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Monitoring of acromegaly: what should be performed when GH and IGF-1 levels are discrepant?

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Summary

Monitoring of a patient with acromegaly requires periodic evaluation of levels of GH and IGF-1, the biochemical markers of this disease. Although the results of these two tests are usually concordant, they can be discrepant and how to proceed when they are can be a challenging clinical problem. In some cases, IGF-1 levels are normal yet GH suppression after oral glucose is abnormal; this pattern may be due to persistent GH dysregulation despite remission. In other cases, IGF-1 levels are elevated yet GH suppression appears to be normal; this pattern may be observed if the cutoff for GH suppression is inappropriately high for the GH assay being used. Various conditions known to alter GH and IGF-1 including malnutrition, thyroid disease and oestrogen use as well as the potential for methodological or normative data issues with the GH and IGF-1 assays should be considered in the interpretation of discrepant results. When a known cause of the discrepancy other than acromegaly is not identified, a clinical decision about the patient's therapy needs to be made. We adjust treatment in most patients whose results are discrepant based on the IGF-1 level, continuing current treatment if it is persistently normal or modifying this if it is elevated. The clinical picture of the patient, however, also needs to be incorporated into this decision. All patients should have continued periodic surveillance of both GH and IGF-1 levels.

Introduction

Active acromegaly is characterized by excess secretion of GH and resultant elevations of circulating levels of GH and IGF-1. Normalization of these hormones is needed to improve the disease's clinical manifestations, signs, symptoms and co-morbidities as well as normalize the patient's life expectancy. Therefore, monitoring of a patient, whether one who is in remission or who is receiving ongoing therapy, relies on an accurate determination of whether or not these excesses are present. This is best accomplished by measurement of both the degree of GH suppression after oral administration of 75 or 100 g of oral glucose tolerance test (OGTT) and serum levels of IGF-1. These tests provide complimentary information, the OGTT assesses neuroregulation of GH secretion and the IGF-1 level, average GH secretion. However, their interpretation is not always straightforward as not infrequently the results are discrepant. While in research studies the conclusions drawn from discrepant results may be somewhat arbitrary and dependent on which test is chosen as the "gold standard" for the comparison, these discrepancies can be clinically important to pursue further. This brief review discusses the potential causes of such discrepant results and a clinical approach to the management of these patients.

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Overview of the biochemical assessment of acromegaly

Monitoring of serum IGF-1 levels in acromegaly patients is essential. When measured properly and compared with a well-characterized, age-adjusted normative database, elevation of the IGF-1 level is a sensitive and specific indicator of persistent disease and normalization should occur with effective therapy. Monitoring of IGF-1 levels can detect mild GH excess.[1,2] IGF-1 normalization also reduces the clinical signs and symptoms of the disease, morbidities such as insulin resistance and glucose intolerance, cardiovascular disease and the excess mortality rate in acromegaly.

Monitoring of GH levels is also essential. The most rigorous method for this, GH suppression after oral glucose (OGTT), is characteristically impaired in active acromegaly. Conversely, when GH falls below a specific cut-off treatment is considered adequate.[3] This nadir GH cutoff has become progressively lower with the use of increasingly sensitive and specific GH assays. Using such assays, GH levels are <0·2 lg/l in most healthy adults with the exception of some young women whose levels are higher.[4–8] Acromegaly treatment should aim for glucose-suppressed GH levels of 1 lg/l or less.[9] A number of studies, using different GH assays, support a cutoff of 1 lg/l.[4,7,10,11] However, as GH levels can be <1 lg/l in some patients with active acromegaly, they could be misclassified by this cutoff. Other studies suggest cutoffs of 0·5 lg/l,[7,12] 0·3 lg/l when using a 22K GH-specific assay[1] or 0·25 lg/l.[6] Clearly, the nadir GH cutoff used to distinguish active disease from remission needs to be assay-specific as considerable assay variability exists.[1,7,13] In a recent study, nadir GH levels in a large group of healthy subjects were measured with three different assays all calibrated to a recombinant human GH standard (98/574) and mean values ranged from 0·13 to 0·015 lg/l.[7] Assay variations in the results of acromegaly samples were also found.[7] Even using the same commercially available GH assay normative cutoffs vary by centre.[7,12] Greater uniformity of GH assay methodology will be needed before completely generalizable criteria can be proposed.[7] Monitoring of acromegaly by combined assessment is preferred in particular when the GH cutoff for the particular assay being used is not clear.

Abnormal GH suppression at normal IGF-1 level

Although the results of GH and IGF-1 levels are often congruent, discrepancies do occur. One pattern of discrepant results, abnormal GH suppression with a normal IGF-1 level, is reported in 9–39% of patients.[1,4,6,7,14] A number of potential causes of this pattern exist (Table 1). Although the mechanism for abnormal GH suppression in patients with acromegaly is unclear, in the setting of a normal IGF-1 this could be due to dysregulation of GH secretion from disruption of its neural or anatomic networks;[15,16] IGF-1 levels could remain normal as the overall amount of GH secretion is normal. GH suppression could also appear to be “abnormal” if the cutoff being used is inaccurate or has not been properly adjusted for the patient’s age, body mass index (BMI) and gender. Nadir GH levels have been found to be lower with increasing age and BMI in a number of studies,[4,7,17,18] while in others this has not been demonstrated.[8,19] Gender-specific nadir GH criteria may also be needed as these levels may be higher in some young women than men.[4,5,8,20,21] Detailed gender, age and BMI-specific GH cutoffs are yet to be developed. Abnormal GH suppression can also occur in conditions other than acromegaly, including chronic renal insufficiency, liver failure, active hepatitis, hyperthyroidism, diabetes mellitus, anorexia nervosa, malnutrition and adolescence.[3] This pattern of discrepancy could also be seen in the setting of conditions that can lower the IGF-1 level such as nutrient deprivation, malnutrition, anorexia nervosa, liver failure, hypothyroidism and poorly controlled insulin dependent diabetes mellitus.[3] One such patient with malnutrition has been reported.[22] Oral oestrogen raises GH, but lowers IGF-1 levels[23] so changes in oestrogen status could alter determination of disease status by IGF-1. Questionable IGF-1 results should also be repeated

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with a different assay of high quality and with carefully derived age-adjusted normative data.[24] Recently developed IGF-1 normative data[25] reveal much lower upper limits than prior assays so incorrect classification of disease status based on erroneously high upper limits of normal could lead to a seemingly normal IGF-1 in a patient with active disease.

When GH is assessed as the mean of serial GH samples collected over a day (day series or curve) this discrepant pattern can also occur.[26–28] In one study, 17% of patients with a mean GH >2·5 lg/ l had normal IGF-1 levels.[29] In a given patient, it is unclear how reliable mean GH levels are for determination of disease status. Mean GH levels <1 lg/l obtained from short sampling strategies are poorly predictive of mean 24-h GH levels[30] and mean 24-h GH levels overlap in acromegaly and healthy subjects.[2,16,27,31] In addition, the cutoff of 2·5 lg/l, which was developed with polyclonal radioimmunoassays[29,32,33] is no longer valid with current assays. An appropriate cutoff of mean GH for use with highly sensitive and specific assays that correlates with IGF-1 levels has not been determined.

The clinical significance of a normal IGF-1 along with abnormal GH suppression is uncertain, but it may be a sign of mild excess GH secretion that is a precursor to recurrence in some patients.[34] In longitudinal follow-up of patients with persistent abnormal GH suppression after surgery, a recurrence, defined by an elevated IGF-1, did occur in 5 of 19[34] and one of three patients.[35] Another group of patients had normal IGF-1 levels and nadir GH levels >0·19 lg/l, above their normal range, at one point in time many years after surgery, but longitudinal follow-up of this group had not been conducted.[21]

Normal GH suppression and elevated IGF-1 level

The opposite pattern of divergent GH and IGF-1 results has also been reported; IGF-1 levels are elevated, but GH suppression is “normal”. Investigations into this pattern have revealed that in many cases GH suppression is actually abnormal when assay-appropriate cutoffs are used. When GH data are compared with cutoffs too high for the assay, the rate of this discrepancy is high, from 24% to 62%.[1,6,14,36,37] For example, using a cutoff of 1 lg/l, inappropriately high for a highly sensitive and specific assay, produces discrepant GH and IGF-1 data in up to 50% of patients.[6,8] Similarly, up to 35% of patients with mean GH <2·5 lg/l on a day series had elevated IGF-1 levels.[28,29,38] However, using appropriate cutoffs, the rate of this discrepancy is low, generally <5%.[1,7,11,36] In patients with elevated IGF-1 levels and normal GH suppression one should also consider whether the IGF-1 measurement could be inaccurate. For example, in the first 3 months postoperatively GH suppression data may be more reliable for predicting long-term remission than the IGF-1 level, which is still falling over this time period.[12,37] We typically perform the OGTT and IGF-1 level to assess disease status 3 months postoperatively. IGF-1 levels are rarely above normal in conditions other than acromegaly, but can be in some adolescents and in pregnancy.[3] IGF-1 assay methodology and normative data should also be considered.

Approach to the patient with discrepant GH and IGF-1 testing

When faced with discrepant GH and IGF-1 results, we typically repeat the testing. As the GH or IGF-1 abnormality is usually mild, we usually do this after 3 or 4 months. In general, we have found the original pattern to persist, but in some patients it may resolve. If available, a laboratory for which well-characterized normative data are available should be used. Possible explanations for the discrepancy as described above should then be sought. In most cases, however, a clear cause of the discrepant pattern cannot be identified. The decision then needs to be made as to which biochemical marker should be the one to guide further monitoring and treatment decisions. In most cases, our therapeutic decisions are guided by the IGF-1 level. As a single measurement, with less variability than GH, IGF-1 levels are easier to monitor frequently. Normalization of IGF-1 correlates with that of the

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morbidities and excess mortality in acromegaly. For example, normalization of IGF-1 is predictive of improvement in insulin resistance. In addition, in patients with normal IGF-1 levels, subtle impairments of GH suppression, GH levels of 0·25–0·1 lg/l, are not predictive of insulin resistance[39] or abnormal glucose levels.[6,21] Although it is controversial whether IGF-1 normalization alone is a sufficient marker for that of mortality in acromegaly,[40] a number of studies have supported the validity of IGF-1.[41–44] Therefore, so long as the patients' IGF-1 levels are persistently normal and none of the issues with IGF-1 levels discussed above are present, it is generally our practice to consider patients with persistently normal IGF-1 levels and abnormal GH suppression in remission and follow them or continue treatment as prescribed. Patients with abnormal GH suppression may be at increased risk of recurrence and we follow them closely. However, data are not available on the use of glucose-suppressed GH levels as an epidemiologic predictor of mortality in acromegaly. There is also insufficient evidence that GH levels need to be suppressed into the range of healthy subjects when the IGF-1 level is normal. In patients undergoing titration of medical therapy and who have persistent symptoms such as insulin resistance despite an IGF-1 level in the upper normal range consideration could be given to reducing this into the mid-normal range; diabetes mellitus control has improved with this adjustment in some of our patients. Further lowering of the IGF-1 level, however, may not be safe as it could be a sign of GH deficiency.[45] In patients with an elevated IGF-1 we typically adjust treatment to normalize this level despite a suppressible GH; even some patients with newly diagnosed disease have very suppressible GH levels.[2] In patients with symptoms or co-morbidities, the decision to treat, even if the biochemical abnormality is mild, is straightforward. It remains controversial, however, whether a mild elevation of IGF-1 level in a patient without symptoms requires treatment.[46] Epidemiological data are not available to guide this decision. The risk–benefit ratio of therapy in such cases needs to be considered on an individual patient basis.

The interpretation of discrepant values should also consider the type of therapy being administered as the implications of the discrepancy can differ depending on the mode of therapy. During somatostatin analogue therapy, both IGF-1 and GH should be monitored, but discrepancies are more common as GH suppression could be less and IGF-1 levels more consistent.[37,47] Some favour only monitoring of IGF-1 for determination of efficacy on somatostatin analogues.[47] Patients on pegvisomant therapy can only be monitored by IGF-1 level. In the patient who has undergone radiotherapy, when GH neurosecretory dysregulation is common, IGF-1 may also be more reliable. In patients with diabetes mellitus, the OGTT is also unreliable and IGF-1 levels are preferred for monitoring. Some have also found measurement of IGFBP-3 to be helpful in cases with discrepancies.[48]

Conclusion

In conclusion, interpretation of discrepant growth hormone and insulin-like growth factor-1 data in the monitoring of patients with acromegaly requires consideration of many factors that influence these levels in general and in patients with acromegaly. Management of such patients needs to be individualized. In general, we base treatment decisions on the serum insulin-like growth factor-1 level result. However, as the aetiology of most discrepancies is not clear we continue to regularly monitor both growth hormone and insulin-like growth factor-1 levels in these patients as discrepancies could herald a change in disease status in some patients. Greater uniformity of growth hormone and insulin-like growth factor-1 assays is needed to help reduce these discrepancies. The long-term clinical significance of discrepant growth hormone and insulin-like growth factor-1 testing in patients with acromegaly requires further investigation.

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Table 1

Causes of discrepant GH and IGF-1 values in patients with acromegaly

"Abnormal" GH suppression with a normal IGF-1 level
Patient in remission
Dysregulation of GH secretion
Disruption of the neural or anatomic networks of GH regulation
Mild or early GH excess?
Causes of abnormal GH suppression other than acromegaly
Chronic renal insufficiency
Liver failure
Active hepatitis
Anorexia nervosa
Malnutrition
Hyperthyroidism
Diabetes mellitus
Adolescence
Cut off for GH suppression inappropriately low for the GH assay used
Patient with active disease
Lowering of the serum IGF-1 level
Nutrient deprivation, malnutrition
Anorexia nervosa
Liver disease
Hypothyroidism
Poorly controlled insulin dependent diabetes mellitus
Oral oestrogen use
Inaccurate IGF-1 normal range – upper limit too high
"Normal" GH suppression with an elevated IGF-1 level
Patient in remission
Falsely elevated IGF-1
Adolescence
Pregnancy
Hyperthyroidism (mild elevation)
IGF-1 assay problems
Early postoperative period
Patient with active disease
Cutoff for GH suppression too high for the GH assay used
Easily suppressible early or mild active acromegaly