLCN7* mutation.[6] However, the serum calcium concentration was normal in our case. The fact that the severity of vision loss stands out from other neurological symptoms as the initial and chief manifestation is special. Further studies on the phenotypes of different mutations and diallelic combinations may provide more insights in the future.

HSCT is an effective treatment for severe or intermediate ARO but contraindicated for some gene mutations. Based on the pathway by which osteoclasts are affected, these genes can be divided into two groups: those that are associated with intrinsic and extrinsic defects.[7] The extrinsic defects comprise only the *RANKL* gene mutations that are expressed in osteoblasts. Osteoblasts are not derived from hematopoietic stem cells. Therefore, HSCT is contraindicated for OS with extrinsic defects and can only help correct the intrinsic pathway.[9] In the intrinsic group, mutations in two genes, *OSTM1* and *CLCN7*, are associated with primary neuropathy.[6] Neurodegeneration is present in all patients with *OSTM1* mutations and a large proportion of patients with *CLCN7* mutations.[6,7] HSCT cannot prevent the progression of neurodegenerative diseases, but it has undesired effects.[9] To make room for donors' hematopoietic stem cells, conditioning regimens by chemotherapy are utilized to eliminate patients' bone marrow before the transplantation, which inevitably causes immunosuppression and regimen-related toxicity.[7,9] Other than regimen-related toxicity, the most common complication of HSCT is infection and graft-versus-host disease (GvHD).[18,19] There are more considerations for HSCT in patient with OS. The patients with OS seem to be more prone to veno-occlusive diseases, which is also one of possible complications of HSCT and can be fatal.[20] Furthermore, the preexisting malformation of cranial structure or hydrocephalus could become more severe and critical, especially during the fluid retention stage early after transplantation or during an

episode of veno-occusive diseases.[9] Therefore, HSCT is contraindicated for *OSTM1* mutations and relatively contraindicated for *CLCN7* mutations under certain circumstances.[9,21] In *CLCN7* mutations without signs of neurodegeneration, HSCT is indicated for the severe type of bone marrow rescue, yet it is still experimental for the intermediate type considering the potential severe complications as described above.[7,9] Consequently, neurological evaluation, including EEG and brain MRI, should be repeatedly performed before conditioning for HSCT.[9] In this case, osseous optic compression was confirmed by MRI. EEG will be arranged and closely followed up with MRI. Concurrently, conditioning for HSCT is also ongoing.

OS is a group of rare disorders that include impaired bone structure, hematologic dysfunction, and visual and neurological impairments. Timely diagnosis, genetic testing, and intervention are crucial for positive clinical outcomes. OS should always be considered a differential diagnosis for unexplained optic nerve atrophy or nystagmus.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent forms from the legal guardians of the patient. In the form, the guardians have given the consent for the images and other clinical information of the patient to be reported in the journal. The guardians understand that the name and initials of the patient will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

Dr. Tzu-Hsun Tsai, an editorial board member at *Taiwan Journal of Ophthalmology*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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