

Rapid assessment of surgical success in patients with acromegaly: GH, IGF-I, or both?

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Neurosurgeons and endocrinologists are happy to be able to tell patients with Cushing's disease, as early as the second or third postoperative day, that surgery on their corticotrophic pituitary adenoma has been successful and that they are almost certainly in remission. This confidence is based on cortisol measurement during the immediate postoperative period: corticotrophin deficiency strongly predicts total removal of the ACTH-secreting microadenoma and, thus, disease remission (1).

Unfortunately, the same is not true for patients with acromegaly. Indeed, a patient might feel far better in the hours following surgical excision of a somatotroph adenoma, based on subjective changes such as less soft-tissue swelling, headache and sweating, but remission cannot yet be objectively confirmed by contemporary hormone assays. Of course, the postoperative decline in GH correlates strongly with the reduction in tumor volume (2). And, because of the short half-life of GH, the serum level falls rapidly after the operation.

As recently reported by Yu *et al.* in *Clin Chem* (3), in keeping with previous studies (4), GH levels fall below their preoperative level in all patients on the first postoperative day (regardless of remission status) and then reincrease on the second postoperative day in some patients. No further significant change occurs between days 2 and 3, indicating that the concentration observed on day 2 represents the stable GH value. However, most patients, whether or not they enter remission, retain GH levels above 0.5 or even 1 µg/L on day 2 or 3 (3).

IGF-I has gained more and more importance for assessing if acromegaly is active or not, thanks to the improvement in its measurement (5) and establishment of reliable normative reference ranges (6). Nevertheless, IGF-I is considered to be even less reliable than GH for predicting acromegaly cure in the immediate postoperative period. Indeed, given its long half-life, which Yu *et al.* calculated to be around 55 h (3), the serum concentration of IGF-I declines slowly and thus remains elevated for many days or weeks after surgery, even when the somatotroph adenoma is completely removed (3,4,7). Current guidelines thus recommend that acromegalic disease status be monitored for at least 12 weeks after surgery, by measuring the IGF-I level (which must normalize) and the GH level during an oral glucose tolerance test (OGTT) (which must be normally suppressed) before concluding that the patient is in remission (8). This is frustrating, for both the patient and the neurosurgeon. Moreover, it can be difficult to reassess GH/IGF-I status 2 to 3 months after surgery when the patient lives far from the hospital.

In their article, Yu *et al.* offer a new possibility for predicting remission of acromegaly very soon after surgery (3). They compared serum IGF-I and GH dynamics during the first 2 or 3 postoperative days between acromegalic patients who were found to be in remission and those who had persistent active disease at the week-8 assessment, which included IGF-I assay and GH measurement during an OGTT. They first confirmed the long half-life of IGF-I, at about 55 h. [Note that, even with new LC-MS technology (9), the

value is similar to the half-life of total IGF-I (about 42 h) that they estimated from Clemmons' dataset, obtained with an immunoassay (10)]. As the rate of postoperative IGF-I decline is very similar from one patient to the next, Yu *et al.* were able to confirm that the higher the preoperative IGF-I level, the higher the IGF-I level on the second or third postoperative day. This held true whether IGF-I was expressed in absolute values, as the Z-score, or as a percentage of the upper limit of normal. Nearly half of all patients who are ultimately considered to be in remission still have IGF-I levels above the upper limit of normal in the immediate postoperative period (3).

Does this mean it is impossible to predict remission from early GH and/or IGF-I levels? Fortunately, probably not! After painstaking analysis, Yu *et al.* found that, on the 2nd or 3rd postoperative day, patients who were considered to be in remission 8 weeks after surgery had a GH level below the 2.5 µg/L cutoff and an IGF-I level <65% of their preoperative level (3). As Yu *et al.* acknowledge in their discussion, they studied a relatively small number of patients (particularly patients who did not enter remission), meaning that the results need to be confirmed in other centers and larger populations. However, if confirmed, their findings would offer a simple means of telling, at the time of hospital discharge, whether or not a somatotroph tumor has been completely removed and the patient will ultimately be in remission, as is already possible in Cushing's disease. This could allow, together with the operative report describing if the tumor has been totally removed or not, not to wait too long for deciding to initiate adjuvant therapy (11).

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