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A review Article

Parameters for Cherubism diagnosis:Clinicoradiographic features, Biochemical ,Cytogenetic ,Immunohistochemistry , and histopathology

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Abstract
Objectives: *Cherubism is a congenital childhood disease of autosomal dominant inheritance. This disease is characterized by painless bilateral enlargement of the jaws, in which bone is replaced with fibrous tissue. The condition has clinical, radiographic and histological features, of which the clinician should be aware a better differential diagnosis in the presence article of a fibro-osseous lesion affecting the bones of the maxillomandibular complex. The purpose of present article paper was to review the literature and to report the most important aspects of cherubism in order to facilitate the study of this disease.*
Material and Methods: *Literature was reviewed about cherubism, emphasizing the relevant clinicoradiographic features and treatment. Literature was selected through the search of PubMed and Scielo electronic databases. The keywords used for search were adolescent, cherubism, cherubism/physiopathology, cherubism/treatment, cherubism/radiography. A manual search of the reference lists of the identified articles and the authors' article files and recent reviews was conducted to identify additional publications. Those studies that described new features about cherubism were included in this review.*
Results: *In total 16 literature sources were searched and reviewed. Studies that described new features about cherubism physiopathology, diagnostics parameter were reviewed.*
Conclusions: *Despite the exceptions, cherubism is a well-characterized disease clinically .but in some cases of a suspicion of cherubism, radiographic examination is essential since the clinical presentation, the site and distribution of the lesions may define the diagnosis. Histopathological examination is complementary. Nowadays, molecular tests should be used for final diagnosis of cherubism.*
Keywords*: adolescent; jaw diseases; cherubism.*

I. Introduction

Cherubism– first showed by Jones (1933) – so received its name because of the angel-like appearance of the patients (chubby and upward directed look). Cherubism is autosomal genetic disorder characterized by abnormal bone tissue in the lower part of the face. starting in early age, both the lower jaw (the mandible) and the upper jaw (the maxilla) appear enlarged as bone is replaced with painless, cyst-like growths. A Point mutation in SH3BP2 detected, so it leads to the degradation of Msx-1 gene, which is plays a role in the regulation of mesenchymal proliferation during craniofacial morphogenesis so occur in jaw[1].

Mangion et al. (1999) and Tiziani et al. (1999) : showed that the gene region responsible for cherubism is located on chromosome 4p16.3.

Ueki et al. (2001) found mutations in the gene for the SH3-bindingprotein SH3BP2, which is located within the critical area in 12 out of 15 families with cherubism. SH3BP2-dependent signal transduction seems to be involved especially in the regulation of elevated osteoclastic and osteoblastic activities during dentition.[2]

According to these observations, Lietman and coworkers detected whether wild-type SH3BP2 progress NFAT translocation, and induce and TRAP activation in RAW cells and whether SH3BP2 mutants found in cherubism patients lead to further increased NFAT and TRAP activation to stimuli the osteoclas that result in bone lesions of cherubism[3] **.**

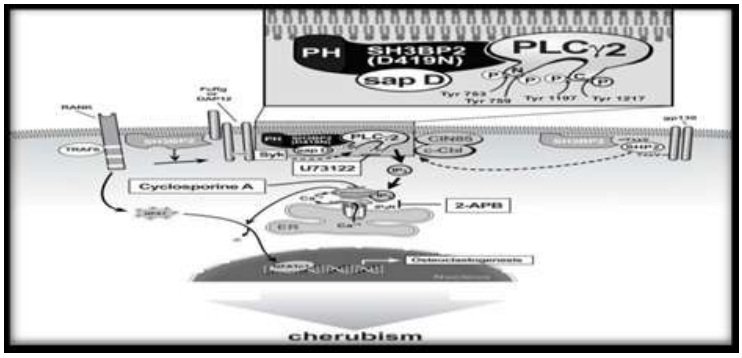
The physiological role of SH3BP2 gene(normal) play a role for instructions to making a protein whose exact function is unknown, although it is known to interact with other proteins in cells. The SH3BP2 protein plays a role in transmitting chemical signals, especially in certain immune system cells and cells involved in the remolding and replace of old bone tissue with new bone (bone remodeling).[4]

The goals of the present paper were to review the literature and to report the most important aspects of cherubism in order to facilitate the study of this disease.

II-Etiopathogenesis

At minimum 11 mutations in the SH3BP2 gene have been detected in patients with cherubism. Each of these mutations changes a single protein making a block (amino acid) in a critical region of the SH3BP2 protein. These molecular changes lead to the formation of an overly active form of this protein. The outcomes of SH3BP2 mutations are still unknown, but researchers believe that the abnormal protein changed critical signaling pathways in cells associated with the maintenance of bone tissue and in certain immune system cells[5].

The overactive protein likely stimuli inflammation in the bones of the jaw and progress the production of an increased number of osteoclasts. An excess of osteoclast contributes to the abnormal destruction of bone tissue in the upper and lower jaws. A combination of bone resorption and inflammation likely underlies the cyst- like growths characteristic of cherubism.[5] the end results of this mutation lead to increased Nuclear factor of activated T-cells (NFAT) and Tartrate- resistant acid phosphatase (TRAP) activation to induce the osteoclastic bone lesions of cherubism. These data suggest that Sh3bp2 function regulates bone homeostasis not only through osteoclast-specific effects but also through effects on osteoblast differentiation and function[6]. figure 1



(figure 1) pathogenesis of cherubism**.**

https://www.google.com.eg/search?q=pathogenesis+of+cherubism&espv=2
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Clinical characteristics and symptoms

Early as 1 year of age, the disease usually occurs between the ages of 2 and 5 years. The cherub-like faces developed from bilateral involvement of the posterior mandible that produces angelic chubby cheeks. "eyes upturned to heaven" appearance that was due to a wide rim of exposed sclerae noted below the iris. The mandibular lesions typically appear painless, bilateral expansion of the posterior mandible that tends to involve the angles and ascending rami. distortion of the alveolar ridgesridges[7].

The initial manifestation signs of the disease are generally diagnosed at about 2 years of age, followed by progressive in growth from 8 to 9 years and resolving after puberty[8] . However, Ashraf and Kalantar suggested that diseases starting from 3 to 7 years of age, growth might be more active after puberty. As well as, the age at the appearing of symptoms differs according to the degree of severity of the disease and degree of deformity. In such cases where the onset of symptoms of cherubism occurs after puberty, the time of remission of the process is expected to be prolonged [9]. In cases where the clinical symptoms are ideal to cherubism, the professional diagnosis should be based on radiographic findings and histopathology, because the clinical features of cherubism at initial examination are similar to other lesions that cause mandible enlargement, such as autosomal dominant osteosclerosis[10] (figure 2&3) .

figure 2 Photograph of a 7 year old boy with cherubism showing bilateral swelling at the mandibular angles. (http://www.ejomr.org/JOMR/archives/2010/2/e2/e2ht.htm

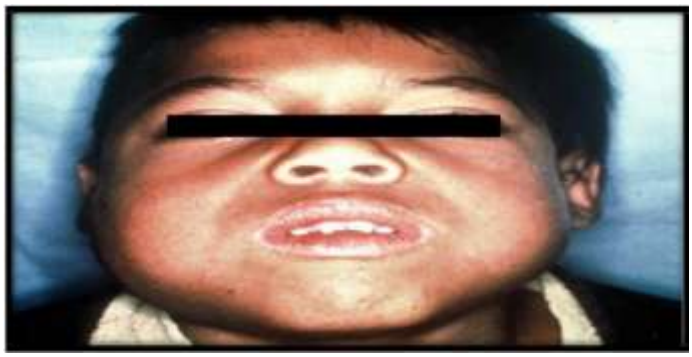

Figure 3. Photograph of a 9 year old boy with cherubism showing bilateral swelling of the angle and ascending ramus of the mandible, stretching the skin in the nasogenial region.
.(http://www.ejomr.org/JOMR/archives/2010/2/e2/e2ht.htm)

Diagnostics
Radiographic

The radiographic appearance might be similar to other lesions containing giant cells hyperparathyroidism[11] . in based on the differential diagnosis, it should be emphasized that, whereas central giant cell lesions involve the central portion of the mandibular body and giant cell tumours rarely affected bone of the maxillomandibular complex, in cherubism the lesions are generally bilateral and involve both the maxilla and the mandible [9].

The radiographic techniques used for the detection the suspected cases of cherubism include a posteroanterior radiograph of the jaws orthopantomography and teleradiography[11]. Computed tomography is a most practical tool uses for the assessment of the damage caused by the process either during the analysis of disease progression or during surgical planning[12] .figure 4&5)

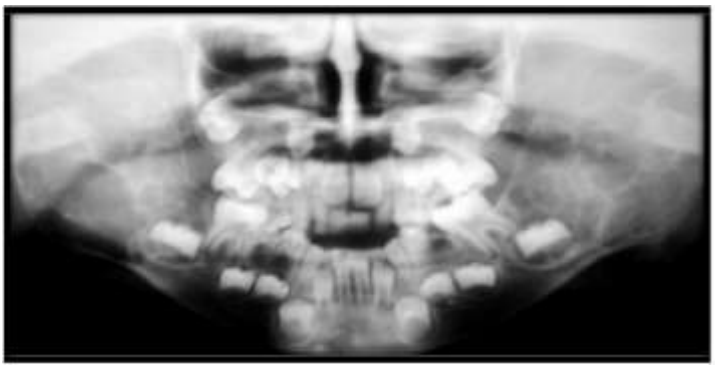

Figure 4 of the same patient as in Figure 2, bilateral swelling caused by expansion related to multilocular bone lesions of the angle and ascending ramus of the mandible and coronoid process.
.(http://www.ejomr.org/JOMR/archives/2010/2/e2/e2ht.htm)

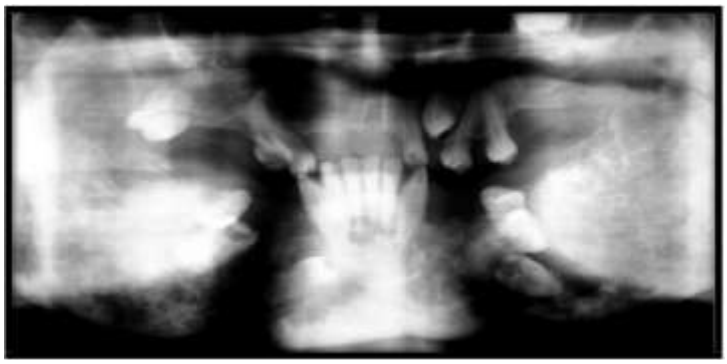

Figure 5 Orthopantomograph of the same patient as in Figure 3, revealing radiographic alterations characterized by greater radiopacity resulting from bone deposition and confirming the lack of involvement of the condylar regions. Note the malpositioning and retention of teeth.
.(http://www.ejomr.org/JOMR/archives/2010/2/e2/e2ht.htm)

Biochemical parameters

The Biochemical parameters limits to normal range but alkaline phosphatase levels might be elevated[13].A constant finding in these patients is the enlargement of submandibular and cervical lymph nodes[13] .

Cytogenetic And Molecular Genetic Findings/Chromosome Analysis

The point mutation in SH3BP2 gene detected by The western blot by which the particular protein or gene can be assessed, by utilizing chromosome examination As a part of this procedure, It utilizes gel electrophoresis to separate local proteins by 3-D structure or denatured proteins by the length of the polypeptide 14 and afterward will be identified the adjusted protein. (figure 6)

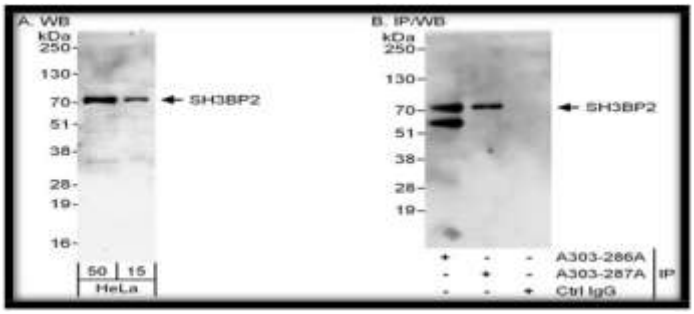

figure6 SH3BP2 mutation detected by using The western blot (http://www.bethyl.com/product/A303-286A/SH3BP2_Antibody)

Immunohistochemistry

Increased expression of **NFATc1** in giant cell lesions of the jaws, cherubism).[14]

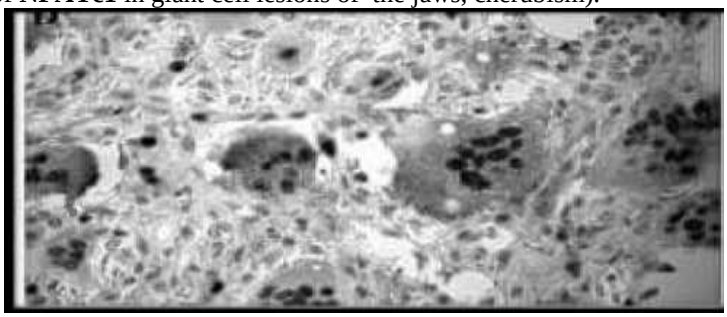

Figure 7 immunohistochemesrty expression of NFATc1 (original magnification, x400.

(https://www.spandidos-publications.com/ol/2/3/571)

TNF- □–positive and **CD14-positive** cells in human cherubism lesions[14].

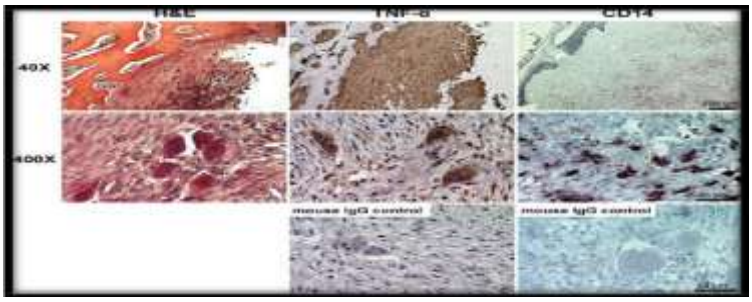

Figure 7 immunohistochemesrty expression TNF-α–positive and CD14-positive.
(https://www.researchgate.net/figure/263016214_fig9_Figure-1-TNF-a- positive-and-CD14-positive-cells-in-human-cherubism-lesions-HE-left)

Histopathology: The microscopic findings of cherubism are essentially similar to those of isolated giant cell granulomas, and they seldom permit a specific diagnosis of cherubism in the absence of clinical and radiologic information. The lesional tissue consists of vascular fibrous tissue containing variable numbers of multinucleated giant cells. The giant cells tend to be small and usually aggregated focally Like the giant cells in central giant cell granulomas, the giant cells in cherubism express markers suggestive of osteoclastic origin. Foci of extravasated blood are commonly present. The stroma in cherubism often tends to be more loosely arranged than that seen in giant cell granulomas15. In some cases, cherubism reveals eosinophilic, cufflike deposits around small blood vessels within the lesion. The eosinophilic cuffing describes to be specific for cherubism. However, these deposits are not present in many cases, and their absence does not exclude a diagnosis of cherubism. In older, resolving lesions of cherubism, the tissue becomes more fibrous, the number of giant cells less prominent, and new bone formation is seen15.

Figure 8 showing atypical histopathology of Cherubism. A histological section from a cherubism lesion demonstrates the typical finding of multinucleated osteoclast-like giant cells (arrows) near bone and within soft fibrous stroma. https://openi.nlm.nih.gov/detailedresult.php?img=PMC3359956_1750-1172-7-S1-S6-1&req=4

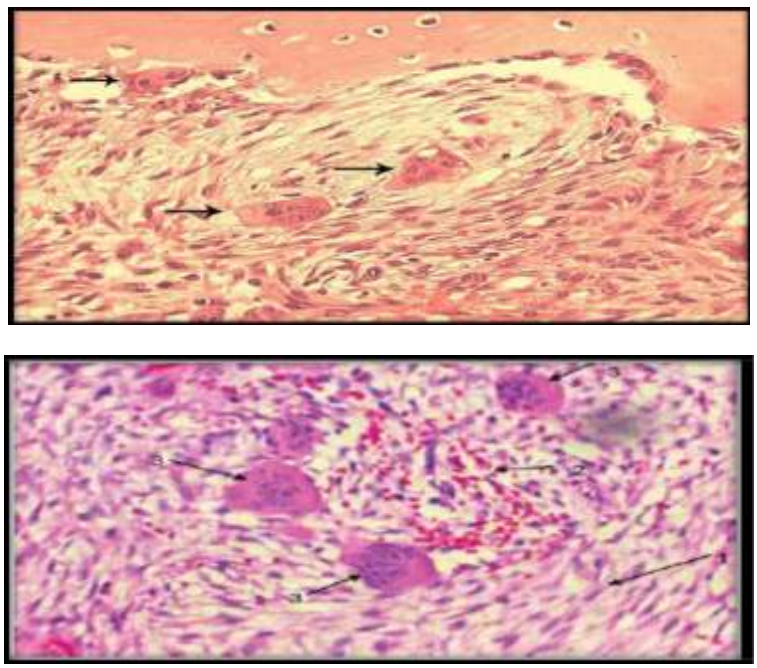

Fig-9: High power view showing the multinucleated cells, blood vessels .
(http://peir.path.uab.edu/library/picture.php?/12475)

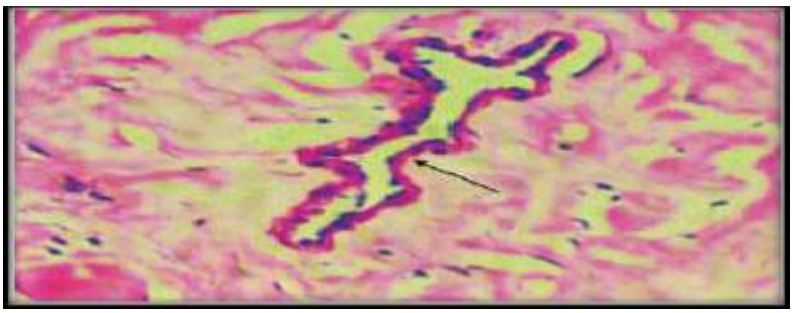

Fig 10 Perivascular eosinophilic cuffing seen in cases of cherubism (http://peir.path.uab.edu/library/picture.php?/12475)

II. Conclusion

Although the cherubism is a clinically well-characterized disease which observed to the appearance of a cherublike face; therefore, this derived the name of the disease. In cases of a suspicion or confusion of cherubism with other similar lesions as giant cell lesion so this parameter used in this review
it will summaries and help in perfect diagnosis. radiographic examination is essential since the clinical presentation and the site and distribution of the lesions may define the diagnosis. Histopathological examination is complementary. Nowadays, molecular tests should be used for final diagnosis of cherubism. Knowledge of the clinical and radiographic alterations and microscopic criteria observed in patients with cherubism is important since the dentist might be the first professional observed and diagnose of this disease

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