

Laboratory investigation of acromegaly: Is basal or random GH > 0.4 µg/L in the presence of normal serum IGF-1 an important result?

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ABSTRACT

Objective: To determine the frequency of indication of the GH suppression test and pituitary magnetic resonance imaging (MRI) in patients with clinical suspicion of acromegaly with GH concentrations > 0.4 µg/L despite normal serum IGF-1. **Subjects and methods:** A total of 160 patients with clinical suspicion of acromegaly with normal IGF-1 were studied. **Results:** Basal GH > 0.4 µg/L was observed in 70/88 women (79.5%). Nadir GH > 0.4 µg/L was found in 21/70 women (30%) and these patients were submitted to MRI, which revealed a microadenoma in 2/21 women (9.5%). In these two women, IGF-1 continued to be normal in subsequent measurements and no clinical progression has been observed so far (time of follow-up until now 4 years). Basal GH > 0.4 µg/L was seen in 33/72 men (45.8%). Nadir GH was < 0.4 µg/L in all of them. **Conclusions:** In patients with clinical suspicion of acromegaly, concern over GH concentration in the presence of normal IGF-1 results in the unwarranted complementary investigation in many cases, and even in possible equivocal diagnoses. It is only in exceptional cases that normal IGF-1 should not rule out acromegaly. *Arch Endocrinol Metab.* 2015;59(1):54-8

Keywords

Acromegaly; laboratory diagnosis; serum IGF-1; basal GH

INTRODUCTION

Acromegaly is an insidious disease which prevalence might be underestimated (1-3). If untreated, acromegaly is associated with high morbidity and mortality; however, when diagnosed and treated adequately, control of the tumor and of hormone hypersecretion is possible in most cases, a fact highlighting the importance of an early diagnosis of the disease.

In the case of clinical suspicion of acromegaly, investigation is traditionally started by the measurement of IGF-1 combined with basal GH (4-23). The disease is ruled out if IGF-1 is normal and basal GH is less than 0.4 µg/L. Thus, diagnosis cannot be ruled out in patients with normal IGF-1 but basal GH > 0.4 µg/L. In this situation, investigation is based on GH suppression test after oral glucose overload (4-23). This strategy is justified by the analytical and normative limitations related to this hormone, conditions that interfere in IGF-1 measurements (reducing it), and cases of acromegaly with normal IGF-1 (5,8,12,17,18,20,23,24). Although the determination of GH concentration increases the sensitivity of patient testing, it is important to evaluate the

consequences of attributing a cut-off for GH concentrations when IGF-1 is normal, i.e., to consider how many subjects are additionally submitted to the GH suppression test and pituitary imaging methods that may lead to an equivocal diagnosis. We emphasize that, except for patients with a typical phenotype or pituitary adenoma, the “clinical suspicion” of acromegaly is prone to the subjective impression of each physician. Therefore, the true probability of the disease among patients submitted to laboratory investigation is variable, with consequences on the predictive value of the tests.

Using current assays and excluding known causes of GH suppression failure, nadir GH > 0.4 µg/L after oral glucose overload is indicative of autonomous GH secretion (5,7,8,11,14-17,19,22,23,25-32).

Using one of the algorithm traditionally recommended for the investigation of patients with clinical suspicion of acromegaly (Figure 1), the objective of this prospective study was to determine the frequency of indication of the GH suppression test and pituitary MRI and the probability of an equivocal diagnosis when GH concentrations > 0.4 µg/L despite normal serum IGF-1 are taken into consideration.

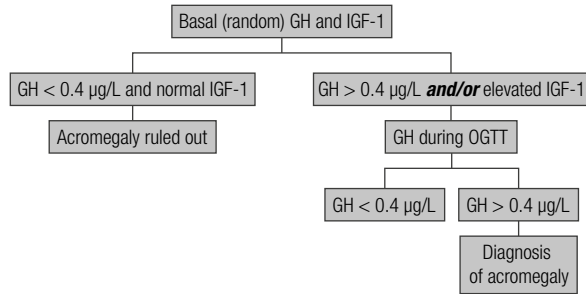


Figure 1. Algorithm of laboratory investigation of patients with a clinical suspicion of acromegaly (4-23).

SUBJECTS AND METHODS

The study and its respective protocol (Figure 2) were approved by the Ethics Committee and informed consent was obtained from all subjects. The study was prospective.

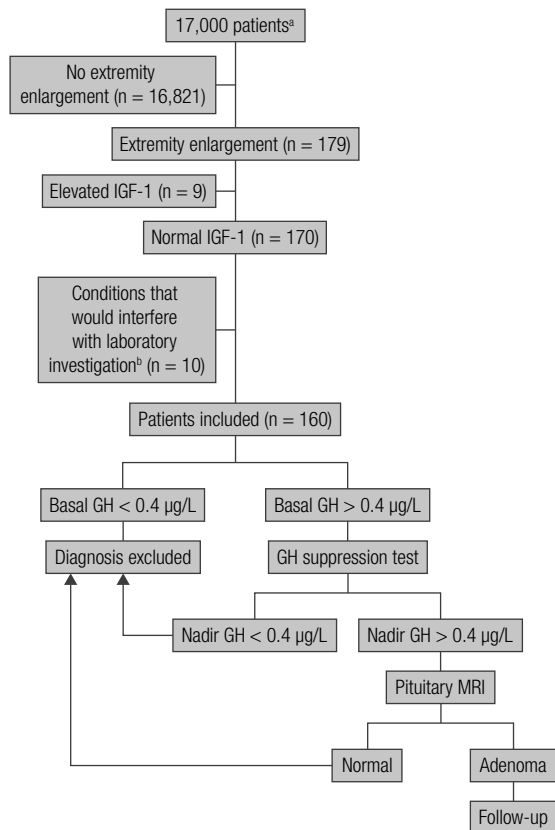
Among the patients seen by general practitioners between July and December 2010 at the nine primary

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 (1.05%) responded positively to at least one of the items of the questionnaire. Specifically for this study, considering its objective, only patients with normal IGF-1 were included ($n = 170$). To avoid interference with the laboratory investigation, patients with *diabetes mellitus*, thyroid dysfunction, kidney or liver disease, anorexia nervosa, weight loss > 5% in the last 3 months and BMI < 18.5 kg/m², and women receiving oral estrogens were excluded ($n = 10$). Thus, the sample consisted of 160 patients who reported enlarged extremities (clinical suspicious of acromegaly), but had normal IGF-1 and presented no conditions that would interfere with laboratory investigation.

Basal GH was measured in the same sample as IGF-1. The latter was normal in all patients (inclusion criteria). When GH levels were > 0.4 µg/L, a new measurement was obtained 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). The samples were collected in the morning after an approximately 10-h fast and the subject rested for 20 min before and during the OGTT. Patients with nadir GH > 0.4 µg/L (5,7,8,11,14-17,19,22,23,25-32) were submitted to MRI of the pituitary using gadolinium as contrast agent.

GH was measured by chemiluminescence assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA). The analytical and functional sensitivities of the assay were 0.01 µg/L and 0.05 µg/L, respectively; with interassay coefficient of variation < 6.6% at concentrations between 0.3 and 17 µg/L. The standard provided by the kit was calibrated against the World Health Organization (WHO) 2nd International Standard (IS) 98/574. The results are expressed as µg/L. IGF-1 was measured by immunochemiluminescent as-



^a 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.

^b *Diabetes mellitus*, thyroid dysfunction, kidney or liver disease, anorexia nervosa, weight loss > 5% in the last 3 months and BMI < 18.5 kg/m², and oral estrogens.

Figure 2. Selection of patients included in the study and its respective protocol.

say (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA). The analytical sensitivity of the assay was 25 µg/L, with intra- and interassay coefficients of variation < 8%. 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 were used (33).

RESULTS

Women (n = 88)

Basal GH > 0.4 µg/L was observed in 70/88 women (79.5%), who were submitted to the OGTT because of this result. Nadir GH > 0.4 µg/L was found in 21/70 women (30%) (Table 1). These patients were therefore submitted to pituitary MRI, which revealed a lesion compatible with microadenoma (hypointense nodule measuring 4 and 6 mm in diameter and showing no contrast enhancement after the administration of gadolinium) in 2/21 women (9.5%). These two women

Table 1. Data of the 21 women with nadir GH > 0.4 µg/L after an oral glucose overload

Age (years)	IGF-1 (x ULN)	Nadir GH (µg/L)	MRI
24	0.90	0.72	Normal
25	0.75	0.45	Normal
25	0.90	0.54	Normal
28	0.70	0.68	Normal
30	0.70	0.45	Normal
34	0.80	0.48	Normal
36	0.70	0.85	Normal
36	0.85	0.47	Normal
40	0.85	0.55	Normal
41	0.80	0.52	Microadenoma (4 mm)
43	0.90	0.42	Normal
44	0.75	0.59	Normal
46	0.80	0.65	Partial empty sella
48	0.70	0.61	Normal
51	0.80	0.47	Normal
52	0.70	0.65	Normal
53	0.80	0.56	Microadenoma (6 mm)
53	0.85	0.45	Normal
54	0.80	0.60	Partial empty sella?
55	0.75	0.42	Normal
58	0.70	0.45	Normal

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ULN: upper limit of normal range; MRI: magnetic resonance imaging.

continue under follow-up (at intervals of 6 months). IGF-1 levels have remained within normal range in subsequent measurements and no progression of clinical manifestations has been observed so far. In addition, reassessment of GH suppression after OGTT, performed after 36 months, still resulted in GH nadir between 0.4 µg/L and 1 µg/L (0.6 and 0.7 µg/L, respectively). The time of follow-up, until now, is 4 years.

Interestingly, nadir GH > 0.4 µg/L on OGTT and indication of pituitary MRI was observed in 14/42 (31%) young or young adult women (age < 50 years) and in 7/46 (15.2%) women ≥ 50 years of age.

Men (n = 72)

Basal GH > 0.4 µg/L was seen in 33/72 men (45.8%), who were submitted to the OGTT because of this finding. Nadir GH was < 0.4 µg/L in all of them, terminating the investigation.

DISCUSSION

The objective of this study, in agreement with the selection criteria and protocol used, was to evaluate the diagnostic workout results in patients with clinical suspicion of acromegaly, with normal serum IGF-1 but with GH concentrations > 0.4 µg/L (4-23). It was not our objective, and the results cannot be used, to define the role of GH (basal or after OGTT) in the diagnostic confirmation of patients with elevated IGF-1. Therefore, this aspect will not be discussed here.

Serum IGF-1 is an excellent marker of GH secretion and is therefore highly sensitive in detecting hypersecretion of this hormone. However, concern exists if acromegaly is ruled out based only on serum normal IGF-1 value (4-23), mainly because of analytical problems and the lack of adequate normal reference values for many assays (5,8,17,18,20,23,33), even in the absence of clinical conditions that interfere (reduce) with serum IGF-1. Therefore, many authors also recommend the measurement of basal GH to rule out the disease (4-23). The present study showed that not ruling out acromegaly diagnosis when serum IGF-1 is normal but GH is > 0.4 µg/L (4-23) lead often to the indication of GH suppression test, and less frequently to MRI, which are expensive procedures and have the risk of providing an equivocal diagnosis, particularly in women.

The present results do not seem to be overestimated. First, because conditions that could increase serum GH

concentrations were rigorously excluded. In this respect, the use of oral contraceptives is common among women and discontinuation for a sufficient period of time is not always advised or possible before laboratory investigation. As a consequence, the frequency of GH > 0.4 µg/L may be even higher than the observed in the present study. Secondly, the finding of lesions compatible with microadenoma upon MRI is also not unexpected since these lesions can be detected in more than 10% of the adult population (34,35). Thirdly, the current consensus is that nadir GH levels > 0.4 µg/L after OGTT are considered to be altered (5,7,8,11,14-17,19,22,23,25-32). Some authors recommend even lower cut-off values such as 0.3 µg/L (5,8,11,15-17,19,23,26), 0.25 µg/L (7), and 0.2 µg/L (14).

As only patients with clinical suspicion of acromegaly based on a specific questionnaire for the detection of extremity enlargement (3) were included in this study, one can not argue that the tests were performed in subjects without clinical indication or that in clinical practice the investigation of cases with GH > 0.4 µg/L and normal IGF-1 would provide different results, i.e., leading frequently to the diagnosis of acromegaly. We emphasize that an earlier diagnosis of acromegaly requires increasing the number of suspicious and investigated cases, which tends to reduce the positive predictive value of the tests.

In view of the importance of diagnosing acromegaly and not delaying the diagnosis, as well as the existence (although uncommon) of cases with normal serum IGF-1 (12,24), in some special situations it is reasonable not to rule out the disease based only on IGF-1 levels within the normal range (Table 2), but the assessment should be complemented by the measurement of GH. However, in most cases GH measurement would not be necessary to rule out the disease.

Table 2. Suggestions for the investigation of subjects with suspicion of acromegaly and normal serum IGF-1

<p>GH concentrations should only be considered in the following situations:</p> <p>(i) Absence of adequate normative data for IGF-1[§]</p> <p>(ii) IGF-1 very close to the upper limit of normal range</p> <p>(iii) Presence of a condition known to reduce serum IGF-1, especially the use of oral estrogens and decompensated diabetes</p> <p>If OGTT is performed, the nadir GH limit of 1 µg/L, in young and young adult women, should be maintained even after ruling out conditions of non-suppression</p>

[§] In adults (29,33,36), normative data for serum IGF-1 should be based on a random selection of at least 1,000 subjects from the background population. The subjects should be selected rigorously, excluding conditions known to interfere with the levels of this hormone [pregnancy, medical conditions (e.g., renal, hepatic and thyroid disease, poorly controlled diabetes, nutritional impairment), medications (e.g., estrogen), body mass index extremes]. The values should be stratified by decade and should include the central 95% interval (2.5-97.5 percentiles).

In conclusion, in patients with clinical suspicion of acromegaly, the use of the recommended algorithm shown in Figure 1 (4-23), which also takes into consideration GH concentrations > 0.4 µg/L in the presence of normal serum IGF-1 as diagnostic, results in the unwarranted complementary investigation in many cases and even in possible equivocal diagnoses (the latter in women). It is only in exceptional cases that normal serum IGF-1 should not rule out acromegaly (Table 2).

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