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Cherubism – new hypotheses on pathogenesis and therapeutic consequences

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SUMMARY. Aims: The hereditary occurrence of cherubism indicates a probable genetic aetiology: a correlation with a mutation in the gene SH3BP2 has been demonstrated. A convincing concept of formal pathogenesis is not yet available. The study was aimed at advancing the understanding of the pathogenesis of cherubism by presenting a case study including genetic findings and an evaluation of the literature. Results and conclusion: Because of its association with the development of the second and third molars, cherubism could be defined as a genetically determined alteration of tooth development. In this context, disturbed PTHrP – PTHrP receptor interaction induced by the mutation in SH3BP2 is discussed. The temporal and spatial determination of the clinical symptoms is explained by an interaction of SH3BP2-dependent signal transduction pathways with jaw morphogenesis (e.g. Hox-gene Msx-1). Because of the disease-induced lack of determination of the cap phase of the second and third molar, a spatial compartmentation, which is necessary for normal dental development, does not take place. This leads to dysregulation of mesenchymal bone building tissue areas, and to the development of giant cell granulomas with high osteoclastic activity.

Because of the genetic determination of cherubism and the associated dedifferentiation of the diseased tissue, a surgical removal should be exclusively restricted to specific indications. Therefore an attitude of wait and see is preferred. © 2004 European Association for Cranio-Maxillofacial Surgery

Keywords: Cherubism; Pathogenesis; SH3BP2; MSX1; Giant cell granuloma

INTRODUCTION

Cherubism – first described by Jones (1933) – received its name because of the angel-like appearance of the patients (chubby and upward directed look). The disease is attributed to an osteopathy also involving odontogenic dysplasia of the jaw bones, a form of fibrous dysplasia of bone and a giant cell granuloma (Burland, 1962; Hoppe et al., 1966). Occasionally, the disease is referred to as cherubism syndrome, since alterations in other bones may occur. It is generally accepted that it is a benign, in most cases hereditary, disease of bone, beginning at the age of 2 or 3 years, progressive in childhood, with a peak at the age of five, and showing spontaneous regression at the end of adolescence.

The diagnosis of cherubism is based on clinical, radiographic and histological findings. The clinical findings are:

- familial occurrence,
- characteristic alterations of the face, with pronounced bilateral involvement of the jaws in early childhood,

- high arched palate and missing second and third molars,
- a cyclical course,
- indolent lymph node swellings,
- spontaneous arrest or regression after adolescence,
- no involvement of the temporomandibular joint.

From a radiographic point of view, a multilocular, cystic, symmetrical expansion of the upper and lower jaws is seen. Computerized tomography shows honeycomb-like lesions of the mandibular cortical bone, with concomitant repair in the mandibular angle area. In the upper jaws, the tuberosity area is affected, with occlusion of the maxillary sinus and elevation of the orbital floor sometimes.

The histology is of limited diagnostic significance. Fibrous hyperplasia and a large number of multinucleated giant cells are noted. Pseudocystic structures are noted especially in the repair phase. The differential diagnosis of cherubism consists of fibrous dysplasia, giant cell granuloma, osteosarcoma, juvenile ossifying fibroma, fibrous osteoma, odontogenic cyst, hyperparathyroidism (Hoppe et al., 1966). Therefore, in addition to the typical histological

features, the bilateral involvement of the jaws, as well as the typical course, and the familial occurrence of the disease are required for a diagnosis of cherubism (*Haunfelder, 1967*). Reports on cherubism without a familial occurrence (*Sitzmann, 1973*) or beginning at the age of 10 (*Hoyer and Neukam, 1982; Opitz and Wittstock, 1990; Pulse et al., 2001*) or immediately after birth (*Mangion et al., 1999*) should be viewed sceptically. By classification three degrees of severity are distinguished (*Fordyce, 1978; Motamedi, 1998*).

The familial occurrence of the disease has been and is still the subject of intense investigation. *Talley (1952)* and *Andersen and McClendon (1962)* showed that two-thirds of the families affected had two or three successive generations affected. In seven families, the diseased members affected one line of siblings only. The authors concluded an autosomal dominant inheritance with 100% penetrance in men and 60 – 80% in women.

Mangion et al. (1999) and *Tiziani et al. (1999)* showed that the gene region responsible for cherubism is located on chromosome 4p16.3. The clinically conspicuous disturbance in osteogenesis and a possible relation to tooth development, as well as the location of the gene in an interval between D4S127 and the telomere of 4p, led to the hypothesis that the genes *FGFR3* and *MSX1*, located in this area, are causative for this disease. Finally, in a larger study, *Ueki et al. (2001)* found mutations in the gene for the SH3-binding protein *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.

Although the genetic cause of cherubism appears to have been identified, an accepted concept for its formal pathogenesis is not available yet. Therefore, it is the aim of this work to advance the understanding of the aetiology and pathogenesis of cherubism. A case study including molecular genetical findings as well as a synopsis of the literature will be presented.

CLINICAL REPORT

A male patient was referred to this department for the first time at the age of 2½ years. There was swelling at the level of the (maxillary) tuberosity on the right side. During the following 3 years, a swelling became noticeable on both sides, especially in the intermaxillary region between the jaws. A high arched palate associated with open bite developed (Fig. 1A,B). A non-painful submandibular swelling of lymph nodes existed on both sides. The most prominent swelling was reached at the age of 5. On orthopantomographs in the 3rd and 8th years, pseudo-cystic alteration, mainly of both the ascending rami of the mandible was noted. The condyles were not affected (Fig. 1C). The 2nd and 3rd molars

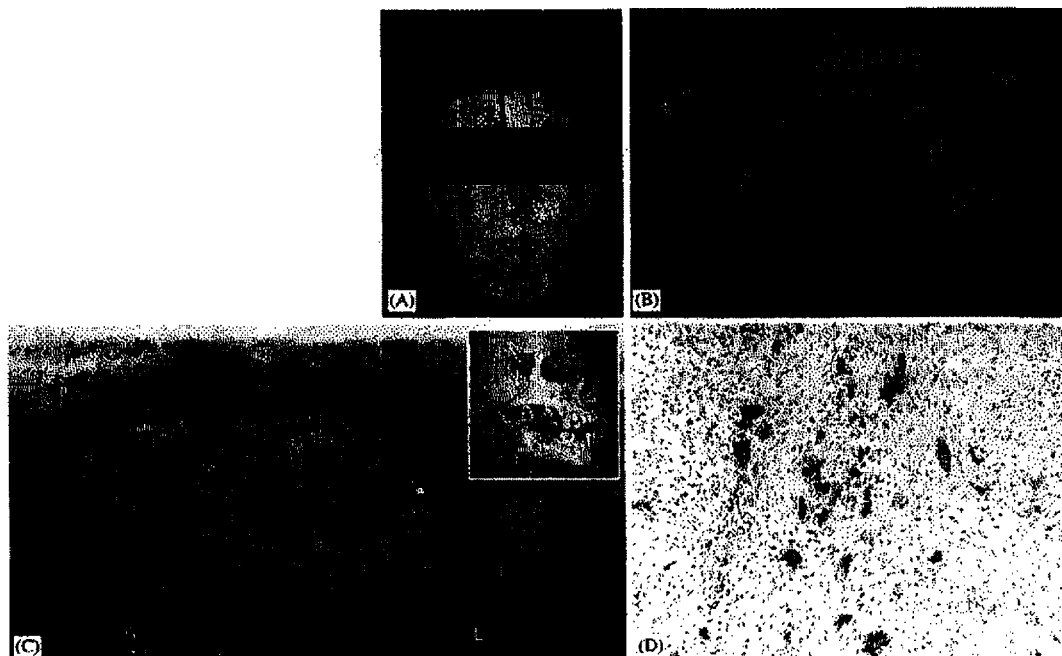


Fig. 1 – A 5-year-old male patient suffering from cherubism: a swelling on both sides, especially of the mandible (A), high arched palate associated with open bite (B); radiograph and CT scan (inset) at the age of 8: extensive pseudo-cystic osteolysis on both sides mainly of the angle of the mandible (C); light microscopy: primarily fibrohistiocytic tissue with multinuclear histiocytic giant cells (D).

never developed. The distal root of the first molar in the left lower jaw was completely resorbed.

To rule out spontaneous fractures, computed tomographic scans were undertaken at ages 5 and 10. CT aspects of skull development of this patient have been published already by *Schleier et al.* (2003). The maxillary sinus was completely occluded on both sides; there was no displacement of the orbital floor and no evidence of a fracture in the mandible. In the ascending ramus and the region of the tuberosity, extensive osteolysis was visible bilaterally (Fig. 1C inset).

Between ages 6 and 10 (annual reviews), the high-arched palate flattened out, and the radio-opacities completely regressed. The patient has been under orthodontic care since the age of 7 years.

At present (aged 12), a tendency for regression was noted, with persistent mandibular swelling and with concurrent growth of the jaws. The open bite was treated successfully by the orthodontists. After establishing the diagnosis based on clinical, radiological, and histological findings, no surgical therapy was performed according to the recommendations of the DÖSAK (German – Austrian – Swiss Registry of Head and Neck Tumours).

FAMILY HISTORY

The father of the patient had suffered familial bilateral giant cell "tumours". In his case, the treatment was conservative. The family history was negative regarding his parents and siblings. The case report of the father was published by *Waurick* (1977). At present, there are no visible pathological changes in the facial profile. On the orthopantomograph only the teeth 43 and 44 were present in the mandible with tooth 44 exhibiting a deformation of the root. The maxilla was edentulous. Both upper and lower jaws were severely atrophic.

HISTOLOGY

Histological processing of tissue samples collected at ages 6 and 11 in connection with primary diagnosis and orthodontic care showed fibrohistiocytic tissue with inclusion of multinuclear histiocytic giant cells. The giant cells were thinly disseminated throughout the fibrous tissue, but did not determine the histological pattern. Immunohistochemical demonstration of tartrate-resistant acid phosphatase (TRAP, antibody clone 26E5; Novocastra Lab. Ltd, UK; Chem Mate™ Kit, Dako, Denmark) revealed the osteoclastic character of these giant cells (Fig. 1D). Histopathology of the specimen obtained from the child at the age of 11, when compared with the specimen at age 6, showed a distinct regression of the tumour. The pseudo-cystic changes are now predominant.

CYTOGENETIC AND MOLECULAR GENETIC FINDINGS/CHROMOSOME ANALYSIS

Cytogenetic and molecular genetic studies were performed using chromosome preparations obtained from cultured peripheral lymphocytes. Chromosome preparations as well as GTG (*G-bands by trypsin using Giemsa*) and CBG (*C-bands by barium hydroxide using Giemsa*) banding were performed according to standard methods described by *Verma and Babu* (1995). In each chromosome preparation, 15 metaphase plates were evaluated. Analysis of the chromosomes revealed a male karyotype (46, XY, 1qh+) in both father and son, without any pathological finding.

FLUORESCENCE IN SITU HYBRIDISATION (FISH)

Fluorescence in situ hybridisation (FISH) was performed according to *Liehr et al.* (1995). For specific demonstration of the chromosome region 4p16.3, the LSI WHS Wolf-Hirschhorn microdeletion probe (LSI WHS region SpectrumOrange/CEP 4 SpectrumGreen, control probe, alpha satellite DNA) was used. As the result of the evaluation of 25 metaphase plates, a deletion in the WHS region 4p16.3 was not evident in father or son (normal karyotype ish 4p16.3 (WHS × 2)).

QUANTITATIVE AND QUALITATIVE ANALYSIS OF MSX-1 EXPRESSION IN PERIPHERAL BLOOD, TOOTH BUD, AND TOOTH FOLLICLE AS WELL AS IN THE GIANT CELL GRANULOMA

For demonstration of expression of the *Msx-1* gene in the patient, total RNA was extracted from peripheral blood using the Total RNA Kit (Qiagen, Hilden, Germany). It was transcribed into cDNA and *Msx-1* expression was analysed by means of polymerase chain reaction (PCR) using primers based on the gene bank sequence of *Msx-1/Hox-7* (Acc. No. M97676). As control for cDNA integrity as well as for semi-quantitative estimation of *Msx-1* expression, beta-actin cDNA was also amplified. PCR analysis revealed that cells from peripheral blood of the patient expressed *Msx-1*. *Msx-1* mRNA could also be demonstrated in the control sample (father of the patient). The tissue samples available for examination, namely, from tooth bud, tooth follicle, and giant cell granuloma, were incubated in RNA lysis buffer (Qiagen, Hilden, Germany) overnight on ice, in order to obtain optimal digestion of the samples. RT-PCR revealed a low level of *Msx-1* mRNA in all samples examined; hence there was no evidence for a lack of expression of *Msx-1*.

SEQUENCING THE SH3BP2 GENE

DNA was prepared from blood samples of father and son. As all mutations known so far were localized in exon 9 of the *SH3BP2* gene, only this exon was sequenced. Sequencing was performed using the ABI Prism-BigDye-Terminator Cycle Sequencing Ready Reaction Kit and exon 9 specific PCR primers on the sequencing machine ABI 3700 (both from Applied Biosystem, USA) as recommended by the manufacturer.

The heterozygous mutation 13369C>A (exchange of cytosine (C) by adenine (A) at position 13369) could be demonstrated in exon 9 of the *SH3BP2* gene of both patients. This mutation causes incorporation of the amino acid histidine (CAC) instead of proline (CCC) at amino acid position 418 of the protein.

DISCUSSION

Cherubism as a result of a disturbance in dental development

Although Jones assumed as early as 1965 that cherubism was an odontogenic lesion, where the growth pressure exerted by dental germs, or exaggerated deciduous tooth resorption were supposed to play a role, a directly odontogenic cause is currently considered as unlikely. Burkhardt and Berthold (1986) have examined the tissue taken from a boy afflicted with cherubism using light and electron microscopy and immunohistology. They found a close relationship with giant cell granuloma of the jaws.

Because cherubism is a location-stable phenomenon found only in the jaws with multiple occurrences, a structure-associated process is a very likely link to the pathogenic mechanism. Conspicuous in this respect is the regular development of giant cell granuloma in all quadrants of both jaws in the area of the molars. In cherubism patients, the second and third molars are also missing. In addition, the cyclic course of the disease is closely linked to the normal development of the second and third molars: The incidence is coincident with the beginning of second molar mineralization (at the age of two or three). Spontaneous regression during adolescence is at the normal conclusion of molar odontogenesis. Furthermore the eponymous symptom of cherubism, the skyward directed gaze, can be explained by excessive tissue formation in association with molar development: The dental germs of the second molars are located rather high in the tuberosities at the age of 2–3 years. Looking at developmental biology, further facts with relevance to understanding cherubism are clear. Thus, the second and third molars are the only dental germs not completely developed at birth. Furthermore, the histological alterations in cherubism only affect structures of the first branchial arch. Considering both the temporal and spatial associations of the clinical course of cherubism with

development of the second and third molars, it may be justified to speculate that the underlying genetic defect of cherubism is disturbing normal development of these teeth and is dysregulating the associated bone formation.

What are the relations between SH3BP2 and dental development?

The patient presented here fulfils the classical and very stringent diagnostic criteria of cherubism with respect to inheritance, physiognomy, radiography, histology and clinical course. In this respect, the finding of a heterozygous mutation in exon 9 of the *SH3BP2* gene matches the earlier results of Ueki et al. (2001). Their hypothesis that cherubism originates from this genetical alteration was confirmed in the case presented. *SH3BP2* was originally described as a tumour suppressor gene with respect to bladder cancer. To date, it is known as a regulator protein of the c-abl oncogene (Bell et al., 1997). Because of its specific domain structure, it is thought to have a role in signal transduction.

So far, however, there is no idea of how *SH3BP2* interferes with regulation of dental development. An explanation of such regulatory action can perhaps be deduced from the genesis of giant cell granuloma, which occurs in other diseases, too, and is important for differential diagnosis. In this respect, true giant cell tumours must be differentiated as well as the so-called brown tumours found in hyperparathyroidism (Van Damme and Mooren, 1994). The latter appear to be induced by a dysregulation of parathormone signal transduction. It may be assumed that the giant cell granuloma-like proliferation in cherubism originates from a similar disturbance in this signal transduction pathway. In fact, it is possible to conclude from a small number of published results of an influence of *SH3BP2* on the regulation of the receptor for parathyroid hormone (PTH) and PTH-related protein (PTHrP): *SH3BP2* interacts with the chaperone protein 14-3-3 (Foucault et al., 2003), which recently was described as a regulatory protein of the type I PTH/PTHrP receptor (Tazawa et al., 2003). Current investigations suggest that the PTHrP – PTHrP receptor interaction is of fundamental importance for the spatio-temporal organisation of bone cells and their osteoclastic function in normal development of the tooth germ and the surrounding alveolar bone, as well as in the dentition (Philbrick et al., 1998, Wysolmerski et al., 2001, Mekaapiruk et al., 2002, Kitahara et al., 2002).

Moreover, the formation of signal transduction protein complexes, or the regulation of non-receptor tyrosin kinases (src, abl) through the src-homology sequences SH2 and SH3 are a fundamental component of eukaryote signal transduction. Increasingly, adaptor proteins are described (e.g. RIN1, 14-3-3), which can, through an SH-based interaction, also serve as a linker to Ras-dependent signal transduction pathways (Han et al., 1997; Wang et al., 2002;

