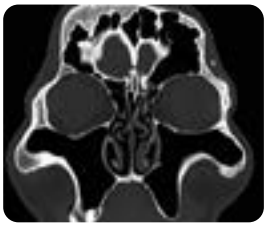

CRANIOFACIAL RADIOLOGICAL FINDINGS IN ACROMEGALY

Hallazgos radiológicos craneofaciales en acromegalia

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Key words (MeSH)
Acromegaly
Growth hormone
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Palabras clave (DeCS)
Acromegalia
Hormona del crecimiento
Imagen por resonancia magnética

Summary

The first medical description of acromegaly was in 1886, by French neurologist Pierre Marie. This rare disease is usually caused by a pituitary adenoma, which has a typical phenotype of overgrowth, craniofacial disproportions and systemic complications, specially in the cardiovascular, respiratory and metabolic systems, secondary to excessive levels of growth hormone and insulin-like growth factor. Radiological detection (computed tomography and magnetic resonance imaging) of these craniofacial features is important, as they provide patients with an early diagnosis and treatment of disease.

Resumen

La primera descripción médica de la acromegalia se hizo en 1886, por el neurólogo francés Pierre Marie. Esta enfermedad, poco frecuente, generalmente la causa un adenoma hipofisario, que activa un fenotipo característico de sobrecrecimiento, causa desproporciones craneofaciales y complicaciones sistémicas en especial en los sistemas cardiovascular, respiratorio y metabólico, secundario a los niveles excesivos de hormona del crecimiento y factor de crecimiento similar a la insulina. La detección radiológica de estos hallazgos craneofaciales, mediante estudios por tomografía y resonancia magnética, son de gran importancia, puesto que brindan a estos pacientes un diagnóstico precoz de la enfermedad, lo cual conlleva instaurar un tratamiento oportuno de esta patología.

Introduction

In 1886, French neurologist Pierre Marie made the first medical description of acromegaly. He coined the term acromegaly, which comes from French and means hypertrophy of the extremities, as this entity is characterized by hypertrophy of the hands, feet, and face. Later, it was discovered that virtually all patients with acromegaly had enlargement of the pituitary gland, and that the hyperfunctioning of the pituitary was secondary to a pituitary tumor (1). Years later it was discovered that the cause of acromegaly was an increase in growth hormone (GH) and insulin-like growth factor (IGF-I). In the early 20th century, surgical resection of the pituitary gland and radiation therapy were performed as treatments for patients with acromegaly. After 1970 medical therapy with dopamine agonists was introduced first, followed by somatostatin analogues and GH receptor blockers (1).

It is a rare disease, which is often under-diagnosed (2). The cause is a pituitary adenoma, in more than 95% of patients and in the remaining 5% it is secondary to a hypothalamic or neuroendocrine tumor (usually of pulmonary or pancreatic origin) leading to somatotrophic hyperplasia and acromegaly (2, 3).

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It progressively produces deformities and causes a wide range of systemic complications, some of which are responsible for increased mortality in untreated patients (4).

The vast majority of GH-secreting pituitary adenomas are sporadic. However, acromegaly can also have a hereditary pattern, by association with other endocrine abnormalities (multiple endocrine neoplasia syndromes type 1 and type 4) or appear as a familial isolated pituitary adenoma (FIPA), which is due to germline mutations of the AIP gene (1). Another related entity is X-linked acrogigantism (XLAG), caused by microduplications on the Xq26.3 chromosome, which encompasses the GPR101 gene, which is highly regulated in pituitary tumors (2).

Acromegaly also affects about 20% of patients with McCune-Albright syndrome (2).

Patients with acromegaly show a characteristic phenotype of overgrowth and craniofacial disproportions. This is because high levels of insulin-like growth factor cause excessive growth of various epithelial and connective tissues, viscera, the cardiovascular and pulmonary systems, and the skin. Decreased intercarotid distance (distance between the common right and left carotid arteries) has been reported. Additionally, excess GH and IGF-1 lead to other pathologies, such as colon polyps, cardiovascular problems, apnea, visceromegaly, metabolic and endocrine disorders (5, 6).

1. Epidemiology

The epidemiological data described in the literature estimate a prevalence of 60 cases per million and an annual incidence of 3 to 4 patients per million (5, 6). Other studies report a total prevalence ranging from 2.8 to 13.7 cases per 100,000 population with an incidence between 0.2 and 1.1 cases/100,000 population (4). It has been established that the higher rates found in recent studies can be attributed to greater awareness of the disease and advances in diagnostic tools (4, 7). It affects men and women equally (5, 6).

The average age at diagnosis is the fifth decade of life, which ranges from 40.5 to 47 years (men: 36.5-48.5 years and women: 38-56 years), with patients under 20 years representing up to 5% of cases (2, 4).

Patients with acromegaly have an increased mortality rate of 30%, secondary to cardiovascular diseases which represent the cause of death in 60% of cases, followed by respiratory diseases in 25% and neoplasms in 15% of cases (4, 8).

2. Clinical manifestations

The most frequent clinical manifestations are distal overgrowth of the extremities (78.8-85.7%) and coarse facial features (71.2-71.4%), macroglossia, skin thickening with symptoms such as headache, hyperhidrosis, arthralgias, snoring, asthenia and carpal tunnel syndrome (7).

Clinical manifestations in acromegaly patients occur by two mechanisms: by the local effect of an expanding pituitary mass and by the direct and indirect effects of excessive secretion of GH and IGF-1, leading to systemic complications and deterioration of quality of life (2).

Headache, one of the local effects of the tumor, is found in approximately 60% of patients; it tends to be intense and disproportionate to the size of the tumor, and can be related to the stretching of the dura mater secondary to tumor growth, invasion of the cavernous sinus and irritation of the trigeminal nerve, or hypersecretion of GH (2, 8).

In cases where pituitary adenomas compress the optic chiasm, visual field alterations will be generated, which begin in the upper half of the periphery of the upper temporal visual fields, and then progress to bitemporal hemianopsia. Persistent compression can result in blindness (2).

Other neurological features, such as hydrocephalus, unilateral exophthalmos (due to orbital invasion) and seizures, are observed in cases of large pituitary adenomas (2).

Systemic manifestations include:

Acral growth: In patients with acromegaly there is excessive growth in the hands and feet, almost in a pathognomonic manner; this is due to an edema in the soft tissues. Osteoarthritis and joint hyperlaxity can also contribute to hand deformities (2).

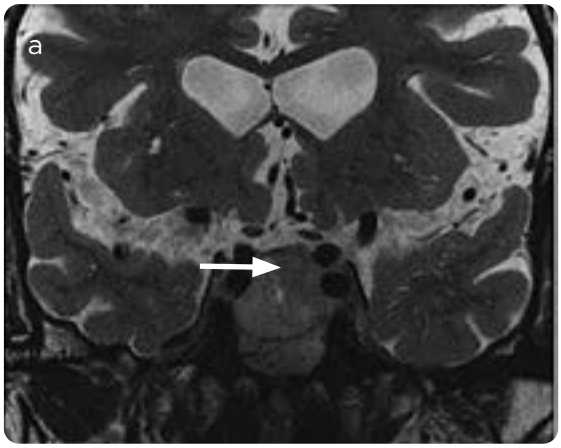
Skin and appendix changes: These alterations contribute to facial and acral deformities. Skin thickening is prominent on the face, hands and feet and is attributed to glycosaminoglycan deposits, increased production of collagen from connective tissue and edema (2, 4).

The increased size of the sebaceous glands leads to hyperhidrosis and bromhidrosis, which can be early signs of the disease and occur in 70% of cases. Acanthosis nigricans due to insulin resistance, psoriasis, Raynaud's phenomenon, hirsutism and hypertrichosis can also be observed (2).

Musculoskeletal changes: Acromegalic arthropathy can affect up to 84% of patients, with inflammation of the joints, hyperlaxity and cartilage thickening. There is an increased risk of vertebral compression fractures which may be accelerated by hypogonadism (2). Additionally, peripheral neuropathy with sensory disturbances in the hands and feet, such as carpal tunnel syndrome, occurs in 20-64% of patients (2). Osteoarthritic changes with bone remodelling, formation of osteophytes, subchondral cysts, decreased joint spaces and periarticular ligament laxity (2). Musculoskeletal pain is frequent and affects the quality of life of these patients (2).

3. Complications of acromegaly

- **Cardiovascular:** The most common feature of acromegalic cardiomyopathy is concentric biventricular hypertrophy. It occurs mainly in the absence of hypertension, but can be aggravated by hypertension and abnormalities of glucose metabolism. In later stages, systolic and diastolic stress dysfunction can be found, as well as valve anomalies (2, 4). Approximately 40% of acromegalic patients suffer from arrhythmias such as paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia and branching blocks (4). These patients have several risk factors for myocardial ischemia, such as: elevated levels of lipoprotein-a, triglycerides, fibrinogen, plasminogen activator inhibitor and tissue plasminogen activator; additionally, high blood pressure is reported in 30-40% of patients, probably due to increased plasma volume, decreased levels of atrial natriuretic peptide (ANP), insulin resistance and diabetes mellitus (4).



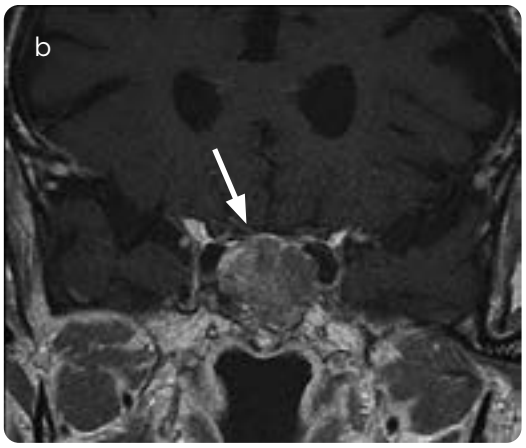


Figure 1. a) MRI, coronal with T2 information: a heterogeneous expansive lesion is observed that occupies and expands the saddle and extends laterally contacting both cavernous sinuses; it corresponds to a pituitary macroadenoma. b) MRI, coronal with T1 information with contrast medium: the lesion highlights the contrast medium in a heterogeneous way (arrows).

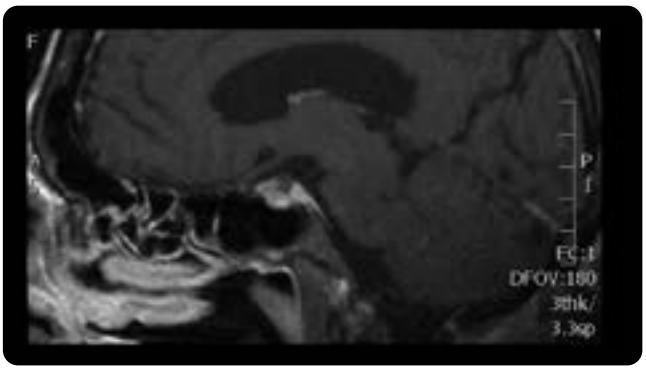


Figure 2. MRI, sagittal with T1 information with contrast medium: alteration in the morphology of the saddle, absence of adenohypophysis and interruption of the infundibulum in a patient with acromegaly is identified.

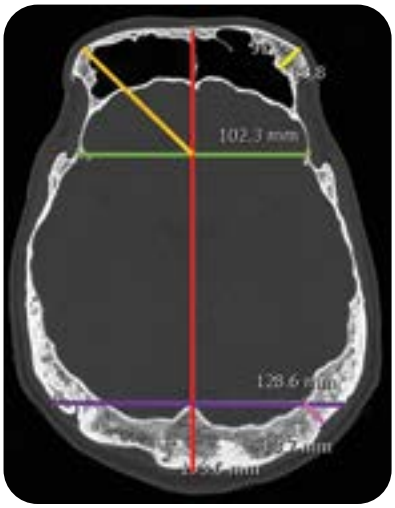
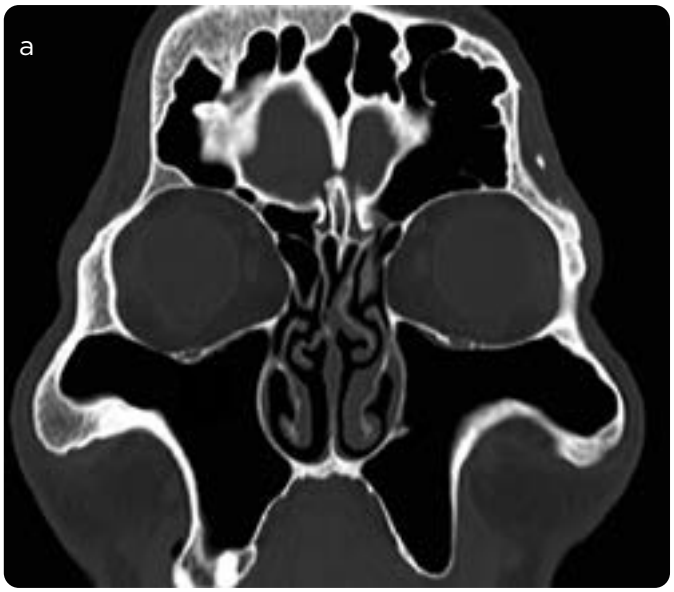


Figure 3. Bone window CT: the appropriate form for measuring the thickness of the frontal and occipital bone table is shown. At the highest level of the sphenoid major wings a line is drawn connecting these two anatomical landmarks (green line) and a line perpendicular to this (red line), a bisector is drawn from the intersection of these lines to the frontal bone (orange line) and at this point the thickness of the frontal cranial vault is measured (yellow line). To measure the occipital thickness, a transversal line is drawn at the height of the most anterior bony projection of the occipital bone (purple line), then a line is drawn at a right angle equidistant between the inner and outer cortices of the occipital cranial vault (fuchsia line).



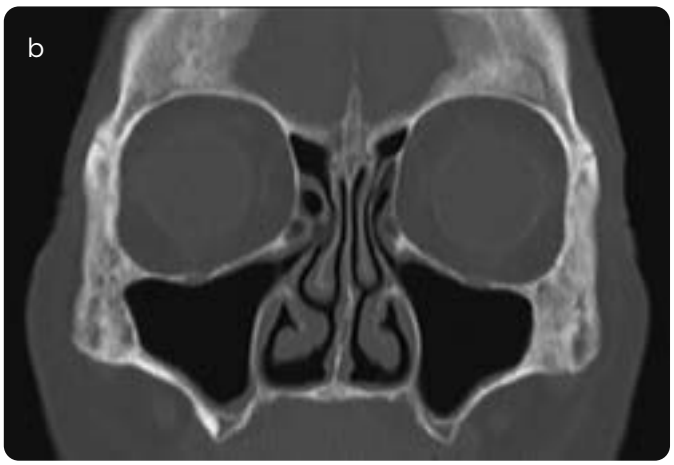
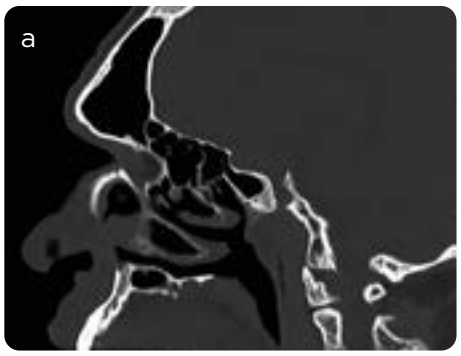


Figure 4. a) Coronal bone window scintigraphy reconstruction: increase in the size of the maxillary and frontal sinuses due to hyperpneumatization in a patient with acromegaly. b) Coronal bone window scintigraphy reconstruction in a patient without acromegaly: note the normal size of the maxillary sinuses in comparison with image a).



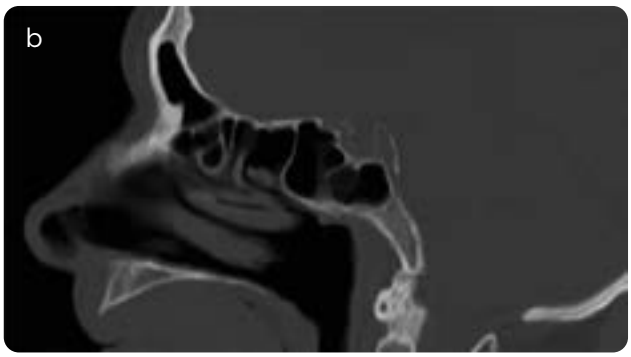


Figure 5. a) Sagittal bone window scintigraphy reconstruction: the increase in the diameter of the frontal sinus by hyperpneumatization is observed in a patient with acromegaly. b) Sagittal bone window scintigraphy reconstruction, in a patient without acromegaly: note the difference in the size of the frontal sinus in comparison with image a).

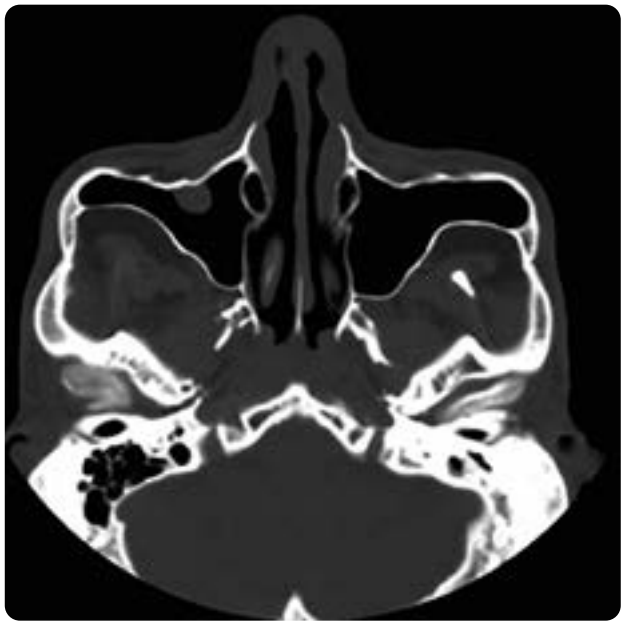


Figure 6. Bone window CT scan of a patient with acromegaly: an increase in the diameter of the maxillary sinuses is observed and, additionally, on the right, a polyp. These are frequent findings in patients with acromegaly associated with hyperpneumatization of the sinuses.

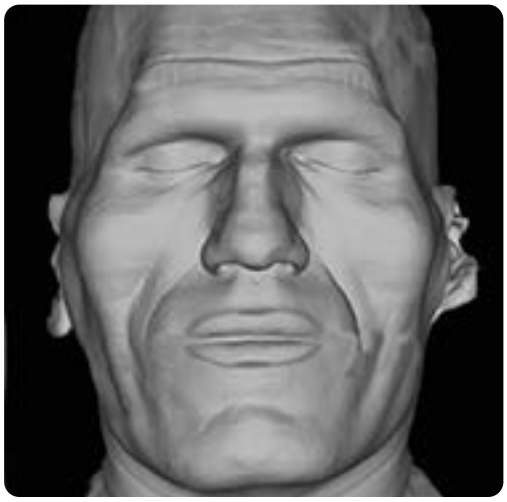
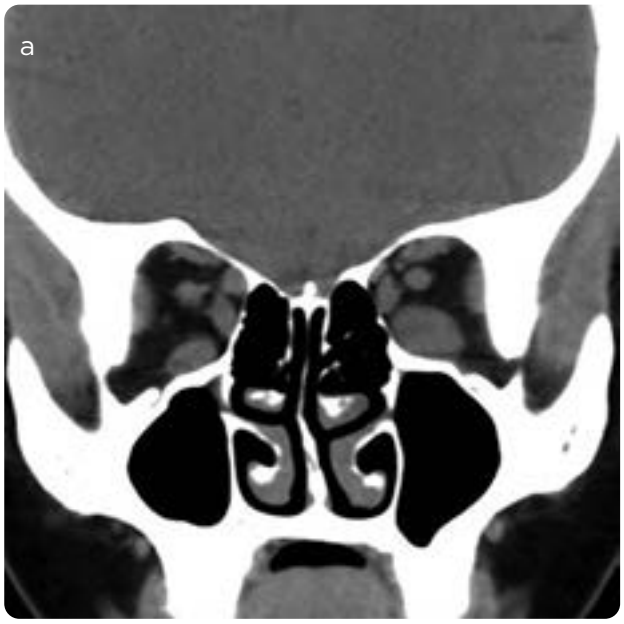


Figure 7. 3D scan reconstruction of the face of an acromegaly patient with some typical facial malformations, such as prognathism, jaw widening, superciliary prominence and nasal hypertrophy.



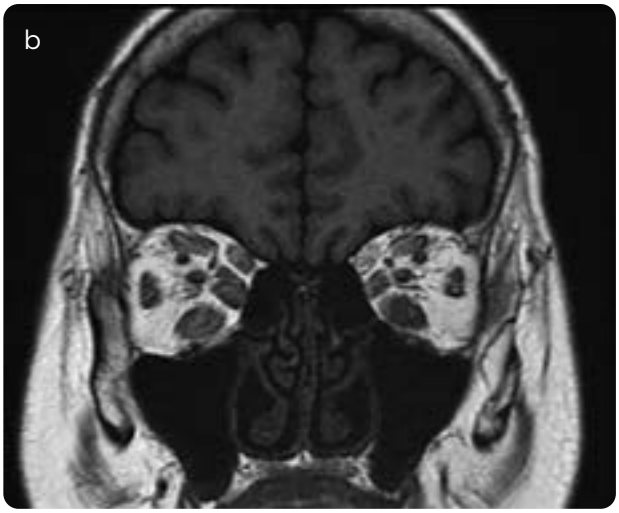


Figure 8. a) Coronal scan reconstruction of a patient with acromegaly: diffuse and bilateral thickening of the orbital muscles, especially the lower rectus. b) MRI, coronal with simple T1 information of a patient with acromegaly: diffuse and bilateral thickening of the extraocular muscles.

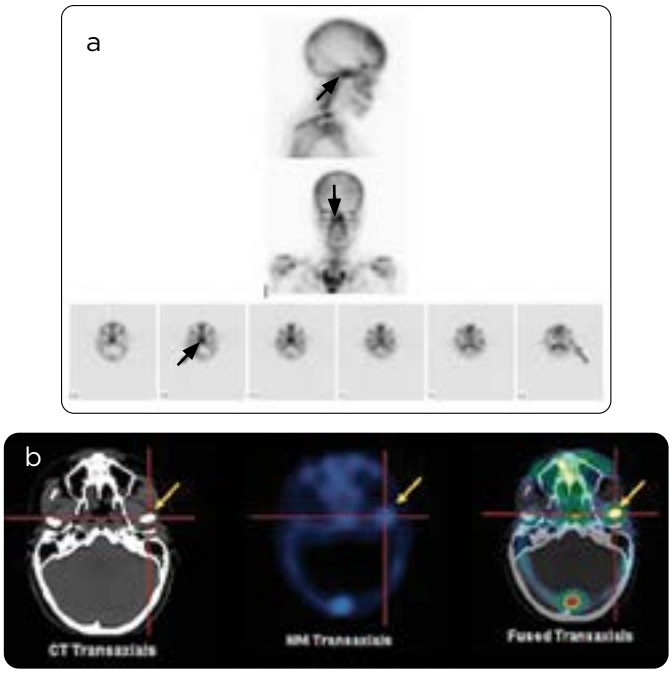


Figure 9. a) Bone scan with SPECT: hypercaptation of the Turkish saddle (red arrow) and of the left mandibular condyle (green arrow) is observed in an acromegaly patient with a pituitary adenoma and condyleal hyperplasia. b) Bone scan with SPECT CT fusion of the same patient: second-hand active condyleal hyperplasia (yellow arrow).

- **Respiratory:** Between 20 and 80 % of acromegalic patients may manifest sleep apnea, with snoring, fragmented sleepiness, daytime sleepiness and morning headache (4). Sleep apnea can predispose to ischemic heart disease, arrhythmias, high blood pressure and strokes. The obstructive type is seen in two thirds of affected patients (due to increased soft tissue in the nasopharynx and other upper airway structures); the remaining third is of the central type (probably due to the direct effects on the breathing centre of elevated GH and IGF-1 levels) (4).
  Narrowing of the airways, disorder of the respiratory muscles, scoliosis in the thoracic spine, overgrowth of the lungs and increased lung volume all result in respiratory dysfunction, usually leading to emphysema and bronchiectasis (4).

- **Metabolic:** Excess GH is associated with insulin resistance, increased gluconeogenesis, lipolysis and decreased peripheral glucose uptake (2, 4), often resulting in glucose intolerance, diabetes mellitus (up to 28-46% of cases) and dyslipidaemia (particularly hypertriglyceridaemia) and an elevated LDL (2).

- **Neoplasms:** In men with acromegaly the risk of developing colon adenomas is increased after the age of 50 years (4). The risk of thyroid nodular disease and thyroid cancer is increased in acromegaly with an OR of up to 7.5 (2). Acromegaly predisposes to benign prostatic hypertrophy, but there is no conclusive evidence that prostate cancer rates increase in this clinical condition. The same is true for breast cancer (4).

- **Gigantism:** This is a rare condition that occurs in 5% of cases of pituitary gland tumors (somatotropinoma). Typically, it is manifested in the second decade of life, the clinical features appear when hypersecretion of GH occurs before the closing of the epiphyseal cartilages and results in excessive linear growth in children, height with more than three standard deviations above the mean for age or more than two standard deviations from the height adjusted to the parents (2). Mutations of the AIP gene are found in 29-50% of cases of gigantism. Recently a new syndrome called X-linked acrogigantism (XLAG) was described, this case of childhood gigantism has a severe clinical phenotype, with an increased growth rate starting at 2-3 months of age (2).

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4. Craniofacial and intracranial radiological findings

4.1 Pituitary adenomas and pituitary stem disruption

In more than 95 % of patients, acromegaly is derived from a functional pituitary adenoma (9), which causes an excess production of GH (growth hormone) which, if not treated, is associated with increased mortality. Macroadenomas (>10 mm) appear in up to 61% of cases (Figure 1), in the remaining 39% microadenomas have been observed (10), as well as an increase in the size of the sella turcica secondary to tumour expansion (6).

Cases of acromegalic patients with hyperprolactinemia have been reported. It should be taken into account that prolactin has a primary amino acid structure similar to that of growth hormone (GH), so it competes weakly for GH-binding receptors, in addition to having biological properties similar to those of growth hormone. Because of its growth-promoting action in various tissues and structures, hyperprolactinemia in acromegalic patients is due to either secretion of prolactin or GH by the tumor, which is seen in up to 50 % of cases, or hyperprolactinemia secondary to compression and disruption of the pituitary stem by the adenoma (11, 12) (Figure 2).

4.2 Increased thickness of the frontal and occipital cranial vault

In order to measure the thickness of the cranial vault in computerized tomography (CT), a transverse line is drawn at the highest level of the major wings of the sphenoid, connecting these two anatomical landmarks and a line perpendicular to it. A bisector is then drawn from the intersection of these lines to the frontal bone and at this point the thickness of the cranial vault is measured at the frontal level. To measure the occipital thickness a transverse line is drawn at the level of the most anterior bony projection of the occipital bone and when this line is in contact with the external cortical bone a right angle is drawn from this equidistant point and this is the measurement of the cranial vault at occipital level (Figure 3) (9).

Apart from the alterations mentioned, an association between acromegaly and Chiari malformation has been reported in the lite-

rature, which proposes that bone overgrowth reduces the volume of the posterior fossa, but these data must be confirmed with additional studies (9).

These measures show that patients with acromegaly have a frontal cranial vault thickening of 1.12 +/- 0.43cm and a bone occipital cortex thickening of 0.75 +/- 0.28cm. These data differ from the values obtained for the population without acromegaly, in which the values for the thickness of the frontal cranial vault are 0.67 +/- 0.27 cm and 0.55 +/- 0.14 cm for the occipital thickness (9) (table 1).

Table 1. Measures of the frontal and occipital bone cortex in patients with and without acromegaly

Cortical bone	Normal values	Values in acromegalia
Frontal	0.67 +/- 0.27 cm	1.12 +/- 0.43 cm
Occipital	0.55 +/- 0.14 cm	0.75 +/- 0.28 cm

4.3 Sinus hyperpneumatization

The anteroposterior measurement of the sphenoidal sinus in patients with acromegaly is 3.31 +/- 0.62 cm, while in patients without the pathology the measurement is 2.92 +/- 0.71 cm. For the maxillary sinus, the measurements in patients with acromegaly were 4.22 +/- 0.30 cm compared to patients without the pathology whose value is 4.06 +/- 0.24 cm (9) (table 2) (figures 4 and 5).

The increase in the diameter of the sphenoidal sinus is a very important variant when performing transsphenoidal surgery, because it makes the surgical approach in the resection of adenomas difficult (9).

Table 2. Antero-posterior (AP) diameter of the sphenoidal and maxillary sinuses in patients with and without synachromegaly

Paranasal sinus	Normal values	Values in acromegalia Sphenoidal
Sphenoidal	2.92 +/- 0.71 cm	3.31+/- 0.62 cm
Maxilla	4.06 +/- 0.24 cm	4.22 +/- 0.30 cm

4.4 Facial alterations

In patients with acromegaly various alterations in the facial bone structure are observed, such as prognathism, malocclusion patterns, lip thickening, jaw widening, superciliary prominence, macroglossia (causing obstructive sleep apnea), dental diastemata and nasal bone hypertrophy; Similarly, several cases have been reported in which, in addition, mucosal hypertrophy, voice thickening due to hypertrophalaryngeal and sinus polyps are present (Figure 6) (6, 9).

Most patients have a 5 to 10 year clinical picture with changes in facial architecture before they are diagnosed with acromegaly. Therefore, in the presence of symmetrical bilateral mandibular prognathism - the mandibular branch is usually more affected than the mandibular body - acromegaly should be considered as a differential diagnosis in CT or MRI studies (Figure 7) (6).

4.5 Orbital involvement

Orbital involvement in acromegaly is a rare finding, up to 5.7% of patients may have campimetric defects, proptosis or diplopia due to restrictive myopathy or, less frequently, secondary to cranial nerve palsy (13).

The imaging findings are a diffuse and symmetrical enlargement of the extraocular muscles, the degree of hypertrophy is related to the duration of the disease and not to hormone levels (13). Histopathological studies show hypertrophy of type 1 fibres and atrophy of type 2 fibres, as a direct result of excess growth hormone secretion (13) (Figure 8).

5. Other imaging techniques

Aunque la RM con medio de contraste paramagnético es la técnica de Although MRI with paramagnetic contrast medium is the technique of choice in the characterization of pituitary adenomas (it identifies adenomas up to 2 mm in diameter), positron emission tomography (PET) offers an anatomical and functional image of the adenoma, since the ligands used in PET provide information for the differentiation of adenomatous tumor tissue from other lesions, such as cysts, fibrosis, necrosis, bleeding and other tumors, such as craniopharyngioma (14).

In patients with acromegaly, PET shows a high tumour index that decreases considerably when medical treatment with somatostatin analogues is introduced, and has therefore been proposed as a tool to monitor the effectiveness of treatment (14).

Total body scan is a useful imaging modality in the detection of pituitary pathology, additionally it allows to infer pathologies associated with acromegaly, such as condylea hyperplasia secondary to the effects of IGF-1 on the temporomandibular joint (15, 16) (figure 9).

6. Discussion and conclusions

Acromegaly is a pathology caused by chronic hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), characterized by multisystemic involvement, especially in the cardiovascular, respiratory and metabolic systems, with the subsequent complications already mentioned.

In addition, these patients have various types of craniofacial malformations, which carry a higher risk of surgical complications when resecting pituitary adenomas by transsphenoidal route, which is why, The radiologist plays a fundamental role in the identification of craniofacial characteristics through CT and MRI studies, as well as in the detection of pituitary adenomas, since their detection gives patients with acromegaly the opportunity for an early diagnosis of the disease and timely treatment, which prevents the complications of the disease.

Reconocimientos

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