An atypical case of craniometaphyseal dysplasia. Case report and surgical treatment

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Summary

Introduction. **Craniometaphyseal dysplasia is a rare hereditary bone disease presenting metaphyseal widening of the tubular bones, sclerosis of craniofacial bones and bony overgrowth of the facial and skull bones. Craniometaphyseal dysplasia occurs in an autosomal dominant (AD) and an autosomal recessive (AR) form.**
Case report. **We present a 32-year-old patient arrived at our unit in May 2009. His main discomfort was a major limitation of the mouth opening, in the context of a craniofacial deformity. Relying on patient's medical history and the performed diagnostic tests, the diagnosis of craniometaphyseal dysplasia was made.**
Conclusion. **After careful evaluation of the clinical case, in accordance with the requirements of the patient, we opted for a surgical treatment aimed at correction of functional limitation of temporomandibular joint and aesthetic improvement of the facial bones. The stability of the clinical results led us to suggest and to undertake the surgical path, also due to the lack of safe and consolidated non-surgical treatments for the specific case.**

Key words: craniometaphyseal dysplasia, ANKH, CMD.

Introduction

The term "osteochondrodysplasia" includes a group of uncommon genetic disorders of bone remodeling, which are characterized by an increased skeletal density. Some of these disorders are relatively ordinary; others, that are less common can also be lethal. Initially, this heterogeneous group of diseases was grouped under the generic term of "*marble bone*" or Albers-Schonberg diseases. From the critical analysis of Gorlin, Spranger and Koszalka (1969), according to the Paris nomenclature, constitutional disorders of bone can be broken down into four subgroups: Osteoscleroses, Craniotubular dysplasias, Craniotubular hyperostoses, Miscellaneous sclerosing and hyperostotic disorders. Craniometaphyseal dysplasia together with Pyle's disease is included in the craniotubular dysplasia group (1).
The definition Craniometaphyseal dysplasia (CMD) was coined by Jackson et al. in 1954 to describe a rare hereditary bone disease presenting metaphyseal widening of the tubular bone, sclerosis of craniofacial bones and bony overgrowth of the facial and skull bones (2-4).
The disease was better framed by Gorlin et al. in 1969, when it was recognized as a separate clinical entity of the autosomal dominant (AD) and autosomal recessive (AR) forms of CMD diseases (5).
Patients with the autosomal dominant form are usually in good general health and they lead a normal lifestyle, their intellect is unimpaired, and have a normal size of the body without evidence of bone fragility. Clinically, the patient may have mandibular prognathism and malocclusion caused by progressive bone overgrowth. Distortion of the face in AR is very severe (2). The paranasal bossing, occurring during childhood, tends to regress with growth. The abnormal growth of the facial bones can lead to nerve compression of the seventh and eighth cranial nerve, with varying degrees of facial palsy and deafness. In AR CMD cranial nerve compression is severe and, in addition, visual loss may result from involvement of the optic nerve (2, 6). In severe forms of the disease, the narrowing of the foramen magnum with compression of the medulla can cause a quadriparesis or death (3, 7).
AD CMD diagnosis is made after the execution of the radiological examinations, in fact clinical signs without radiological investigation are not exhaustive. Radiographic features in AR CMD include non-sclerotic widening of the metaphysis with cortical thinning and sclerosis of the skull; in adulthood, sclerosis may be

especially evident along the cranial sutures (8). The paranasal bony bossing, featured during childhood, may give an appearance of hypertelorism. The air sinus obliteration and the mandibular prognathism are common (2).
The widening of the methaphysis is more visible at the lower end of the femur, the metaphyseal flaring results in an Erlenmeyer flask appearance in childhood, and a club-shaped deformity in adulthood (3, 7). The bones of the pelvis and spine are normal and in the chest a slight modeling defect of the medial portion of the clavicles and the costochondral junctions may be found (2).
Although radiographic examinations are necessary to make the diagnosis of CMD, the bone abnormalities shown are not pathognomonic of CMD; indeed Pyle's disease, craniodiaphyseal dysplasia and frontometaphyseal dysplasia may have similar radiological findings. A genetic analysis is therefore necessary to provide a definitive diagnosis (3, 9).
ANKH is the only gene which is known to be associated with CMD: sequence analysis of ANKA detects mutations in about 90% of affected individuals.
The autosomal dominant form is linked to chromosome 5p15.2-p14.1, within a region harboring the human homolog (ANKH) of the mouse progressive ankylosis gene (ank) (3, 10). ANKH encodes a 429-amino acid multipass transmembrane protein that is involved in transport or cotransport of intracellular pyrophosphate (PPi) into extracellular matrix (8, 11, 12). Experimental studies have shown that CMD mutations in ANK lead to decreased PPi levels in bone extracellular matrix, which in turn cause increased density and progressive thickening of cranial bones (11, 13).
AR form of CMD has been mapped to a 7cM interval on chromosome 6q21-22 (11, 14).
AR form is more severe, more difficult to diagnose, and rarer than the dominant form (3). The CMD is in differential diagnosis with Methaphyseal dysplasia (Pile's disease), Craniodiaphyseal dysplasia, Paget's disease, osteopetrosis (as previously mentioned).
Pile's disease is an autosomal recessive disease presenting gross metaphyseal widening, and where pelvic bone and thoracic cage are expanded (1, 7).
The skull is spared, apart from a broadening of the supraorbital rims, which is normally associated to this disease (7, 9).
The patients are clinically normal, except for valgus deformities of the knees. Craniodiaphyseal dysplasia is characterized by a more significant flaring of the diaphyseal region, without metaphyseal involvement, with severe sclerosis and hyperostosis of the skull.
There is a medical therapy for CMD, based on the control of calcium homeostasis and the regulation of the activity of osteoclasts and osteoblasts, through the consumption of somatostatin, calcitriol, calcitonin, or a low calcium intake (3, 6, 8).
Calcitonin therapy reduces bone resorption by inhibiting osteoclast activity and secondarily by impeding bone formation through feedback coupling to limit osteoblast activity, the long-term results are a reduction of bone remodeling without a change in bone density.
The low oral intake of calcium promotes, instead, a state of hypocalcemia that stimulates the osteoclasts activation. Calcitriol has the function to stimulate bone absorption, activating the osteoclasts. Somatostatin seems to have a role in slowing the hyperostosis progression (7, 8).
Surgical treatment is intended to correct the deformity of the skull and providing cranial nerve decompression. However, the removal of sclerotic bone is rather complicated and it often does not produce the desired results, showing relapse. Nerve decompression addressing the facial nerve and optic nerve is a complex surgery, which is not without complications and risks. However, surgical management obtained good results in conductive hearing loss due to ossicular fixation, with an improvement of hearing (7, 8).

Case report

The patient LS, male, 32 years old, referred to our unit in 2009. His chief complaint was a major limitation of his mouth opening, in the context of a craniofacial deformity.
The anamnestic evaluation reported natural birth from non consanguineous parents. The birth weight was 3,450 kilos. By the age of 3, the patient reported an initial appearance of gingival hypertrophy and frontal bossing.
From early childhood, mental and physical development was slowed compared to his peers, with a delay in speech and in locomotion.
At the age of 10, the patient presented dorso-lumbar S Italic scoliosis with a moderate rotation of the lumbar bodies, associated with a misalignment of the pelvis, where the right iliac wing was raised compared to the contralateral.
One meaningful piece of date in the remote pathological anamnesis is the hospital admission, to a pediatric clinic of another centre, when he was 11 years old, for a diagnostic work up for a possible genetic syndrome, suggested by a skull X ray analysis. Those radiographic examinations showed a severe thickening of the cranial bones and an alteration of the bony density of the maxillary bones.
From the performed diagnostic tests (spine, hands, elbows, chest, pelvis, skull and legs X-ray; rx opt; Ct skull; blood tests; chromosome map and ophthalmology examination), the diagnosis was a dysplasia of Mellnick-Needles. This diagnosis has been recently excluded.
When he was 18 years old, the patient was subjected to the Wechsler Intelligence test for adults, showing slight mental retardation. Over the years, the bilateral hearing loss due to poor transmission progressively become worse with the persistence of a walking drag with incorrect right limb. The skull deformities also increased over the years, especially the frontal, mandibular and mastoid hyperostosis.

At the time of hospitalization in May 2009, the examination showed bone bossing in the frontal, mastoid and occipital regions, bone bossing of smaller thickness at the angles and mandibular symphysis.
The CT allowed us to highlight, in addition, the subversion of the normal anatomy of the temporomandibular joints in the lower jaw, which was causing limitations in the mandibular movements. The inspection of the oral cavity highlighted a class II type malocclusion, associated with gingival hypertrophy and hyperostosis of the upper and lower alveolar bone. The patient also presented skin folds in the nuchal region (Figs. 1, 2). The patient had, moreover, hearing loss with severe bilateral transmission deficit and an X-ray of the knee showed a deterioration of the bony component with cortical thickness reduction and widespread reduction in calcium content.
After careful evaluation of the clinical case, in accordance with the requirements of the patient, we opted for a surgical treatment aimed at correction of functional limitation of temporomandibular joint and aesthetic improvement of the facial bones.
The patient was subjected to 2 surgeries under general anesthesia. In the first, performed in May 2009, the patient was subjected to partial right mastoidectomy, right coronoidectomy and removal of multiple exostoses of the right mandibular body.
In the second surgery, performed one month after the first, we proceeded to left coronoidectomy and to the removal of the massive cranial exostoses, which were in the frontal area (a median one and a lateral one) and at the level of the right superior orbital frame (Fig. 3).
Histological examination showed fragments of lamellar cortical bone which was mature compact, dense with medullary component containing blood forming

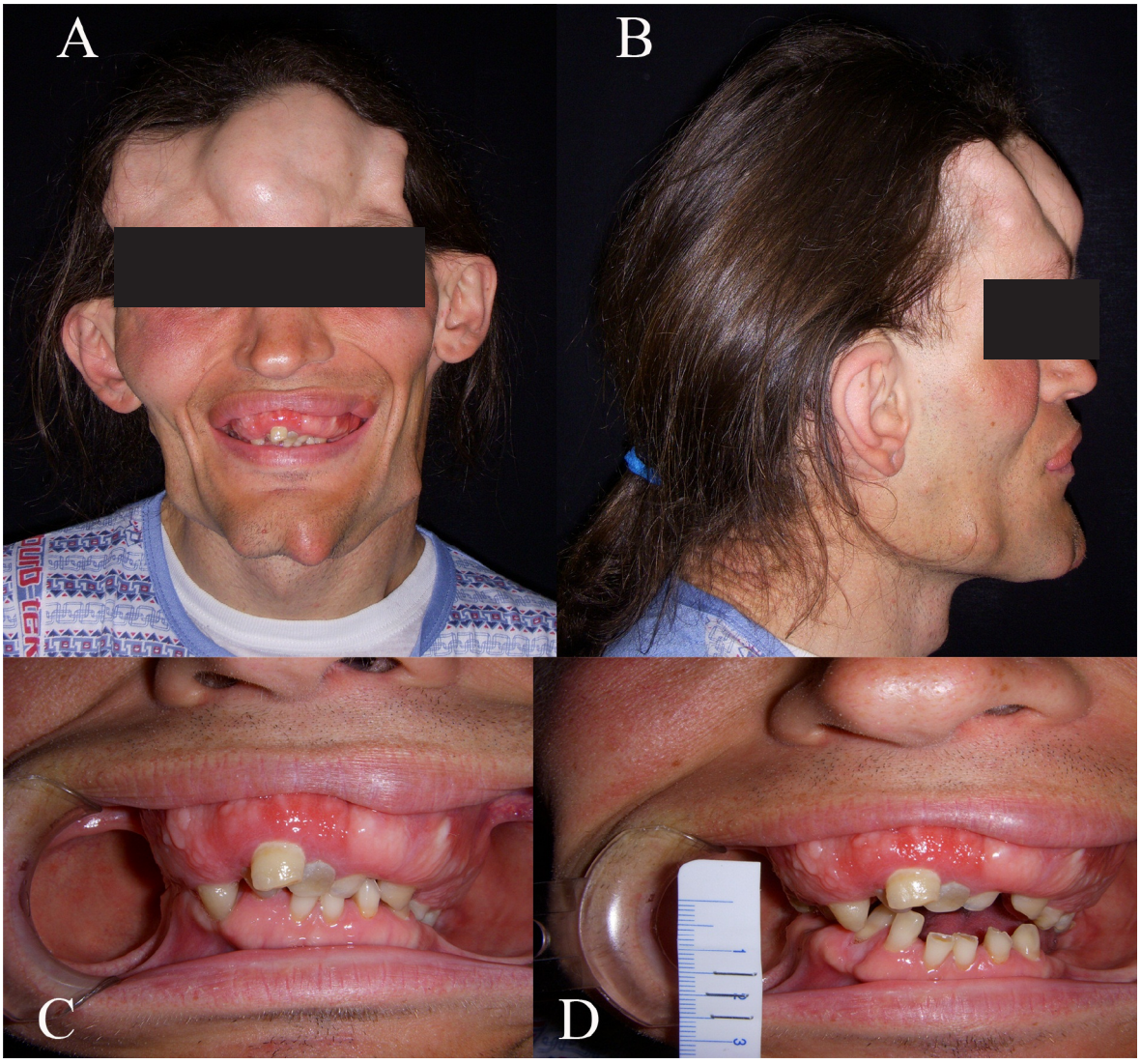

Figure 1. (A, B) Clinical aspects; (C) Intraoral view showing gingival hypertrophy, hyperostosis of the upper and lower alveolar and bone; (D) Major limitation of the mouth opening.

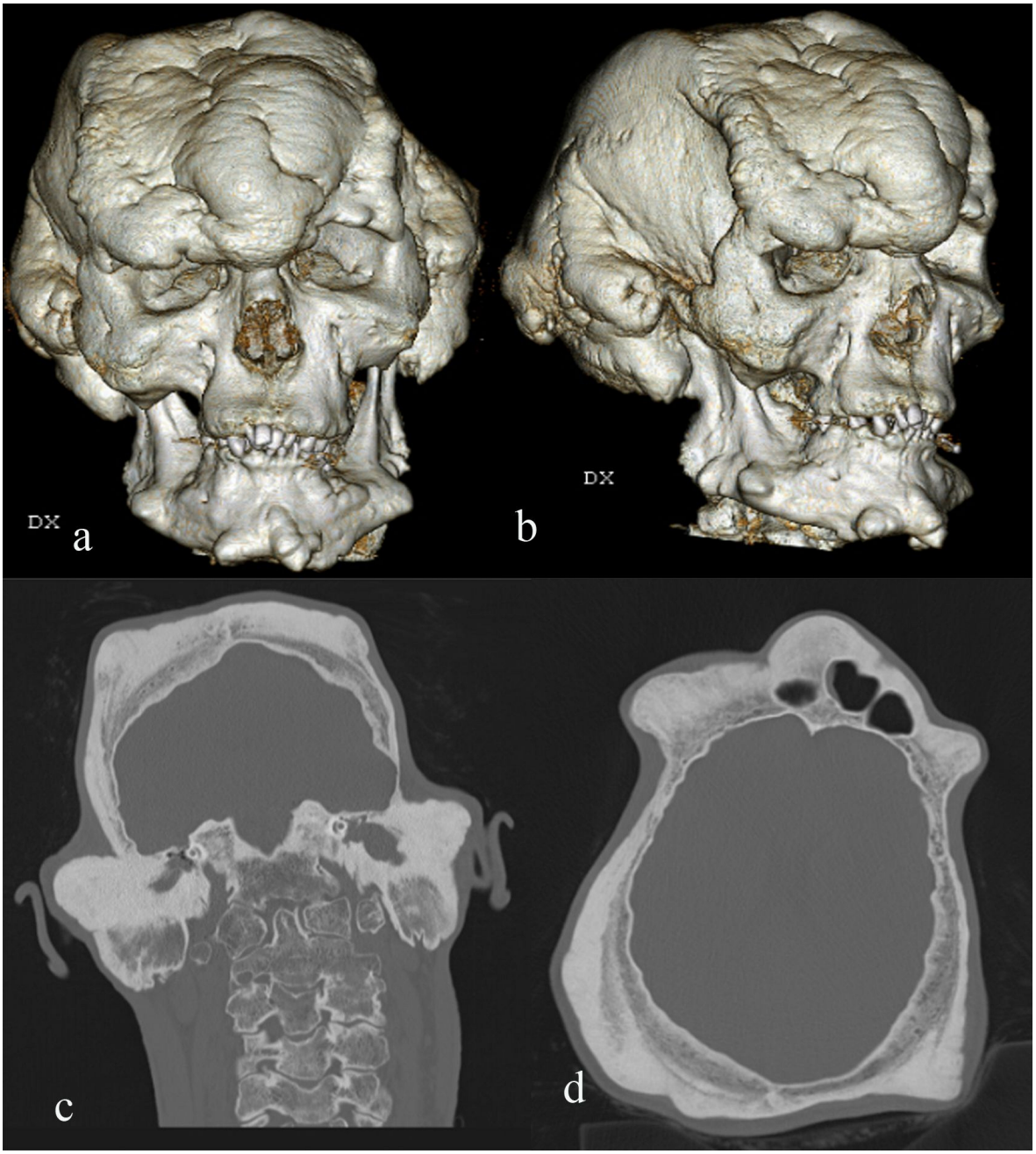

Figure 2. (a-d) 3D CTscan showing bone bossing in the frontal, mastoid and occipital regions and bone bossing of smaller thickness at the angles and mandibular symphysis.

tissues and adipocytes; those findings are compatible with osteoma. During the first surgery a sampling of skin from the nuchal region has also been performed with a diagnostic outcome of small chronic dermal fibrosis with mild periadnexal inflammation and papillomatosis of the epidermis.

To complete diagnosis, we decided to subject the patient to a genetic study, which was negative for explorable syndromic genetic diseases.

At the moment, the patient is being followed up with monthly checks. After 2 years there is no relapse of the disease in the resected areas. There is a good mandibular function and, thanks to the correction of facial aesthetics, the patient has improved his social relations (Fig. 4).

Discussion and conclusions

The dysplastic disease which affects facial bones, and particularly diseases presenting abnormal growth of bone or fibro-osseous tissue, often generates serious

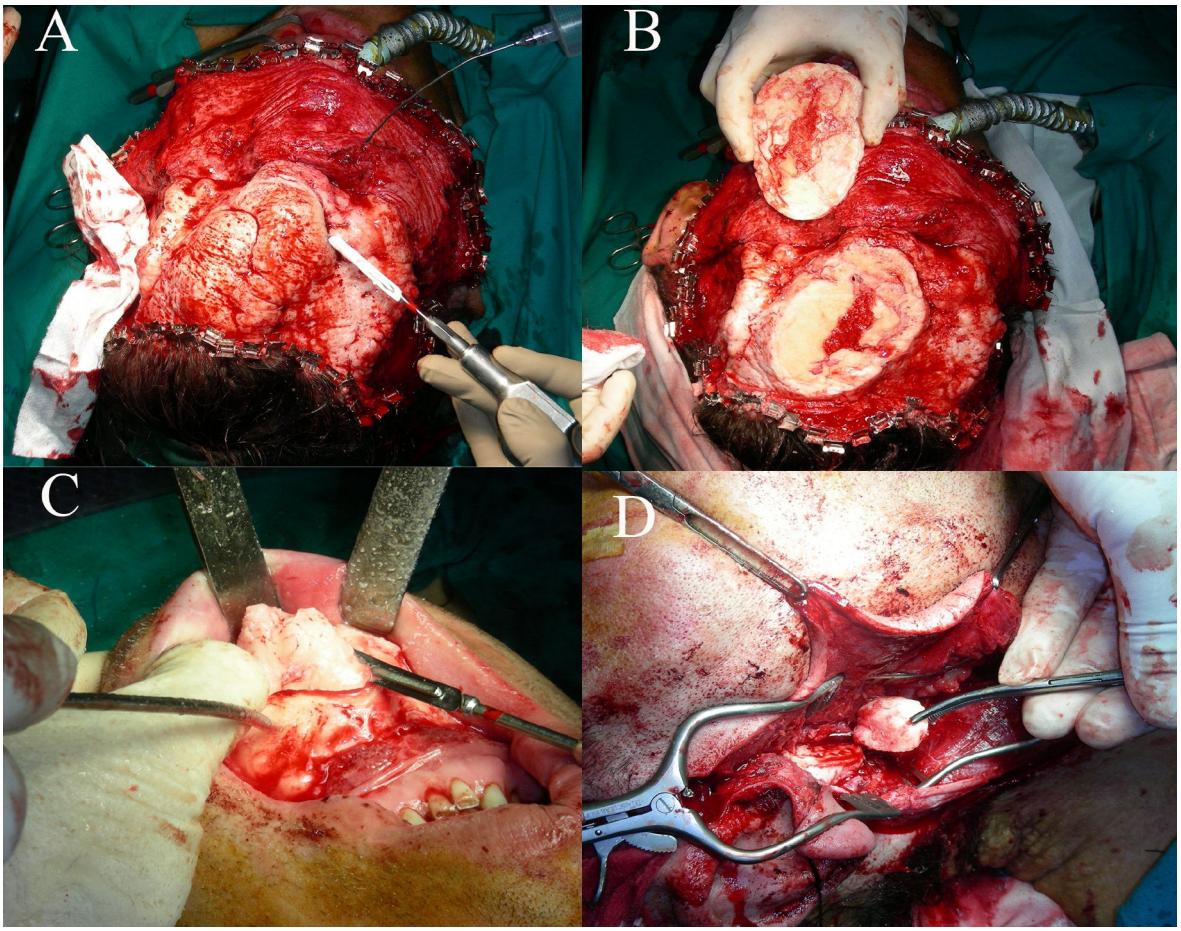

Figure 3. (A, B) Frontal bone resection; (C) Mandibular symphysis resection; (D) Mastoid resection.

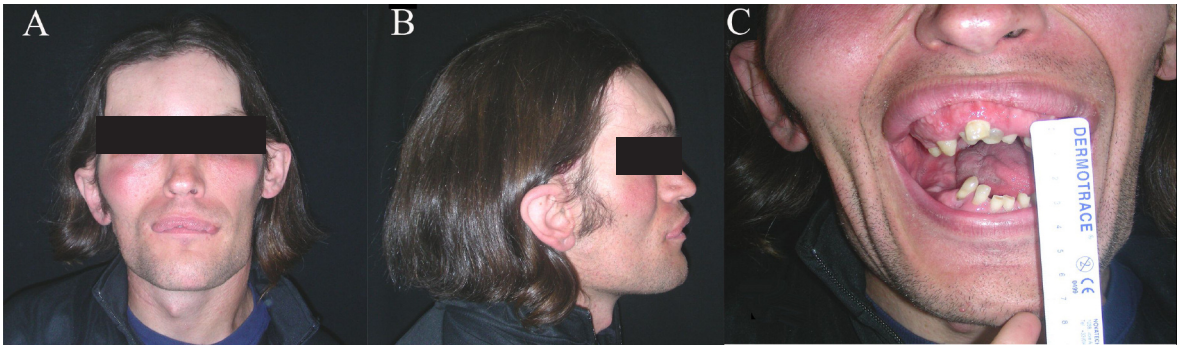

Figure 4. (A, B) Post-operative clinical aspects; (C) Post-operative mandibular function.

functional problems originating from a mutated eurhythmy of the face which causes psychological and social issues.

A diagnosis of these forms is often very difficult and it is not rare to find cases with sporadic genetic mutations which are not yet classifiable in existing syndromes or can be defined as new kind of diseases or variation of existing ones.

In the case we reported, apart from a dutiful clinic and nosological framework of the disease, we had a significant clinical need for function and aesthetics arising from the patient.

Our choice for a surgical approach, even if a genetic confirmation was not provided, derived from a careful clinical and radiological evaluation of the pathology.

Therefore, we chose, with a first surgery, to unlock the mandibular function and partially reshape facial bones to improve patient's aesthetics.

In the second surgery, we performed a global remodeling of the face, particularly of the voluminous

frontal and mandibular sinuses.
The histological examination of excised bone and the clinical controls, showing no relapse, confirmed the correct indication for the programmed surgery.
The stability of the clinical results led us to suggest and implement the surgical path, also because of lack of safe and consolidated non-surgical treatments for the specific case.
Currently, we are performing other genetic analysis, more specific, to identify a possible genetic mutation which might help us to frame this particular form into CMD or assess it as a new rare form of the disease.

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