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Etiologic Aspects and Management of Acromegaly

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ABSTRACT

Acromegaly is a systemic disease with various etiologies. It can occur as a sporadic or, more rarely, as a familial disease. Numerous complications such as endocrine, cardiovascular, respiratory, metabolic, osteoarticular and neoplastic disturbances occur and must be taken into account when establishing a therapeutic strategy. For this reason, the decision as to a treatment modality of acromegaly must be followed by a thorough evaluation of the patient and once the diagnosis of complications is settled, adequate treatment should be instituted. Follow up of the patients requires periodical re-assessment of complications' status. **(Arq Bras Endocrinol Metab 2005;49/5:626-640)**

Keywords: Acromegaly; Etiology; Treatment; Management; Complications

RESUMO

Aspectos Etiológicos e Manejo da Acromegalia.
A acromegalia é uma doença sistêmica com diversas etiologias. A grande maioria dos casos se manifesta de forma esporádica, e uma minoria tem transmissão familiar. Além disso, a acromegalia pode ser acompanhada de várias complicações como alterações endócrinas, cardiovasculares, respiratórias, metabólicas, osteoarticulares e neoplásicas que devem ser consideradas quando a estratégia de tratamento for estabelecida. O acompanhamento dos pacientes requer reavaliações periódicas do *status* das complicações. Neste artigo serão abordados os aspectos etiológicos e o manejo da acromegalia. **(Arq Bras Endocrinol Metab 2005;49/5:626-640)**

Descritores: Acromegalia; Etiologia; Manejo; Tratamento; Complicações

ACROMEGALY IS A WELL-CHARACTERIZED syndrome resulting from elevated levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I). However, this proves to be a heterogeneous disease with various etiologies, although some of them are quite rare, as it will be discussed below. Manifestations include acral enlargement, increased perspiration, arthralgia and paresthesias. The disease also presents systemic complications such as hypertension, cardiomyopathy, respiratory and metabolic disturbances. For this reason, a thorough evaluation must be made once the diagnosis is settled and adequate follow up requires periodical re-assessment of complications' status. The management of the acromegalic patient will be discussed next.

ETIOLOGY

GH Hypersecretion

GH hypersecretion of pituitary origin – sporadic

Acromegaly, in the majority of the cases, occurs as a sporadic disease usually caused by a GH-secreting pituitary adenoma (somatotropinoma) or rarely as part of the McCune-Albright syndrome (table 1).

Different types of GH-secreting pituitary adenomas, characterized in accordance with their hormone expression and ultrastructural features, may be responsible for distinct clinical presentations of acromegaly (table1). Somatotropinomas are monoclonal in origin (1) and the most common genetic alteration involved in their pathogenesis is the activating *gsp* mutation. This somatic mutation is found in up to 40% of the patients (2). Other genes that may be involved are *pRb*, *p27/KIP1*, *PTTG* and a tumor suppressor gene located at chromosome region 11q13 distinct from *MEN1* (3).

Pure somatotropinomas are the most frequently found (60% of the GH-secreting pituitary adenomas) and can harbor densely or sparsely distributed cytoplasmic granules that stain positive for GH. Densely-granulated somatotropinomas are acidophilic, occur in older individuals, grow slowly and present in an insidious manner. On the other hand, sparsely-granulated somatotropinomas are chromophobic, occur in younger individuals and grow faster. Mixed GH-cell and prolactin (PRL)-cell adenomas are formed by two distinct cell types and may appear acidophilic, partly acidophilic or chromophobic, depending on the granularity of the two components. They correspond to 25% of the GH-secreting pituitary adenomas and cause acromegaly with moderately increased serum PRL levels. Mammosomatotroph cell adenomas are the most common tumor type in children and adolescents with gigantism and constitute 10% of the GH-secreting pituitary adenomas. They are acidophilic, the cells are well differentiated and contain both GH and PRL granules. Serum PRL levels are normal or moderately increased. Acidophil stem cell adenomas are very infrequent (< 5%), rapidly growing and invasive tumors. They originate in the acidophil stem cells, the common precursors of somatotrophs and lactotrophs, and express both GH and PRL. These tumors have relatively low hormonal activity and the clinical presentation may be similar to that of a non-functioning pituitary adenoma or marked by hyperprolactinemia, since PRL is the major product of tumor cell secretion. Pluri-hormonal somatotropinomas, which are either monomorphous or plurimorphous, are rare (< 5%) and may express GH with any combination of adrenocorticotrophic hormone (ACTH), glycoproteic hormones and/or a-subunit (4) (table 1).

Ectopic GH-secreting adenomas may originate from pituitary remnant tissues in the sphenoid sinus (5), temporal bone and nasopharynx (6). The presence of this ectopic tissue is explained by pituitary development from Rathke's pouch, which originates in the nasopharynx and migrates to its normal location in the sella turcica (table 1).

Somatotroph carcinomas are extremely rare and their diagnosis is based on the identification of distant metastases (7). Tumors exhibiting mitotic activity, hypercellularity and nuclear pleomorphism without metastases should not be misdiagnosed as malignant, even if they are rapidly growing and invasive (7,8) (table 1).

The McCune-Albright syndrome is caused by an early somatic activating mutation in the gene *GNAS1* that encodes the ♦ subunit of the GTP-binding protein (Gs♦). The severity of the disease depends on the percentage of mutant cells in different embryonic tissues (9). It is characterized by the triad of polyostotic fibrous dysplasia, café-au-lait spots and sexual precocity. Other endocrine manifestations are hyperthyroidism, hypercortisolism, acromegaly/ gigantism, hyperprolactinemia, hyperparathyroidism and hypophosphatemic rickets/osteomalacia. Acromegaly may be due to an adenoma or to mammosomatotrophic hyperplasia (10,11) (table 1).

GH hypersecretion of pituitary origin – familial

Acromegaly, in the minority of the cases, occurs with familial aggregation either as isolated familiar disease (Isolated Familial Somatotropinoma – IFS) or as a component of a multiple endocrine neoplasia syndrome that includes Multiple Endocrine Neoplasia type 1 (MEN-1) and Carney Complex (CNC) (12) (table 1). IFS is defined by the presence of at least two cases of acromegaly or gigantism in a family that does not exhibit MEN-1 or CNC. A tumor suppressor gene located at chromosome 11q13, distinct from *MEN-1*, has been implicated in its pathogenesis (13,14). Somatotropinoma is a component of the MEN-1 syndrome, which also includes hyperparathyroidism and enteropancreatic neuroendocrine tumors (12). Somatotropinoma, in the context of MEN-1 syndrome, is usually multicentric. The diagnosis of MEN-1 requires the presence of a least two of the three major components of the syndrome (15). This autosomal dominant

Table 1. Etiology of acromegaly.

Hormone excess	
GH	
	Pituitary – sporadic
	Pure somatotropinomas:
	Densely granulated
	Sparsely granulated
	Mixed GH-cell and PRL-cell adenomas
	Mammosomatotroph cell adenomas
	Acidophil stem cell adenomas
	Pluri-hormonal somatotropinomas
	Ectopic GH-secreting pituitary adenomas (sphenoid sinus, temporal bone and nasopharynx)
	Somatotroph carcinomas
	McCune Albright syndrome
	Pituitary – familial
	Isolated familial somatotropinoma (IFS)
	Multiple endocrine neoplasia type 1 (MEN-1)
	Carney Complex (CNC)
	Extra-pituitary
	Ectopic pancreatic islet cell tumor; non-Hodgkin's lymphoma
GHRH	
	Hypothalamic
	Hamartomas, gliomas and gangliocytomas
	Ectopic
	Carcinoid tumors, pancreatic cell tumors, small-cell lung carcinomas, pheocromocytomas, medullary thyroid carcinomas, adrenal adenomas, breast and endometrial carcinomas.

syndrome is due to loss of function of the tumor suppressor gene *MEN-1*. Carney complex also exhibits an autosomal dominant inheritance pattern and arises from inactivation of the tumor suppressor gene *PRKAR1A* (protein kinase A type 1 alpha regulatory subunit) or by a genetic alteration in an oncogene, not yet identified, located at chromosome 2p16 (16-18). It is manifested by heart, skin and breast myxomas, spotty mucocutaneous pigmentation, schwannomas, primary pigmented nodular adrenocortical disease (PPNAD), testicular and thyroid tumors, as well as somatotropinomas (12,15,16). In patients with CNC, histopathological examination has revealed adenomas, tipically multicentric, with staining for GH (predominantly), PRL and occasionally for other hormones. Adenohypophyseal hyperplasia has also been seen (19). The diagnois of CNC is based on the recognition of at least two of the components of the complex (15,16). Rarely, MEN-1 and CNC may occur as sporadic diseases (12).

GH hypersecretion of extra-pituitary origin

Acromegaly has been described in a patient harboring a GH-secreting intramesenterioc islet cell pancreatic tumor (20) and in another with a non-Hodgkin's lymphoma (21) (table1). In these extremely rare cases, normal sized or reduced pituitary is seen on magnetic resonance imaging (MRI) and GH is not responsive to TRH administration (20). Finally, other tumors may stain positively for GH, like lung, breast and ovarian adenocarcinomas (22,23). However, acromegaly has not been described under these circumstances to date.

GHRH HYPERSECRETION

GHRH hypersecretion of hypothalamic origin

Hypothalamic tumors like hamartomas, gliomas and gangliocytomas may secrete GHRH and cause somatotrophic hyperplasia or even a somatotropinoma (24,25) (table 1).

GHRH hypersecretion of ectopic origin

Carcinoid tumors, pancreatic cell tumors, small-cell lung carcinomas, pheocromocytomas, medullary thyroid carcinomas, adrenal adenomas, breast and endometrial carcinomas may also secrete GHRH. In these cases, acromegaly is caused by somatotrophic hyperplasia. Carcinoid tumors, mainly bronchial in origin, represent most of the tumors associated with ectopic GHRH secretion (26-28) (table 1). Acromegaly in MEN-1 patients is rarely caused by GHRH production from a pancreatic islet cell tumor rather than by a somatotropinoma (29).

Management of acromegaly

As stated before, acromegaly is a systemic disease and causes endocrine, cardiovascular, respiratory, metabolic, osteoarticular and neoplastic morbidities besides increasing mortality (1.26 - 3 times the general popu-

lation mortality) (30-32). On the other hand, diagnosis is made 7 to 10 years after symptoms begin. Therefore, as soon as the diagnosis is settled and treatment of acromegaly is defined, a careful evaluation of the anterior pituitary function and of acromegaly related complications are important aspects of the management of this disease.

Defining the treatment of acromegaly

Treating acromegaly is a challenging task and should be carried on by a multi-professional team, including an endocrinologist, a neurosurgeon and a radiotherapist.

Treatment options include: surgical resection of the adenoma by transsphenoidal approach, medical management and conventional or stereotaxic radiotherapy. Craniotomy for the adenomectomy is rarely necessary (33). Further details on each of these treatment modalities can be obtained at Donangelo et al. (34). The objectives of the treatment are to restore GH secretion and/or action to normal, reduce IGF-I levels to age- and gender-matched controls, relieve signs and symptoms of the disease, minimize complications, control tumor growth, preserve anterior pituitary function and prevent tumor recurrence. The ultimate goal is to reduce mortality to general population rates which can be accomplished by obtaining GH levels less then 2.5ng/mL and normalization of IGF-I for age and sex (30,31,35). Recent epidemiological studies have suggested that lower GH levels should be pursued (1ng/mL) (32,36).

The best treatment option for each patient should be chosen based on clinical, biochemical and radiological characteristics of the disease, as well as the patient's preference. An algorithm for the treatment of acromegaly is showed in figure 1. The first question to be answered is whether surgical approach has curative potential. If this is the case, transsphenoidal adenomectomy should be performed and the disease status reassessed in the following 3 months. If the patient is cured, then he/she should be regularly followed and evaluated for co-morbidities. If the cure is not achieved, then adjuvant medical therapy should be started. Hormone hypersecretion is controlled (GH< 2.5ng/mL) with surgical management in 86-91% of the patients bearing microadenomas and in 46-52% of the patients with non-invasive macroadenomas (35,37,38). On the other hand, if surgical cure is improbable, medical therapy should be the first option. Two questions that still awaits for controlled-randomized clinical trials to be designed for this purpose are: 1) If pre-treatment with somatostatin analogs (SA) can improve surgical outcome, and 2) whether surgical debulking of the tumor should be done, even if surgical cure is unlikely. In a retrospective study which involved 52 patients, Colao et al. (39) showed that patients with uncontrolled disease by somatostatin analogs as a primary therapy (mean ± SEM GH: 22.7 ± 4.5ng/ml; mean ± SEM IGF-I: 2.2 ± 0.1 Upper Limit Reference Values - ULRV) presented better results in terms of biochemical control after surgical debulking of the tumor (7.7 ± 1.6ng/ml and 1.3 ± 0.1 ULRV, respectively).

Three classes of drugs are available for the treatment of acromegaly: dopamine agonists, SA and GH receptor antagonists (40) (table 2). During medical

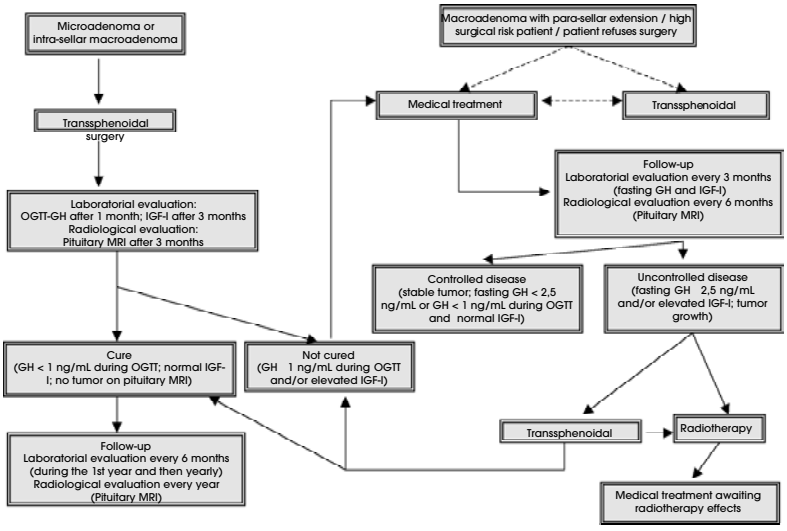

Figure 1. Algorithm for the treatment of acromegaly. Note: Dashed lines represent therapeutic approaches still not established in the literature.

Table 2. Drug options for the medical treatment of acromegaly.

Drug class	Drugs	Suitable patients
Dopamine agonists		
	Cabergoline	Mixed GH/PRL secreting tumors; patients with slight elevations of GH and IGF-I levels (GH < 20ng/mL and IGF-I < 750ng/mL); combination therapy in SST analogs partial responders.
SST analogs		
	Octreotide LAR	As a primary or adjunctive treatment (see figure 1).
	Lanreotide SR	
GH-R antagonist		
	Pegvisomant	Patients resistant to SST analogs (isolated or combined use).

SST – somatostatin; GH-R – growth hormone receptor.

treatment, hormonal levels should be assessed every 3 months and imaging studies (preferentially MRI) should be performed every 6 months. If the disease is controlled, this routine should be maintained and MRI can be done yearly. However, if the disease is not controlled, drug doses should be increased, the drug class should be changed and/or combination therapy (2 drug classes) should be started.

Somatostatin analogs are the most commonly used drugs for the medical treatment of acromegaly (table 2). Octreotide LAR adequately controls GH and IGF-I levels in 60-75% of the patients (41,42) and tumor shrinkage has been seen in up to 61% of the patients when used as an adjunctive therapy and up to 100% of the patients when used as a primary therapy (43). In some instances, cabergoline, a dopamine agonist, may be successfully used, such as in patients bearing mixed GH/PRL secreting tumors and in patients with slight elevations of GH and IGF-I levels (GH< 20ng/mL and IGF-I< 750ng/mL), in which GH and IGF-I control rates are around 50 – 57% (44,45). The control rates with the use of bromocriptine are unacceptably low, making it an unsuitable therapeutic option (46). Cabergoline can also be used in combination with depot SA in patients partially-responsive to the latter (47). Pegvisomant represents the newest class of drugs available for treatment of acromegaly and has proven to be the most effective in terms of IGF-I normalization (97%) (48). However it exerts no direct action over the tumor mass in such a way that questions have been raised as whether pegvisomant treatment could lead to tumor growth. This seems not to be the case, but more experience with the use of this drug should be accumulated to enlighten this subject (48).

Selective estrogen receptor modulators (SERMs) like tamoxifen and raloxifene have been shown to reduce IGF-I in small series of acromegalic patients. Tamoxifen was able to normalize IGF-I in 31% (4/13) of the patients (males and females) and raloxifene in 54% (7/13) of the female and 25% (2/8) of the male patients (49-51). Also, estroprogestinic pill has been shown to normalize IGF-I levels in 50% (4/8) of the female patients (52).

Radiotherapy is, in most cases, a third-line treatment for acromegaly, being indicated to patients not cured by surgery and resistant or intolerant to medical treatment. Even if normalization of IGF-I levels occurs in up to 89%, this takes approximately 10 years and may be accompanied by hypopituitarism, radionecrosis, cognitive deficits, optic nerve damage and other central nervous system malignancies (40,53,54). Radiosurgery seems to be a better option when radiotherapy is required because the results are seen earlier than with conventional radiotherapy (33,55) and probable side-effects are minimized by lesser exposure of normal brain tissue to radiation.

High cost is an inconvenience of the treatment with SA. Therefore, the ability to predict which patients will achieve "safe" GH levels and IGF-I normalization would be advantageous. The usefulness of the acute test with subcutaneous octreotide has been extensively investigated (56-63) and even intravenous octreotide has been used for this purpose (64). A positive response is considered when GH levels fall at least 50%. Some authors use 50mg and others use 100mg of octreotide as a test dose and distinct results are found. Therefore, it is still under debate whether the test is capable to distinguish the patients that will achieve "safe" GH and normal IGF-I levels during long term SA therapy. As an alternative, once octreotide LAR binds with high affinity to somatostatin receptor subtypes 2 and 5 (SSTR2 and 5), the analysis of the SSTR gene expression profile in the tumor may help select the patients with better chance to respond to these drugs (65).

New drugs have been developed and are under

investigation for clinical use, such as SOM-230, a "universal ligand" of somatostatin receptors (SSTR), with high affinity with SSTR1, SSTR2, SSTR3 and SSTR5 and somatostatin analogs with selective specificity for SSTR1 (BIM-23296 and CH 275) and SSTR5 (BIM-23206 and BIM-23268) (66,67). A chimeric molecule with ligand properties to both SSTR2 and D2 dopamine receptor (BIM23A387) has also been developed and proved to be highly effective in reducing GH secretion in vitro (68). More recently, tri-selective chimeric molecules with activity at SSTR2, SSTR5 and D2 dopamine receptor (BIM-23A758, BIM-23A760 and BIM-23A761) have shown enhanced efficacy in suppressing GH and PRL from SA-resistant somatotropinomas (69).

Assessment of GH/IGF-I axis

As stated before, during medical treatment, GH/IGF-I axis should be evaluated every 3 months. Although GH supression to less than 1ng/mL during an oral glucose tolerance test (OGTT) is one of the biochemical criteria of disease control (70), performing this test every 3 months is very uncomfortable for the patients. It is important to mention that with the highly sensitive GH assays that are being used nowadays, the cut-off nadir of 1ng/mL during an OGTT is too high and it has been demonstrated that a more appropriate cut-off nadir is approximately 0.25ng/mL (71). Since GH is released in a pulsatile manner, whether a single random blood sample is representative of the 24-hr GH secretion by the somatotropinoma is discussed. Sampling during a GH surge or during a valley could result in falsely discordant GH and IGF-I results. To circumvent this problem a number of "GH profile protocols" has been used in the literature, but no standardization has been proposed (72-74). In our outpatient clinic, GH mean is calculated from 5 samples collected over a 2-hr period (every 30 min) and IGF-I is assessed in the first sample. However, we observed that the first GH from the profile correlates quite well with the mean (r^2= 0.953; p= 0.000) (data not published) and concluded that this test should only be applied to patients with GH levels around 2.5ng/mL and discordant GH and IGF-I levels in order to be useful and cost-effective.

Real discordance between GH and IGF-I levels has been seen in 8-23% of the patients during SA treatment (42,75). A previous study from our group revealed discordant results in 19.2% (10/50) of the patients (76). In all of them, GH levels were < 2.5ng/mL and IGF-I was increased. This can be explained by tonic GH stimulation over IGF-I secretion, delayed normalization of IGF-I values following treatment or by the presence of non-immunoreactive GH molecules with biological activity. On the other hand, discordance with elevated GH and normal IGF-I levels seems to be the result of bioinnactive GH molecules being secreted by the tumor and detected by the GH assays. When discordant GH and IGF-I are detected, a careful evaluation of symptoms and signs of disease activity should guide the therapeutic decision.

Evaluation of the anterior pituitary function

Anterior pituitary function should be evaluated at diagnosis because compression of the normal pituitary tissue, stalk and/or hypothalamus by the macroadenoma may cause hypopituitarism, which may add significant morbidity to the patients. Hypogonadism, manifested by amenorrhea or reduced libido, is found in over 50% of the patients (77,78) and may result in reduced bone mass (79). Thyrotroph and corticotroph failure are present in nearly 15% and 5% of the patients, respectively (80).

Surgical management and radiation therapy may also cause hypopituitarism, although sometimes surgery or even somatostatin analogs therapy may correct hypopituitarism by reducing compression.

Anterior pituitary function should be re-assessed every 6 months during follow-up. For thyrotrophic and corticotrophic evaluation, measurement of serum free T4, thyroid-stimulating hormone (TSH) and 8AM plasma cortisol, respectively, should be carried out. A cortisol value greater than 18µg/dL invariably indicates an intact corticotrophic axis and a value lower than 5µg/dL indicates hypocortisolism. Values between 5 and 10µg/dL indicate the possibility of hypocortisolism and a stimulation test should be done, optimally with insulin induced hypoglycemia and alternatively with a low dose synthetic ACTH. Cortisol values between 10 and 18µg/dL should be further investigated according to clinical signs and symptoms. Gonadotrophic evaluation, with measurement of estradiol or testosterone, besides FSH and LH, is indicated only in patients with irregular menses or sexual dysfunction. In menopaused women, low LH and FSH levels already confirm hypogonadism. Measurement of prolactin levels is also recommended. Hyperprolactinemia is observed in 30-40% of the patients as a result of GH-PRL-secreting adenomas or stalk compression and galactorrhea may or may not ensue.

A comprehensive strategy for the treatment of

acromegaly should aim at maintaining normal anterior pituitary function and, if necessary, adequate hormone replacement therapy should be given.

Evaluation of acromegaly related complications

Cardiovascular system

Mortality in acromegaly is increased mostly because of cardiovascular complications, responsible for 50-60% of the deaths (30,32). The cardiovascular system complications include: hypertension, acromegalic cardiomyopathy, arrhythmias, coronary artery disease (CAD) and endothelial dysfunction.

Hypertension is considered one of the major negative predictors of survival in acromegaly (36,81). Its prevalence has been reported to range from 18 to 60% in different clinical series (81-83), with a mean prevalence of about 35% (84). In a study from our group its prevalence was 47.5% (85). Hypertension in acromegaly is generally mild, uncomplicated, and easily controlled with standard antihypertensive medications (84).

Chronic GH and IGF-I excess affects cardiac morphology and performance inducing a specific cardiomyopathy (86-88). Its prevalence is variable, between 25% and 100% in different series, which is related to the different populations studied (86,89-92). Its most common feature is left ventricular hypertrophy (LVH) (93,94), which was present in 57.5% of our patients (85). In that study, hypertension and IGF-I were independent determinant factors of LHV (85).

Systolic and diastolic dysfunction are functional consequences of acromegalic cardiomyopathy. At diagnosis, alteration of the diastolic filling at rest is common. Impairment of the ejection fraction after exercise can be recorded in 73% of patients (87). In the advanced stage, systolic disorders become more relevant. Ventricular dilatation is a less common complication, with poor prognosis, that occurs in later stages of the disease (95).

Cardiac valve disease, specially mitral and aortic are other cardiac abnormalities reported (92). In a recent study, Colao et al. (96) demonstrated a high prevalence of mitral and aortic valve dysfunction in acromegalic patients, compared with controls (86% vs. 24%).

Ectopic rhythm, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia, sick sinus syndrome and ventricular tachycardia are more frequently recorded in acromegalic patients than in control subjects (97). In particular, complex ventricular arrhythmias were found in 48% of acromegalic patients as compared with 12% of controls (98). Herrmann et al. (99) found a prevalence of late potentials significantly higher in patients with active acromegaly than in the control group.

The prevalence of CAD varies between 3 and 37% in different series (100). Studies of post-mortem heart-catheterization showed involvement of small vessels with thickening of the intramural vessels in up to 22% of cases (101). Holdaway et al. (36) recently showed that myocardial infarct was the main cause of death in acromegalic patients.

Significant increase of the carotid intima-media thickness without an increased prevalence of atherosclerotic plaques have been reported in acromegalics (102). Increased concentration of IGF-I might be involved in the lack of susceptibility to atherosclerosis in some acromegalic patients (103).

The management of acromegaly should include a careful evaluation of cardiovascular function and morphology at the diagnosis and during the follow-up. Our patients have their blood pressure measured in every appointment and ECG, Holter ECG, Doppler echocardiogram, and Doppler ultrasound of the carotids are done at diagnosis (table 3). Coronary artery disease is investigated if signs and/or symptoms of ischemic cardiopathy are present. Other diagnostic methods are: equilibrium radionuclide angiography, coronary angiography and cardiac magnetic resonance. The Doppler echocardiogram and Doppler ultrasound of carotid should be done every 12 months during the follow-up of an uncontrolled acromegalic patient.

Treatment of the cardiovascular complications of acromegaly is based on controlling the activity of acromegaly, once studies suggested that its progression can be arrested by achieving biochemical control of the disease (104-107). In addition, hypertension, arrhythmias and systolic dysfunction requires specific treatment. Their follow-up and therapeutic management are similar to that of the general population (108).

Respiratory system

Respiratory disorders account for up to 25% of mortality in acromegaly, being second only to cardiovascular events (81,109). The most typical and probably relevant respiratory complication in acromegaly is the sleep apnea (SA), defined as the presence of more than five episodes of apnea or hypopnea lasting at least 10 seconds for each hour of nocturnal sleep. When associated with daytime somnolence, it characterizes the sleep apnea syndrome (SAS). SAS can lead to serious consequences including increased fatal road accidents and reduced overall quality of life (110), besides an elevated cardiovascular risk (111), which is mostly due

Table 3. Screening of acromegaly complications.

Complications	Evaluation/Diagnostic Tests
Cardiovascular System	BP measurement Eletrocardiogram (ECG) Doppler Echocardiogram Doppler ultrasound of the carotids Holter ECG
Respiratory System	Epworth score Polysomnography Cavum MRI
Glucose metabolism **Non-diabetic**	 OGTT Fasting insulin (HOMA-IR)
Diabetic	Fasting glucose HbA1c C peptide
Osteoarticular	Clinical evaluation X-ray* Ultrasonography*
Cancer ♦	Colonoscopy

BP= blood pressure; MRI= magnetic resonance imaging; OGTT= oral glucose tolerance test; HbA1c= hemoglobin A1c.
* If necessary.
♦ Screening for prostate, breast and female genital tract cancer should follow the recommendations for the general population.

to the presence of ischemic cardiopathy, hypertension, stroke, pulmonary hypertension, and cardiac arrhythmias (112-114). With the more extensive use of polysomnography, an increasing prevalence of SA has been recorded in acromegaly over the years: from 20-30% to 60-70% or more nowadays (115).

There are two types of SA: a central type manifested by apneic events without an inspiratory effort, indicating reduced central respiratory drive; and an obstructive type characterized by repetitive obstruction of the upper airway, leading to apneic events despite ongoing inspiratory efforts. Both types of SA result in oxygen desaturation and arousals from sleep. The mixed type of SA, previously described, is not regarded anymore (116). The polysomnographic evaluation of 25 of our *de novo* acromegalic patients revealed a SA prevalence of 88% (22 patients), higher than described in the literature. In addition, out of the 22 patients with SA on polysomnography, 21 had predominantly obstructive apnea and only one had predominantly central apnea (data not published).

Therefore, in our acromegalic patients, we recommend to perform overnight polysomnography and cavum MRI at diagnosis in order to identify the presence of SA and possible related anatomic abnormalities (table 3). In patients with confirmed SA, we also screen for SAS with the Epworth Scale Questionaire (117). A score greater than 10 is considered a risk factor for the performance of regular activities, due to excessive daytime sleepiness.

The relationship between SAS and the biochemical activity of acromegaly is not clear. Some authors have reported the persistence of SAS in acromegalic patients, besides reduction or normalization of GH levels after treatment (118-122). However, some studies showed a marked improvement in SAS after treatment with both short and long-acting somatostatin analogs, even in patients not properly controlled (119,123), suggesting that octreotide may exert direct effects on the respiratory control (124) or on the upper airway (reducing soft tissues edema) (120,125). This action seems to be unrelated to the GH-lowering effects of octreotide (124).

Thus, it is advisable to repeat polysomnography and cavum MRI in acromegalic patients 6 months after disease control with surgery or medical therapy with octreotide LAR. The use of continuous positive airway pressure (CPAP) maintains the upper airway permeability, preventing its collapse, mainly in the inspiratory phase. Its use should be recommended in acromegalic patients with persitent SAS despite treatment of acromegaly. A new polysomnography should be performed after 1 year of continuous therapy with CPAP.

Glucose metabolism

The anti-insulin effects of GH cause carbohydrate intolerance and secondary diabetes mellitus (DM) in, respectively, 50% and 10-30% of the acromegalic patients (126-129). Data from 72 newly diagnosed patients followed in our outpatient clinic revealed impaired glucose tolerance (IGT) in 18.1% and DM in 27.8%.

Active acromegaly is frequently characterized by the presence of insulin resistance (IR). Although the precise mechanisms remain poorly understood, the IR in acromegaly is characterized by defects in the ability of insulin to suppress hepatic glucose production and by impairment of glucose uptake and oxidation into peripheral tissues (130). A study using homeostasis model assessment (HOMA) to evaluate IR demonstrated that HOMA-IR was higher in acromegalic patients than in healthy controls (131). In a study of our group in which 20 newly diagnosed acromegalic patients without diabetes were evaluated, mean HOMA-IR was 4.0 ± 3.2 (RV:2.1 ± 0.7) (data not published). Hyperinsulinemia and insulin resistance may play an important role on the cardiovascular risk of acromegalic patients (132).

Recently, Kasayama et al. (133) described that insulin sensitivity is reduced to a similar extent in acromegalic patients with normal glucose tolerance and those with impaired glucose tolerance or diabetes. However, compensatory beta cell hyperfunction appears to counterbalance the reduced insulin sensitivity only in those with normal glucose tolerance.

At diagnosis of acromegaly, carbohydrate metabolism should be assessed by fasting and two-hour glucose during an OGTT, and fasting insulin in order to obtain HOMA-IR (table 3). Oral glucose tolerance test should not be undertaken if the patient already has the diagnosis of DM. Laboratorial evaluation should be done every 6 months in patients with uncontrolled disease. In diabetic patients, we currently perform the measurement of fasting glucose, glycosylated hemoglobin (HbA1c) and C peptide at diagnosis and every 3 months (table 3). At physical examination, the abdominal circumference, height and weight should be recorded.

Carbohydrate intolerance and DM improve rapidly with lowering of GH after surgery. Somatostatin analogues therapy are able to inhibit in a similar manner pancreatic insulin and glucagon secretion, as well as GH secretion in acromegalic patients. These metabolic effects are responsible for complex results on overall glycemic control, mainly depending on the balance between the improvement of GH-dependent insulin resistance and the suppression of insulin and glucagon secretion (131). Therefore, acromegalic patients in regular use of somatostatin analogues must be evaluated more carefully (131,134).

Treatament of impaired glucose tolerance and DM in acromegaly should include dietary approach (135), physical activity (136) and pharmacologic treatment in the same way that for the regular type 2 diabetic patient (137).

Osteoarticular system

Articular manifestations are frequent clinical complications and a leading cause of morbidity and functional disability in acromegaly (97). At presentation, 60-70% of the patients have involvement of large peripheral joints (shoulder, knee, hip) and about 50% have axial arthropathy affecting mainly the lumbar area (138-140). The most common sign of acromegalic arthropathy on examination is crepitus (97).

Excess circulating GH and IGF-I, as well as locally produced IGF-I, stimulate the articular chondrocytes leading to replication and matrix synthesis. As a result, thickening of the cartilage occurs, accompanied by widening of the articular space and alteration of joint geometry. The latter is worsened by synovial hypertrophy that results from GH and IGF-I action over the periarticular structures (141). At this point, arthropathy can be reversed by adequate treatment of acromegaly and control of disease activity (97). As disease progresses, the cartilage surface develops progressively enlarging fissures, the fibrocartilage proliferates and calcifies, resulting in osteophyte formation. Finally, an irreversible thinning of the articular cartilage occurs, resulting in narrowed joint space (141). Radiological evaluation reveals joint space widening early in the disease, whereas long-standing acromegaly is characterized by the narrowing of joint spaces, osteophytosis, and other features of osteoarthritis (141).

Periodic clinical evaluation of arthropathy is recommended and imaging studies such as X-rays and/or ultrasonography should be done if necessary (table 3). Treatment with somatostatin analogs have already been shown to improve signs and symptoms of arthropathy. Colao et al. (142) showed that treatment with octreotide decreased cartilage thickness and, in a subsequent study with lanreotide, clinical improvement was observed in all patients with normalization of plasma IGF-I (143).

Thus, one should focus on early diagnosis of acromegaly in order to start treating the disease when joint involvement is still reversible. Later in the course, symptomatic relief of the pain should be offered to the patients as well as other strategies,

such as physical therapy, local steroid injections or, in advanced cases, surgical intervention (including joint replacement).

Cancer

The association between acromegaly and cancer has been extensively investigated and is still under debate. Evidence from a large series (31) suggests acromegaly modifies the progression of existing malignancies but their role in tumorigenesis is still unproven (145). The most well established association between acromegaly and neoplasia is with colon cancer. It appears that acromegalics are at risk for benign and malignant colonic tumors that occur at a younger age than in the general population (146-150). In addition, patients who are found to harbor a colonic neoplasia are at risk for recurrence (149). In a study by our group, the evaluation of 30 patients (22 women) with 39.6 years (± 14.3), revealed hyperplastic polyps in 16.7% (5 patients) and adenomatous polyps in 13.3% (4 patients). No adenocarcinomas were found (151).

Hyperplastic polyps have little malignant potential. Risk factors for progression to colonic cancer include: multiplicity (> 20), size (> 10mm), high grade dysplasia and concomitant adenomas (152). Adenomatous polyps are considered premalignant lesions and the pathogenesis of colon cancer seems to involve the progression from adenomas to carcinomas, a process that takes approximately 10 years (153).

In our outpatient clinic, every acromegalic patient undergoes colonoscopic examination at diagnosis (table 3). If colonoscopy is normal or only a few hyperplastic polyps are found, the patient has no family history of colon cancer and GH/IGF-I levels are under control, colonoscopy is repeated every 5 years. However, if adenomatous polyps are found or the patient has a positive family history or hormonal levels are not adequately controlled, repeat examination is done every 3 years (154). The colonoscopic examination is always performed by the same experienced colonoscopist. This is a very important issue because large bowel lenght and loop complexity makes colonoscopic examination in acromegalics a technically difficult task which can increase the risk of serious complications (155).

Screening for breast and female genital tract cancers as well as for prostate cancer should follow the recommendations for the general population.

In conclusion, acromegaly is a heterogeneous disease and numerous aspects should be considered before deciding the treatment modality. In addition, careful evaluation of its associated complications should be done and appropriate therapeutic interventions undertaken.

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