Journal of Medicine in the Tropics (2015) 17:1:42-45

Journal of Medicine in the Tropics

Case Report

Cherubism: Case report and review of literature

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Abstract

Cherubism is a rare autosomal dominant genetic defect of bone remodeling which characteristically affects the mandible alone or both the mandible and the maxilla and does not occur in any other bone of the body. Nasal obstruction may occur in patients with cherubism as a result of involvement of the middle concha. Cherubism like any other genetic disease is incurable. Treatment, therefore, is based on the natural and clinical course of the disease.

Key words: Bone remodeling, cherubism, genetic disease, rare

Introduction

Cherubism, a rare autosomal dominant defect affecting mandibular and maxillary bone remodeling, was first described by Jones in 1933.[1] He likened it to the characteristic fullness of the cheeks and upward gaze of the eyes similar to the angelic look of the cherubs.[2,3] Other synonyms include familial multilocular cystic disease of the jaws, familial fibrous dysplasia and familial multiple giant cell lesions of the jaws.[2-4] To the best of our knowledge only 300 cases from available studies have been reported in the English literature.[5,6]

Epidemiologically, painless, often symmetrical, bilateral jaw swellings appear from 2 to 7 years after birth. Themandible may be affected either alone or in combination with the maxilla.[1,3,7] The tumor, thereafter, enlarges rapidly up to the age of 7 and then begins to regress as patient approaches puberty and subsequently adulthood. Males are more commonly affected than females with 100% penetrance in 2:1 ratio.[8] Sporadic occurrence due to spontaneous mutation may occur and this accounts for about 40% of cases.[1] Submandibular lymphadenopathy, occlusal derangement due to missing teeth, impacted teeth, spacing and early exfoliation of primary teeth are other clinical findings.[1,3]

We present a case of this rare disease occurring in a 7-year-old child.

Access this article online	
Quick Response Code:	Website: www.jmedtropics.org
	DOI: 10.4103/2276-7096.148699

Case Report

A 7-year-old male child was presented to our clinic by the mother having observed a rapidly progressive painlessjaw swelling of 3 years duration. The swelling was said to have developed spontaneously at the angle of the mandible spreading to involve its body as well as the maxilla bilaterally. Pyrexia, night sweats and cough were all negative clinical findings. There was, however, a positive history of nasal obstruction. There was no history of such swelling in other siblings or relatives and patient had no other known systemic illness.

On examination, the patient was otherwise healthy looking except for a diffuse swelling that involved the ramus, angle and body of the mandible bilaterally but not crossing the midline. Involvement of the maxilla bilaterally gave the characteristic "chubby cheek" appearance [Figure 1]. Skin overlying the lesion was normal in texture and

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color. Submandibular and submental lymph nodes were palpable, multiple, discrete and non-tender. Intraorally, the swelling exhibited bucco-lingual expansion, from the region of the lower first premolars to the retromolar areas bilaterally. Mucosa overlying this lesion was not ulcerated and the underlying bone had an "egg shell crackling" sound on palpation. Similar bilateral swellings could be seen in the region of maxillary first molars posteriorly. There were few standing teeth of mixed dentition present as

6, C, 2	2, C, 6
D, 2	1, 2, D

The teeth were generally not mobile but displaced. Other intraoral structures appeared clinically normal and further systemic examination yielded no significant findings. An impression of cherubism was made based on these clinical findings.

The CT scanogram [Figures 2 and 3] showed extensive expansile lytic lesion involving the mandible and maxilla with internal septae. There is involvement of the inferior margin of both orbits, lateral margin of the nasal cavity on the right and both maxillary sinuses. There is an extensive brilliantly enhancing hypodense mass causing marked expansion and thinning of the mandible, maxilla, maxillary sinuses as well as the posterior aspect of the sphenoid sinus. The demonstrated cerebral and cerebellar hemispheres and the ventricular system of the brain and the extra axial fluid spaces are withinnormal limits.

Full blood count, serum calcium, calcitonin, alkaline phosphatase and parathyroid hormone assays done were within reference ranges.

Incisional biopsy was requested for and done under local anaesthesiavia a transoral approach with two samples taken separately from the upper and lower jaw lesions and sent for histopathological analysis. Histological reports

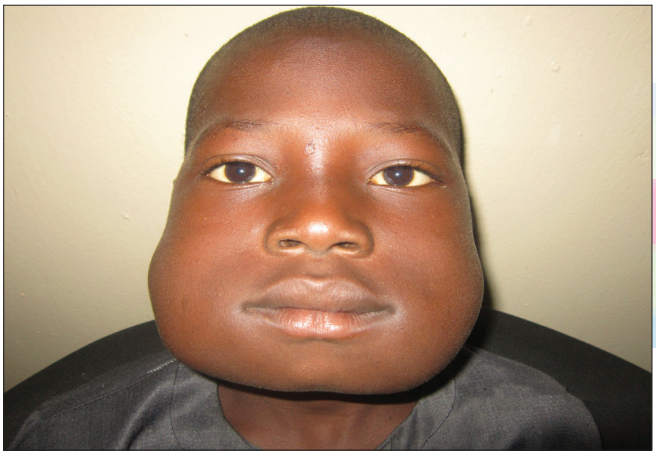

Figure 1: Facial profile of the patient

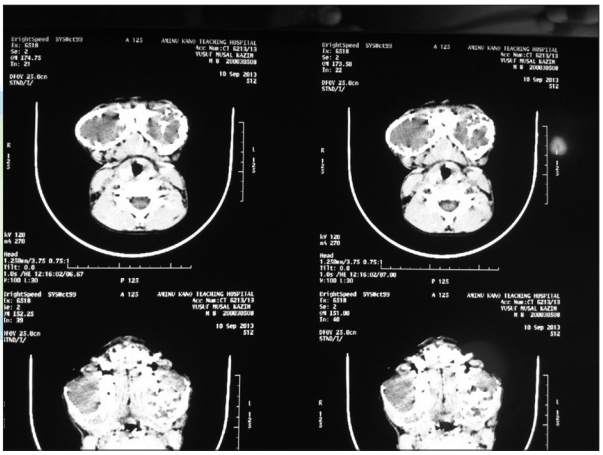

Figure 2: A CT scanogram showed extensive expansile lytic lesion involving the mandible and maxilla with internal septae

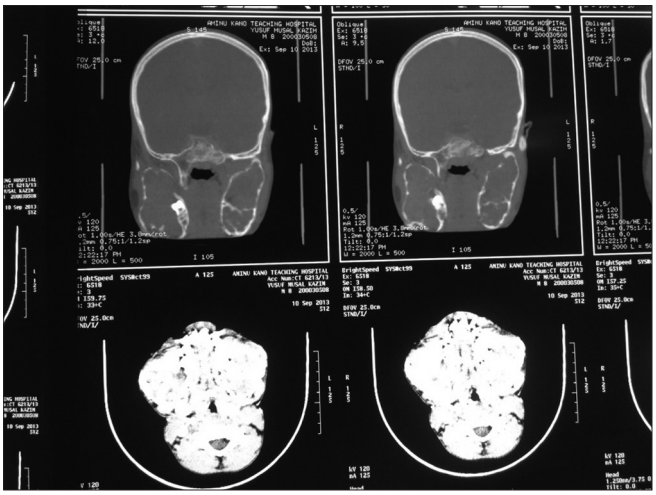

Figure 3: An extensive brilliantly enhancing hypodense mass causing marked expansion and thinning of the mandible, maxilla, maxillary sinuses as well as the posterior aspect of the sphenoid sinus

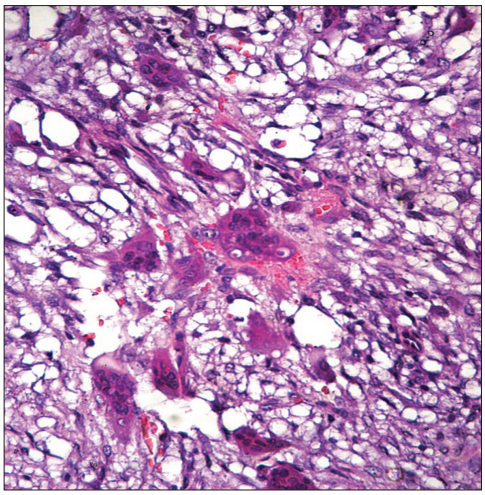

Figure 4: Histological report revealing several multinucleated giant cells dispersed in a loose fibrous connective tissue that exhibited lymphocytic infiltration and extravasation of red blood cells

for both specimens revealed several multinucleated giant cells dispersed in a loose fibrous connective tissue that exhibited lymphocytic infiltration and extravasation of red blood cells consistent with cherubism [Figure 4]. The parents were counseled and the patienthas since been on a biannual follow up for the past 1 year.

Discussion

Cherubism, a rare bony dysplasia may be familial or sporadic in 60 and 40% of cases respectively.[1,3] The case reported in this paper may be one of the sporadic types as no previous occurrence was found in the patient's siblings or relatives.

The age of onset of the swelling in our patient was consistent with those reported in the literature.[1-4]Mengand Yu[5] however, reported 6–10 years as age of onset in a review of 24 cases. In terms of sex, males are more commonly affected than females.[8] Papadaki *et al*.,[6] however, found an equal male to female ratio and because of the rarity of the disease in the world it is difficult to specify the disease frequency though cases have been reported across all racial and ethnic groups. Furthermore, Unequal penetrance between males and females should be considered a historical artifact, which is based on misinterpretation of a thorough clinical investigation. The delayed disease onset and misdiagnosis of adult patients with a mild form of cherubism may have contributed to this misconception. This view is similar to what was reported by Reichenberger *et al*.[9]

A molecular pathogenesis of cherubism has been proposed, with the detection of a mutation in the gene encoding SH3-binding protein 2 (SH3BP2) and possible degradation of the Msx-1 gene which is involved in the regulation of mesenchymal interaction during craniofacial morphogenesis.[9-11] The mutations identified have been traced to exon 9 from position 415 to 420. It is believed that the different clinical manifestations of cherubism are due to the changes secondary to mutations or incomplete penetrance.[10] Genetic studies could not be carried out in our patient due to non-availability of facilities for such as at the time of this report.

Mineral metabolism has been observed to be normal in patients with cherubism. Serum levels of calcium, parathyroid hormone, calcitonin and alkaline phosphatase are typically within normal range. However, some reports have documented a rise in the serum levels of TNF-α in patients with cherubism.[6,12] Hematological and blood chemistry investigations carried out in our patient was consistent with reports in the literature.

Clinically, painless submandibular lymphadenopathy and nasal obstruction as reported in this case are frequent features of cherubism.[1-5]

In terms of classification, Seward and Hankey[13] in 1957 categorized cherubism into four grades based on the severity and location of the disease as follows:

- Grade 1 – Bilateral involvement of the mandibular body, and ramus sparing the condyles.
- Grade 11 – Bilateral involvement of maxillary tuberosities in addition to grade 1.
- Grade 111 – Massive involvement of the entire maxilla and mandible except the condyles.
- Grade 1V – Involvement of both jaws plus the condyles.

This classification was rather not exhaustive in its entirety. Raposo–Amaral[14] simplified the grading system of Motamedi *et al*.,[15] and added a 6th Grade to describe the involvement of the orbits. While these latter classification systems describe the extent of lesions, it is not universally accepted. This is because of the biologic behavior and clinical uniqueness of cherubism in each patient, Papadaki *et al*.,[6]identified important parameters to be considered by clinicians: rate of growth, size, cortical bone perforation or thinning, tooth displacement and the functional deficits.

Involvement of the orbital process of the maxilla and the subsequent upward displacement of the eye resulting in "sclera show" as well as the "chubby cheek" due to maxillary expansion prompted the name, "cherubism" is seen in the classic description of the Grade 111 type.[13] The patient [Figure 1] in this report was categorized into Grade III based on clinical and radiological findings. Cherubism, like most other fibro-osseous diseases of the jaws, requires a combination of clinical, radiological and histopathological features to arrive at a diagnosis rather than histologic as the latter appear similar for all fibro-osseous lesions.[1,2,5] Lesions which appear clinically and microscopically similar to cherubism and from which it must be differentiated include hyperthyroidism, giant cell granuloma, aneurysmal bone cyst, Noonan syndrome and Jaffe-Campanacisyndrome.[1,3,5] Hyperthyroidism can be excluded by serum calcium and alkaline phosphatase analysis which are usually elevated.[1,2,3] Other lesions in the differential diagnosis of cherubism have unilateral presentations.[1-5] Histologically, eosinophilic perivascular cuffing of collagen is considered characteristic of cherubism.[6-8] This feature, however, is frequently absent and only seen in about 40% of cases.[1,6-8] The histopathological description of our case report did not reveal this feature.

Cherubism, as with any other genetic disease is not curable.[1,5] Treatment should therefore be based on the known natural course and clinical behavior of individual cases.[1-6] The policy of waiting for disease regression (natural course), followed by the evaluation of physiological bone remodeling, is the most recommended.[11,16] However, it is

still uncertain whether this approach is the most effective one since only a few cases of long-term follow-up have been reported.[1-6,11,16]

Surgical interventions in the form of osseous recontouring and curettage may be necessary to restore function and aesthetics since curettage has been suggested to stimulate bone replacement.[1-4] Sometimes, severe nasal obstruction may lead to airway concerns thereby necessitating the removal of the middle conchae and turbinates.[1]

Radiation therapy has been abandoned as a treatment of choice for cherubism because of the potential risk of osteoradionecrosis or even malignant transformation of the process resulting in osteosarcoma.[17,18]

In terms of medical therapy clinical evidence is lacking in the use of calcitonin in the treatment of cherubism but *in vitro* experiment has shown promising result by inhibiting bone resorption by multinucleated giant cells in cherubic tissues although further investigations are needed.[6,10]

Antiangiogenic therapy using daily low dose interferon alpha has been shown to prevent recurrence of aggressive giant cell tumors of the jaws as reported by Kaban *et al*.,[19] and could be useful in the treatment of cherubism although this report has not been validated.

Ongoing research strongly suggests that abnormal inflammatory responses are an important component of the pathophysiology of cherubism. Research in a mouse model suggests that high levels of tumor necrosis factor- (TNF-) in the circulating blood system contribute to the progression of cherubism.[6,9,20] A therapy to reduce TNF- levels could be possible if this hypothesis holds true in humans as well.

Conclusion

We have reported cherubism a very rare incurable genetic defect observed in a 7-year-old boy who is still being followed up in our clinic on conservative management as treatment is based on the natural and clinical course of the disease.

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How to cite this article: Idemudia AB, Olushola AI, Akinwale E, Taoheed AA, Sikiru LH, Kevin O. Cherubism: Case report and review of literature. J Med Trop 2015;17:42-5.

Source of Support: Nil, **Conflict of Interest:** None declared.