

# Screening for acromegaly in adult patients not reporting enlargement of the extremities, but with arterial hypertension associated with another comorbidity of the disease

*Rastreamento de acromegalia em pacientes adultos não relatando crescimento de extremidades, mas com hipertensão arterial associada a outra comorbidade da doença*

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## ABSTRACT

**Objective:** To determine the value of acromegaly screening in adult patients not reporting enlargement of the extremities, but who present arterial hypertension associated with at least one other comorbidity of the disease. **Subjects and methods:** Patients seen by general practitioners at primary health care units were evaluated. Among the patients without extremity enlargement, those with recently diagnosed arterial hypertension associated with at least one other comorbidity were selected. **Results:** A total of 1,209 patients were submitted to laboratory investigation. Elevated IGF-1 was observed in 22 patients. Eighteen patients had adequate suppression of growth hormone (GH). No GH suppression was observed in four women with confirmed elevated IGF-1. In the latter, IGF-1 and nadir GH were only slightly elevated, magnetic resonance showed a normal pituitary, and chest and abdominal computed tomography revealed no tumor, and no intervention was performed. **Conclusion:** In patients with arterial hypertension without known pituitary disease, acromegaly is unlikely in the absence of enlargement of the extremities. *Arq Bras Endocrinol Metab.* 2014;58(8):807-11

## Keywords

Acromegaly; screening; arterial hypertension; enlargement of the extremities

## RESUMO

**Objetivo:** Determinar o valor do rastreamento de acromegalia em pacientes adultos sem aumento de extremidades, mas com hipertensão arterial associada a pelo menos uma outra comorbidade da doença. **Sujeitos e métodos:** Pacientes vistos por clínicos em unidades primárias de saúde foram avaliados. Entre pacientes sem aumento de extremidades, aqueles com hipertensão arterial diagnosticada recentemente e associada a pelo menos uma outra comorbidade foram selecionados. **Resultados:** Um total de 1.209 pacientes foi submetido à investigação laboratorial. IGF-1 foi elevado em 22 pacientes. Dezoito pacientes apresentavam supressão adequada do hormônio do crescimento (GH). Ausência de supressão do GH foi vista em quatro mulheres com IGF-1 repetidamente elevado. Nestas, IGF-1 e nadir do GH foram apenas discretamente aumentados, ressonância magnética revelou hipófise normal, tomografia computadorizada de tórax e abdome não revelaram tumor, e nenhuma intervenção foi realizada. **Conclusão:** Em pacientes com hipertensão arterial sem doença hipofisária conhecida, acromegalia é improvável na ausência de aumento de extremidades. *Arq Bras Endocrinol Metab.* 2014;58(8):807-11

## Descritores

Acromegalia; rastreamento; hipertensão arterial; aumento de extremidades

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## INTRODUCTION

Acromegaly generally has an insidious onset and its prevalence may be underestimated (1-3). If untreated, the hypersecretion of growth hormone (GH) is associated with clinical complications and increased mortality (4,5). In contrast, when acromegaly is diagnosed and treated adequately; tumor control, control of hormone secretion, prevention of the onset of complications, and improvement of existing comorbidities are possible in most patients (4-7). The importance of an early diagnosis is therefore unquestionable.

However, since acromegaly is a rare disease, the establishment of strategies designed to increase the diagnosis and to permit early detection in a rational and cost-effective manner is a challenge (3). Agreement regarding the need to investigate hypersecretion of GH exists for patients with a typical phenotype or imaging results compatible with pituitary adenoma (8). Except for these cases, there are no objective recommendations as to which patients should be evaluated for acromegaly (9-17), and the "clinical suspicion" is subject to the personal impression of each physician, which is influenced by academic background, degree of suspicion, experience with the disease, and motivation to diagnose it. In an attempt to encourage early detection, some authors and guidelines recommend acromegaly to be investigated in subjects with two or more comorbidities associated with the disease (18,19). Considering its high prevalence in the general population, arterial hypertension is one of these comorbidities that would be interesting to study.

The objective of this study was to determine the value of acromegaly screening by serum IGF-1 measurement in adult patients without known pituitary disease and not reporting enlargement of the extremities, but who present arterial hypertension associated with at least one other comorbidity of the disease (18,19).

## SUBJECTS AND METHODS

The study and its respective protocol were approved by the Ethics Committee of our institution and informed consent was obtained from all subjects. The study was prospective.

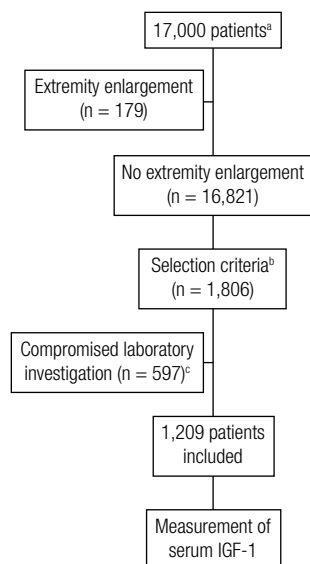
Among the patients seen by general practitioners between July and December 2010 at the 9 primary health care units of the city of Belo Horizonte (one per Sanitary District), subjects of both genders ranging in age from 18 to 70 years without known pituitary

disease, and excluding pregnant women, were initially evaluated (n = 17,000). The medical records of these patients were analyzed and personal interviews were conducted, including the application of a questionnaire for the detection of extremity enlargement (3). The items of the questionnaire were: Has your shoe size increased over the last 5 years? Did you have to change your wedding ring or ring over the last 5 years because it became tight? The interviews were conducted and the questionnaires were applied by nursing students enrolled in the School of Nursing (3).

One hundred seventy nine patients responded positively to at least one of the items of the questionnaire and the results of these patients have been published previously (3). Among the 16,821 patients who responded negatively to two items of the questionnaire, 1,806 subjects with recently diagnosed (< 5 years) arterial hypertension requiring antihypertensive medication, associated with at least one other comorbidity of acromegaly, were subsequently selected for this study. These comorbidities were (18,19): (i) nonspecific chronic headache (for example, migraine and hypertensive headache were not considered); (ii) generalized and persistent excessive sweating; (iii) diffuse arthralgias associated with some radiologic alteration (20) in the absence of known rheumatological disease (reported by the patient, suspected, or confirmed in the medical record); (iv) chronic fatigue not explained by any other underlying disease (among the diagnoses reported by the patient or present in the medical record); (v) bilateral paresthesias (Carpal tunnel syndrome); (vi) recently diagnosed *diabetes mellitus*.

Because of the possibility of interference with laboratory assessment, patients with known kidney or liver disease, patients with anorexia nervosa, patients presenting weight loss > 5% in the last 3 months and BMI < 18.5 kg/m<sup>2</sup>, or women receiving oral estrogens were excluded. The remaining 1,209 patients comprised the final sample (Figure 1).

Serum IGF-1 was measured in all patients included in study. Acromegaly was ruled out if serum IGF-1 was normal for sex and age. When IGF-1 levels were elevated, a new measurement was obtained and combined with the measurement of GH during an oral glucose tolerance test (OGTT) (GH before and 30, 60, 90 and 120 min after the oral administration of 75 g anhydrous glucose). Patients with persistently elevated IGF-1 associated with nadir GH  $\geq$  0.4  $\mu$ g/L (4,5,9,10,12,15,16,19,21) were submitted to magnetic



<sup>a</sup> Patients seen by general practitioners at primary health care units, ranging in age from 18 to 70 years, without known pituitary disease and excluding pregnant women.

<sup>b</sup> Patients with recently diagnosed (< 5 years) arterial hypertension requiring antihypertensive medication, associated with at least one other comorbidity (18,19).

<sup>c</sup> Patients with known kidney or liver disease, patients with anorexia nervosa, patients with weight loss > 5% in the last 3 months and BMI < 18.5 kg/m<sup>2</sup>, or women receiving oral estrogens.

**Figure 1.** Selection of patients included in the study.

resonance imaging (MRI) of the pituitary using gadolinium as contrast agent. The samples were collected in the morning after an approximately 10-h fast, with the subject resting for 20 min before and during the OGTT.

GH was measured with a chemiluminescence assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA) with an analytical sensitivity  $\leq 0.05$   $\mu\text{g/L}$ . The standard provided by the kit was calibrated against the World Health Organization (WHO) 2<sup>nd</sup> International Standard (IS) 98/574. The results are expressed as  $\mu\text{g/L}$ . IGF-1 was also measured with a chemiluminescent assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA) with an analytical sensitivity of 25  $\mu\text{g/L}$  using standards calibrated against the WHO IS 87/518 preparation, and previously established reference values stratified by sex and age based on a sample of 1,000 subjects rigorously selected in the same town where the study was conducted (22).

## RESULTS

Among the 1,209 patients submitted to laboratory investigation of acromegaly, 613 were women and 606 were men. Patient age ranged from 20 to 70 years (me-

dian 51 years). In addition to arterial hypertension (inclusion criterion), the comorbidities (18,19) detected in the patients are shown in table 1. Elevated serum IGF-1 levels for sex and age were observed in 22 patients. When the measurement was repeated, three patients presented normal IGF-1 and adequate suppression of GH in the OGTT. Fifteen of the 19 patients with persistently elevated IGF-1 had adequate suppres-

**Table 1.** Comorbidities (18,19), in addition to arterial hypertension (inclusion criterion), detected in the 1,209 patients included in the study

Comorbidity	Number of patients
Chronic headache	675 (55.8%)
Diabetes mellitus	331 (27.3%)
Chronic fatigue	278 (23%)
Diffuse arthralgias	274 (22.6%)
Paresthesias (Carpal tunnel syndrome)	263 (21.7%)
Excessive sweating	150 (12.4%)
Number of comorbidities	
1	615 (50.8%)
2	480 (39.7%)
$\geq 3$	124 (10.2%)

**Table 2.** Results of the 19 patients with persistently elevated IGF-1

Patient	Sex	Age (years)	IGF-1 (x ULN)	Nadir GH ( $\mu\text{g/L}$ )	Number of comorbidities (in addition to arterial hypertension)
1	Male	65	1.2	0.1	1
2	Male	61	1.15	0.1	1
3	Male	44	1.22	0.15	2
4	Male	39	1.08	0.18	2
5	Male	37	1.1	0.2	1
6	Male	53	1.05	0.22	1
7	Male	65	1.2	0.2	2
8	Male	48	1.05	0.2	1
9	Male	35	1.1	0.16	2
10	Female	61	1.08	0.18	1
11	Female	52	1.15	0.2	2
12	Female	50	1.08	0.2	1
13	Female	45	1.21	0.24	2
14	Female	36	1.05	0.28	1
15	Female	60	1.1	0.3	1
16	Female	42	1.07	0.5	2
17	Female	58	1.12	0.56	3
18	Female	35	1.28	0.68	2
19	Female	38	1.15	0.85	1

ULN: upper limit of normal.

sion of GH in the OGTT (patients 1-15 in Table 2). No GH suppression in the OGTT was observed in four women with confirmed elevated IGF-1 (patients 16-19 in Table 2). Since serum IGF-1 and nadir GH were only slightly elevated, MRI showed a normal pituitary and chest and abdominal contrast-enhanced computed tomography revealed no tumor, no intervention was performed. These four patients continue under follow-up (clinical assessment and measurement of IGF-1 at intervals of 6 months), with the absence of symptom progression and observation of stable IGF-1 levels in three and subsequent spontaneous and persistent normalization of IGF-1 in one patient (patient 16 in Table 2). The time of follow-up until now is 3 years.

## DISCUSSION

The currently available therapies (surgery, somatostatin analogs, GH antagonists, dopamine agonists, radiotherapy) permit the control and occasional cure of tumors and hormone hypersecretion, as well as the improvement and even reversal of comorbidities, in most patients with acromegaly (4-7). This chance is even higher when the disease is detected early. The fact that acromegaly is underdiagnosed (1-3) or diagnosed late (23) continues to be the problem. Most patients report that they have sought medical care due to manifestations of the disease before the diagnosis was finally suspected (23,24). Therefore, the problem does not seem to be the lack of seeking medical care on the part of patients, but rather the lack of familiarity of health professionals with the manifestations of acromegaly, who do not remember this hypothesis when treating patients with suspicious signs and/or symptoms (3). This fact is supported by the observation that, even in screening studies, the cases detected already exhibit an exuberant phenotype, but the disease had not been suspected by the physicians (1-3), probably due to the rarity of the condition.

Objective recommendations as to which subjects should be investigated for acromegaly may improve detection of the disease. This is the case of patients with imaging findings compatible with pituitary adenoma (8). Subjects with a “suspicious phenotype” are also recommended for investigation, but there is no objective definition of this phenotype (9-17), which is left to the personal impression of each physician.

Enlargement of the extremities is an early and almost universal manifestation of acromegaly (23-29). In fact, a previous study suggested that the presence of this

finding evaluated by two simple questions is an objective, simple and cost-effective method to define a “suspicious phenotype” (3). The present study determined whether this manifestation would be sufficiently sensitive to detect acromegaly in patients without a known pituitary tumor which, if confirmed, would support the validity of this parameter (growth of the extremities) as a criterion to indicate investigation for acromegaly. At the same time, this criterion was compared to the recommendation proposed by other authors, i.e., the investigation of subjects with two or more comorbidities (18,19). In view of its high prevalence in the general population, arterial hypertension is one comorbidity that would be interesting to study.

We observed no case of acromegaly among 1,209 adult patients without a known pituitary tumor who did not report growth of the extremities, although they presented two or more comorbidities [arterial hypertension associated with at least one other comorbidity] as proposed by some authors (18,19). It should be noted that additional criteria were adopted to increase the specificity of these manifestations. This result highlights the importance of growth of the extremities while, at the same time, weakens the cost-effectiveness of investigating acromegaly in subjects without a known pituitary tumor in the absence of that manifestation.

We cannot rule out acromegaly in patients with elevated serum IGF-1 based on adequate normative values (22) in two measurements, in the absence of pregnancy, hyperthyroidism and puberty, and accompanied by the lack of GH suppression in the OGTT. However, we believe that the disease is unlikely in the four patients of our series with this finding considering the presence of only slightly elevated serum IGF-1 and nadir GH and the absence of a tumor on MRI. In fact, cases of acromegaly with GH suppression in the OGTT exhibited apparent adenoma on MRI (27-32). Furthermore, ectopic production of GHRH is unlikely in the presence of the biochemical findings cited, normal MRI (no hyperplasia), and absence of a tumor on chest and abdominal CT scans (33). Corroborating the absence of disease, the four patients continue without symptom progression and with stable IGF-1 levels (no intervention). Cases of patients with unexplainable elevated IGF-1 and without acromegaly have been reported by other authors (32,34).

The results of this study indicate that acromegaly is unlikely in patients with arterial hypertension and without known pituitary disease in the absence of growth

of the extremities and that this finding can be used to select patients who should be submitted to investigation for GH hypersecretion (3).

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