Cherubism: A Case Report with Surgical Intervention

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Abstract. *Cherubism is a rare benign, autosomal-dominant hereditary fibro-osseous condition predominantly affecting the jaws. Symmetrical cyst-like expansions of the jaws cause the characteristic facial swellings. The disease is often associated with severe malposition of teeth. The gene for cherubism is src homology 3 binding protein 2 (SH3BP2) located on chromosome 4p16.3. The repeated experience of this self-limiting disorder in affected individuals published in the medical literature has resulted in a wait-and-see strategy regarding therapeutic options. Indeed, cessation and regression of even large bone expansions can be expected in early adulthood. Nevertheless, severe facial disfiguring and functional impairment can make surgical intervention necessary. This report details the surgical procedures carried out in a patient with progressive and disfiguring jaw expansions at the end of adolescence, the mutation of SH3BP2 gene, and the limited effect of surgically assisted orthodontic tooth movement in a patient with disease-associated impaired tooth development and tooth eruption.*

Cherubism is a rare benign, autosomal-dominant hereditary fibro-osseous condition predominantly affecting the jaws (1-3). The term 'cherubism' was introduced by Jones (1-3) and refers to the characteristic painless osseous extensions to the orbit causing a scleral show and the impression of an upward-directed look, similar to the facial appearance of angels as illustrated on Baroque style paintings. However, mandibular cherubism is more frequent than maxillary (4). Until recently, differential diagnosis of cherubism from other expansive jaw lesions was difficult (3, 5). For example, consensus on differential diagnosis of fibrous dysplasia and cherubism was difficult to achieve prior to the genetic characterization of both entities (6).

Recently, cherubism was ascribed to the src (sarcoma) homology 3 binding protein 2 (*SH3BP2*) gene on chromosome 4p16.3 and recognized as a genetically defined entity distinguishable from other lesions of the jaw (7-9). The tumorous expansion can give rise to extensive facial malformations. However, the entity is considered non-neoplastic (4). On radiographs, this entity is characterized by areas of predominantly symmetrical cyst-like radiotransparency, preferentially affecting the mandibular angles and ramus (10). Histologically, the space-occupying jaw lesions represent giant cell granuloma (GCG) (11).

It is generally accepted that cherubism is a self-limiting disease starting in early childhood (4). In the third decade of life, signs of involution of the tumour-like lesions can be expected (4, 11). Therefore, many authors suggest a wait-and-see policy and seek to move away from surgical intervention in affected individuals (10, 12). However, severe jaw malformation can have a heavy impact on physical functions, and social and psychological development in children and adolescents, and therefore can force an early decision on ablative surgery in such cases (13-15), with reported exceptions to this strategy indicating the reluctance for bone surgery even in severely expansive lesions of the jaw (16). A further indication for locally restricted surgical intervention is severe malposition and retention of teeth in order to allow orthodontic treatment (11, 17). This report details the surgical treatment of a patient with cherubism with growth spurts of the granuloma during puberty.

Case Report

Medical history and radiology. A 7-year-old boy was admitted to the Department of Oral and Craniomaxillofacial Surgery, Hamburg University Hospital, for treatment of cyst-like lesions visible on pantomogram. His parents reported to have noticed their son's full cheeks from early childhood (Figure 1A and B). This impression was substantiated by

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Key Words: Cherubism, giant cell granuloma, *SH3BP2*, jaw tumour, bone tumour, jaw surgery, immunohistochemistry, mutation analysis.

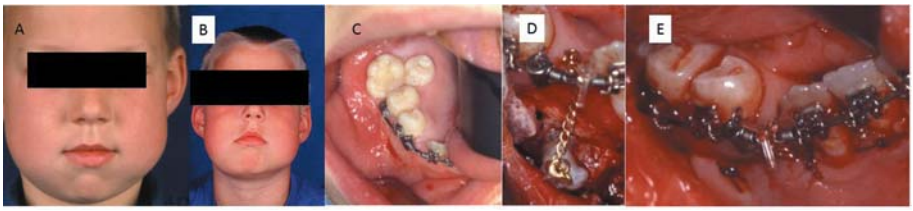

Figure 1. *En-face photograph of the patient at the age of 10 years (A) and 13 years (B), with characteristic swelling of the cheeks. Oral findings showing malposition of erupted permanent teeth (C) and surgical-orthodontic preparation to perform upward movement of the right inferior canine (D, E).*

photographs of the patient taken in his first years of life. His facial appearance had changed to having very prominent chubby cheeks during the preceding months. Furthermore, he had noticed bony protrusions of the mandible. He exhibited a mixed dentition, with no molars appearing in the oral cavity. On the pantomogram, large osteolytic lesions were found to be affecting the mandible and the ramus, angle and molar/premolar region exhibited extensive cyst-like osteolytic zones. The condyles were not affected. No tooth germ of wisdom teeth was present and all molars were partially or completely retained. Figure 2 shows representative radiographs taken during the course of treatment.

Surgery. It was decided to obtain a bone biopsy to establish the diagnosis. Intraoperatively, after exposing the right vestibular side of the mandible, the egg-shaped osseous boundaries of the cystic lesions comprised of a soft, immediately disintegrating and bleeding, dark-red granulomatous tumour. After taking a biopsy of this region, the wound was closed by primary intention. Healing was uneventful. Tissue samples were fixed in buffered formalin and sent for histological analysis to the Department of Pathology. After establishing the diagnosis of cherubism, we refrained from further interventions, expecting a self-limiting bone alteration. The patient was advised of the need for regular follow-up and consultative orthodontic support.

At the age of 10 years, the permanent mandibular first molars still had not penetrated the alveolar mucosa and had to be surgically exposed to allow for orthodontic treatment. This procedure had to be repeated for the right lower first molar a few months later. No further surgical intervention was performed and the lower first molars erupted into the oral cavity, despite root distortions. Five years later, at the age of 16 years, the deeply displaced right lower canine was surgically exposed to allow the fixation of orthodontic devices (Figure 1C-E). During the follow-up, the expected cessation and re-ossification of the osteolytic mandibular lesions did not occur. Indeed, the lesions exhibited radiological progression and the lower face showed further disproportional growth. Additional computed tomograms disclosed a predominance for the mandible to be affected compared to the maxilla (Figure 2D). In the maxilla, widened periodontal spaces were noted in the molar regions.

At the age of 17 years, mandibular cystic lesions were excised *via* an oral route. After vestibular mucoperiostal incision reaching from the right second molar to the left first premolar, GCG was scraped from the bubble-like cavities. Intraoperatively, the mandibular nerve was infiltrated by tumorous tissue and the continuity of the nerve had to be microsurgically reconstructed.

At the age of 18 years, a submental approach was chosen to reduce recurrent extensive cystic lesions of the mandible due to rapidly recurring facial swellings.

At 19 years of age, again operative reduction for recurrent bone tumour was performed and additionally a Le-Fort-I osteotomy was chosen to reduce sinusal tumour. The osteotomy was extended to three-piece maxilla to adjust the contour of the hypoplastic maxilla to the reshaped mandible and to close the open bite. Segments were fixed with miniplates and monocortical screws. Orthodontic treatments for upper right first molar, lower right canine, and lower right first molar were judged to be have been ineffective. These teeth were extracted. Six months later, the osteosynthesis plates were removed. At that time, the pantomogram disclosed a marked re-ossification of the mandible (Figure 2G). The maxillary segments showed complete reunion. A biopsy of the maxillary sinuses revealed chronic sinusitis without evidence of GCG. Healing was uneventful in all surgical procedures.

Histology, immunohistology and genetics. The specimen of the cyst-like tumour proved to be solid lesions with typical findings allowing the diagnosis of GCG in all samples. Histological investigation of the extracted and displaced right lower canine with adjacent soft tissue revealed a GCG adhering to a tooth unaffected by GCG.

The tumour cells were immunoreactive for CD68 and CD163, but negative for S-100, actin, CD1a, CD34, β-catenin, p53 and B-cell lymphoma 2. Mitotic activity in terms of Ki67 labelling index was low. Genetic analysis

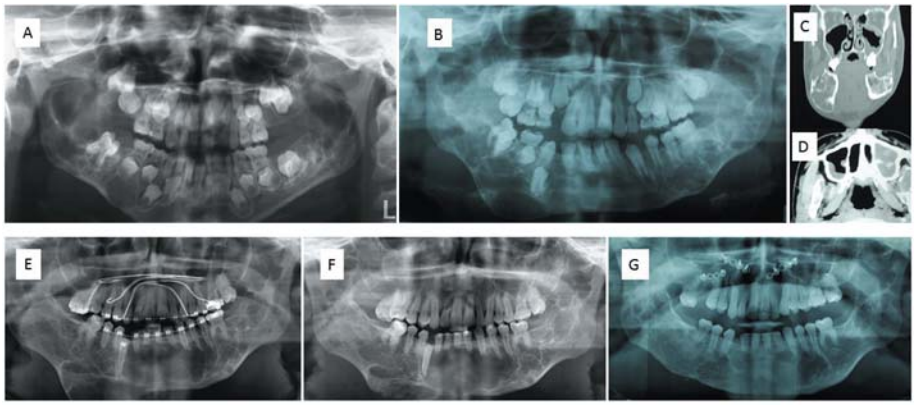

Figure 2. *Radiographs depicting the facial skeleton of the patient at 7 (A), 11 (B, C, D), 17 (E), 18 (F), and 19 (G) years of age. Pantomograms show the jaw alterations over time. The mandible is more affected than the maxilla. Early radiographs also show bilateral expansions of the dorsal parts of the maxilla (A) that are not visible any more at the age of 17 years (E). A, B, D-G: In the ramus, the condyles were excluded from osteolysis throughout the period of observation, but radiotransparency and loss of contour was very advanced in both coronoid processes. At the age of 19 years, some contouring of the coronoid processes had occurred (G). The anlage of the right lower canine is displaced inferiorly (A) and extrusion of the completely developed tooth failed (E-G). Note the exaggerated growth of the right anterior side of the mandible directed caudally (D). After repeated osteotomy, the anatomically re-shaped contour of the basal mandible remained stable (G).*

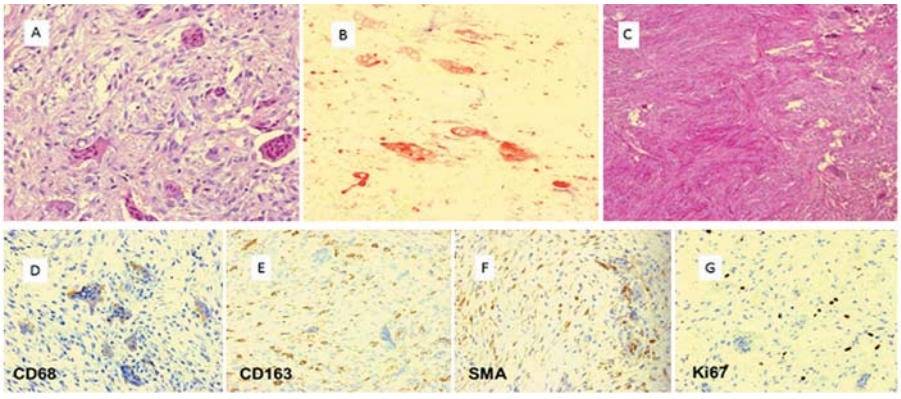

Figure 3. *Histology and immunohistochemistry of giant cell granuloma in cherubism. A: Microscopic analysis showed fibroblastic proliferation with multinucleated giant cells with no atypia. B: The giant cells exhibited positive reaction to tartrate-resistant acid phosphatase, demonstrating their osteoclastic nature (hematoxylin-eosin). C: Focal regions exhibited dense collagen fibres and appeared to be somewhat less cellular (elastica van Gieson). Immunohistochemical analyses were performed: antibody against CD68 highlighted osteoclasts (D), antibody against CD163 identified intralesional mature macrophages (E), antibody against smooth muscle actin decorated myofibroblastic characteristics of some of the lesional fibroblasts (F), and antibody against Ki67 revealed the low proliferative activity of the lesion (G) (magnification, ×200).*

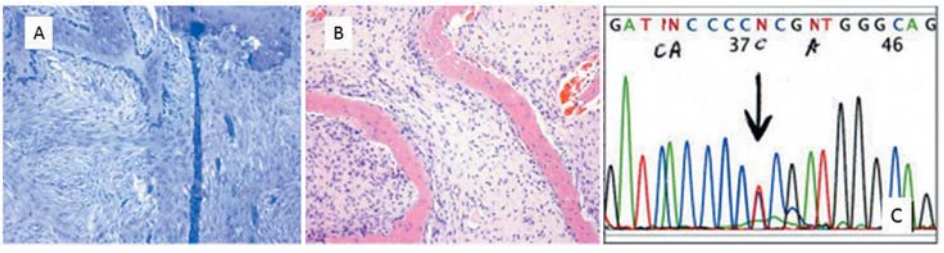

Figure 4. *Bone trabeculae adjacent to the giant cell granuloma in cherubism shows seams of activated osteoblasts and a lack of Sharpey-like collagen fibres (A) (toluidine blue) when compared to fibrous dysplasia (B) (toluidine blue) (magnification, ×100). The mutation of the src homology 3 binding protein 2 (SH3BP2) gene on 4p16.3 is depicted in (C).*

confirmed a mutation in exon 9 of *SH3BP2* gene showing a missense mutation (c.1253C>T) in codon 418 resulting in a substitution of proline to leucine (p.P418L). Histochemical staining and immunohistochemical findings are shown in Figures 3 and 4.

Discussion

The report details the temporary effect of surgery on the external appearance of an individual affected by growth spurts of cherubism during adolescence and the limited effect of orthodontic tooth movement of retained teeth in close proximity to osteolytic jaw lesions. However, the temporary relief from excessive bone extension and consequent deformation was judged to be worth the interventions. The close association of cherubism with tooth development was obvious in this case. However, it remains speculative whether this condition could be traced back exclusively to anomalies of dentition (10). The genetic event is related to cells arising in the jaw bones in the strict sense and not to odontogenic progenitor cells (7-9). Furthermore, extracranial manifestations of lesions similar to the GCG in cherubism have occasionally been reported (5). Surgical therapy has to be individually tailored and should not create unrealistic expectations. The scale of Seward and Hankey (18) with modifications is used for estimating the severity of cherubic bone alterations and expectations concerning the natural course of the lesions (19). According to this classification the patient was suffering from second-degree cherubism (without cherubic lesions of the anterior maxilla). The circumstances that paved the way to diagnosis of cherubism have rarely been reported. Some reports describe a situation where the patient could not bear their appearance as a reason to seek surgical relief (13). On the other hand, the number of cases which are incidentally diagnosed following routine dental radiographs detecting typical jaws lesions is probably high (20).

There are several reports on surgery for cherubism (11, 17, 21). It is generally accepted to refrain from surgery for cherubism due to the experience of self-limiting jaw growth in this condition (5). In addition, the phenotype can vary widely and it is believed that many patients with cherubism exhibit only mild effects on their facial appearance by expanding jaws or can even have normal facial proportions (22). Furthermore, the cherubic appearance of patients is expected to be reduced impressively due to involution of the bubble-like distensions of the jaws in early adulthood (5). However, a recent follow-up study on adults with a history of cherubism called this belief into question (19). In fact, this study described a high rate of jaws with regions of deformed bone and altered bony structure in adults with cherubic phenotype. The findings were restricted to the anterior mandible (19). Persisting radiotranslucency in patients with cherubic phenotype had already been reported by Zachariades *et al*. (23) and mild bone expansion persisting over long periods of time was also already known (11). Significant correlations were calculated for the relationships between the grade of cherubism and the maximum buccal bone expansion and for the age of normalization of affected bone (11). Nevertheless, the altered bony structure recognized as such may not be the actual indication for surgery, rather the change of self-perception of patients, in particular during phases of bone growth, is a crucial factor in deciding for surgery. Furthermore, the self-reflection of the patient about how others perceive their altered face and the experience of "looking ridiculous" (13, 24) has to be considered in the decision-making for surgery. Indeed, facial disfigurement is an accepted indication for surgery (5). Severe forms of cherubism presenting an aggressive course with impaired swallowing or breathing self-evidently require surgical intervention (13-15, 21). However, even extensive bone growth in cherubism may not necessarily be accompanied by breathing impairment (13). Nevertheless, reports on surgical procedures show that measures are predominantly confined to excochleation of the soft-tissue lesions entirely filling the vesicular osseous distensions. Eventually, the bone is trimmed to achieve a nearly anatomical shape (17), as was also performed repeatedly in the present case.

Curettage and more conservative surgical measures were the dominating procedures in reports based on larger clinical studies (11, 21) and are recommended in notifications of expert centres (5, 9, 11). Surgical interventions should not necessarily be postponed until after puberty (21), but this attitude is still not generally accepted (12). Extensive reduction of the soap bubble-like expansive bones is not recommended in order to avoid pathological fractures (13). Furthermore, bony islands are needed as centres of re-ossification following curettage. Debulking procedures may necessitate tracheostomy (14), but not regularly (13). Access to the bone may require extra-oral incisions in cases with very extensive jaw lesions, in particular in order to control bleeding (13). The mandible is preferentially affected in cherubism, however, the name-giving facial aspect is caused by maxillary lesions (5) and is characteristic, but not pathognomonic (25). Some authors prefer a two-stage procedure in patients affected in both jaws, reducing the granuloma and expansive bone separately in one jaw at each operation (26), but the superiority of this procedure has not been confirmed by others up to now.

In a population-based longitudinal study, none of the surgically treated patients who underwent minor procedures experienced enhanced active growth of lesions (11). On the other hand, occasional reports of rapid regrowth after surgery (23, 27) has moved some authors to question the indication for minor surgical interventions (12). In individual cases, it

remains speculative whether surgery truly induced tumour progression or whether surgery was performed in a patient becoming symptomatic in a phase of growth spurt that continued after surgery. Indeed, we assume from the present case the extraordinarily strong growth rate after puberty and emotional distress of the patient to be the main causative factors for recurrent surgical therapy in adolescents.

Orthognathic surgery. Orthognathic surgery can be performed in adolescents to correct severe skeletal deformities of the jaws in cherubism (28). This procedure is technically demanding and screw-retaining bone might be very difficult to find adjacent to the osteotomy lines in patients with concurrent osteolytic zones. However, permanent bone healing and stable positioning of jaws was achieved at least in one reported case (28). One genioplasty was also mentioned (11) and in the list of procedures mentioned in the report on cherubism treatment published by Meng *et al*. one case of osteoplasty was noted, without further specification of the procedure (21). In the present case, Le-Fort I osteotomy was performed to adjust the jaw relationship. The histological investigation of soft-tissue samples of the maxillary sinus did not reveal GCG. However, at that age, the patient did not have a midfacial swelling.

Implant dentistry. Restoration of the dental arch by means of insertion of dental implants into the affected bone was occasionally reported in an adult, underlining the principal ability of this bone to be equipped with hard tissue resistant to the occlusal forces impinging on an implant-supported prosthesis (29). Dental implants as a means of restoring chewing function were already described by von Wowern (11), but no information about the permanence of this reconstruction was reported. In the latter case, depicting a severe mandibular hypodontia and functional edentulism on adequate radiographs from the age of 15 and 23 years, respectively, implant dentistry was started in the fifth decade of the patient's life. These cases indicate the uncertainty as to when and how to allow functional loading of the jaws in cherubism. On the other hand, a population-based study revealed five patients with implant-supported prosthetic reconstructions, including one case with implant failure (17). These authors also reported on implant insertion into multilocular radiolucent regions but did not stress the success rate of these implants inserted at recipient sites usually at risk of losing implant retention (17). Furthermore, onlay bone grafting combined with implant dentistry proved to be successfully applied in one adult patient with cherubism (30).

Hypodontia. Missing teeth are a characteristic finding in cherubism (11). The permanent molars are preferentially affected (11), as also found in the present case. However, hypoplasia was not very distinct in our case. Indeed, hypodontia does not necessarily affect the chewing function (11) but the number of patients who are in need of prosthetic restorations in early phases of life is high (17). In this period of life, the dental findings requiring prosthetic treatment are very likely to be related to a disease-associated lack of permanent teeth, or to teeth positions unsuitable for functional integration into the tooth arch (17).

Tooth transplantation. Resorption of dental roots after tooth transplantation in a case of cherubism occurred many years after transplantation and were judged unlikely to be related to the bone disease (11). In another case of successful tooth transplantation in cherubism, the follow-up period of 2 years appears to be too short to allow for a definite conclusion on the success of tooth preservation in the new jaw region (31).

Orthodontic treatment. Reports on orthodontic treatment for cherubism are sparse (11, 22). Orthodontic treatment anterior to the lesions was reported to be successful in two cases (11). A further case report described the successful appliance of orthodontic devices to extrude a retained lower second molar that verged on the distal portion of the tooth to the granuloma of the mandibular angle (22). On the other hand, the eruption of teeth may be delayed but not necessarily impossible, as seen in the eruption of the mandibular molars in the present case. However, debulking of jaw lesions covering retained and dystopic teeth may be inefficient at provoking eruption of teeth, even with orthodontic devices, and eventually tooth extraction cannot be avoided (11). This decision had to be made in the present case, after long-lasting application of extruding forces on the retained right lower canine. In the present case, root resorption of mandibular incisors was evident and related to the disease. Maintenance of teeth was achieved by applying adequate orthodontic support after curettage of the anterior lesions.

Oral soft-tissue lesion. Oral mucosa usually remains intact but occasionally, oral ulcer can occur caused by oral tumour extension and occlusal bone pressure (12).

Adjuvant therapy. Pharmacological treatment in cherubism is not advocated (5). Intralesional calcitonin treatment gave inconsistent results (5). Radiotherapy is not a therapeutic option (5); development of osteosarcoma was reported in a case of cherubism subjected to radiotherapy of the jaw (11).

Histology. Biopsy of the cystic bone lesions may be essential in establishing diagnosis (20, 21). Indeed, in our opinion, diagnosis of cherubic jaw lesions requires expert histological confirmation (25). Furthermore, molecular genetic analysis in suspected sporadic cases of cherubism may be necessary in order to rule out central GCG, a sporadic disease of

unknown aetiology, occasionally occurring with multilocular mandibular lesions (12, 14). In this situation, histological and radiological features may be insufficient to allow these entities to be distinguished (17). As can be derived from larger studies, the referral of patients for surgery points to a generally accepted need for surgical exploration in order to clarify diagnosis: 22/24 in Norway (17), 14/17 in China (21), and 18/18 in Denmark (11). However, current guidelines claim histological verification of the lesion to be unnecessary, with reference to the characteristic radiological findings (5). This assessment is on the one hand convincing and may reduce the diagnostic burden on affected individuals, in particular children. On the other hand, it is well known that cherubic phenotypes can be mimicked by other jaw tumours that require extensive surgical intervention (25) or other therapeutic strategies (32). Eosinophilic vascular cuffing was reported to be a characteristic but not obligate finding in soft-tissue specimens in cherubism otherwise diagnosed as a central GCG (5, 12, 33). In the present case, the immunohistological findings support the microscopic diagnosis addressing the content of the cyst-like jaw lesions as GCG.

Genotype/phenotype correlation. At present, no genotype to phenotype correlations are known for cherubism. In addition, further mutated genes might be involved in the establishment of the phenotype (5, 9). The SH3BP2 mutation in this sporadic case is known in familial cherubism (17) but evidence for mutation of this gene in sporadic cases appears to be limited using both blood samples and tissue (17).

Conclusion

Cherubism is a self-limiting bone disorder with preference for foam-like bone hyperplasia preferentially affecting the jaws. Surgical intervention may be necessary to relieve patients from an unsightly appearance.

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