Case Report

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Familial Fibrous Dysplasia in Two Subsequent Generations in a Family

Dentistry Section

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ABSTRACT

Cherubism also known as familial fibrous dysplasia is a rare, non neoplastic, self-limiting fibro-osseous disorder commonly affecting the jaws in children and young adults. It is also described as familial multilocular cystic disease and familial benign giant cell tumour of the jaw. It is characterised by bilateral, painless swelling involving the mandible giving a cherubic (angel like) appearance. As it is a rare disorder, it is challenging to determine the disease frequency. A familial disorder like cherubism is more likely to be of autosomal dominant trait and shows 100% male sex predilection compared to female which is 50-70%. Although, cherubism becomes noticeable in childhood (2-7 years of age), the treatment is however contentious as the disorder is believed to regress gradually after the onset of puberty and surgical intervention is to be decided based on aesthetics or functional difficulties. Numerous researches have been conducted to prove that cherubism is a genetically mediated disorder and the chromosome mapped is 4q16.3. This paper describes a case of an 11-year-old girl with cherubism and also encountered in two subsequent generations of a family, the father and his three children. The genetic and pedigree analysis carried out in this family proves hereditary basis in better understanding the genetic association related with the disorder. All the patients were educated about the disorder and were advised for surgical management after the onset of puberty.

Keywords: Benign, Cherubim, Familial multilocular cystic disease, Fibro-osseous lesion, Genetic predisposition

CASE REPORT

An 11-year-old girl reported to the Oral Medicine Department of Saveetha Dental College and Hospital with a complaint of painless bilateral swelling in the lower jaw since the age of five years. Initially, the swelling was small and gradually increased over the years. There was no history of pain, difficulty in mastication, toothache, or any discharge from the swelling. The patient was apparently healthy. No treatment was done for the swelling till date. She now reported with concerns of unaesthetic facial appearance.

A. Family history: Patient's father who was 30 years of age during the time of reporting had similar condition and surgical recontouring of the jaws was done in his childhood. The patient also reported having two siblings a younger sister and a younger brother of nine and seven years respectively, who also had similar condition since childhood. This established familial inheritance pattern of the mandibular swelling in subsequent two generations of the family.

B. Examination: The patient and her two siblings were examined and all three had diffuse swelling present bilaterally in maxilla and mandible, irregular in shape with dull margins extending superioinferiorly from infraorbital margin to the lower border of mandible bilaterally and from the tragus of the ear till the ala of the nose anteroposteriorly on both sides. Nasolabial fold was obliterated bilaterally. The skin over the swelling was normal with no secondary changes, discharge, or pigmentations. The swelling was non tender, hard in consistency, smooth surface with diffused edges and the skin over the swelling was pinchable. Multiple, bilateral, palpable, non tender and firm submandibular groups of lymph nodes were also evident on palpation [Table/Fig-1].

C. Radiographic examination: Baseline Orthopantomogram (OPG) was advised for the patient and her siblings. All panoramic radiographs uniformly reveal diffuse bilateral multilocular radiolucencies present in maxilla and mandible with a well-defined periphery with cortical bone thinning and bilaterally extending to the condylar and coronoid process [Table/Fig-1].

Multislice Computed Tomography (CT) showed a diffuse, bilateral, multilocular hypodense area with wispy septae and cortical bone expansion in the maxilla and mandible in the axial view. The coronal view showed condyle, coronoid and ramus destruction, and the 3D reconstructed image showed the extent of the osteolytic lesion [Table/Fig-1].

D. Genetic mutation analysis: Current literature states 80% of affected individuals with cherubism have a mutation in exon 9 of the SH3BP2 gene. Genetic analysis was performed from the collected blood samples of the patient, her parents and her two siblings.

- Primer: Sense 5'-AAATGGTCCTGCCTTCCTCT-3'
  Antisense 5'- GAG GCT GAC GGT GTC AGT
- Amplification conditions: Initial denaturation- 94°C for two minutes

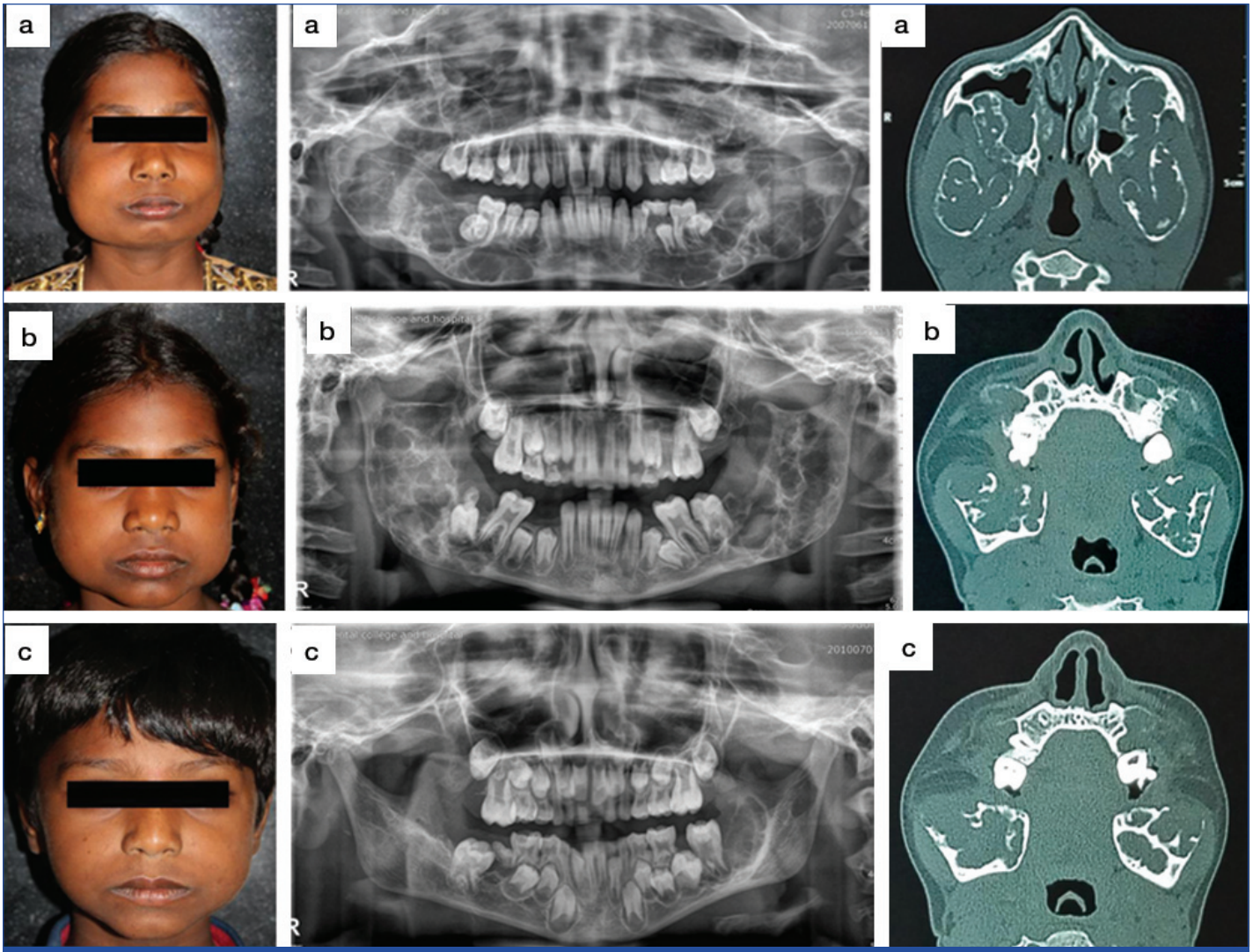
Amplified- 35 cycles of 94°C for 30 seconds followed by a final extension at 72°C for 10 minutes [1].

The result showed the Deoxyribonucleic Acid (DNA) sequencing of the Polymerase Chain Reaction (PCR) amplification product of exon 9 indicated a heterozygous point mutation. Alteration in only a single base pair from alanine to glycine was seen [Table/Fig-2]. A genogram was designed based on family history and genetic information. Family history revealed the patient's grandfather (generation I) presented with cherubism followed by the patient's father (generation II) who has 25% of the penetrance of the disease and all the three children (generation III) has 100% penetrance of the disease [Table/Fig-2].

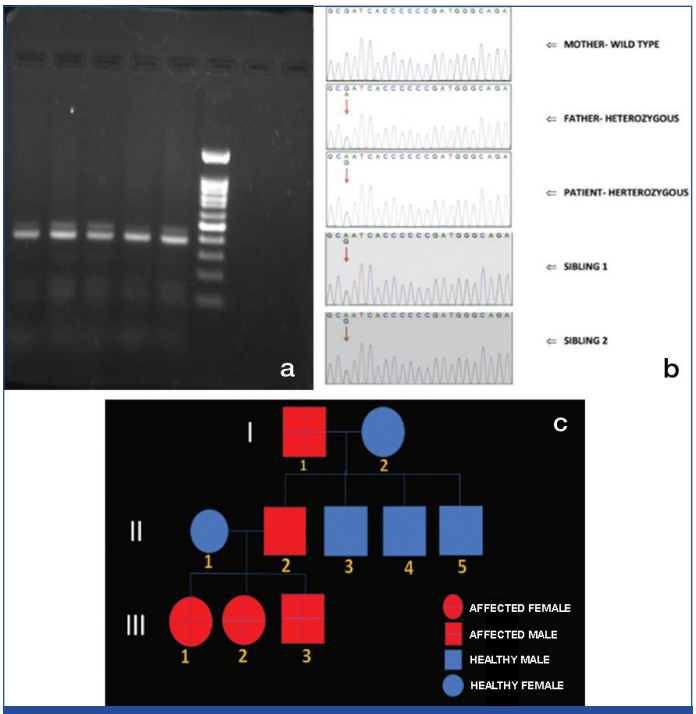
As the patients reported in this paper were young and had not attained skeletal maturity, surgical treatment was not advised. However, the patients were reassured, educated about the disorder, the familial preponderance and were advised to undergo surgical contouring and aesthetic corrections after attaining skeletal growth.

DISCUSSION

According to the World Health Organisation (WHO), cherubism belongs to a group of non neoplastic bone lesions that affect only the jaws [2]. Globally, many terms have been coined for cherubism,



[Table/Fig-1]: Shows the profile picture, OPG and CT images (axial section) of the patient (a) and her siblings (b and c).



[Table/Fig-2]: Shows the exon 9 amplified to 400 base pairs, gene analysis results and pedigree chart.

such as familial multilocular cystic disease and familial benign giant cell tumour of the jaw. As cherubism is considered a part of family of fibrous-osseous diseases, some authors even refer to this disorder as "familial fibrous dysplasia". In 1933, William A. Jones of Ontario first recognised multilocular cystic jaw disease in a Jewish-Russian family of three affected family members. The nomenclature of the term "cherubism" comes from the word "cherub" who means sweet, innocent baby or little angel, showing a perfect round cheek with eyes facing up exactly giving an angelic look by capturing the clinical features of the child's disease precisely [3].

The first signs of disease symptoms are generally observed about two years of age, then the growth accelerates at 8-9 years of age and spontaneously ceases shortly after puberty. However, the clinical or radiological features of cherubism are not apparent until 14-36 months of age [4]. On radiographs, cherubim are a bilateral, expansive, multilocular, radiolucent lesion clearly separated by the cortical bone of the mandible. Radiologically cherubism is like hereditary craniofacial fibrous dysplasia, a subtype of fibrous dysplasia. To date, hereditary tooth germ changes have been identified in 80% of the cherubism population. Mutation occurs in the gene encoding SH3 binding protein 2 (SH3BP2) and is mapped to chromosomal region 4q16.3 [5]. Cherubism is a rare hereditary autosomal dominant benign disorder of childhood. The name was derived from the cherubs of Renaissance art which showed similar full round cheeks and the eyes gazing upwards giving the children and young adults peculiarly grotesque, or cherubic appearance. Cherubism is also referred to as familial fibrous dysplasia of the jaws, but the recent gene mapping has proven it to be a separate entity at the molecular level [6]. Literature states that the cherubism cases reported as of 2017 were estimated to be approximately 300 in number. Because of its rarity in existence, it is difficult to determine a disease frequency for this disorder. However, the extragnathic skeletal involvement is rare in cherubism. In 1983, Davis GB et al., reported some rare occurrences of multiloculated cystic lesions in other bones, namely, anterior ribs, upper humerus and upper femoral necks [10].

The symmetrical appearance with multilocular, expansile, radiolucent lesions present in the mandible and/or maxilla typically appears at the age of 2-7 years. In the early stages of the disease, the swelling of the submandibular lymph nodes can contribute to the fullness of the face, which can be appreciated in present case as well [7]. The characteristic eyes tilted upwards appearance exposing the sclera below the iris can be caused by the soft fibrous dysplastic tissue in the lesions which infiltrates the orbital floor on expansion. Because of the orbital floor involvement, the associated inferior and lateral recti muscles and the intraconal space of the orbits may also get involved. If the lesion extends up to the orbit, rarely there can be a loss of eyesight due to the optic nerve atrophy [7]. However, in this case, there was no "eyes raised towards heaven" appearance.

The condition clinically presents with the child having normal appearance at birth and the orofacial signs and symptoms slowly begin during the 2nd or 3rd year of life. A classic bilateral, symmetrical deformity of the face due to multiple cystic lesions involving both the right and left mandible is the main diagnostic criterion. It is believed that the disease progresses until the onset of puberty and shows gradual regression in adulthood. Solitary lesions or some varying degree of deformity might persist into adulthood, and a few aggressive versions of cherubism have also been described in the literature [8].

In 1978, D.G. Arnott suggested a grading system for cherubism depending on location and the severity of involvement of jaws [9]. Based on Arnott's grading system, Ramon and Engelberg proposed a grading system for cherubism based on the extent of the involvement during the time of evaluation as:

- Grade 1- Involvement of both mandibular ascending rami
- Grade 2- Same as grade 1 plus involvement of both maxillary tuberosities
- Grade 3- Massive involvement of whole maxilla and mandible, except the condylar processes
- Grade 4- Same as grade 3 with the involvement of the floor of the orbits causing orbital compression [10].

Based on the classical grading system, which is followed worldwide, the entire family in this case series fits in the grade 2 cherubism category where there is involvement of mandibular ascending rami and involvement of maxillary tuberosities bilaterally.

Radiographically, cherubism is characterised by bilateral, expansive, multilocular, radiolucent lesions clearly delimited by cortical bone expansion in the mandible as seen in our patients [11]. Alterations of the bone tend to begin in the mandibular angle extending to the ascending ramus of the mandible and may sometimes involve the body of the mandible, which at times can displace the mandibular canal, and even in some cases involvement of the coronoid process is evident. The complete involvement of the maxilla is less frequent and less extensive. In severe cases, orbital bone infiltration can occur leading to exacerbated exophthalmos which can limit the ocular movements. Multiple retained deciduous teeth are commonly seen along with hanging and/or floating teeth, also known as floating tooth syndrome. Present patient's first sibling, the younger sister, presented with floating teeth which were clear in the OPG. Computed Tomography (CT) scan is the primarily employed imaging technique essential for establishing a diagnosis and for an adequate course of action. Keeping this in mind, we advised our patient for a CT scan, and the results have proven to show the extent of the osteolytic lesion in the 3D reconstructed image. It aids in identifying the extent of bone involvement. Dental anomalies such as delayed eruption, displacement of teeth, root resorption, are also known to be present [11].

Cherubism with multiple familial presentation had reported mutations in the exon 9 of the SH3 binding protein 2 (SH3BP2) genes on chromosome region 4q16.3. The molecular pathogenesis is based on the interaction between disrupted Parathyroid Hormone-Related Protein (PTHrP) receptors (due to mutations in SH3BP2) and the activity of the Homeobox protein MSX-1. Therefore, the temporal and spatial termination of clinical manifestations is explained by SH3BP2-dependent signaling pathways that impede jaw morphogenesis. During the odontogenesis of the 2nd and 3rd molar in cap stage, there is no spatial compartmentation which is necessary for normal development, leading to cause dysregulation of mesenchymal bone formation and thus to the development of formation of giant cells granulomas which contains osteoclasts [12]. The result of the gene analysis of our patient showed the heterozygous point mutation only in a single base pair, from alanine to glycine. As there is no evidence in the literature of the disease causing mutation outside exon 9 in the SH3BP2 gene which highlights the specificity in the diagnosis of the disease [12].

Diagnosis of cherubism is primarily based on factors such as age, family history, radiographic findings, biochemical analysis, and molecular analysis. However, recent advances have shown that the risk of developing cherubism during pregnancy can be detected by DNA analysis that is performed on fetal cells obtained either via amniocentesis which is usually done during the 15-18 weeks of gestation or via chorionic villous biopsy which is done about 10-12 weeks of pregnancy. Studies have shown that the SH3BP2 mutation that causes the disease can be detected by pre-implantation genetic testing available to families with or suspected of having cherubism [13].

The differential diagnoses for cherubism are fibrous dysplasia, Ramon syndrome, Noonan syndrome, fragile X syndrome (Martin-Bell syndrome), and giant cell granuloma [14].

Treatment for cherubism is contentious and not standardised. Because it is a self-limited disease, invasive treatment should be postponed until complete skeletal maturity is completed. Surgery is not recommended for patients with grade I and II cherubism, but biopsy and surgical treatment can be given if tissue dilation causes problems with the airway or masticatory capacity. Surgical managements can vary from a simple impacted teeth extraction to more aggressive resection of the lesion. Evaluating the extent and severity of the disease prior to the surgical intervention. It should be performed meticulously to assess the areas of bone weakness in order to avoid any bone fractures or infections. Calcitonin therapy has been proven to be effective in remission of lesions and is administered as an intranasal spray instead of a subcutaneous injection. The reason for administering calcitonin is that it inhibits giant cell osteoclastic activity [15].

CONCLUSION(S)

This paper presents cherubism in two generations of a single family establishing the familial pattern of inheritance. Performing the genetic sequencing can be a helpful tool in educating the patient on disease progression and severity.

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