Abstract
Cherubism is a rare hereditary non-neoplastic bone disease characterized by clinically evident bilateral, painless enlargements of the jaws, said to give the patient a cherubic appearance. Here we report the case of cherubism in a 5 year-old girl who complained of painless bilateral swelling, noticed by her parents three months back. Panoramic radiography and CT images exhibited bilateral multilocular radiolucent areas with cortical expansion. Histopathologic examination revealed proliferating fibrous connective tissue containing numerous multinucleated giant cells.

Keywords: Cherubism, autosomal dominant, familial.

INTRODUCTION
Cherubism, or familial intraosseous fibrous expansion of the mandible, is a genetically-mediated disorder first reported in 1933. The word ‘Cherubism’ refers to the spherical facial appearance of angels painted in the Renaissance era. [1,2] It is characterised by the presence of giant cells and fibrous tissue proliferation. Cherubism is a non-neoplastic hereditary bone lesion characterized by a spherical and symmetrical chubby facial appearance, bilateral painless swelling of the maxilla and mandible, resulting in a fullness of the cheeks and retraction of the lower eyelids, giving an upward turned appearance of the eyes – comparable to a cherub angel. It is an autosomal dominant inheritance in 80% of familial patterns. Typically, the mandible is primarily affected and, in 60% of cases, maxilla is also involved. Children are normal at birth. At the age of 14 months to 5 years, a symmetric enlargement of the jaws begins, progressing until puberty. [3-5]

Here we report a case of 5 year-old girl with a history of bilateral swelling of the mandible.

CASE REPORT
The parents of a 5 year-old child came to the department of Oral Medicine and Radiology of Oxford Dental College, Bangalore, with complaint of bilateral swelling in the cheek region since 3 months. As the baby was chubby since birth, they could not make out the difference in the present swelling and there was no history of trauma. Three months back, parents and friends started noticing differences in the face of the baby. There was no increase in the size of swelling, but they felt hardness in swelling. Parents visited a local physician who advised radiological investigations and biopsy for swelling. They were apprehensive about teeth eruption and came for a second opinion to our college. Family history reveals that girl’s father had similar painless bilateral mandibular swelling during his childhood, and later on, at the age of 13, surgical intervention was carried out for aesthetic purposes.

The general physical examination detected no abnormality in any system. On extra-oral examination, bilateral swelling was noticed in the lower 3rd of the face, causing fullness of the cheeks. Skin over the swelling appeared normal (Fig. 1). On palpation, it was bony-hard in consistency and non-tender. Bilateral submandibular lymphnodes were enlarged and non-tender. Intra-orally, bilateral obliteration of the buccal vestibule was noticed, extending from the 1st molar to the retro molar region, due to buccal
cortical plate expansion (Fig. 2). Based on the family history and on classical findings, provisional diagnosis of Familial Cherubism of mandible was arrived at.

Tooth buds of permanent 1st molars were embedded within the radiolucency, giving a floating tooth appearance (Fig. 3). CT also revealed the same features in the mandible without involving maxilla (Fig. 4). According to the radiographic grading given by Ramon and Engelberg [11], diagnosis of grade I Cherubism was given. Serological investigations revealed increase in alkaline phosphatase level (165 IU/ml) and normal serum calcium levels. Incisional biopsy confirmed the clinical diagnosis of Cherubism.

Fig. 1. Extra-oral photograph showing bilateral facial swelling

Fig. 2. Intra-oral photograph revealing buccal cortical plate expansion

Fig. 3. (a) Panoramic radiography, (b) PA mandible showing multilocular radiolucency with floating tooth appearance extending to the condyles

After a vivid clinical review, the parents of the child were informed about the benign nature of the swelling, about its familial pattern, possible regression and delayed eruption, crowding and missing of permanent teeth, and advised yearly follow up.
The first description of Cherubism was made by Jones, who analyzed the familial occurrence of painless enlargement of the jaws in three siblings. [1] According to the World Health Organization, Cherubism, belonging to a group of non-neoplastic bony lesions affecting only the jaws, is an autosomal dominant inheritance, with 100% occurrence in males and 50 to 70% in females. [2,3] The molecular gene pathogenesis proposed demonstrated SH3BP2 gene mutations, mapped to locus 4p16.3, and causing disfunction of the Msx-1 gene, involved in the regulating mesenchymal interaction in craniofacial morphogenesis. [2] The SH3BP2 mutation is thought to lead to parathyroid hormone receptor (PTHr) signaling and Msx-1 activation. No spatial partitioning takes place in the cap stage of the second and third molars, which is necessary for normal dental development, leading to disfunction of mesenchymal bone formation, development of multinucleated giant cells and abundant deposition of fibrohistiocytic tissues. [6,7] Disfunction of Msx1 stops in the end of molar development, leading to remineralization of lesions. [2] Perivascular fibrosis leading to mesenchymal disorders and reduced oxygenation is the most widely accepted theory evidencing the pathogenesis of cherubism. [8]

**DISCUSSION**

It is a benign, self-limiting fibro-osseous disorder characterized by bilateral expansion of the mandible, maxilla, or of both. The lesions are usually symmetrical and painless. Frequently, Cherubism is accompanied by dental arch and dental eruption abnormalities. The rounded facies and occasional upward cast of the eyes, with exposure of the sclera below the pupil, is due to enlargement of orbital floor and fragile support of the lower lids, with a superior globe displacement and sclera exposition, giving the “eyes-to-heaven appearance”. This classical clinical characteristic is not observed in every patient. Our case, for example, had only mandible involvement. [3,5] Affected children appear physically and mentally normal at birth, with no clinically or radiographically evident disease until 14 months to 3 years of age, when bilateral jaw expansion begins. [9] Typically, the earlier the lesion appears, the more rapidly it advances, becoming progressively larger until puberty. Lesion regression is expected to occur spontaneously by the end of puberty, being solved by middle age. [2]

**Dental abnormalities**

Early exfoliation of deciduous teeth, impaction or displacement of teeth, ectopic tooth eruption, agenesis of the permanent teeth, mainly (second and third molars) due to involution of their germs, delayed eruption of the permanent teeth and, in severe cases, root resorption of teeth occurs. [7,9,11] All these features results in malocclusion, as well as in problems of phonation and swallowing, the latter being exacerbated by flattening or inversion of the palatal cleft. [7]
Biochemical parameters

The haematological parameters, such as serum calcium and phosphorus concentrations, are usually within normal limits, only the alkaline phosphatase levels may be elevated. [1,7,9,10,16] Our case revealed a high level of alkaline phosphatase and normal serum calcium levels.

Radiographic features

Radiographically, lesions appear as cystic multilocular radiolucencies clearly bounded by cortical bone and distributed bilaterally in the posterior quadrants of the mandible and maxilla, often beginning near the angle of the mandible and spreading to the mandibular ramus and body. Maxillary lesions may concomitantly occur, usually in the maxillary tuberosity region. [1,7,11] Our case demonstrated lesions confined to mandible body and ramus. Frequently, teeth appear as displaced and impacted, and root resorption is observed; frequently, the mandibular canal is also displaced. [7]

Radiographic grading of Cherubism

Several grading systems have been proposed to describe the severity of cherubism. Arnott suggested radiographic staging for the lesions of Cherubism according to their location and degree of expansion. [12] Ramon and Engelberg modified grading based on the area of involvement, as follows: [8]

- **Grade I**: involvement of both mandibular ascending rami.
- **Grade II**: involvement of both maxillary tuberosities, as well as of the mandibular ascending rami.
- **Grade III**: massive involvement of the whole maxilla and mandible, except the coronoid process and the condyles, resulting in considerable facial deformity.
- **Grade IV**: grade 3 plus the involvement of the floor of the orbits, causing orbital compression.

The grade may change, depending on the results of follow-up examination.

Differential diagnosis of Cherubism

[8,10,16]

The histological features are non-specific, showing fibrous hyperplasia and multinucleated giant cells, which are also seen in other bone diseases, such as brown tumor of hyperparathyroidism, giant cell tumor, and central and peripheral giant cell granuloma. [2,3,5,10]

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<tr>
<th>CLINICAL ENTITY</th>
<th>DIFFERENTIATING FEATURES</th>
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<tr>
<td>Fibrous dysplasia</td>
<td>It is not usually familial, being observed quite late, between 10 and 30 years of age, it does not show the typical “cherubic” look, and the lesions do not tend to regress after puberty. In addition, the multiloculated, ground-glass lesions of fibrous dysplasia are rarely as symmetrical as the cherubic lesions.</td>
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<td>Central giant cell granuloma</td>
<td>It closely mimics cherubism, occurring between 10 and 30 years of age. Radiologically, the central giant-cell granuloma lesions have a predilection to involve the anterior mandible, they are rarely bilateral or symmetrical, the involvement of the posterior part of either mandible or maxilla being unusual</td>
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<tr>
<td>Brown tumours of Hyperparathyroidism</td>
<td>It is rare in the jaw region. Multiloculated radiolucent lesions may be seen with cortical bone thinning, but they are not symmetrical or bilateral.</td>
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<td>Familial gigantiform Cementoma</td>
<td>It is a rare disorder, involving mandible and maxilla. The lesions are focal in distribution, predominating in the maxilla, being frequently extended to the orbits and nasal septum.</td>
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Cytogenetic and molecular studies, such as fluorescence, in situ hybridization and quantitative analysis of Msx-1 expression in different tissues, are used in cherubism diagnosis. [13]

TREATMENT

Cherubism is generally a self-limiting lesion, which spontaneously regresses with age. Jaw remodelling continues through the third decade of life, at the end of which the clinical abnormality may be subtle. The frequency of remodelling is unknown, since most of the recorded cases have been surgically treated before reaching puberty. Conventional treatment of cherubism includes jaw contouring, curettage of the lesions, and management of dental disharmony. Curettage alone or in combination with surgical contouring has been considered the treatment of choice, and some authors have reported a massive growth of the lesion after surgery, especially when performed during the active growth phase. Liposuction has been used to change the contour of the jaws in patients with cherubism. [3-5] Some authors point medical therapy in the form of calcitonin, as a possibility to curtail the disease and obviate the need for surgery. Calcitonin has been shown to cause inhibition of osteoclast resorption by multinucleate cells in cherubic tissue in vitro. [14] The daily use of 200 IU salmon calcitonin via nasal spraying for cherubism has been recently reported. [13] Based on the genetic mutations related to the disease, gene therapy is expected to play a role in future treatments. [2]

CONCLUSIONS

Cherubism is a rare, giant-cell-containing lesion of the jaw bones. In cases of suspicion of cherubism, radiographic examination is essential, since the clinical presentation and the location and distribution of lesions may define the diagnosis. Histopathological examination is complementary. Nowadays, genetic tests should be used for final diagnosis of cherubism. Knowledge of the clinical and radiographic alterations observed in patients with cherubism is important, since the dentist might be the first professional representative to diagnose this disease.

References