Growth Hormone Replacement in Adults with Cured Acromegaly: Ready for Prime Time?

Growth hormone deficiency (GHD) may eventually occur in the majority of patients with cured acromegaly as a consequence of pituitary surgery and/or radiation therapy [1].

Several studies have suggested that unreplaced GHD in patients with cured acromegaly (acroGHD) is associated with abnormal body composition (increased total and visceral adiposity), abnormal cardiac function, increased serum C reactive protein levels, and impaired quality of life (QoL) in comparison with patients with cured acromegaly who are GH sufficient [2-3]. These findings suggest that the phenotype of patients with acroGHD may be similar to that of deficient adults whose GHD is caused by other etiologies and raise the possibility that GH replacement might be of benefit in this population.

The paradigm of replacement therapy in deficient patients with prior history of hormone excess is certainly familiar to endocrinologists, who routinely replace glucocorticoids in patients with Cushing’s disease that were rendered adrenally insufficient as a result of pituitary surgery and/or radiation therapy. Similarly, levothyroxine replacement is advised in patients with Graves’ disease that developed primary hypothyroidism as a result of thyroid surgery and/or radioiodine therapy. So, should GH replacement be offered to patients with acroGHD?

The effects of growth hormone (GH) replacement in a population of patients with acroGHD have been examined in several studies, which have generally been of limited size and/or duration. Some studies have suggested beneficial effects of GH replacement in patients with acroGHD, including improvements in body composition, serum lipids and QoL [4-9]. In contrast, other studies have found little evidence of benefit [10] or raised concerns regarding the cardiovascular safety of this therapy in patients with acroGHD [8].

To further evaluate the effectiveness and safety of GH replacement in patients with acroGHD, a team of investigators has recently analyzed data extracted from a large, international, pharmaco-epidemiological database of adult patients with hypopituitarism of diverse etiologies who have been receiving GH replacement [11].

Computerized searches identified an “effectiveness population”, including 115 adults with acroGHD and a control population of age, gender and body mass index (BMI) - matched patients, consisting of 142 adults with GHD and history of clinically non-functioning pituitary adenoma (NFPA). All patients had stringently defined GHD, based on the diagnostic criteria recommended by the Growth Hormone Research Society [12], and had been receiving GH replacement for at least 75% of the study period. Changes in serum lipids and QoL in response to GH replacement were retrospectively analyzed in this population.

In addition, the safety of GH replacement was assessed in the entire database population of patients with acroGHD on GH replacement (164 adults) in comparison with the entire database population of patients with GHD and NFPA (2469 adults) receiving GH replacement, as well as several external reference groups drawn from the general population [including the World Health Organization “Global Burden of Disease” (WHO GBD), “Cancer Incidence in Five Continents”, the Kronoberg County Study, the US National Health Interview Survey, the KORA S4/F4 and the Bruneck Study, as well as the MONICA Augsburg Cohort Study].

The median GH replacement dose was 0.3 mg daily in both groups (acroGHD and NFPA) at the end of the 5 year observation period and serum insulin-like growth factor 1 (IGF-1) standard deviation scores (SDS) were comparable and physiologic in both groups (Figure 1). There were also comparable decreases in total and low density lipoprotein (LDL) cholesterol levels in both groups (Figure 2A and 2B). Quality of life scores, assessed by the QoL-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire, continued on page 2

Figure 1. Serum IGF-1 SDS levels in GHD adults with acroGHD or NFPA, measured at baseline as well as 5 years after the initiation of GH replacement [11]. Copyright 2014, The Endocrine Society.
showed comparable improvements in both groups during the same period (Figure 3).

Reassuringly, safety analyses showed that all-cause mortality in patients with acroGHD was similar to that in the general population (ratio between observed/expected [O/E] cases [95% confidence intervals] = 1.32 [0.70 - 2.25]). All cause mortality was lower in patients with NFPA [O/E ratio = 0.58 (0.48 - 0.70)] than the general population, perhaps reflecting a healthier group selected for GH replacement.

Somewhat less reassuringly, cardiovascular mortality was increased in patients with acroGHD (O/E ratio = 2.89 [1.16 - 5.92]) in comparison with the general population. In contrast, cardiovascular mortality was lower in patients with NFPA (O/E ratio = 0.68 [0.48 - 0.94]) than the general population, yielding a standardized mortality rate (SMR) ratio of 4.23 (1.89 - 9.47) between patients with acroGHD and NFPA (P = 0.0004). These findings remained robust to adjustments for history of hypertension, diabetes mellitus, dyslipemia and cardiovascular disease at baseline, or after the exclusion of patients with cardiovascular or cerebrovascular disease at study entry. Of note, cerebrovascular mortality was not increased in either group (acroGHD or NFPA) in comparison with the general population.

The incidence of diabetes mellitus was higher in both groups (acroGHD and NFPA) than the general population (acroGHD patients: O/E ratio = 3.84 [2.31 - 5.99]; NFPA patients: O/E ratio = 3.86 [3.43 - 4.33]), and increased with higher BMI at study entry. However, there was no difference in the incidence of diabetes mellitus between these two groups. Similarly, there was no difference between patients with acroGHD and NFPA with regards to the incidence of all malignancies combined, benign or malignant brain tumors, incident cardiovascular or cerebrovascular disease.

What can we make of these findings? The data from the present study affirm several possible benefits of GH replacement in patients with acroGHD, including potentially salutary effects on serum lipids and QoL. However, body composition (fat mass, lean body mass and bone mineral density), cardiovascular function or exercise capacity were not assessed in this study, owing to lack of sufficient data in the database.

With the exception of a possible increase in cardiovascular mortality, the findings of this study suggest that the safety of GH replacement in patients with acroGHD is comparable to that in patients with GHD and NFPA.

It should be kept in mind that patients with active GH excess are at increased risk of cardiovascular morbidity and mortality (13-14). It remains unclear whether the increased cardiovascular mortality among patients with acroGHD receiving GH replacement, noted in the present study, is associated with their history of previous GH excess or with subsequent GH replacement. It may also be noted that the present study represents a retrospective analysis of observational data rather than a randomized clinical trial, which is the gold standard for assessing efficacy and safety. In addition, a control population of patients with acroGHD, who

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**Figure 2A.** (Top) Change from baseline in total cholesterol levels in GHD adults with acroGHD or NFPA, measured over 5 years after the initiation of GH replacement (11).

**Figure 2B.** (Middle) Change from baseline in LDL cholesterol levels in GHD adults with acroGHD or NFPA, measured over 5 years after the initiation of GH replacement (11).

**Figure 3.** (Bottom) Change from baseline in QoL-AGHDA scores in GHD adults with acroGHD or NFPA, measured over 5 years after the initiation of GH replacement (11). A decrease in QoL-AGHDA score denotes an improvement in QoL. Copyright 2014, The Endocrine Society.
An Unusual Case of Acromegaly: the Disappearing Macroadenoma

Lisa B. Nachtigall, MD

A generally healthy 34 year old man with a recent history of hypertension came to medical attention during a June hospitalization in Virginia for “heat exhaustion” and the worst headache of his life following routine military training exercises. He also reported visual disturbance, fever, nausea and vomiting and underwent an MRI of the brain which showed a large pituitary mass measuring 3.2 cm x 1.8 cm x 2.5 cm and abutting the undersurface of the optic chiasm (Figure 1 a and b). Approximately three weeks later, he was seen at MGH for further work-up and management. Retrospectively, he reported a four year history leading up to the acute episode of carpal tunnel syndrome and enlargement of his brow, hands, and feet requiring increasing sizes of his wedding ring and combat boots. He also noted the development of skin tags on his neck and underarms.

His exam was notable for typical features of acromegaly including a large jaw, coarsening of facial features and broadened nose, frontal bossing, and enlarged hands with thickened metacarpalphalangeal and proximal interphalangeal joints. Visual fields were intact by exam and by formal visual field testing by neuro-ophthalmology. The clinical diagnosis was acromegaly, based on classic findings on history, physical exam and the presence of a pituitary macroadenoma. He was scheduled for surgical resection of what was thought to be a growth hormone secreting pituitary macroadenoma. IGF-1 level was obtained on the day of his initial neuroendocrine evaluation and was surprisingly normal at 311 [reference range: 114-492 ng/ml]. Other anterior pituitary tests were normal including cortrosyn stimulation, thyroid function tests and prolactin level, with the exception of a low morning testosterone of 209 [270-1070 ng/dl].

The patient opted to defer neurosurgery for three months in order to complete his reserve training and during that interval received three doses of lanreotide 90 mg IM monthly for a presumptive GH secreting macroadenoma. A pre-operative repeat MRI three months later was performed to guide resection and showed involution of the tumor (Figure 1 c and d). There was marked interval decrease in size of heterogeneously enhancing sellar mass to 1.2 cm SI by 1.6 cm RL by 1.1 cm AP. The surgery was cancelled. In the subsequent 12 months and with no further therapy, the patient’s physical features of acromegaly regressed and his hypertension resolved. MRI showed complete involution of the tumor two years later with no additional therapy (Figure 1 e and f). IGF-1 remained normal and random growth hormone was 0.39 [2-6 ng/ml]. All of his anterior hormone tests were normal including cortisol > 18 mcg/dl, free thyroxine, and testosterone, which had increased into the mid-normal range.

In summary, this patient presented with clinical evidence of acromegaly, likely secondary to a pituitary macroadenoma, and hypogonadism and had spontaneous resolution of acromegaly due to a possible apoplectic event (e.g., bleeding and autoinfarction of the adenoma). Gonadal function also spontaneously recovered. In retrospect, the severe headache and “heat exhaustion” just before presentation likely represented apoplexy. It is also possible that the three doses of lanreotide contributed to tumor shrinkage, but of note, IGF-1 was normal before the medication was used.

Spontaneous resolution of acromegaly due to presumed apoplexy, while rare, has been reported in the medical literature in over 25 cases [1-5], beginning in 1986 [6] before wide spread use of pituitary MRI and including case reports that date back to the 19th century, when complete regression of features of acromegaly in the Mexican governor of California Pio Pico was explained by presumed apoplexy. Photographs of Governor Pico from 1873 show no signs of acromegaly compared with 1857, when classic features of acromegaly had been evident [7]. In these prior case reports of apoplexy associated with remission of acromegaly, a wide range of precipitating factors were proposed, including anticoagulation [8], cerebral angiography [9], contrast dye [10], diabetes mellitus [3] and thyroid surgery [11]. However this is the first case report to my knowledge, in which intensive physical training was associated with the onset of symptoms of apoplexy and presumed regression of acromegaly.

Most cases in the literature were reported before the availability of MRIs [2], or were in patients diagnosed after tumor involution [4], or included patients who underwent surgical intervention despite spontaneously normalized growth hormone after apoplexy [3]. Thus, few reports demonstrate complete spontaneous resolution of a macroadenoma by imaging [2, 5]. In the patient described here, his decision to postpone surgery provided the opportunity to capture the natural history of his tumor resolution on MRI scans following presumed apoplexy and three doses of medical treatment.

While hypopituitarism has been reported to occur in the majority of patients following apoplexy associated with acromegaly remission [2], this patient has recovered gonadal axis function and maintained normal pituitary function of the other hormone axes. Importantly, he has had no recurrence of his pituitary macroadenoma on MRIs up to three years after the initial presentation. It is possible that the tumor had a dramatic response to three doses of long acting somatostatin analog. However, the medication is unlikely to explain all of his clinical improvement since the IGF-1 was already normal before the somatostatin analog was administered. Additionally, there has been no progression of tumor and no ele...
vation of IGF-1 or GH over three years of follow up. While a period of remission has been reported in a small minority of patients with acromegaly following chronic somatostatin anal-

glog treatment for at least 14 months [12-14], it is rare to remain in remission for three years after stopping somatostatin [13] and remission has not been reported after only three doses.

This is an unusual case of acromegaly because most patients require surgery and/or long term medical therapy to control large tumors but this patient had spontaneous regression of the large adenoma and/or after three months of medical therapy. The normal IGF-1 prior to medical therapy with somatostatin ana-

logue suggested that his disease spontaneously improved prior to any therapy. In addition, apoplexy is usually associated with a decrease in pituitary function, and in this patient, gonadal function recovered and other pituitary axes remained normal. He will be monitored carefully for recurrence, but so far is doing very well on no pituitary-related medications and MRI remains stable three years after he experienced the episode of severe headache and exhaustion.

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were not receiving GH replace-

ment, was not available in the database. Inclusion of such a control population would likely be helpful in order to further elucidate the cardiovascular safety of GH replacement in patients with acroGHD and should be considered in future studies.

References

SAVE THE DATE

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Physicians with questions may contact the PPIS at 617-726-3965 or 1-888-429-6863 e-mail pituitary.info@partners.org
The PPIS has received educational grant support from Concept Therapeutics and Ipsen Biopharmaceuticals, Inc.
**RESEARCH STUDIES AVAILABLE**

Patients may qualify for research studies in the Neuroendocrine Clinical Center. We are currently accepting the following categories of patients for screening to determine study eligibility. Depending on the study, subjects may receive free testing, medication and/or stipends.

<table>
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<th>SUBJECTS</th>
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| Adults with GHD | • Long acting GH replacement study  
• Assessing bone microarchitecture | Beverly MK Biller, MD  
Karen Pulaski Liebert, RN  
Nicholas Tritos, MD |
| Adults with Cushing’s disease | • Treatment study assessing the effect of an investigational medication on cortisol levels | Beverly MK Biller, MD  
Karen Pulaski Liebert, RN |
| Adolescent and young adult athletes | • Investigating impact of hormonal alterations on menstrual function and bone density | Madhu Misra, MD  
Anne Klibanski, MD  
Kathryn Ackerman, MD |
| Adolescent girls with anorexia nervosa | • Investigating the impact of new therapies on bone density | Madhu Misra, MD  
Anne Klibanski, MD  
Kathryn Ackerman, MD |
| Girls and young women with low-weight eating disorders 10-21 years old | • Investigating food motivation pathways and appetite regulating hormones in relation to eating behaviors disease outcome | Madhu Misra, MD  
Elizabth Lawson, MD  
Kamryn Eddy, PhD |
| Women with anorexia nervosa | • New therapies  
• Cross-sectional bone density study | Karen K Miller, MD  
Anne Klibanski, MD |
| Women ages 18-40 with a history of anorexia nervosa | • Investigating hormones and brain circuitry involved in appetite | Elizabeth Lawson, MD  
Anne Klibanski, MD |
| Men and women with active or treated acromegaly | • Quality of life  
• Cross-sectional bone density study  
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Pouneh Fazeli, MD  
Karen Pulaski Liebert, RN  
Nicholas Tritos, MD |
| Girls and women with current anorexia nervosa or a history of anorexia nervosa, ages 10 and up | • Investigating genetics of appetite-regulating and stress hormones | Elizabeth Lawson, MD  
Karen K Miller, MD  
Anne Klibanski, MD  
Madhu Misra, MD |
| Healthy girls and women, ages 10 and up | • Investigating genetics of appetite-regulating and stress hormones | Elizabeth Lawson, MD  
Karen K Miller, MD  
Anne Klibanski, MD  
Madhu Misra, MD |
| Healthy normal-weight and obese men | • Effect of oxytocin on caloric intake | Elizabeth Lawson, MD |
| Men with hypopituitarism | • Characterization of oxytocin deficiency | Elizabeth Lawson, MD |
| Healthy normal-weight women | • Cross-sectional bone density study | Pouneh Fazeli, MD  
Anne Klibanski, MD |
| Healthy slightly overweight men and women | • Investigating the effects of fasting on adipose tissue distribution | Pouneh Fazeli, MD |
| Obese women | • Cross-sectional bone density study | Pouneh Fazeli, MD  
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| Overweight and obese women and men | • Investigating GH and bone health | Karen K. Miller, MD |
| Obese men and women | • Investigating the effect of acipimox, a medication to decrease free fatty acids, on skeletal muscle mitochondria | Hideo Makimura, MD |
| HIV positive men and women with and without metabolic abnormalities | • Assessment of coronary artery atherosclerosis  
• Growth hormone and growth hormone releasing hormone  
• Assessment of long-term GHRH  
• Assessment of epinephrine on metabolic abnormalities  
• Assessment of menopausal transition  
• Statin therapy for coronary plaque | Steven Grinspoon, MD  
Janet Lo, MD  
Katie Fitch, FNP  
Takara Stanley, MD  
Suman Srinivasa, MD |
| Adults with moderate-to-severe psoriasis about to be started on etanercept (Enbrel) by their treating dermatologist | • Assessment of cardiovascular and metabolic health | Markella Zanni, MD  
Steven Grinspoon, MD |

*The Neuroendocrine Clinical Center is involved in many different research studies. Types of studies and enrollment status changes frequently, so please call our office (617-726-3870) or check our webpage (massgeneral.org/neuroendocrine) for more information about potential studies which may not be listed here.*
Facilities
The Neuroendocrine Center is located on the 1st floor [Suite 112] of Zero Emerson Place at the Massachusetts General Hospital. A test center is available for complete outpatient diagnostic testing, including ACTH (Cortrosyn) stimulation; insulin tolerance; CRH stimulation; oral glucose tolerance and growth hormone stimulation testing. Testing for Cushing’s syndrome can also be arranged, including bilateral inferior petrosal sinus ACTH sampling for patients with ACTH-dependent Cushing’s syndrome.

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A weekly interdisciplinary conference is held to discuss new patients referred to the Neuroendocrine Center and to review patient management issues. It is a multidisciplinary conference, attended by members of the Neuroendocrine, Neurology, Neurosurgery, Psychiatry and Radiation Oncology services. Physicians are welcome to attend and present cases.

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Scheduling
Outpatient clinical consultations can be arranged by calling the Neuroendocrine Center Office at [617] 726-7948.

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The Neuroendocrine Clinical Center Welcomes Dr. Alex Faje
Dr. Faje earned his medical degree at Vanderbilt University School of Medicine, completed his residency training at the University of Michigan and fellowship in endocrinology at the Massachusetts General Hospital. At MGH, Dr. Faje sees patients with pituitary and neuroendocrine disorders in the Neuroendocrine Clinical Center as well as consulting on inpatients, teaching and maintaining involvement in clinical research studies.