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review

ACROMEGALY AND MODIFICATIONS OF THE CRANIOFACIAL COMPLEX: ORAL IMPLICATIONS

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SUMMARY

Acromegaly is a rare acquired endocrine disorder linked to hypersecretion of the growth hormone, which induces a progressive somatic disfigurement on the face and on the limbs. Changes in the craniomaxillofacial complex are one of the main indicators of the disease and are therefore a key feature for an early diagnosis. This article, after a short introduction on the ossification processes involved, describes the main modifications of the craniofacial complex induced by acromegaly on both hard and soft tissues. The most relevant odontostomatological aspects of the disease are then discussed, together with the important role of the dentist/orthodontist in its early diagnosis and treatment.

Key words: acromegaly, ossification, odontostomatology.

Introduction

Acromegaly is a rare disease of the adult age listed among the acquired endocrine disorders and linked to uncontrolled hypersecretion of the growth hormone (GH). The disease manifests itself with a progressive somatic disfigurement mainly located on the face and on the upper and lower limbs (1). Its prevalence is 40-70 cases per million, with an annual incidence of 2-4 cases per million. It is associated with cardiac arrest, cerebrovascular diseases, diabetes mellitus, sleep apnea, and arthropathy, with an increase in mortality risk (2).

Ever since it was defined in its modern sense, dating back to Pierre Marie in 1886 (3), craniofacial features were considered the most peculiar clinical characterizations of the disease. Indeed, Pierre Marie himself described his first clinical cases emphasizing how the changes in the craniofacial features of the disease manifested themselves by somatically disfiguring the affected subjects. In describing two of his clinical cases, he used the following words: "Her face at this time also underwent changes, … so that when the patient returned home none of her relatives could recognize her…", "The lower jaw is well developed…", "The borders of the orbits are very thick, also the frontal eminences, making between them and the upper border of the malar bone a deep depression...", "The nose is large. The lower jaw is very thick…" (3-5).

Changes of the craniomaxillofacial features are therefore pathognomonic in defining the modifications of the acromegalic subject. They are mainly represented by the thickening of the superciliary arches and a frontal bossing with hypertrophy, leading to a depression in the zygomatic bone region. Another sign is given by the enlargement and thickening of the zygomatic bone. The Guidelines of the American Association of Clinical Endocrinologists (6) underlines how maxillofacial changes are among the main indicators of the presence of the disease and occur in 74% of acromegalic subjects (Table 1) (7).

Table 1 - Clinical features of acromegaly.

Feature	Percent
Acral enlargement	86
Maxillofacial changes	74
Excessive sweating	48
Arthralgias	46
Headache	40
Hypogonadal symptoms	38
Visual deficit	26
Fatigue	26
Weight gain	18
Galactorrhea	9

Adapted from Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pitutary tumor registry: a novel clinical resource. J Clin Endocrinol Metab. 2000;85:168-174.

Physiopathological bases of craniofacial modifications

To understand the pathogenetic mechanisms of this complex syndrome, which interferes with craniofacial growth and bone metabolism, we must call attention to the two distinct types of physiological bone growth in the craniofacial complex: the endochondral ossification and the intramembranous ossification (8). In both ossification processes, mesenchymal tissue is replaced with bone tissue. However, while in the intramembranous ossification there is a direct passage from mesenchymal tissue to bone, in the endochondral ossification the process goes through an intermediate cartilaginous phase. The intramembranous growth can in turn be sutural or endosteal/periosteal, depending on the anatomical growth site.

In the craniofacial complex we can identify four distinct growth areas, summarized in Table 2. The cranial vault, which includes the covering bones of the outer upper surface of the brain, undergoes a sutural growth. The cranial base, represented by the bone floor that lies below the brain and which outlines the separation between the skull and the face, presents an endochondral development. In the nasal-maxillary complex, consisting of the nose, including the nasal-maxillary sutures, of the maxilla, with the palatine bone segments, and of the small associated bones, the development is both sutural, with the addition of bone at the level of the sutures connecting the maxilla to the cranial base and to the skull, and periosteal, with a bone remodeling mechanism associated with apposition and reabsorption processes. In the mandibular bone, next to a periosteal growth that sees phenomena of bone apposition and reabsorption at the level of the segments of the ramus and of the mandibular body, we find an endochondral growth affecting the condylar cartilage that covers the mandibular condyle surface at the temporomandibular joint level.

Considering the described growth mechanisms, it is important to define the onset of GH disorders in relation to age. In the prepubertal age, disorders related to the hypersecretion of GH are known as gigantism. The peculiarity of this disease is given by the fact that it manifests itself at a stage where bone growth is still ongoing and

Table 2 - The four growth sites in the craniofacial complex with the corresponding growth mechanisms.

Site	Growth mechanisms
• **Cranial vault** Bones covering the outer upper surface of the brain	**Sutural**
• **Cranial base** Bone floor under the brain. It also represents the dividing line between the skull and the face	**Endochondral**
• **Nose-maxillary complex** Nose, maxilla, and small associated bones	**Periosteal and sutural**
• **Mandible**	**Periosteal and endochondral**

therefore the epiphysis of long bones are not yet welded. In this case the somatotropic stimulus determined by the hypersecretion of GH will be responsible for an acceleration of the endochondral ossification with a lengthening of long bones. Subjects affected by gigantism will reach an adult height even in excess of 2.5 m, maintaining however harmonic body proportions.
In acromegaly, the hypersecretion of GH begins after the pubertal age. In this case the welding of the epiphyseal plaques, which usually occurs around 18-20 years, has already completed the bone growth. Therefore, the somatotropic stimulus, unable to influence the endochondral ossification, will act only on the periosteal and endosteal growths, with consequent thickening and enlargement of the bones starting from the periosteum (4). Subjects affected by acromegaly will therefore present an overall disharmony of the body proportions.

Modifications of the cranio facial complex in acromegaly

In the acromegalic adult subject, the mechanisms described above translate into an important thickening of the cranial bones associated with hyperostosis phenomena mainly localized at the level of the cephalic end, i.e. the splanchnocranium. The result is a massive appearance with a disproportionate volume increase of the splanchnocranium compared to the neurocranium, altering the 1/1 harmonic volumetric relationship typical of the adult (Table 3). Therefore the disharmony of the face in relation to the skull is determined by an increased volume of the splanchnocranium, a vertical elongation of the face, and a tendency to brachycephaly (Table 4), resulting in a real asymmetry and disproportion in the relationship between face and skull.
Similarly to what happens in normal development, acromegaly also activates the growth-related periosteal functional matrices. Under the influence of the hypersecretion of hypophyseal somatotrophic hormone, osteoblasts become hypersensitive to tensions and pressures exerted by the muscular system. As a consequence, the sites of muscular insertion, the articular surfaces, and the apophyses become further sites of growth phenomena with addition of neogenic tissue induced by the functional stimulus. This process activates several microskeletal units, such as the condyle, which suffers the tensions of the external pterygoid muscle, the coronoid process, influenced by the temporal muscle, and the mandibular angle, stressed by the masseter muscle (9).
Based on the mechanisms described, the alterations of facial structures in acromegaly include a thickening of the outer surface of the skull bones, a thickening with hypertrophy of the frontal bones which causes the typical prominence of the superciliary arch, an enlargement of the nasal sinus, and a widening of the maxilla at the level of the zygomatic bone. Morphological changes in the mandible include an evident prognathism, an increased perimeter of the lower dental arch, the lengthening of the condyles and of the coronoid process, the thickening of the cortical bone, an increase in the thickness and height of the alveolar process, and a reduction in bone porosity (10-12). Often, but not always, the mandible grows with an acceleration similar to that observed during the peak of adolescent growth (13).

Table 3 - Neurocranium to splanchnocranium volume ratio development during normal craniofacial growth.

Age	Neurocranium/splanchnocranium volume ratio
1 year	3/1
3 years	2/1
13 years	3/2
Adult	1/1

Table 4 - Craniofacial manifestations of acromegaly.

- Face to cranium disharmonic ratio
- Splanchnocranium volume enlargement
- Vertical elongation of the face
- Tendency to brachycephaly

Craniofacial anomalies cause an alteration of the extraoral clinical appearance of acromegalic subjects with marked facial lines and thickening of the lips and of the nasal ala. At the intraoral level there are changes in soft tissue with macroglossia and an increase in the volume of salivary glands (12).
To complete the clinical picture, the orodental signs include horizontal interdental alveolar bone loss, with consequent presence of diastemata, and hypercementosis. The latter, rather than to a secondary hormonal stimulus, could be linked to a functional response to structural morphological changes (14-16).

Odontostomatological aspects of acromegaly

Mandibular prognathism, caused by the proliferation of condylar cartilage and the growth of the mandibular ramus, is a constant component of craniofacial changes in the acromegalic subject. It follows an alteration of the jaw bones which translates into an anomaly of the occlusal relationship between the upper and lower dental arches, with the establishment of a class III malocclusion. The severity of the malocclusion tends to worsen over time and is therefore related to the duration of the disease (16).
A clinical sign linked to the tendency to compensate for excessive mandibular growth is the extrusion of the posterior molars, which, combined with the increase in the thickness and height of the alveolar processes, contributes to increase the lower facial height and the angle between the ramus and the body of the mandible (15).
Prognathism is often associated with an increase in the volume of the tongue, with the possible presence of furrows on the mucosal surface. Macroglossia can in turn induce diastemata at the level of the lower dental arch (15). The enlargement of the tongue and of the cutaneous tissues of the lips also induces problems related to swallowing, chewing, phonation, and breathing (17). While some studies reported an expansion of the maxillary alveolar bone and of the mandibular bone associated with the increased lingual pressure, the majority of the literature does not include an augmented transverse diameter of the upper jaw among the facial features of acromegaly (18).
A complication of acromegaly, also of odontostomatological interest, is the obstructive sleep apnea syndrome (OSAS) (19-21). In this case, the determining factors of the syndrome are macroglossia and facial skeletal and soft tissue abnormalities, such as laryngeal and soft palate hypertrophy, which favor the narrowing of the upper airway (15, 22).
The shape of the dental crowns is usually normal, while the roots of the posterior molars can increase their volume as a result of hypercementosis (15). Root resorption was also observed: this is usually generalized but sometimes it can be limited to specific dental groups (23).
Finally, recent studies report that the hypersecretion of GH associated to acromegaly, by stimulating the thickening of gingival tissues and alveolar bone, could have a protective effect against advanced chronic periodontitis (24, 25).

Role of the dentist in acromegaly

The clinical picture characterizing acromegaly is typically that of a slowly progressive disease that causes significant changes in the thickness and shape of hard and soft tissues of the upper and lower limbs and of the cephalic extremity. It manifests itself with an insidious onset that may be associated with clinical signs that lack specificity and which are therefore not pathognomonic *per sé*. An example can be represented by the patient's difficulty in inserting rings on his fingers or putting on shoes (12). The main problem is, therefore, that the diagnosis can be difficult and delayed over the years, with a consequent worsening of the outcome of the disease. According to the literature, the onset of the disease is slow and the interval between the appearance of the first symptoms and the diagnosis is 6-10 years (26, 27).

However, changes and anomalies in the craniofacial growth can represent the first perceived debilitating clinical signs: while for the enlargement of the extremities macroscopic alterations are necessary before the patient perceives them as pathological, at the level of the oral cavity even small variations in shape and size represent the first "disabling" clinical signs as they alter the stomatognatic functions of swallowing, mastication, phonation, and breathing (17, 28).
The dentist, the orthodontist, and the maxillofacial surgeon must therefore be aware of all the main clinical signs of acromegaly as patients will initially contact them for the treatment of the orodental and maxillofacial problems related to this disease, thus placing these professional figures in the crucial position of diagnostic "sentinel". In a first clinical approach, the observation of a progressively worsening malocclusion in adulthood must always induce the dentist/orthodontist to raise the diagnostic suspicion of acromegaly, with immediate referral of the patient to endocrinological specialist examination (6).
From a therapeutic point of view, all surgical procedures, such as the maxillofacial correction of the dental malocclusion, should be postponed pending the normalization of GH levels (6). Orthodontic therapies can, on the other hand, be applied as supportive therapies aimed at recovering and restoring the oral functions compromised by the pathology.

Conclusion

Acromegaly is a rare disease induced by hypersecretion of the growth hormone and is associated with a significant increase in mortality. It manifests itself with a progressive modification of the somatic features that mainly affects the upper and lower limbs and the face.
Craniofacial modifications and orodental manifestations include the thickening of the skull bones, prominent superciliary arches, mandibular prognathism, macroglossia, hypertrophy of the soft palate and of the larynx, the thickening of the lips, hypercementosis, apical root resorption, and dental diastemata, with impaired swallowing, mastication, phonation, and breathing.
The onset and the progressive aggravation of the craniofacial modifications and of the orodental clinical signs usually induce the acromegalic patient to consult the dentist as the first specialized medical figure. The dentist then assumes the key role of "sentinel" in the early diagnosis of acromegaly. It is therefore essential for the dentist to be able to recognize the main clinical signs of acromegaly in order to hypothesize a suspected diagnosis with referral to endocrinological specialist examination.

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