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Orphan disease: Cherubism, optic atrophy, and short stature

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Abstract

A 12-year-old female presented with complaints of progressive visual impairment in both her eyes. On clinical examination, she was short for her age and her ophthalmoscopic examination revealed bilateral optic atrophy. Computed tomography of the patient revealed multiple expansile lytic lesions of mandible suggesting cherubism. The optic atrophy was confirmed on magnetic resonance imaging, which additionally revealed bilateral retrocerebellar arachnoid cysts. This association of cherubism with optic atrophy and short stature was grouped as orphan disease by National Institutes of Health and only one case was reported in the literature so far.

Key words: Cherubism; fibrous dysplasia; optic atrophy; short stature

Introduction

Jones[1] first described this disorder as "familial multilocular cystic disease of the jaws," in 1933. The term "cherubism" was coined later describing the rounded facial appearance that was reminiscent of cherubs depicted in Renaissance art. Cherubism was considered as a variant and part of fibrous dysplasia in the 19th and early 20th centuries. However, with the advent of genomic research and gene sequencing methods, cherubism had proven to be a distinct form of skeletal dysplasia. Mangion *et al*.[2] and Tiziani *et al*.[3] later discovered that cherubism was due to dominant mutations in *SH3BP2* gene on chromosome 4p16.3. Cherubism was thought to be self-limiting and most of the patients will become normal by adulthood. But persistence of the fibrocystic lesions and dysmorphic facial features was not so uncommon.

Case Report

A 12-year-old girl presented with complaints of progressive visual impairment in both her eyes for the past 1 year. On clinical evaluation, she was found to be short for her age with her height measuring 135.2 cm corresponding to 0.16 percentile. Fundoscopic evaluation revealed bilateral pale chalky white disc pallor, which was more on the left side, suggestive of optic atrophy [Figure 1].

The patient was further imaged for evaluation of bilateral optic nerve atrophy. On magnetic resonance imaging (MRI), optic nerves were thinned out (left > right). However, no altered signal intensity within the nerves was seen [Figures 2 and 3]. Incidentally, bilateral retrocerebellar arachnoid cysts were also seen. The globes, optic chiasm, rest of the neuroparenchyma along with sellar region were unremarkable.

The patient also complained of fullness in the cheek with dysmorphic facial features. On evaluation with computed tomography (CT), the patient showed bilateral almost symmetrical expansile lesions involving body, rami,

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and coronoid processes of the mandible. The lesions predominantly showed lytic areas [Figures 4 and 5] with sparing of condyloid processes [Figure 5]. There were no lesions in the maxilla, optic canals, or in the skull.

Biochemical and hormonal evaluation of the patient for short stature was unremarkable. She also had normal secondary sexual characters and the examination of her genitourinary system was within normal limits [Figure 6].

Discussion

Cherubism had been first described as a subtype of fibrous dysplasia, termed as hereditary craniofacial fibrous dysplasia by Cornelius and Bianchi.[4,5] It was considered as the same group of disorder because it shows radiographic similarities with fibrous dysplasia. Ueki *et al*.[6] discovered a series of point mutations resulting in amino acid substitutions in the SH-3 binding protein SH3BP2 on chromosome 4p16.3 in patients of cherubism accounting for the disease. Affected children appear normal at birth and usually develop bilateral painless jaw swellings. These lesions begin in first several years of life, with a range of 14 months to 12 years.[7] The disease usually undergoes gradual resolution of the lesions with partial or complete remineralization. On resolution these may appear isodense or sclerotic to the adjacent normal bone. Some of the lesions may persist or undergo partial resolution, which may result in dysmorphic features. In 1992, Marck and Kudryk[8] proposed grading system for cherubism based on lesion locations [Table 1].

Histological examination of these lesions shows abundant multinucleated giant cells scattered in a stroma of vascularized fibrous connective tissue, which can be seen in other conditions such as giant cell tumor, brown tumor, and giant cell granuloma. Hence histopathological examination had limited value in the diagnosis of cherubism.

Cherubism can cause optic atrophy, which is usually due to the mass effect in the optic chiasm or optic nerve by

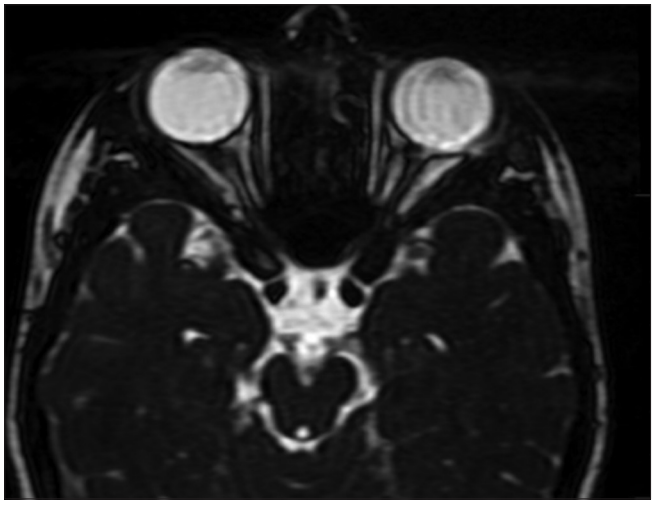

Figure 1: Axial T2 MR image showing bilateral thinned out optic nerves with prominent optic nerve sheath fluid

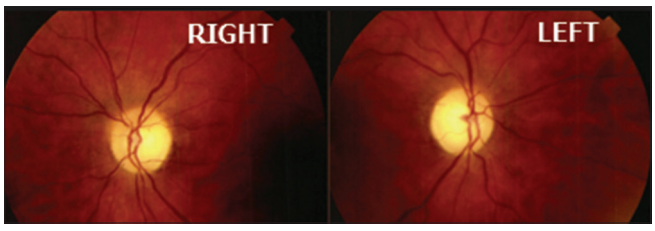

Figure 3: Fundoscopic image showing bilateral optic disc pallor suggestive of optic atrophy predominantly on the left globe

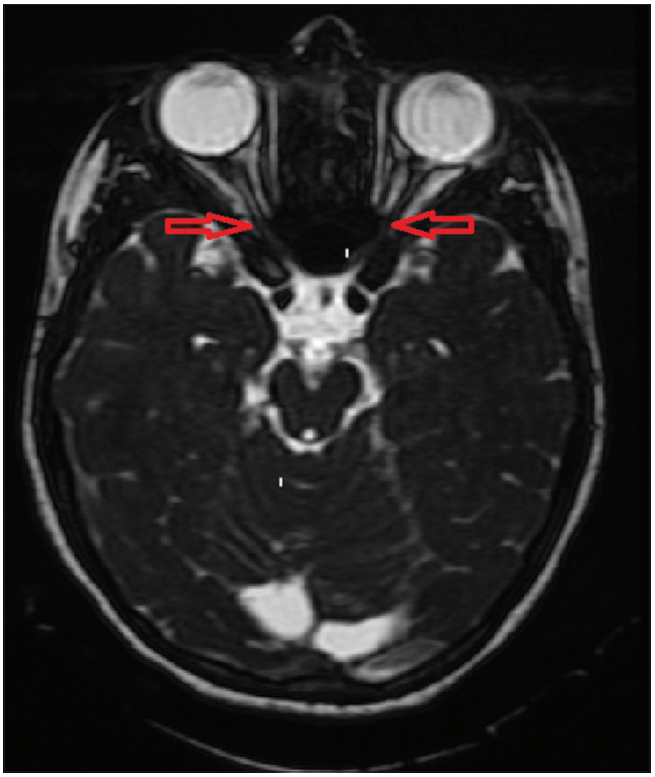

Figure 2: Axial T2 weighted images showing thinned out bilateral optic nerves (arrows)

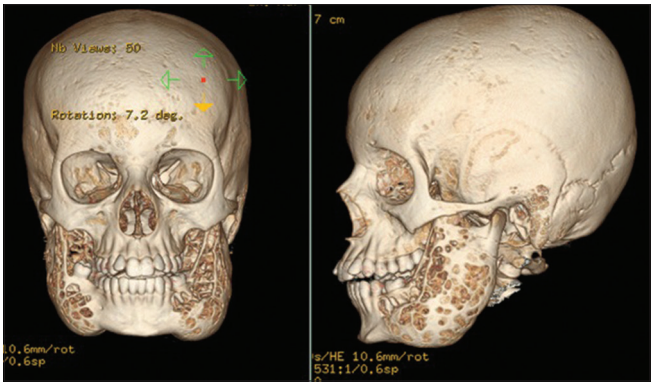

Figure 4: Volume rendered images showing bilateral symmetrical expansile lesions giving rise to "Soap bubble" appearance

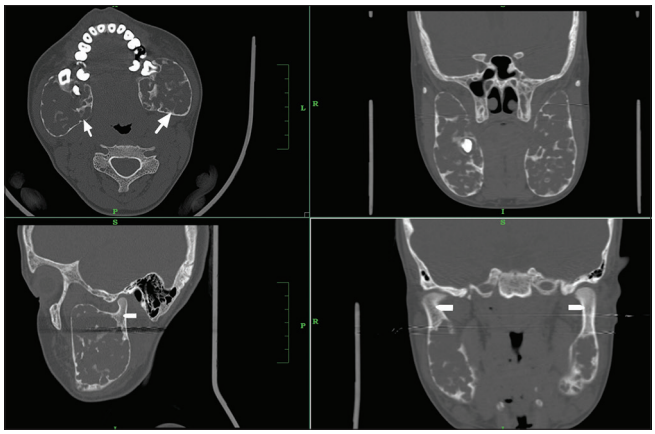

Figure 5: Axial, Coronal and Sagittal CT images showing bilateral symmetrical expansile predominantly lytic lesions involving the body, rami and coronoid processes of bilateral mandible (arrows). Typical sparing of condyloid process of mandible (arrow heads) seen

Table 1: Marck and Kudryk grading of cherubism

Grades	Lesion characteristics
Grade I	Bilateral involvement of mandibular rami
Grade 2	Involvement of both mandibular rami and maxillary tuberosities
Grade 3	Involvement of the entire maxilla and mandible except for the condyles
Grade 4	Involvement of the orbits with ocular disturbances as well as the grade 3 lesions

the lesions extending into skull base. Most of these optic atrophies are unilateral and asymmetrical in the reported literature.Cherubism may be associated with genetic diseases such as Ramon's syndrome, Jafe Campanacci syndrome, Fragile X syndrome, Neurofibromatosis, and Noonan's syndrome.[9-14] Only one case of cherubism associated with bilateral optic atrophy and short stature had been reported in the literature.[15] Cherubism associated with optic atrophy and short stature is listed as rare disease by the Office of Rare Diseases of the National Institutes of Health. In our case, incidentally, bilateral retrocerebellar arachnoid cysts were also detected. No syndromic association had been found comprising cherubism, optic atrophy, and short stature, and even in our case we did not have any features to suggest a syndromic association of these findings.

Conclusion

Cherubism alone is a rare disease and its association with optic atrophy and short stature had been reported by only one case in the literature so far. The association of bilateral retrocerebellar arachnoid cysts in our case may be incidental. Hence cherubism, optic atrophy, and short stature is an orphan disease and we are reporting one of its kind.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

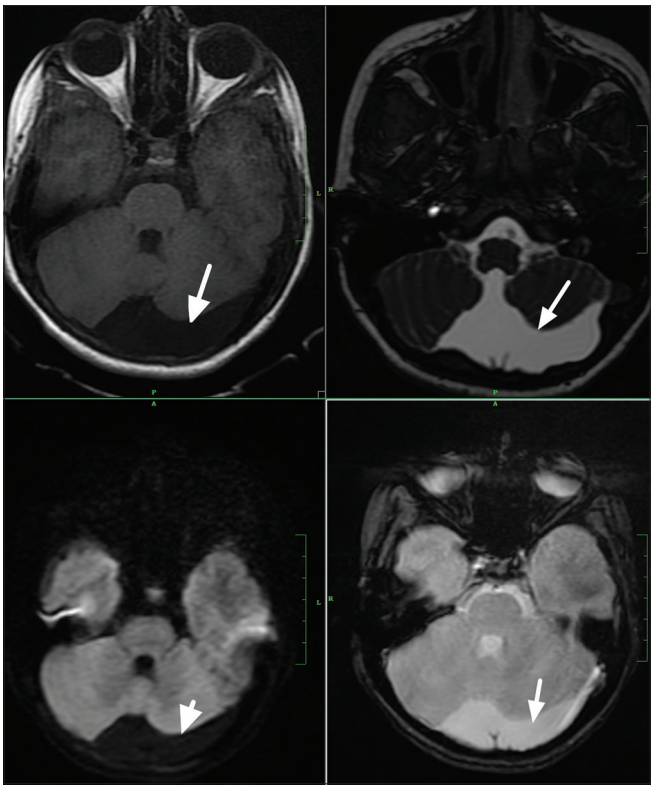

Figure 6: Axial sections of posterior fossa showing Retrocerebellar arachnoid cyst with classical CSF appearance on all images (Hyper in T2, Hypo in T1 and no DWI restriction) with mass effect over both cerebellar hemispheres

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Conflicts of interest

There are no conflicts of interest.

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