MANAGEMENT OF ENDOCRINE DISEASE

GH excess: diagnosis and medical therapy

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Abstract
Acromegaly is predominantly caused by a pituitary adenoma, which secretes an excess of GH resulting in increased IGF1 levels. Most of the GH assays used currently measure only the levels of the 22 kDa form of GH. In theory, the diagnostic sensitivity may be lower compared with the previous assays, which have used polyclonal antibodies. Many GH-secreting adenomas are plurihormonal and may co-secrete prolactin, TSH and α-subunit. Hyperprolactinaemia is found in 30–40% of patients with acromegaly, and hyperprolactinaemia may occasionally be diagnosed before acromegaly is apparent. Although trans-sphenoidal surgery of a GH-secreting adenoma remains the first treatment at most centres, the role of somatostatin analogues, octreotide long-acting repeatable and lanreotide Autogel as primary therapy is still the subject of some debate. Although the normalisation of GH and IGF1 levels is the main objective in all patients with acromegaly, GH and IGF1 levels may be discordant, especially during somatostatin analogue therapy. This discordance usually takes the form of high GH levels and an IGF1 level towards the upper limit of the normal range. Pasireotide, a new somatostatin analogue, may be more efficacious in some patients, but the drug has not yet been registered for acromegaly. Papers published on pasireotide have reported an increased risk of diabetes mellitus due to a reduction in insulin levels. Pegvisomant, the GH receptor antagonist, is indicated – alone or in combination with a somatostatin analogue – in most patients who fail to enter remission on a somatostatin analogue. Dopamine-D2-agonists may be effective as monotherapy in a few patients, but it may prove necessary to apply combination therapy involving a somatostatin analogue and/or pegvisomant.

Introduction
Acromegaly
Historical reports of giants such as Goliath cannot be definitively verified, but the most significant reputed giant from Roman times was the emperor Gaius Julius Verus Maximus (1). Wier (2) was the first researcher to provide an accurate medical description of acromegaly – hypersecretion of growth hormone (GH) in adults after epiphyseal fusion – in the sixteenth century. Marie (3) recognised and named acromegaly as a distinct clinical entity in 1885 (4). The diagnosis of acromegaly requires...
biochemical confirmation of abnormal GH and insulin-like growth factor 1 (IGF1) levels. The same parameters are used for therapeutic decisions, i.e. initiation or termination of particular treatments. For these reasons, reliable epidemiologically and statistically proven criteria of normalcy for GH and IGF1 are necessary (5).

**GH regulation and assays**

GH is an anabolic hormone that is synthesised and secreted by the somatotroph cells of the anterior lobe of the pituitary gland. It is a member of the GH (GH1) gene family, which includes placental GH, prolactin (PRL) and the placental lactogens. GH secretion is pulsatile in nature in all species (Fig. 1).

Most currently used GH assays are designed to estimate only the 22 kDa form of GH. However, plasma contains more than 100 variants of GH, where the free 22 kDa form constitutes about 21% of the total GH volume in plasma (6), and the second most abundant variant of GH is the 20 kDa form. The previous use of polyclonal antibodies has resulted in higher levels of GH compared with monoclonal assays (7, 8), but no significant difference has been reported between the 20 kDa:22 kDa ratios in healthy controls and patients with acromegaly (9). By contrast, Lima et al. (10) demonstrated that acromegalic patients display an increased proportion of the circulating 20 kDa GH isoform. With this being the case, the use of an assay specific to 22 kDa GH may underestimate the tumour production of total GH (10). The measurement of GH levels in pregnancy is a challenge, especially in acromegaly, due to the homology between pituitary GH and placental GH. However, redesigning an immunometric assay by changing the capture and signal antibodies may be a successful strategy for measuring GH levels in pregnancy (11).

**Serum IGF1 levels**

GH status is an important determinant of circulating IGF1 levels in non-starving, non-catabolic humans (12), and around 75–80% of serum IGF1 is liver derived (13). IGF1 is not pulsatively secreted, and the long half-life makes IGF1 a good candidate for quantifying the integrated GH secretion (14, 15). Faje & Barkan (16) have recently reported that the correlation between plasma IGF1 concentrations and mean 24-h GH concentrations is dependent on basal GH levels and that GH pulses do not determine plasma IGF1 levels.

IGF1 levels are conventionally determined using a RIA after extraction and separation from interfering IGF-binding proteins (17). Sephadex G-75 acid gel filtration is the gold standard for this separation, but because of the expenses involved in this process, an acid–ethanol extraction is often used instead (18). A paper by Kay et al. has described the use of a method for estimating IGF1 levels based on stable isotope dilution ultra HPLC–tandem mass spectrometry. Although their results are promising, the method cannot be recommended for clinical use before a full evaluation has been carried out (14). According to Frystyk et al. (19), the number of assays for IGF1 has expanded dramatically and, thanks to the worldwide distribution of commercial IGF1 assays, in particular, virtually every endocrine laboratory now has the capacity to carry out measurements of immuno-reactive IGF1 levels. However, as these researchers outlined in their survey (19), the measurement of IGF1 levels is still not a routine biochemical procedure.

**IGF1 levels, insulin and regional body composition**

BMI exerts a strong negative effect on GH secretion in healthy individuals (20), and in contrast to GH levels, total, free and bioactive IGF1 levels are often all within the reference interval in obese individuals (21). There is no definitive explanation for the relatively high IGF1 levels in obese individuals, but we know that IGF1 levels are mainly determined by GH and insulin levels (22, 23) (Fig. 2). Theoretically, there may be a direct or indirect association between regional fat deposits and IGF1 levels. We have reported that the homoeostasis model assessment of insulin resistance (HOMA-IR) and adiponectin levels were respectively positively and negatively associated with central fat mass and, in particular, subcutaneous abdominal fat (24) in relatively lean men from the Odense Androgen Study (25). In regression analyses using the same population of young men, subcutaneous abdomen
and thigh fat deposits were found to be positively associated with IGF1 levels. In contrast to the associations between IGF1 levels and subcutaneous fat deposits, intramyocellular lipid levels of the thigh were inversely associated with IGF1 levels (23). In patients with acromegaly, where GH and IGF1 levels are increased, Freda et al. (26) reported that male patients ($n = 15$) had significantly higher levels of intramyocellular lipid than controls (130 males, aged 18–84 years). These findings emphasise the differential associations between GH/IGF1 levels and regional fat deposits.

In patients with acromegaly, both GH and insulin levels are usually high, resulting in increased IGF1 levels in the fed state (27). However, prolonged fasting promotes functional resistance to GH (28), and IGF1 levels may thus appear normalised in fasting patients with acromegaly (29).

**Pituitary adenomas: genetics and fetal antigen 1**

Pituitary tumours are benign in most cases, and although aggressive local growth may occur, most tumours do not progress to true malignancy with demonstrable extracranial metastases (30) (Fig. 3). Cellular senescence is a possible mechanism for the low incidence of pituitary carcinomas in GH-secreting adenoma patients (31). Cellular senescence is distinguished by a largely irreversible cell cycle arrest and constitutes a strong antiproliferative response, which may be triggered by DNA damage, chromosomal instability and aneuploidy, loss of tumour-suppressive signalling or oncogene activation (32).

Approximately 4–5% of pituitary adenomas occur in a familial setting (33). Both multiple endocrine neoplasia type 1 (MEN1) and Carney’s complex (CNC) are syndromes that involve the pituitary gland. Multiple endocrine organs are involved in MEN1 as well as in CNC, whereas tumours only occur in the pituitary gland in familial isolated pituitary adenoma (FIPA) patients (34). FIPAs may be caused by a mutation in the aryl hydrocarbon receptor-interacting protein (AIP) gene (35), a mutation that was identified in 2006 (36). The functional evaluation of AIP mutations is consistent with a tumour-suppressor role for AIP (37), and a relatively low penetrance has been reported (4, 38). A high prevalence of germline AIP mutations has very recently been observed not only in young patients, particularly in acromegaly, but also in prolactinoma patients (39). Therefore, it seems appropriate to screen a patient with a GH-secreting adenoma for an AIP mutation if the patient is below the age of 40 years when symptoms appear (40).
Menin mutations are generally accepted as the main gene mutations involved in MEN1. While 5–10% of patients with MEN1 do not have any mutation in menin, some of these patients may have mutations in the cyclin-dependent kinase inhibitor 1B (CDKN1B) gene (41, 42), and this has given rise to a new MEN4 or MENX syndrome, as it is commonly known. Apart from pituitary adenomas, parathyroid tumours may be found, and tumours in reproductive organs have also been reported, along with incidences of renal and adrenal tumours (42).

In 1988, a new protein – fetal antigen 1 (FA1) – was isolated from second-trimester amniotic fluid (43). FA1, which is also named delta-like 1 homologue or preadipocyte factor 1, is postnatally restricted to neuroendocrine cells: pituitary gland, adrenal cortex, testes, ovaries and β-cells of the pancreas (44). The circulating FA1 is proteolytically cleaved from the transmembrane protein (45); the main function of the transmembrane protein is inhibition of the differentiation and proliferation of preadipocytes (44). FA1 is expressed throughout the development phase of the pituitary gland and becomes predominantly restricted to GH cells within the adult gland (46). For example, its role in pituitary tumour development is not clear (47). A common secretory and stimulatory pathway for GH and FA1 has not been established (48). Although FA1 levels may hypothetically be higher in acromegaly, and somatostatin analogue therapy may reduce FA1 levels, the elevated GH levels in patients with acromegaly are not reflected in high FA1 levels (48). These findings may be due in part to increased clearance of FA1 in acromegaly (49, 50). Nevertheless, FA1 levels did decrease in six of seven acromegalic patients, who had a significant reduction in GH levels during 4 weeks of octreotide therapy (51). This effect on FA1 levels may be due to a decrease in GH or IGF1 levels per se or to a direct effect of octreotide on FA1 secretion (48).

**GH excess and hyperprolactinaemia**

The low prevalence of acromegaly – ~40–60 per million (52) – and the slow progression of signs and symptoms often delay the diagnosis of this condition. A patient may seek medical advice due to sleep apnoea, cardio/cerebrovascular disease or endocrinological complications such as diabetes mellitus or osteoporosis. A rheumatologist may initially see the patient on account of arthralgia, swollen hands and feet, or carpal tunnel syndrome. On rare occasions, the change in physical appearance is observed by the patient himself/herself or by relatives. An increasing number of patients are diagnosed with acromegaly secondarily to a pituitary incidentaloma, and even though the frequency of acromegaly is low in pituitary incidentaloma patients, it is still necessary to exclude GH excess in all cases (53).

GH-secreting adenomas may be plurihormonal, and hyperprolactinaemia is found in 30–40% of acromegalic patients (54), and the adenoma may also co-secrete thyroid-stimulating hormone (TSH) and/or α-subunit (55). Reversible transdifferentiation, i.e. interconversion of somatotrophs and lactotrophs, has been described in pregnancy (56) and in pituitary hyperplasia (57). Pituitary hormone secretion from an adenoma is a dynamic process, and acromegaly may thus be diagnosed in a patient with hyperprolactinaemia (58). Similarly, GH hypersecretion may be detected despite not being accompanied by obvious clinical stigmata of acromegaly. Asa et al. (59) have elegantly shown that variable amounts of GH and PRL are released from different subclasses of adenomas from the acidophil cell line in vitro. A large surgical series on tentative prolactinomas has described similar serum PRL levels in patients with or without PRL staining in the adenoma (60). A total of 31 adenomas from female patients stained positive for GH, and one of the tumours did not reveal any PRL. Unfortunately, the paper did not present any data on serum GH and IGF1 levels (60).

A recent paper by Wang et al. (61) has reported that women with GH–PRL-secreting adenomas often have relatively low serum GH levels and that these adenomas are associated with higher incidences of menstrual disorders and galactorrhoea compared with GH-secreting adenomas. In patients with hyperprolactinaemia, we found that three of 78 patients developed acromegaly (58). In line with the paper by Sakharova et al. (62), our findings highlight the need for careful endocrine evaluation of patients with a prolactinoma (58). A yearly measurement of serum IGF1 levels may be an appropriate screening test, although some patients may have increased GH levels in spite of having normal IGF1 levels (63). The diagnosis of GH excess/acromegaly in a patient with hyperprolactinaemia would indicate a change of therapy. Some of these patients may be treated exclusively with a somatostatin analogue, as we have previously reported that octreotide treatment for 4 weeks normalised PRL levels in patients with acromegaly and hyperprolactinaemia (51). However, surgery may be indicated in some cases.

**Treatment goals in acromegaly**

Treatment goals in acromegaly include normalisation of GH and IGF1 levels, tumour removal, significant
review of tumour size or stable tumour size, normal pituitary function (substitution therapy), reduction of comorbidities, improved quality of life and normalisation of excess mortality (64). With regard to the normalisation of GH levels, the optimal suppressed GH levels during an oral glucose tolerance test (OGTT) or the optimal basal nadir GH levels have not been defined, but different cut-offs have been reported: GH nadir during an OGTT: <1 μg/l (65) or <0.4 μg/l (66), or basal GH levels: <2.5 μg/l (67) or <1 μg/l (68). It is important to consider the GH assay and gender when evaluating the results of an OGTT, as Markkanen et al. (69) reported significantly higher GH levels in women than in men. The relationship between GH levels and mortality in acromegaly has been studied (70, 71, 72). A reduction of measured GH levels to <2.5 μg/l was sufficient to achieve normalisation of mortality rates in two studies (70, 71). GH levels had to be reduced to <1 μg/l for normalisation of the increased mortality in acromegaly in another study (72). The effect of therapy could not be reliably estimated by IGF1 levels (70). Nevertheless, we have to rely on the measurements of IGF1 levels in patients receiving pegvisomant therapy, as it is not yet possible to monitor endogenous GH levels using routine GH assays on account of cross-reaction with pegvisomant. A recent debate has focused on the biochemical follow-up of acromegalic patients receiving somatostatin therapy, where GH and IGF1 levels may be highly discordant. During treatment with somatostatin analogues, the predominant discordance has been found to be between a high GH level and a normal IGF1 level (67), resulting in the proposal of a new term – extra-hepatic acromegaly – in a recent paper: ‘Somatostatin analogues may normalise serum IGF1 levels in the presence of elevated GH actions in extra-hepatic tissues, which may result in persistent disease activity in some patients’ (27).

Medical therapy for acromegaly

Surgery is generally the first-line therapy for acromegaly, and it is the only therapy that may lead to lasting remission. The high number of macroadenomas (80%) combined with the follow-up time of 9.8 years (median) may explain the low postoperative normalisation rate of IGF1 levels (38.8%) reported by Schofl et al. (52). Their results explain the need for adjuvant therapy in a large proportion of patients immediately after surgery or during follow-up.

Radiotherapy in the form of conventional fractionated radiotherapy, stereotactic radiosurgery (including gamma knife surgery), cyberknife therapy or proton beam is required for the treatment of a few patients with acromegaly.

By contrast, medical treatment is quite often indicated as adjuvant therapy, and a somatostatin analogue is usually the first drug of choice (52). Two somatostatin analogues are available: octreotide long-acting repeatable (LAR) and lanreotide Autogel. No blinded, randomised study that has compared octreotide LAR with lanreotide Autogel in de novo acromegalic patients has been published. There is a risk of selection bias when patients included in a study tolerate and respond fully or partially to a particular somatostatin analogue. We carried out a randomised, open, cross-over study in ten patients on octreotide LAR or lanreotide Autogel therapy for 12 months (73). Octreotide LAR and lanreotide Autogel produced comparable effects if patients were good responders to previous octreotide LAR therapy. In partial responders – i.e. patients with increased GH levels – octreotide LAR was more efficient than lanreotide Autogel in reducing GH levels. IGF1 levels were comparable in both therapies (73). We found individual differences in the susceptibility to develop subcutaneous nodules and adverse gastrointestinal effects (73). Our results suggest that a switch between somatostatin analogues may be beneficial in individual patients, if i) the patient is a non-responder or ii) the patient develops subcutaneous nodules at the injection site and/or adverse gastrointestinal effects (73).

Tumour removal or reduction of tumour size is another important goal of therapy for acromegaly. Octreotide LAR has been found to induce clinically relevant tumour shrinkage in more than half of patients with acromegaly (74). Overall, a total of 32.8% of patients experienced a variable degree (10–77%) of tumour shrinkage during lanreotide sustainable release (SR) or lanreotide Autogel (75) therapy.

The prediction of a clinically relevant response to somatostatin analogue therapy is of interest. The acute octreotide test is not a reliable tool for making clinical decisions; however, the test has relatively low sensitivity and specificity in predicting long-term responses to octreotide LAR (76). Heck et al. (77) reported that hyperintensity on T2-weighed MR scans is associated with a sparse granulation pattern on immunohistochemistry and that hyperintensity may predict a worse response to octreotide LAR therapy and the possible impact on clinical decision-making has to be verified.

Surgery is required for the pathological characterisation of adenomas. Human GH-secreting adenomas express predominantly somatostatin receptor subtype 2 (sst2A) and to a lesser extent subtype 5. It has recently
been demonstrated that the expression of SST2A protein correlates positively with the biochemical response during somatostatin analogue treatment in GH-secreting adenoma patients (78). Resistance to somatostatin analogue therapy may often be observed in patients carrying a mutation in the AIP gene, and these adenomas are usually sparsely granulated (79). Patients without an actual AIP mutation, but with low AIP expression in the adenomas, are more frequently resistant to somatostatin analogue therapy (79). The interaction between AIP status and somatostatin analogue therapy may explain some of the cases, where although the number of sst2 is high, adenomas prove to be resistant to somatostatin therapy (79).

Somatostatin analogues have been used by Auriemma et al. (80) as primary therapy, particularly in patients with macroadenomas who are at an increased risk during surgery or who refuse surgery. The duration of preoperative somatostatin analogue therapy has been individualised (81).

Presurgical randomised studies comparing surgery with octreotide LAR (82) or lanreotide SR (83) treatment have generated promising results (84).

Pasireotide, the new somatostatin analogue, may be more efficacious in some patients because of its multi-receptor targeting of somatostatin receptors 1–3 and, in particular, receptor 5 (85). In a randomised clinical phase II trial on 60 patients with acromegaly, 27% of the patients were found to display a biochemical response after 3 months of pasireotide treatment. The definition of a biochemical response was GH level(s) ≤2.5 g/l and normalisation of IGF1 levels (85). Future studies and clinical experience will determine the impact of this new somatostatin analogue.

Pegvisomant, a 191-amino acid compound, was initially developed as a new GH analogue, but it is an effective GH antagonist. Pegvisomant closely resembles GH, and so most currently available assays cross-react with it (86). Pegvisomant decreases IGF1 levels effectively in most patients, as demonstrated by the fact that IGF1 levels were normalised in 87 of 90 patients with acromegaly when pegvisomant (10–40 mg/day) was administered for 12–18 months (87). However, pegvisomant does not reduce tumour size; ~2–3% of patients treated with pegvisomant exhibited a significant increase in tumour size (88). Nevertheless, combination therapy with somatostatin analogues results in a clinically relevant decrease in tumour size in about 20% of patients, although an elevation in the levels of transaminases may occur in 11–15% of patients (89).

The risk of diabetes mellitus is increased during pasireotide therapy, primarily on account of reduced insulin levels and reduced incretin responses, although pasireotide had no effect on insulin sensitivity (90). Insulin levels may also be reduced during octreotide LAR or lanreotide Autogel therapy, but the risk of diabetes is relatively low. Pegvisomant therapy may actually improve insulin sensitivity (91).

Dopamine agonists were the only class of pharmaceutical agents available for the medical treatment of acromegaly until the 1980s. Cabergoline, a second-generation dopamine agonist, has few adverse effects in most patients (92). However, a large register study of Parkinson’s disease carried out in 2007 has documented an increased risk of valvulopathy in patients treated with a cabergoline dose higher than 3 mg/day (93), and Zanettini et al. (94) reported an association between cumulated doses of cabergoline and valvulopathy. From 2008 to the present, 16 clinical studies have been published on dopamine agonists – primarily cabergoline – and valvulopathy in patients with hyperprolactinaemia (95). The conclusions from these clinical studies were reassuring, and a register study found no association between clinically significant cardiac valve disease and cabergoline therapy in patients with hyperprolactinaemia (96). Furthermore, a relevant retrospective paper has reported no relationship between cabergoline therapy and cardiac valve regurgitation or remodelling in acromegaly (97).

So when should cabergoline therapy be used in the context of acromegaly today? i) Cabergoline may be used as add-on therapy for a patient who has not reached the target GH and IGF1 levels on either somatostatin analogue (73) and for whom pegvisomant therapy is not possible on account of adverse effects or non-availability of pegvisomant. ii) Moreover, cabergoline may be used as monotherapy if somatostatin analogue and pegvisomant therapy is not a viable option, and cabergoline therapy may also be efficacious in patients with normal PRL levels (98).

Temozolomide and GH excess

Aggressive pituitary tumours are associated with substantial morbidity and mortality. These tumours exhibit continued growth despite multimodal therapy, including surgery and radiotherapy (99). Temozolomide (TMZ), synthesised in 1984, is an alkylating agent that can be administered orally with 100% bioavailability. TMZ has a remarkable ability to cross the blood–brain barrier, and it was first used to treat malignant gliomas (100). The critical methyl adduct produced by TMZ and responsible for the greatest
cytotoxicity is the lesion at 06-guanine, which is repaired in the presence of 06-methylguanine-DNA methyltransferase (MGMT). The regulation of MGMT expression is not fully understood (99), and MGMT status as a biomarker for the responsiveness of pituitary tumours to TMZ treatment is still the subject of debate (99). A correlation between low MGMT levels and TMZ efficacy has been demonstrated in brain tumours, melanomas and neuroendocrine tumours (101). A review has concluded that immunohistochemistry for MGMT appears to be a promising, readily available technique for guiding therapeutic decisions and predicting response to TMZ therapy (102). Others do not recommend the use of MGMT molecular analysis, however, because the predictive value is too low to influence the clinical decision about treatment with TMZ in individual cases (103, 104). These different conclusions may be explained by problems with the sensitivity and specificity of determining MGMT status (99).

A total of 40 cases have been published on TMZ therapy of pituitary tumours, and four of these 40 cases involved GH hypersecretion (105). In our case – where the patient had a mixed pituitary carcinoma with hyperprolactinaemia and acromegaly – the MGMT values were low. The patient responded to therapy and is still alive and in remission (106). The other three of four cases had high MGMT values and did not respond to TMZ (105).

No other cytostatic agents have proven effective in treating pituitary carcinomas. Two recent papers have reviewed the literature on TMZ and pituitary tumours (101, 107). Ravero et al. (101) focused on pituitary carcinomas and aggressive tumours, while Whitelaw et al. (107) devoted their attention to dopamine agonist-resistant prolactinomas. Both papers (101, 107) noted the lack of evidence and long-term data and emphasised the need for caution.

Conclusion

The diagnosis of acromegaly was described more than 125 years ago, but new aspects are still being reported. For example, the AIP gene – a gene involved in acromegaly – has only recently been discovered. Patients who display GH excess before the age of 40 years are advised to undergo genetic screening. GH adenomas frequently co-secrete PRL, so hyperprolactinaemia may be diagnosed before GH excess becomes apparent in some patients. Therefore, it seems appropriate to measure IGF1 levels once a year in patients with prolactinomas. Two somatostatin analogues are available for acromegaly: octreotide LAR and lanreotide Autogel. Switching between the analogues may prove beneficial if i) the patient has failed to reach his/her biochemical target or ii) the patient displays an adverse response to one of the analogues. The effects of pasireotide, a new, multi-receptor somatostatin analogue, have not yet been fully established, and the decrease in insulin levels during therapy is a source of concern.

Pegvisomant therapy may normalise IGF1 levels in a large proportion of patients for whom radiotherapy has been indicated previously, but tumour size is not reduced during pegvisomant therapy and the levels of transaminases may increase during combination therapy with a somatostatin analogue.

Studies of four cases where TMZ has been used in acromegaly have been published. Only one patient with low MGMT status responded to treatment. This patient had a malignant pituitary tumour with co-secretion of PRL. On this basis, the results of TMZ therapy in acromegaly are not promising.

Acromegaly is a rare disease, but it is reassuring to note that research regarding diagnosis – including genetic predisposition – and with regard to medical therapy has made great strides over the last 30 years.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by a research grant from the Novo Nordisk Foundation.

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Received 28 June 2013
Revised version received 14 October 2013
Accepted 21 October 2013