Cherubism: A Rare Case Report and Literature Review
Avinash Tamgadge, Neha Modak, Sudhir Bhalerao, Sandhya Tamgadge

Abstract
Cherubism is a rare developmental jaw condition that is generally inherited as an autosomal dominant trait with high penetrance but variable expressivity. It is a benign disease of bones affecting the jaws and giving a characteristic cherubic appearance to the patient. Recent genetic studies revealed that cherubism is a genetically mediated disorder first reported at 1933. It is a self-limiting bony growth which usually begins to slow down when the patient reaches five years of age, and stops by the age of 12 - 15 years. At puberty the lesion begins to regress. The treatment of cherubism is still controversial and it is said that the disease will regress itself and after regressing if any asymmetry is there then the bony deformity can be corrected by decortications of bone and osseous shaving. This article presents a rare case report of 12 years old child who had started developing cherubism from the age of five years and till the age of twelve years showed no signs of regression. Also it involves review and recent development in the literature of cherubism.

Key words: Bone Diseases; Fibrous Dysplasia of Bone; Cherubism; Genetic Diseases; Inborn; Congenital; Hereditary; Neonatal Diseases and Abnormalities.

Introduction
Cherubism belongs to a group of non-neoplastic progressive hereditary bone lesions affecting only the jaw bones of children according to the WHO classification. Cherubism, first described by Jones in 1933, as a benign self-limiting fibro-osseous disorder characterized by bilateral symmetrical painless expansion of the mandible, maxilla, or both. This expansion results from rapid bone degradation followed by extensive bone remodeling. Skin over the swelling is stretched, pulling the lower eyelids down and exposing a line of sclera. A rim of sclera may be visible beneath the iris, giving the classic ‘eye raised to heaven’ appearance. The name cherubism was applied to this condition because the facial appearance is similar to that of the plump-cheeked little angels depicted in Renaissance painting.

Cherubism is a familial disease with typical age of onset being two to five years. This jaw lesion is progressing gradually until puberty, stabilizes spontaneously and then eventually regresses. It presents as an autosomal dominant trait with 100% penetrance in males and 50 – 70% penetrance in females. Initially called as ‘familial fibrous dysplasia of the jaws, disseminated juvenile fibrous dysplasia’ but this term should be avoided because cherubism has no relationship to the fibrous dysplasia of bone and recent genetic investigations have proved it as to be separate entity at the molecular level. This patient had reported presented with the Cherubic disease at an age which was slightly more than the normal age. Hence a lot of study is to be done to know the actual genetic treatment for this genetically mediated disease.

Case Report
A 12 years old male patient reported to the Department of Oral Medicine and Radiology with the complaint of bilateral swelling of the face. The patient was normal at birth but at the age of seven years, a bilateral swelling was observed on both sides of the face which gradually increased in size. The parents of the child had taken the patient to a physician who had started treating him for hypothyroidism with Altroxin. After few months the patient stopped taking any treatment or medication from the physician. Patient’s family history was noncontributory. Systemic examination revealed no abnormality. Extraoral examination of the face showed severe bilateral expansion (Figure 1a). The face was giving chubby appearance on inspection. On palpation the swelling was bony hard in consistency.
Submandibular lymph nodes were also enlarged bilaterally.

The Orthopantomogram revealed a multilocular lesion which was radiolucent with radiopaque areas and it involved the symphysis menti, body of mandible, and the ascending rami bilaterally (Figure 1b). Floating and multiple impacted teeth were also evident on the radiograph. A computerized tomographic (CT) scan showed extensive expansile remodeling of the mandible, with internal trabeculations and a mildly sclerotic matrix (Figure 1c). There was no cortical break, fracture, or periosteal reaction seen within the jaw bone. Bilateral condylar extension was characteristically absent. CT scan also clearly depicted the absence of extraosseous soft tissue extension.

Hematological and biochemical investigations were performed. The results showed an erythrocyte sedimentations rate of 8 mm/1st hour, serum alkaline phosphatase of 450 IU/L, T3 of 1.43 ng/mL, T4 of 6.50 µg/dL, thyroid stimulating hormone of 3.59 µlu/ML. Since thyroid function tests were normal, it was decided to discontinue the earlier Altroxin therapy. Blood urea level was 20.0 mg/dl and serum creatinine level was 0.70 mg/dL and all were under normal limits. Serum calcium level was 9.44 mg% which was under normal limit.

Incisional biopsy was also performed. Histopathologically findings revealed highly cellular fibro-vascular connective tissue. The cellular components consisted of abundant plump fibroblast like cells with multinucleated giant cells interspersed between them. Some areas of local hemorrhage were also noticed within the connective tissue (Figure 1d). Mixed types of inflammatory cells were evident. Clinical, histopathological and radiological diagnosis confirmed the final diagnosis of cherubism. Cherubism is a genetically mediated disorder which gets corrected with age and usually gets resolved after puberty. After doing a vivid clinical review, it was decided that the patient will be kept under observation till he attains puberty.

Discussion
First description of familial multilocular cystic disease of the jaws was coined on 1933. Jones first described the familial occurrence of a painless enlargement of the jaws in three siblings. Jones later in 1938 reported, observations on the same family under the title “familial multilocular cystic disease of the jaws” and coined the term “Cherubism” after the cherubs of Renaissance art for the full round cheeks and “eyes upturn to heaven” giving the children a peculiarly grotesque, cherubic appearance.

Gene SH3BP2 for cherubism has been mapped to chromosome region 4q16.3. Normally SH3BP2 encodes the adapter protein SH3-domain binding protein. It is required in several intracellular protein tyrosine kinase–dependent signaling pathways during hematopoietic cell differentiation and function. SH3BP2 positively regulates the activity of the transcription factor [NFAT] which is involved in osteoclastogenesis [Lietmanetal 2006]. But the abnormal gene products are formed in cherubism by mutations in the SH3BP2 gene with its location on Chromosome 4q16.3. This mutation activates TNF expression in myeloid cells, causes both bone loss and inflammation.

Clinically, cherubism represents normal at birth with the onset between 14 months and five years. However the severe cases are evident at birth. It progresses until puberty, and usually progression stops after puberty. There is regression of bone lesion i.e., the resolution of the disease without treatment in many cases. There is cherubic appearance with fullness of the lower half of the face (Checks and Jaw) with retraction of the lower lids by the stretched skin over the checks pulling down the lower eyelids. Consequently a thin line of sclera is exposed beneath and the eyes appear to be raised to heaven. Mandible is most commonly involved with the involvement of the maxilla in 60% of cases. There is premature loss of deciduous teeth, root resorption and displacement of permanent dentitions, displaced tongue affecting speech, mastication swallowing and respiration. All the above physical and clinical alterations can lead to psychological impairment.

Cherubism is reported to be associated with some well described syndromes, including Neurofibromatosis type1, Noonan like / multiple giant cell lesion syndrome, Ramon syndrome, and Jaffe-Campanacci syndrome. The patient in our report presented with a bilateral painless swelling.
extensive, multilocular areas of reduced density, with a few intervening irregular bony septae and thinning of the cortical rims.\textsuperscript{6-10} About 60 - 70\% of the lesions may be mildly sclerotic and upto 70\% may demonstrate internal trabeculae.\textsuperscript{10} These multilocular areas of diminished densities are later replaced by irregular patchy sclerosis, with progressive calcification. The classical ground-glass appearance of the lesions is a result of the presence of small tightly compressed trabeculae.\textsuperscript{8,9} In our case, patient shows diffuse, bilateral, multilocular mixed radiolucent/radiopaque lesion radiographically, which extends from the angle of mandible to the ramus and body.\textsuperscript{3,8,9}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{The extraoral Photograph showing cherubic appearance owing to the bilateral painless expansion of mandibular jaw (a). Orthopantomogram reveals multilocular appearance of the mandibular jaw with numerous unerupted and displaced teeth (b). The axial CT image shows multilocular mixed radiolucent/radiopaque lesion within the entire mandibular jaw giving ground glass appearance (c). The photomicrograph showing osteoclasts-like giant cells lie in a fibroblastic background with hemorrhagic zone within mesenchymal tissue (d).}
\end{figure}

Seward and Hankey\textsuperscript{8,11} have proposed a grading system based on the radiographic location of the lesions in the jaws. It is as follows:

\textbf{Grade I}: Involvement of bilateral mandibular molar regions and ascending rami, mandible body, or mentis.

\textbf{Grade II}: Involvement of bilateral maxillary tuberosities (in addition to grade 1 lesions) and diffuse mandibular involvement.

\textbf{Grade III}: Massive involvement of the entire maxilla and mandible, except the condyles.

\textbf{Grade IV}: Involvement of both jaws, including the condyles.

According to this grading system, our patient showed Grade I disease.

CT clearly depicts the extent of the mandibular and maxillary lesions as compared to plain radiographs; the anatomic complexity makes interpretation of radiographs of the facial bones difficult.\textsuperscript{8,10} A fibro-osseous, mildly sclerotic matrix is typically seen, with expansile remodeling of the bone and cortical thinning.\textsuperscript{8,10} The lesions in our patient showed a mildly sclerotic matrix. Some reports have also documented soft-tissue density material on CT scan.\textsuperscript{8,12} In our patient, none of the osseous lesions showed adjacent periosteal reaction or an associated soft-tissue mass. Though sparing of the mandibular condyles
has been described as a pathognomonic feature of cherubism, condylar involvement is often seen on CT scan.\textsuperscript{8,13} Condylar involvement was, however, absent in our patient.

There are very few reports describing the magnetic resonance imaging features of cherubism,\textsuperscript{8,10,12} which are usually nonspecific. The lesions have been described as being homogenously isointense or heterogeneous on T1W images and heterogeneously isointense or hyperintense on fat-suppressed spin-echo T2W images.\textsuperscript{8,10,12}

Microscopically, the lesions show numerous multinucleated giant cells and vascular spaces which are randomly distributed against a background of highly cellular connective tissue.\textsuperscript{9} The cellular stroma contains focal deposits of hemosiderin pigments. All these histological features are appreciated in our case. Eosinophilic collagen perivascular cuffing can be seen in some cases and this perivascular hyalinolysis is considered pathognomonic for cherubism.\textsuperscript{14,15} Histochemical and immunohistochemical characterization of the multinucleated giant cells reveals that these are osteoclasts since they are positive for tartrate-resistant acid phosphatase and express the vitronectin receptor.\textsuperscript{9}

Differential diagnosis for cherubism is fibrous dysplasia, brown tumor of hyperparathyroidism, infantile hyperostosis,\textsuperscript{4} familial gigantiform cementoma, true giant cell tumor, central giant cell reparative granuloma,\textsuperscript{4,10} and central giant cell granuloma.\textsuperscript{10} Cherubism and craniofacial fibrous dysplasia can be distinguished clinically and radiographically. Cherubism is characterized by bilateral mandibular involvement, limitation to the maxilla and mandible, and involution at the time of puberty.\textsuperscript{10} Clinical features of cherubism, like swollen cheeks, upward turning of the eyes, and dental derangement, is typically not present in fibrous dysplasia. Histologically, numerous multinucleated giant cells are seen in patients with cherubism, while they are rarely seen in fibrous dysplasia.\textsuperscript{8}

Normal level of serum calcium, phosphorus, and alkaline phosphatase along with clinical features rules out hyperparathyroidism.\textsuperscript{4,6} Infantile cortical hyperostosis may affect siblings and present with bilateral jaw enlargement. Occurring at a younger age than cherubism and radiographs show bilaterally symmetric cortical thickening caused by marked periosteal new bone formation without any loculation or lucent lesions.\textsuperscript{4} Familial gigantiform cementoma is a rare osseous disorder in which the lesions are primarily located in the maxilla and cause focal enlargement rather than diffuse involvement. Histologically, multinucleated giant cells are absent and the lesions contain cementum.\textsuperscript{8,10} Central Reparative Granuloma has a predilection to involve the anterior mandible.\textsuperscript{4} Central Giant Cell Granuloma develops in anterior mandible in young females. True giant cell tumors occur in the older age group 20 to 40 years of age and most commonly occurs as a solitary lesion located at the metaphysis of long bones particular by the knee. Rarely involves the jaw bones and rarely has bilaterally symmetrical distribution.\textsuperscript{4}

Now days advanced investigative modalities include ‘Molecular genetic testing’ which is use to confirm the diagnosis is a proband with the suggestive clinical findings and typical radiologic and/or histologic manifestations.\textsuperscript{4} ‘Pre-implantation genetic diagnosis’ may be available for families in which the disease causing mutation has been identified. For pregnancies at increased risk of developing cherubism can be identified by analysis of ‘DNA extract’. ‘DNA banking’ is also recent technique where DNA is typically extracted from white blood cells and can be used for possible future. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using ‘sequencing’, ‘restriction fragment analysis.’

Being a self limiting condition, treatment is mainly for the esthetic needs and for unerupted teeth. In our case, we are keeping the patient under observation and if the lesion does not regress fully by the age of thirteen years then the patient will be sent to a surgeon for cosmetic surgery. Curettage is the surgery of choice. Simple contouring of lesions produces good cosmetic appearance. Liposuction has also been used to achieve good contour. Surgery gives good immediate results as it arrests the active growth of remnants of cherubic lesions. Radiotherapy is contraindicated because of fear of retardation of jaw growth osteoradionecrosis and chances of malignant degeneration. Medical therapy like calcitonin is theoretically appropriate but without proven result. The recent
advancement in the treatment of Cherubism is the genetic therapy.\textsuperscript{2,4}

Conclusion

Basically this article discusses a rare case report of 12 years old child who had presented the cherubic disease at an age slightly more than normal age. The case which is reported in our department showed all classical signs of cherubism with bilateral expansion of the jaw. Apart from the clinical presentation, radiographic as well as histopathological examinations also confirm the diagnosis of it. Nowadays, genetic tests should be used as confirmatory tests for the final diagnosis of cherubism. Being a self-regressing condition, we’ll follow the wait and watch policy and if necessary we’ll do the surgical correction as per the requirements.

Author Affiliations

1. Dr. Avinash Tamgadge, Prof. and Head, 2. Dr. Neha Modak, Post Graduate Student, 3. Dr. Sudhir Bhalerao, Prof. and PG Guide, 4. Dr. Sandhya Tamgadge, Prof. and PG Guide, Department of Oral and Maxillofacial Pathology, Padmashree Dr. D. Y. Patil Dental College and Hospital, Sector 7, Nerul, Navi Mumbai, Maharashtra, India – 400706.

Acknowledgement

We would like to thank the staff members of the oral pathology department for their support & cooperation.

References


Corresponding Author

Dr. Avinash Tamgadge, Professor and Head, Department of Oral and Maxillofacial Pathology, Dr. D.Y. Patil Dental College and Hospital, Sector 7, Nerul, Navi Mumbai, Maharashtra, India. Pin- 400706 Ph- +91 9222199770 Email: avinash.pt@gmail.com

Source of Support: Nil, Conflict of Interest: None Declared.