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AGGRESSIVE CHERUBISM: LONG-TERM CLINICORADIOLOGIC FOLLOW-UP AND A NEW CLASS PROPOSAL IN ITS GRADING

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ABSTRACT

Background: Cherubism is a rare autosomal dominant disorder characterized by fibrous tissue replacement of the bone at the mandibular rami and maxillary tuberosity.

Aim of the study: This study was conducted to assess the clinical and radiographical features of cherubism (familial and nonfamilial) during and at the end of the progressive period of the disease; and the relation between the grade and the clinical course of the disease.

Patients and methods: Five (3 males and 2 females) patients with an age range of 4-14 years at the time of diagnosis with cherubism were included in this study. The patients were graded initially and at the end of the follow-up period according to the grading system developed by Raposo-Amaral and were followed up clinically and radiographically for an average of 10 years.

Results: Two patients who were diagnosed at an early age and classified as grade VI cherubism, showed aggressive early manifestation of the disease. The patients who were diagnosed at elder age and had the same classification (grade I) showed mild course of the disease, one of these patients continued mild the whole period of follow-up with no changes in the grade and total improvement after puberty. The other patient became grade III with more enlargement of the mandible and involvement of the condyles.

Conclusion: The patients who initially present with minimal involvement should only be followed up regularly and those with severe function and/or esthetic affection should be strongly considered for surgery.

KEYWORDS: Cherubism; Follow-Up Studies; Aggressive; Clinical; Classification.

INTRODUCTION

Cherubism is a rare autosomal dominant related to mutations in the gene encoding the binding protein SH3BP2. Characterized by the presence of symmetrical soap bubble, expansile radiolucencies of the mandible. Affected children look normal at birth. The fibrous tissue expansions of the mandible and maxilla usually appear between 2 and 7 years of age, later the lesions increase in size until puberty,

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revert, fill with woven bone, and remodel until the age of 30. [1,2] Jones et al., a Canadian radiologist, first reported the disease (1933)[3] and defined the condition as a familial multilocular cystic disease of the jaws. However, shortly thereafter he suggested the term cherubism to designate the appearance of the patients due to their similarity to the cherubs in Renaissance art. [4]

In addition to facial deformities, other complications may present including vision loss, airway obstruction, and chewing difficulty due to changes in the development and appearance of teeth.[5] Tooth abnormalities found in cherubism patients may include agenesis, lack of eruption, ectopic impaction, displacement, and root resorption.[6]

WHO categorized cherubism in the group of benign osteo-fibrous lesions, distinguishing it from osteo-cementum lesions and fibrous dysplasia for its unique clinicoradiological features. [7] Grading system for cherubism suggested describing the location and severity of the lesions. The first system distinguished three grades[8,9]. Many grading systems developed with several subdivisions over the years. The grading system of Motamedi, [10] was simplified and added a 6th Grade to define the involvement of the orbits by Raposo-Amaral. [11]

Cherubism has a major influence on involved children and their families. Particularly in aggressive cases with a severe facial deformity and functional complications. However, the majority is self-limiting and needs no surgical intervention apart from longitudinal clinical and radiographic observation, which should continue into adulthood. The aim was to assess the clinicoradiological features of cherubism (familial and nonfamilial) and the relation between the clinical course and the grade of the disease on long-term follow-up.

PATIENTS AND METHODS

This observational longitudinal study included nine patients diagnosed with cherubism (3 females and 6 males). They were first examined in the period between January 2010 – December 2012 at Oral & Maxillofacial Surgery Department clinics, Faculty of Dentistry, Mansoura University. Patients were followed up clinically and radiographically for an average of 10 years. All patients were questioned about family history to determine the patients with a familial background. Clinical examination counted in; (1) Patient facial form. (2) Assessing the shape of the jaws buccally and lingually (normal or expanded) by clinically palpating jaws against the rest of facial bones. (3) Teeth status: normal or missed (either aplasia or surgical removal of ectopic impaction), malformed, or presence of root resorption, and (4) Submandibular lymph nodes examination and neck ultrasound was done when needed. [12]

Radiographic examination of bone structure: either (normal or the existence of multilocular radiolucencies or sclerotic) done by panoramic radiograph regularly and multislice CT scan at first diagnosis and the end of follow- up. The patients were graded initially and at the end of the follow-up period according to the grading system developed by Raposo-Amaral. [11] (Table 1) All patients did a biochemical analysis of serum calcium, phosphorus, parathyroid hormone, and alkaline phosphatase. Histopathology was done to verify the diagnosis by incisional biopsy or during postoperative routine procedures in seven patients; the other two refused the biopsy because their clinical features were not noticeable. No treatment was initiated for any of the patients; only minor surgical corrections were performed when needed. All patients included in the study signed informed consent and the ethical committee approved the study.

RESULTS

Results after 10 years of follow-up were available for five patients only as the others were not committed to regular follow-up visits. The patients (2 females, 3 males) were between 3 and 9 years of age at the beginning of clinical evidence of the disease (Table 2). With the mean age of 5.6

at the time of diagnosis. Family history revealed 3 familial cases; (two siblings and their cousin). Biochemical tests were normal for all patients, except (patient 4) who showed high alkaline phosphatase and serum phosphorus at initial presentation. Histopathological examination done for patients (1, 2, and 4) confirmed the diagnosis of cherubism; patients (3 and 5) refused to perform the biopsy. The disease expression varies greatly between patients, therefore facial appearance, tooth status, and radiographical bony changes were presented separately:

Patient 1: A 14 -year-old boy first presented to the department clinic at the age of 4. Family history was negative until 2 years after follow-up. At that time, the patient's younger brother was diagnosed with cherubism. No abnormalities were detected on physical examination. Extraoral examination showed the normal color of the face, painless bilateral symmetrical enlargement of the mandible, and no ophthalmic abnormalities. (Fig1: A) Intraoral examination presented intact and normally colored overlying mucosa, the mandibular alveolar ridge bilaterally had mild enlargement on the buccal and lingual sides, and the teeth in the upper and lower jaws were all present in normal alignment except tooth 72. Panorama and reconstructed 3D CT scan revealed multiple well-delineated multilocular cystic-like lesions with a thin cortical outline affecting the entire mandible, sparing coronoids, and condyles, and affecting maxillary tuberosities. Tooth buds of the lower anteriors were floating in a large radiolucent lesion in the anterior part of the mandible. (Fig1: B, C) Patient classified as grade II class1 cherubism.

At age 6, the teeth (16, 46) were unerupted and still in a high position. The left eye presented upward gaze and there was a slight retraction of the eyelids that caused exposure of the rim of the sclera below the iris. After 2 years, the enlargement in both jaws markedly increased. Panorama presented the involvement of both coronoids, agenesis of teeth (37, 47, 38, and 48). The maximum growth was between 8 and 10 years. (Fig1: D) At age 10, the mandibular lesions were curetted bilaterally in another institution. The lesion removal was more on the left side, resulting in a bad esthetic of the patient and an abnormal lower inferior border.

TABLE (1): Showing Raposo-Amaral cherubism-grading system (2007) with the addition of a new subdivision.

Grade I: Mandibular lesions without root resorption. (With 5 subdivisions)
Grade II: Lesions involving both jaws without root resorption. Class 1: the mandible and maxillary tuberosities are involved. Class 2: lesions in the mandible and anterior maxilla Class 3: the mandible and entire maxilla.
Grade III: Aggressive mandibular lesions with root resorption Class 1: one lesion in the mandibular body Class 2: multiple lesions of the mandibular body Class 3: one lesion in the ramus Class 4: multiple lesions of the mandibular rami Class 5: lesions involving the mandibular body and rami *Class 6: class 5 and may include the coronoid and condyle
Grade IV: Lesions involving both jaws with root resorption. (With3 subdivisions)
Grade V: The rare, aggressive, and deforming juvenile cases involving the jaws, and may include the coronoid and condyles.
Grade VI: The rare, aggressive, and extensively deforming juvenile lesions involving the jaws and orbits

**** New subdivision proposed by the authors***

During the 4 years of follow-up period after surgery, the patient had no relapse of the lesions. However, the patient and his parents were not satisfied with his appearance after surgery. The disease was still progressing in both jaws, more

in the maxilla at the right side. (Fig1: E) Dental abnormalities were; buccal displacement of upper teeth, dilacerations in teeth (13, 22), impacted (15, 24), resorption in (12, 14), and there was a high arched palate. The CT revealed marked expansion and distortion of both jaws causing encroachment on the orbital floor with bilateral proptosis, as well as maxillary sinuses and hard palate, with multiple bony defects. (Fig 1: F-I). Currently, the patient was classified as grade VI with the involvement of coronoids. (Table 3)

Patient 2: A 12 -Year-old boy was diagnosed at 4 years with grade VI cherubism. On physical examination, no abnormalities were detected. Extraoral, there was a painless bilateral symmetrical enlargement of the mandible. Eyes presented upward gaze and bilateral lower lid scleral show giving the patient the classic cherubic face. The submandibular and cervical lymph nodes were palpable. Intraoral examination showed intact and normal colored overlying mucosa; bilateral mandibular expanded alveolus buccally and lingually. Teeth in both jaws were in normal alignment with loosening of the lower posteriors on both sides. CT showed expanding multiloculated cystic lesions affecting the four-jaw quadrant. The expanding maxillary bones encroach on and obliterate the maxillary sinuses and on the inferior aspect of both orbital cavities. During the first two years of follow-up, the patient manifested rapid expansion of the bony lesions in both maxilla and mandible. Neck US showed multiple bilateral enlarged cervical lymph nodes with distorted shape and eccentric hilum.

At age 8, the lesional parts compressed on the orbital floor bilaterally were surgically removed. No palpable submandibular and cervical lymph nodes. From age 8 to 12, the mandibular expansion increased more on the right side. The stretching of the skin over the massively expanding bony lesions caused more exposure of the sclera below the iris. A large number of teeth were exfoliated in both jaws. CT scan of the patient showed soap bubble appearance lesions in the entire mandible except condyles, and in the entire maxilla, agenesis of

TABLE (2) Patients' gender, age at diagnosis, type of intervention, and follow-up period.

Patients	Gender	Age (yrs.)	Intervention	Follow-up period
1	Male	4	Biopsy, surgical removal of peripheral giant cell lesion, and curettage central lesions	10
2	Male	4	Biopsy, curettage of maxillary lesions compressing orbits.	9
3	Female	8.5	No intervention	10
4	Female	3	Biopsy, curettage of maxillary lesions Compressing orbits.	10
5	Male	9	No intervention	10

TABLE (3) patients' grading according to modified Raposo-Amaral grading system.

patients	Initial classification	Current classification
1	Grade II class1	Grade VI
2	Grade VI	Grade VI
3	Grade I class 4	Grade III class 6
4	Grade VI	Grade VI
5	Grade I class 4	Grade I class 4

teeth [37,38,47,48]. Most of the teeth were floating in the lesional spaces in the mandible. The patient grading did not change. (Table 3).

Patient 3: An 18-year-old female patient was diagnosed at the age of 8.5; the patient showed bilateral symmetrical mandibular swelling with the fullness of the face. Intraorally, all teeth in the upper jaw were normally aligned, whereas, in the mandible, tooth 74 was exfoliated. CT scan revealed markedly expansile osteolytic lesions involving both ascending rami and angles, encroaching upon the adjacent parts of the body on both sides with marked thinning of the overlying cortex and endosteal scalloping. Tooth 75 was floating in cyst-like spaces, and teeth (36, 46) still did not erupt and were deeply seated in the jaw lesions. Normal maxillary bone and clear maxillary antra. The patient was in grade I class 4. At the age of 10, the teeth (36, 37) were in position and there was more bilateral expansion at the mandibular angles. After puberty, the disease progression did not stop, but the rate was slower. Extraoral at the age of 18, the patient displayed asymmetrical expansion involving the whole mandible, large on both mandibular angles, and more on the right side. There was a slight discrepancy in the normal tooth eruption pattern with the extreme extension of the mucosa anteriorly. Panorama showed endosteal scalloping in both rami and root resorption in the lower incisors and tooth [43]. The patient was classified as grade III class 6, a new subdivision that was proposed by the authors in Raposo-Amaral classification because of the involvement of the condyles. (Fig 2) & (Table 1&3)

Patient 4: A 24-year-old female patient first presented to the department clinic at age 14 (after puberty), she was already diagnosed at the age of 3 in another medical institute. The family history was not contributory. From previous radiographs, the patient was classified as Grade VI. At the age of 7, the patient performed surgical removal of lesional parts compressing the optic nerve to relieve the pressure. Extraoral examination showed bilateral asymmetrical enlargement of the mandible and maxilla that was hard and non-tender on palpation and the facial skin was extremely stretched. Iris of the left eye was completely hidden under the upper lid and the patient can see only by the right eye. (Fig 3: a). The patient had tremors in her hands and head for 2 years and suffered from seizures caused by medications taken for the treatment of the tremors. Intraoral examination revealed massive alveolar enlargement and gingival hypertrophy in both jaws, incompetent lips with exposure of the maxillary ridge. The mandibular expansion resulted in a posterior displacement of the tongue.

CT of the maxillofacial bone showed an expansile, multilocular radiolucency with a soap-bubble appearance distributed in the whole mandible except the condyles. Maxillary bone markedly expanded and entirely obliterated the nasal cavity, the nasopharyngeal airway, paranasal sinuses, and encroached on the inferior wall of the orbits causing bilateral proptosis. Presence of pressure erosion of the entire outer cortex in both jaws. (Fig 3: b, c)

Panorama could not be used in regular follow-ups because of the huge size of the mandible and tremors of the patient's head, therefore multislice CT scans were used instead. At age 16, there was more increase in the mandibular expansion bilaterally, the hard palate was completely obliterated by the lesions, and the upper anterior teeth were more displaced. At age 19, the patient reached a stationary phase with no active growth. At 20 to 24, the size of the swelling was stable. Intraorally still were massive gingival and alveolar enlargement bilaterally in the mandible, new eruptions, and exfoliations of the anterior teeth in both jaws. (Fig 3:d,e,f) CT presented cortical reossification in the mandible and maxilla. Large areas of patchy sclerosis were present in the whole mandible. (Fig 3: g, h) Patient grading at the end of the follow-up period was unchanged.

Patient 5: A 20-year-old male patient examined at age 9 complained of bilateral mandibular swelling and unerupted posterior teeth. Extraoral, there was

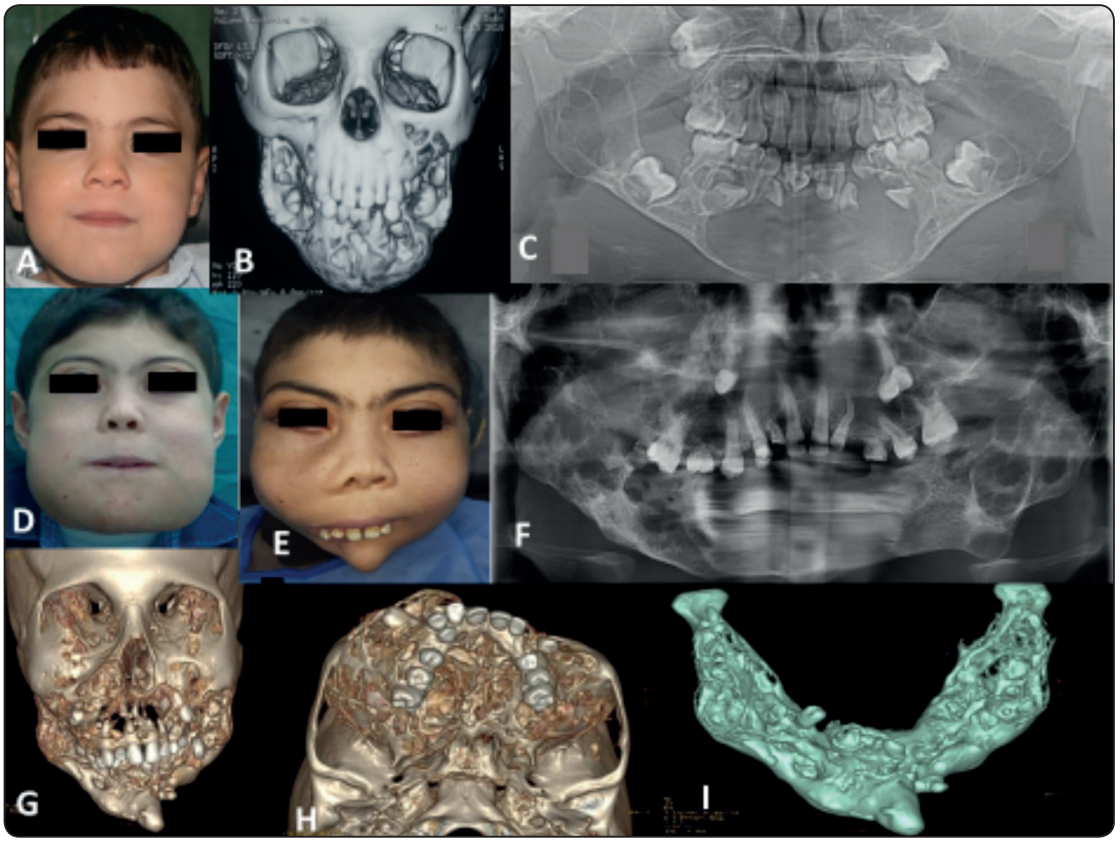

Fig. (1) (A-I): (A) Clinical (B) Reconstructed 3D-CT (C) Panoramic views for (patient 1) at age 4 showing bilateral mandibular swelling, multilocular radiolucent lesions involving the entire mandible (sparing coronids and condyles), and involving maxillary tuberosities and orbital floor. (D) Patient at age 10 showing large bilateral mandibular swelling before curettage of mandibular lesions, (E) Current clinical (F) Panoramic (G, H, I) Reconstructed 3D-CT views of the patient at 14 years showing a massive increase in maxillary expansion more in the right side, and involvement of coronoid processes.

a mild swelling on the left side; skin color was normal, and no ophthalmic abnormalities. Intraoral examination showed intact and normal colored overlying mucosa, teeth in the upper jaw were normally aligned, and in the mandible, teeth 36 and 46 were unerupted. CT of the maxillofacial bone showed an expansile, multilocular radiolucency with a soap-bubbles appearance in both rami and angles. The patient was classified as grade I class 4 with no change in grading at the end of the follow-up period. The mandibular expansion continued slowly until puberty and then regressed at age 17 with total improvement in facial appearance without any surgical intervention.

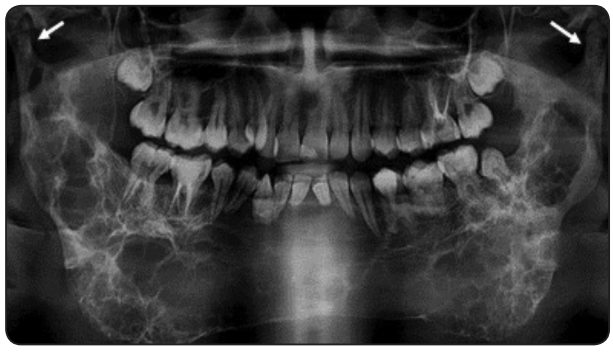

Fig. (2): Panoramic radiograph of (patient 3) at age 18 showing multilocular radiolucencies at both mandibular rami, angles, and anterior part. Root resorption in teeth (31,41,43). Involvement of the condyles (arrows).

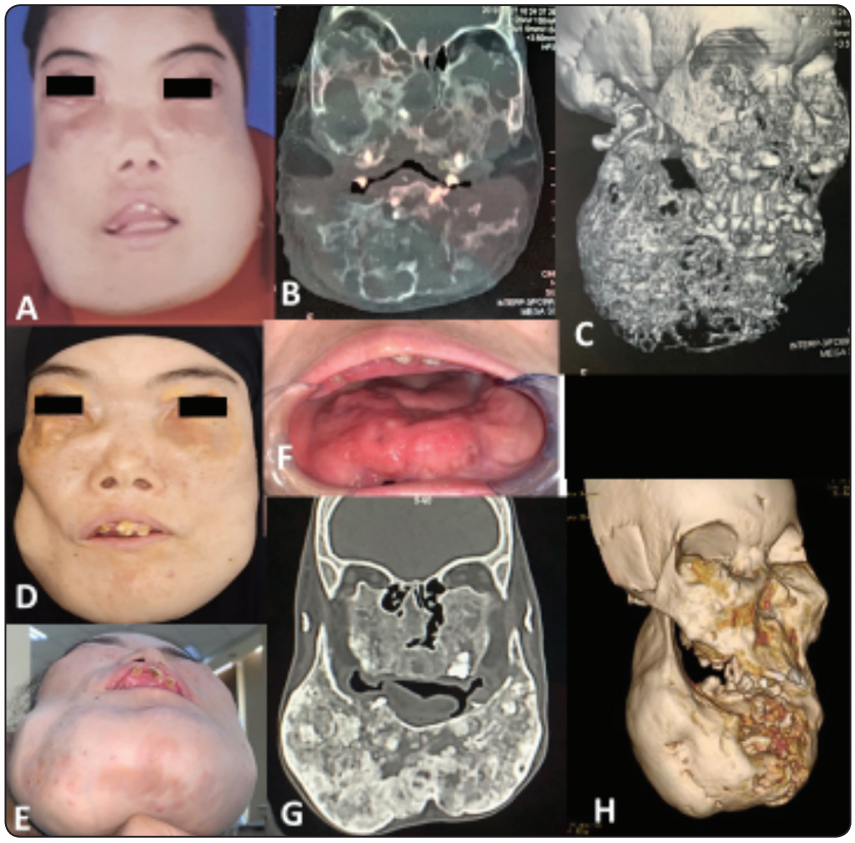

Fig. (3) (A-H): (A) Clinical (B) Frontal CT (C) Reconstructed 3D-CT views of (patient 4) at age 14 showing bilateral mandibular swelling and eyes to heaven appearance. Multilocular radiolucent lesions extension and pressure erosion in both jaws' cortex and encroachment on orbital floor. (D, E) Clinical (F) Intraoral current views at age 24 showing persistent huge mandibular swelling, gingival hypertrophy, and backward tongue displacement. (G) Frontal CT (H) Reconstructed 3D-CT showing patchy sclerosis in large areas of both jaws, nearly complete reossification of outer cortex.

DISCUSSION

Cherubism is a rare, autosomal dominant genetic condition. Progressive painless bilateral enlargement of the jawbones characterizes the disease. The natural history of cherubism varies according to severity. Typically, clinical or radiographic findings are not apparent until the age of 14 months to three years of age. The severity and clinical expression of the disease range from no clinical manifestations to distressingly deforming mandibular and maxillary overgrowths that can affect vision, airway, and speech.

Clinically, all patients had symmetrical swelling in the mandible at the beginning of the disease. Three cases showed diffuse maxillary involvement; that caused the 'eye-to-heaven' appearance. Two of these cases presented this appearance early at the age of 4, whereas the third case was at 10. These findings were similar to several reports that showed severe cases of cherubism, in which the fibro-osseous lesions in the maxilla extend into the inferior and/or lateral orbital walls. [13-15] Different degrees of malocclusion and abnormal dentition were found in all patients; like early loss of deciduous teeth, unerupted, displaced, dilacerated, or absent permanent teeth. The teeth may have a floating appearance on the radiograph as in a study by Suhanya et al. al. [16] and the same as presented in three of our patients (1, 2, and 4).

The biochemical markers are usually within normal range, so they might help to distinguish cherubism from hyperparathyroidism, in which all markers are raised. Alkaline phosphatase and serum phosphorus levels were elevated in patient 4 at the time of initial presentation. However, this is predictable in young age persons. (Kaugars et al.)[17]assumed that the deviations might be due to the patient's inability to consume a normal diet.

Radiologically, CT scan results showed total bony reossification and normal radiographic appearance in (patient 5) at the age of 20, comparable to a study by Papadaki et al.[1] Also showed patchy sclerosis in large areas of both jaws and nearly complete reossification of the outer eroded cortex in (patient 4), but still with the characteristic cherubic appearance at the age of 24.

Seward and Hankey, [9] suggested a grading system for cherubism that has been used in several studies and added with some subdivisions in other studies.[18-20] Raposo-Amaral, [11] presented a clinical classification of VI degrees of disease expression, this classification was the closest to describe our patients' state. However, we proposed a modification to this classification by adding a new subdivision in Grade III, where class 6 was added, the same as class 5 plus involvement of coronoids and/or condyles.

The more early the lesions appear, the more rapidly it progresses as evident in three of our patients diagnosed early at age 3 and 4 years, two patients (2 and 4) were grade VI aggressive cherubism from initial diagnosis till the end of the follow-up, while the third (patient 1) was grade II class 1 and developed to grade VI. Clinically presented as massively growing and extensively deforming expansion with eyes raised to heaven's look. Radiographically, justified by the severe extension of the bony lesions in the mandible and maxilla, perforation of wide areas of the bony cortex, involvement of the orbits, and root resorption. Two of these patients (2 and 4) underwent surgical curettage of maxillary lesions affecting the orbits and vision before puberty like Ricalde et al.[21] who stated that surgical intervention should be done in individuals who have local aggressive lesions associated with complications. The grade often increases on follow-up examination, as observed in (patient1 and 3). Patient 3 was Grade I class 4 at the age of 8.5, then progressed to Grade III class 6 cherubism at the end of the follow-up period. Clinically evident as mild symmetrical bilateral mandibular swelling that progressed without remission until early adulthood to severe bilateral asymmetrical swelling at the right mandibular angle. Radiographically, there were perforations and disruption in large areas of the mandibular cortex, marked root resorption in the lower anteriors, and involvement of the condyles in accordance with many studies. [18-23]

Patient 5 was Grade 1 at age 9 and presented mild progression until puberty, regression at 17, and improvement without any residual deformity at the age of 20. This finding was parallel to a study by Meng et al., [23] who indicated that reaching the normal state is faster in patients of Grade I than those of higher grades.

The duration of the active process of bone destruction varies between affected individuals; follow-up results showed progressive bony destruction in patients (3 and 4) after puberty until early adulthood, unlike most cases that regress without intervention after puberty. [24-26] However, post-pubertal actively expanding lesions were also reported. [27]

Management of cherubism should be according to the disease natural course and clinical behavior of the individual cases. Curettage in the mandibular lesions that was done for (patient 1) before puberty, achieved good results as no relapse in the bony lesions was noticed. This result was consistent with other reports [11, 23, 28] and in contrast with some authors who stated cases in which surgery during the rapid growth phase should be avoided due to quick relapse. [29-32]

CONCLUSION

The wide presentations of cherubism make it difficult to find a treatment protocol suiting all. Therefore, patients, who initially present with minimal involvement as grade I should only be followed up regularly and those with severe function and/or esthetic affection should be strongly considered for surgery even in the progressive period of the disease.

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