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REVIEW ARTICLES

Young-onset acromegaly and gigantism: Causes and clinical features of growth hormone overproduction

Acromegalia e gigantismo em idade pediátrica: Causas e manifestações clínicas do excesso de produção de hormona do crescimento

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ABSTRACT

Depending on the age of onset, the excessive release of growth hormone (GH) – most commonly by a pituitary tumor – and subsequently of insulin-like growth factor 1 (IGF1) can cause acromegaly and gigantism.

The purpose of this study was to describe the clinical manifestations and main known causes of GH overproduction.

GH-releasing hormone and IGF1 can result in a series of physical traits and comorbidities due to hormonal imbalance and somatic overgrowth. To date, several syndromes and genetic mutations have been linked to the etiology of acromegaly.

Keywords: acromegaly; gigantism; cause; clinical feature

RESUMO

A acromegalia e o gigantismo são doenças raras causadas pela secreção excessiva de hormona do crescimento – mais frequentemente causada por um tumores hipofisário – e subsequente produção excessiva de fator de crescimento semelhante à insulina 1.

O objetivo deste estudo foi rever as manifestações clínicas e principais causas conhecidas de produção excessiva de hormona de crescimento.

A ação da hormona de crescimento condiciona sinais e sintomas dependentes, entre outros, da fase de crescimento do doente, isto é, da patência ou encerramento das epífises ósseas na altura do aparecimento da doença. Estão atualmente identificadas várias síndromes e mutações genéticas associadas à etiopatogenia da acromegalia.

Palavras-chave: acromegalia; gigantismo; causa; manifestação clínica

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INTRODUCTION

Although giants have been part of global mythology for millennia, it was not until 1567 that the first clinical case was reported. Moreover, it was not until the 19th century that the French neurologist Pierre Marie coined the term acromegaly, and the Italian physician Roberto Massalongo correlated its causes to a secreting pituitary tumor.[1] Nowadays, it is well established that the excessive release of growth hormone (GH), resulting in hypersecretion of insulin-like growth factor 1 (IGF1), results in somatic growth and impaired metabolic function, being associated with increased morbidity and mortality.[1-3] If this pathogenic mechanism occurs during infancy, before epiphyseal closure, it usually increases the individual's linear growth, causing gigantism. On the other hand, if it occurs after epiphyseal closure, the effects are only noticed throughout the years, as the individual suffers from soft-tissue hypertrophy and other physical changes.[1-3] In the last few years, a number of reports based on different geographical areas and health systems have provided information about these conditions, indicating a prevalence of 2.8–13.7:100,000 and an incidence of 0.2–1.1 cases:100,000.[4,5] The epidemiological data on gigantism and young-onset acromegaly is sparse, mainly due to their rarity. It has been reported that 2.4–22.2% of patients with GH overproduction are aged under 19 years old.[4,5] In the pediatric population, GH-secreting pituitary adenomas (termed somatotropinomas) can occur either sporadically or, most frequently, as part of various endocrine neoplasia syndromes. In exceptionally rare cases, GH hypersecretion can be induced by a GH-releasing, hormone-secreting ectopic neuroendocrine tumor. Diagnosing GH overproduction can be challenging, particularly in adolescents, given the progressive development of phenotypical attributes in a period of life where disproportionate growth of hands, feet, and changing facial features might seem appropriate. Therefore, there is usually a delay between the time when the first symptoms are noted and the diagnosis.[6-8] Reviewing the available literature, Holdaway and Rajasoorya estimated that this delay ranged from 6.6 to 10.2 years, with an average of eight years.[6] Thus, raising clinical awareness of this entity is of utmost importance to foster prompt diagnosis and improve patients' prognosis.

OBJECTIVES

The aim of this study was to review the various clinical manifestations and main known causes of growth hormone overproduction.

DEVELOPMENT

The clinical features of acromegaly are attributed to the local effects of an expanding pituitary mass, as well as to direct and indirect effects of excessive GH and IGF-1 secretion, which can lead to systemic complications and impaired quality of life.[9,10] Local tumor effects include headache (in about 60% of patients), visual field disturbances upon compression of the optic chiasm, and other neurological features only found in huge pituitary adenomas, such as hydrocephaly, unilateral exophthalmos, or seizures.[11] As the term 'acromegaly' suggests (acral: extremity; megaly: enlargement), systemic manifestations include the excessive growth of hands, feet, and orofacial features, like pronounced brow protrusion, creasing of the front head, enlargement of the nose and ears, thickening of the lips, skin wrinkles and widening of nasolabial folds, as well as mandibular prognathism leading to dental malocclusion and increased interdental spacing.[1,2] Macroglossia is a frequent finding and contributes to respiratory complications.[1,2] Moreover, the condition can also be associated with several comorbidities and nonspecific symptoms, like fatigue, excessive sweating, menstrual disturbances, and joint pain in 30-70% of patients.[1] Biventricular hypertrophy, valve disease, arrhythmia, cardiomyopathy, hypertension, and congestive heart failure are examples of cardiovascular complications. Effects on the respiratory system may include sleep apnea, snoring, and airway obstruction with subsequent ventilatory dysfunction. On the skeleton, the condition frequently causes carpal tunnel syndrome, arthropathy, vertebral fractures, articular cartilage thickening, and loss of sensitivity due to nervous system impairment. Colonic polyps or dolichomegacolon are typical findings in the gastrointestinal system and why colonoscopy and screening for colon neoplasia are recommended when acromegaly is diagnosed.[1-4] Additionally, the presence and growth of a pituitary tumor, typically more aggressive when compared to adulthood-onset acromegaly, can commonly cause headaches, excessive prolactin production, hypopituitarism and, in some cases, visual impairment due to mass effect.[1-3] Other findings related to GH and IGF1 overproduction are hyperphagia, metabolic disturbances such as insulin resistance (acanthosis nigricans), poor glucose tolerance, diabetes mellitus, and dyslipidemia. Reproductive disorders, such as precocious puberty and hypothyroidism with consequent thyroid goiter, are also signs that should raise suspicion of GH overproduction in pediatric age.[1,2]

Gigantism is a rare condition occurring in 5% of somatotropinomas that results from excessive exposure to these hormones before closure of the epiphyseal cartilages. In these patients, increased skeletal growth velocity is more than three standard deviations above the mean for age and height or more than two standard deviations above the estimated mean parental target height. Without treatment, patients may also develop spinal and skeletal deformities and rib cage distortion.[1-3,5-7]

GH overproduction in acromegaly is most commonly caused by a GH-secreting tumor. However, in rare cases, it can also be caused by pituitary hyperplasia or ectopic secretion of GH or GH-releasing hormone.[1-2]

If the origin of GH excess is the pituitary gland itself, it is most commonly due to a pituitary adenoma or, less frequently, to a pituitary carcinoma. GH overproduction may also originate in a pancreatic

islet cell tumor or lymphoma or be caused by inappropriate GH replacement or overdose.[1]

When a hypothalamic or pancreatic carcinoid tumor produces GH-releasing hormone, pituitary hyperproduction of GH is induced, increasing the production of IGF1 protein by the liver. IGF1 is ultimately responsible for the symptoms associated with acromegaly.[1,4] At least 46% of cases of excessive GH production of pituitary origin have an identifiable genetic cause.[1-3]

Cases of acromegaly caused by pituitary tumors associated with paragangliomas and phaeochromocytomas can also rarely be due to mutations in the genes coding the succinate dehydrogenase (SDH) complex (*SDHA*, *SDHB*, *SDHC,* or *SDHD*), which act as tumor suppressors. These three tumors together are known as the 3PA syndrome. According to series published in the literature, almost 50% of carriers of mutations in the SDH complex genes are unaffected, while most of the other 50% have non-pituitary disease. Nonetheless, about 1% of known carriers will eventually develop a pituitary adenoma. Among these, 28% have been reported to have GH excess and thus acromegaly, but none has been shown to develop symptoms before puberty.[1,3]

Multiple endocrine neoplasia type 1 (MEN1) syndrome has also been linked to acromegaly. About 1.2% of acromegalic patients have an inactivating mutation in the MEN1 gene, a tumor suppressor that controls the cell cycle and regulates oxidative stress. This syndrome is characterized by the development of hyperparathyroidism, pituitary adenomas, and neuroendocrine tumors. About 40% of carriers have prolactin-secreting macroadenomas. When also producing excessive GH, these patients can present acromegaly- or gigantism-associated signs (≈10%).[1-3] Mutations in the *CDKN1B* gene, responsible for MEN4 syndrome (which has similar clinical features to MEN1), have also been reported in some patients with pituitary adenomas. However, the prevalence of this syndrome, either in cases of pituitary tumors or acromegaly, is very rare.[1-3]

The Carney complex is another syndrome that can lead to acromegaly in approximately 10-15% of patients .[1-3] In most cases (60-70%), it is caused by mutations in the *PRKA1A* gene.[2] Other symptoms include pigmented skin/mucosae lesions, cutaneous and cardiac myxomas, and primary pigmented nodular adrenocortical disease.[1,3] Many patients also show thyroid, testis, and adrenal tumors. GH is oversecreted in 80% of Carney complex patients, primarily due to multifocal hyperplasia of somatotroph pituitary cells instead of pituitary adenomas.[3] It should also be noted that Carney complex is a familial disease in about 70% of cases and is transmitted as an autosomal dominant mutation. Hence, some reported cases manifest gigantism.[3]

McCune-Albright syndrome (MAS), caused by postzygotic mosaicism in the *GNAS1* gene, is linked to acromegaly in 20–30% of cases. MAS is concomitantly characterized by polyostotic fibrous dysplasia, *café au lait* spots, and precocious puberty, which may be caused by tumors with autonomous hormone secretion, namely of prolactin and GH.[1-3,13] Skull base fibrous dysplasia has been a highly consistent finding in most MAS patients with acromegaly.[5] Other prevalent clinical features include Cushing's syndrome (rarely) and thyroid nodules, which may lead to thyrotoxicosis.[2,3,13] Approximately 10–20% of MAS patients show acromegaly features, and the mean age at diagnosis is 24 years. Among these, 64% are diagnosed during adulthood, and their final height is generally normal, even in precocious puberty cases, which are expected to lead to short stature due to early closure of epiphyseal plates. Around 85% of patients diagnosed before the age of 16 years show accelerated growth, and more than half have precocious puberty. No cases of inheritance in humans have been reported.[13]

Aryl hydrocarbon receptor-interacting protein (AIP) gene mutations are associated with familial isolated pituitary adenomas (FIPA) and with sporadic GH-secreting pituitary adenomas. These tumors usually arise in younger patients (more than 75% are under 30 years at diagnosis) and in males and tend to be more aggressive and therapy-resistant.[1-3,14] In 76.5% of these patients, adenomas secrete GH or GH and prolactin, although rare cases of adrenocorticotropic hormone and thyroid-stimulating hormone secretion have also been reported.[2,3] Additionally, patients more often develop macroadenoma with extracellular extension.[14] Importantly, AIP mutations can be found in at least 33% of all acromegalic patients under 18 years old.[3] However, the genetic cause in most families with FIPA is still unknown. Genetic screening for AIP mutations is recommended in patients with positive family history, in pediatric patients, and in patients who intend to have children, aiming for an earlier diagnosis and improved treatment.[14]

Finally, X-linked acrogigantism (XLAG) is a newly described syndrome that starts in early childhood, causing acromegaly and gigantism in virtually all affected patients before the age of five years. XLAG was pinned as the cause of these conditions in 80% of prepubertal cases, which showed a very increased growth and weight gain rate, with patients linked to this etiology being generally taller than those with other etiologies.[2,15] XLAG is responsible for 10% of all cases of pituitary gigantism and is the second genetic cause of FIPA, accounting for the second largest group of childhood-onset acromegalic patients.[2,3] It originates in a duplication of the *GPR101* gene in chromosome Xq26.3, resulting in somatotroph cell hyperplasia or GH- and prolactin-secreting pituitary adenomas.[1-3,15,16] These mutations seem to be unique to each patient and result from a replication error.[15,16] Contrarily to patients with AIP mutations, patients with XLAG are more frequently female, and their rapid growth usually begins around one year of age, although it can be sooner, at two to three months.[1] The severity of the disease is further increased by the presence of high levels of GH-releasing hormone, which suggests hypothalamic implication in its pathogenesis.[15] Although most cases are sporadic, the duplication can be inherited from mother to son. In sporadic males, mosaicism in somatic cells has also been found in variable proportions, with a similar disease severity and growth rate to constitutional duplication cases.[15]

Table 1 - Germline and somatic GNAS mutations associated with acromegaly and gigantism (adapted from Gadelha *et al.*)[17]

Disease	Gene Mutation/Genetic Alteration	Gene Location	Prevalence in Acromegaly (%)	Phenotype
FIPA/AIP	AIP	11q13.3	50% in homogeneous FIPA 4% in sporadic acromegaly 29% in gigantism	Isolated pituitary tumor
FIPA/X-linked acrogigantism	*GPR101*	Xq26.3	0–4.4% in acromegaly 10% in gigantism	Isolated pituitary tumor
Multiple endocrine neoplasia type 1	*MEN1*	11q13.1	1.2% in acromegaly 1% in gigantism	Hyperparathyroidism, pituitary tumor, pancreatic neuroendocrine tumors
Multiple endocrine neoplasia type 4	*CDKN1B*	12p13.1	rare	Hyperparathyroidism, pituitary tumor, pancreatic neuroendocrine tumors
McCune–Albright Syndrome	Mosaic *GNAS* mutation	20q13.3	5% of gigantism patients	Classic triad: fibrous dysplasia, cafe- au-lait macules, precocious puberty
Neurofibromatosis type 1	*NF1*	17q11.2	rare	Neurofibromas, cafe au-lait macules, freckling, Lisch nodules, optic glioma
Deficiency of the X-link immunoglobulin superfamily member 1	*IGSF1*	Xq26.1	Not estimated	Acromegalic facial features organomegaly in adulthood
Sporadic somatotropinomas	Somatic *GNAS* mutation	20q13.3	40%	Isolated pituitary tumor
Pituitary adenoma and PPGL association	*SDHx* *VHL* *MEN1* *RET*	SDHA 5p15.33 SDHB 1p36.13 SDHC 1q23.3 SDHD 11q23.1	rare	Association between PPGL and pituitary tumor
	MAX	14q23.3		
Carney Complex	*PRKAR1A*	17q22-24	1% among gigantism	Acromegaly, cardiac and cutaneous myxomas, PPNAD, lentiginosis
	CNC2 locus	2p16		

CONCLUSION

A better understanding of the causes and mechanisms of acromegaly and gigantism has been crucial to improve the treatment and quality of life of affected patients. The most recent genetic findings of these disorders in pediatric age have been of utmost importance to control overgrowth and disease aggressiveness, as well as associated comorbidities. Raising awareness of these entities and avoiding diagnostic delays should thus be a continuous goal. In addition, given the still great proportion of unknown genetic causes of acrogigantism in young patients, further studies in the area should be performed.

AUTHORSHIP

Raquel Vaz de Castro – Conceptualization; Investigation; Methodology; Writing –original draft

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