

CASE REPORT

Cherubism: a case report

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Abstract

Cherubism is a familial benign fibro-osseous disease of the jaws. On radiography, the lesions exhibit bilateral multinuclear radiolucent areas. Histopathology reveals multinucleated giant cells in the background of proliferating fibrous connective tissue. Mutations in the SH3BP2 gene are identified as the cause of cherubism. A 12-year-old girl with prominence of the lower face was investigated. Her chief complaint was her facial appearance with asymmetrical swelling of the cheeks. Clinical and radiographic examinations, and biopsy, biochemical analysis and genetic investigations were performed.

Keywords: mandibular enlargement, cherubism, genetic heterogeneity.

Introduction

Mandible consists of two equal halves, which normally develop symmetrically. The two halves of the mandible ossify in the midline of the mandible during the second year of life. The great varieties of mandibular anomalies depend on the very complex growth mechanism of the mandible regulated by specific combination of genetic and non-genetic factors [1]. Most patients with cherubism have germline mutations in the gene encoding SH3BP2, an adapter protein involved in adaptive and innate immune response signaling. The more complex the formation of a structure, the more opportunities for abnormality. Misregulation of mandibular growth leads to anomalies of the mandible’s size, morphology and position in the craniofacial skeleton creating functional and esthetic problems. Mandibular enlargement is often part of a disease or syndrome and occasionally can occur isolated. We describe the case of a 12-year-old girl with prominence of lower face. Marked chubbiness of the face arose as result of mandibular enlargement found to be in association with other symptoms such as facial lentiginosities, short stature, broad chest, bone marrow hypoplasia, thrombocytopenia and autoimmune myxedema. The patient presents signs and symptoms, which overlap with other conditions having different etiologies and treatments. The combination presents some diagnostic challenges. Previous studies have not found similar association of symptoms. Our aims were to find out the cause of mandibular deformity and to avoid misdiagnosis and inappropriate treatment.

Materials and Methods

The research was conformed to the ethical guidelines of the Declaration of Helsinki, on the principles for medical research involving human subjects. Written

informed consent was obtained from patient’s parents. Written informed consent was obtained from the patient’s parents for use any accompanying images.

Family study and clinical examination

A direct interview and examination of all available relatives of the patient were carried out. Information concerning present or past symptomatology of the family members was collected. Extra-oral and intra-oral examinations were performed too. Radiological examination was required in this case.

Biopsy and histological examination

Biopsy was performed to establish histopathological diagnosis. An incisional biopsy was done removing a sample of bone tissue from the left mandibular angle. After the biopsy specimen was obtained, it was sent to histological examination. Hematoxylin and Eosin (HE) staining procedure was used. We used a Nikon Eclipse E200 microscope with 10×, 20× and 40× magnification objectives. Images we captured using a Nikon Coolpix L28 digital camera.

Conventional karyotyping

Peripheral blood samples were cultured using overnight and synchronized culture and processed by conventional cytogenetic procedures with GTG banding. In each case, at least 20 metaphases were analyzed and the karyotypes were described according to ISCN 2013 (*International System for Human Cytogenetics Nomenclature*).

DNA samples and molecular analysis

The blood sample was collected by venipuncture in a vacutainer with EDTA. The blood sample was processed for genomic DNA extraction using Wizard[®] Genomic DNA Purification Kit according to the manufacturer

recommendations (Promega, USA). Molecular analysis consisted of PCR amplification and direct sequencing of exons 3, 4 and 9, an intron–exon boundaries of SH3BP2 gene harboring all variants reported to date [2]. The reference sequence and exon numbering are according to GenBank accession number NM_003023.4 with the A of the ATG start codon on position 1.

Results

A 12-year-old girl is the only child to non-consanguineous parents with low socio-economic status. She attends normal school. Her chief complaint was facial appearance with swollen cheeks, round and asymmetrically full lower face. In August 2012, the patient was referred by her pediatric endocrinologist to the Department of Oral and Maxillofacial Surgery for surgical evaluation and treatment (if necessary).

Family study

There was no family history of prominent facial swelling or similar disorders in first or second-degree relatives of affected girl. The disorder seems to be occurred sporadically within the family. Both parents were healthy.

Clinical findings

Review of patient's medical history revealed significant findings. The child was normal at birth. Physically and mentally development was normal until the age of 3, when mother noticed a slowly growth in stature and weight of her daughter. Medical investigations revealed an autoimmune myxedema. Best results were obtained after administration of replacement therapy with Levothyroxine. At that time, additional hematological abnormalities were reported such as hypoplastic bone marrow and thrombocytopenia. Long-term follow-up has been recommended and patient was monitored regularly during treatment for hematological abnormalities. At age 4, the patient had enlarged submandibular lymph nodes and was diagnosed as epidemic parotitis. The girl's mother reported that the onset of facial deformity was unusual, first presented with unilateral swelling then developed bilateral but asymmetric. The girl was about 7-year-old when facial swelling became apparent. The enlargement slowly progressed to its present size. Facial asymmetry has gradually become more evident. The girl was concerned about her facial appearance becoming anxious and low self-esteem. She stated that "her face does not look like other children". Extra-oral head and neck examinations revealed fullness of the lower face, painless enlargement at the angles of mandible, bilateral swelling but right side was more prominent than the left side (Figure 1), no evident enlarged lymph nodes under mandible. Skin pigmentation as dark-freckles was found on middle face but not on scalp or neck. Except painless swelling of the lower face and facial freckles, unremarkable features were reported: no ocular abnormality, normal ears and neck. Speech, mastication, swallowing, vision and breathing were generally within normal limits.

Intra-oral examination revealed normal soft tissue of the mouth, normal tongue, normal palate and no delayed eruption or missing teeth. Poor occlusion was noted. No extension of the swelling in the mouth was observed.

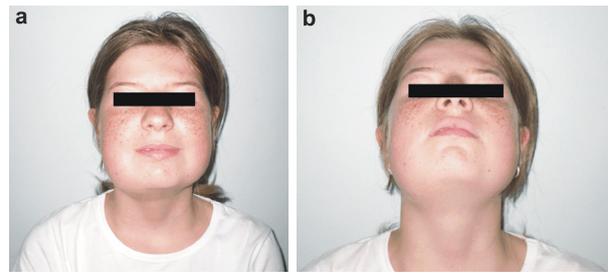


Figure 1 – Facial appearance (a – frontal and b – submental images) showing asymmetrical swelling of the cheeks caused by unequal mandibular enlargement (the right side is more prominent than the left one).

Radiological findings

Panoramic radiograph showed clearly that the facial enlargement is the result of abnormal bone pattern in the mandible. Radiological examination revealed bilateral multilocular radiolucent areas within the bone. The lesions are restricted to the angle and body of mandible (Figure 2). Maxilla was not involved.



Figure 2 – Panoramic radiograph revealing radiolucent lesions (white arrows) in the mandible (no involvement of the maxilla).

Biochemical markers such as calcium, phosphorus and alkaline phosphatase were within normal limits.

At the time of examination no mental retardation, no abnormalities of skin and hair, no cardiovascular anomalies and no other bones or joints were affected.

Biopsy and histological changes

Histological examination reported the replacement of the normal bony structure with fibrous tissue containing a reduced number of multinucleated giant cells scattered in a fibrovascular stroma of nuclear spindle-shaped cells (Figure 3). Hemorrhagic areas, few macrophages, deposits of hemosiderin, small vessels are lined by endothelial cells and eosinophilic collagen perivascular cuffing were identified too. Six months after the initial biopsy the patient course seemed to be stabilized. Histological findings are not distinctive for any benign giant cell tumor of the jaw [3]. So, it cannot be diagnosed by histology alone [4]. Not all authors share the same opinion [5].

Conventional karyotyping

Chromosome analysis test showed a normal karyotype female (46,XX).

DNA samples and genetic testing

No DNA variants that could contribute to the phenotype were identified in the SH3BP2 gene by sequencing (benign variants are not reported). However, this result does not exclude SH3BP2 variants as variants outside of

the analyzed region or variants not detectable by sequencing might be present.

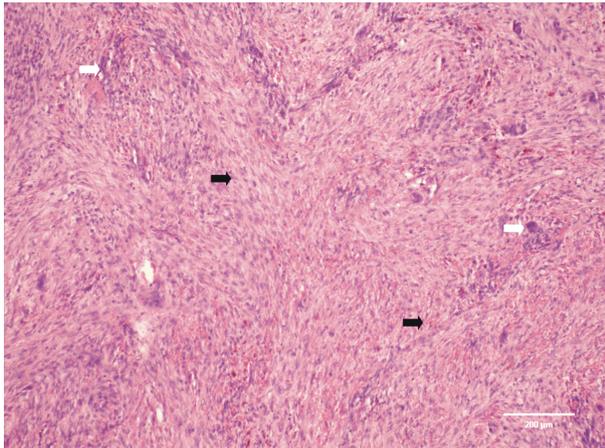


Figure 3 – *Histological examination: multinucleated giant cells (white arrows) randomly distributed in a fibrovascular stroma of nuclear spindle-shaped cells (black arrows) (HE staining, $\times 100$; Scale bar represents 200 μm).*

Discussion

The patient expresses a less severe clinical phenotype with common and occasional findings for some bone disorders with mandibular deformity involvement. None of these features is pathognomonic for any condition mentioned below. Enlarged face due to swelling of the mandible/maxilla is a common finding in cherubism [6, 7] but has also been found in association with Noonan syndrome with multiple giant-cell lesion syndrome [8, 9], Ramon syndrome or neurofibromatosis. Moreover, jawbone lesions with multinucleated giant-cells are also described in central giant-cell granuloma and fibrous dysplasia. All these conditions form part of differential diagnosis creating potential management difficulties [10]. We carefully excluded one by one, separately, some of the mentioned conditions based on comparisons between our results and those from literature review. Noonan syndrome (NS) is clinically and genetically heterogeneous. In excluding Noonan syndrome (NS) we relied on the lack of key features such as ocular (the most common features of NS) and cardiovascular anomalies, and later childhood typical facial appearance [11–13]. Short stature (common feature in NS), lentigines (uncommon feature in NS but also seen in Leopard syndrome – syndrome allelic to NS caused by different missense mutations in PTPN11, a gene encoding the protein tyrosine phosphatase SHP-2 located at band 12q24.1), thrombocytopenia and auto-immune myxedema (uncommon features in NS) are positively correlated with NS [14]. Genetic testing was considered but literature review shows that knowledge of the phenotype can help to predict the likely causative gene [15]. PTPN11 mutations (50–60% of patients with NS) express pulmonary stenosis, short stature, pectus deformity, factor VIII deficiency and typical face [16, 17]. SOS1 mutations (10–15% of patients with NS) cause multiple ectodermal features but normal growth and intelligence [16]. RAF1 mutations are correlated with hypertrophic cardiomyopathy [18]. KRAS mutations are associated with short stature and severe mental retardation

[17]. BRAF and MAP2K1 mutations are associated with more severe cardio-facio-cutaneous findings [19]. All these genes are known to be involved in the Ras/MAPK (mitogen-activated protein kinase) signal transduction pathway. Ramon syndrome, which is characterized by short stature, intellectual disability, and gingival fibromatosis, was excluded too [20, 21]. The patient presented no major criteria of Ramon syndrome except short stature.

Fibrous dysplasia was excluded too based on clinical findings: benign giant-cell lesions localized asymmetrically in the maxilla rather than the mandible. Moreover, patients with cherubism have a prominent number of multinucleated giant cells, which are rarely seen in fibrous dysplasia [22].

Central giant-cell granuloma might be considered but radiological findings facilitate the differential diagnosis. The lesions in case of cherubism are multilocular whereas in central giant-cell granuloma the lesions are unilocular [23, 24].

In order to diagnose the case, we correlate clinical degree of the disorder, radiographic and histopathological findings of the lesion, genetic testing results, course of the disease and literature review. Failure to find out relevant clinical findings associated with NS, Ramon syndrome or other similar disorders and our previous experience [25] suggested that the case was to be diagnosed with cherubism. Additional clinical features of the patient could be occasional in this case. Furthermore, the patient presented only mandible involvement, stabilized facial course and did not show mental retardation or a well-characterized pattern of organ involvement. SH3BP2 gene is the only one in which mutations are currently known to cause cherubism [2, 23, 26, 27]. Molecular genetic testing is appropriate for diagnostic confirmation if the clinical findings do not meet clinical and radiological diagnostic criteria. Molecular genetic testing did not identify any SH3BP2 mutation. Failure to identify a SH3BP2 mutation in 20% of affected individuals suggests possible genetic heterogeneity [26].

Follow-up was recommended with regular medical checkups in order to identify any change of patient's disorders evolution.

Conclusions

Based on patient age and details of clinical, radiographic and histological findings cherubism was suspected. Gene testing confirmed the absence of a mutation in SH3BP2 gene. Failure to notice suggestive clinical findings associated with other genetic disorders and the review of the literature indicated that the case was to be diagnosed with cherubism.

Acknowledgments

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Author contribution

All authors contributed extensively to the work presented in this paper. All authors discussed the results and implications and commented on the manuscript at all stages.

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