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Cardiac Disease in Acromegaly

Janet Lo, M.D.

Patients with acromegaly are known to have reduced life expectancy. Prior to effective treatment for acromegaly, more than 80% of acromegalic patients died of cardiovascular disease before age 60 (1,2). Even in the modern era with available therapy, mortality in active acromegaly is still increased about two- to three-fold and the major cause of death remains cardiovascular disease, comprising 40 to 60 percent of mortality in acromegalic patients (3). Several studies have shown, however, that mortality rates can be decreased to levels expected in the general population by normalization of serum growth hormone (GH) and insulin-like growth factor (IGF-I) (3,4,5,6).

Huchard first described cardiac abnormalities associated with acromegaly in 1895 (7), not long after Marie's initial description of acromegaly (8). In addition to myocardial hypertrophy and congestive heart failure, other cardiovascular disorders prevalent in acromegalic patients include hypertension, diastolic dysfunction, valvular heart disease, ventricular arrhythmia, and endothelial dysfunction. Post-mortem pathological studies found the increase in heart size was related to duration of acromegaly and occurred in both hypertensive and nonhypertensive patients (9). Cardiac histopathology showed myocardial hypertrophy (in 93% of patients examined), interstitial fibrosis (85%), and lymphomononuclear cell infiltrate (59%).

Possible etiologic factors for cardiac hypertrophy in acromegaly include hypertension, direct hormonal effects of growth hormone or IGF-I, or the combination of hypertension and hormonal effects. Hypertension, a well-established cause of left ventricular hypertrophy, is very common in acromegaly. In normal rat heart *in vivo*, the administration of recombinant IGF-I causes ventricular chamber enlargement and hypertrophy in a dose-responsive manner (10). Some authors have proposed a separate entity of "acromegalic cardiomyopathy" since hypertrophic cardiomyopathy can be seen independent of hypertension, diabetes mellitus, valvular heart disease, or atherosclerosis in acromegaly. Early on, as the myocardium hypertrophies, diastolic dysfunction is detectable. Later, ventricular remodeling with chamber enlargement and systolic heart failure can ensue.

The prevalence of regurgitant valvular heart disease, especially aortic valve regurgitation and mitral valve regurgitation, is increased in acromegaly compared to controls matched for sex, age, left ventricular function and presence of hypertension and correlates with the duration of acromegaly (11). Pathologically, myxomatous degeneration is seen in surgically removed valves (11). It appears that valvular heart disease in acromegaly may be irreversible, in contrast to the reversibility of ventricular hypertrophy (11).

Is coronary artery disease increased in acromegaly? Associated complications of hypertension, diabetes mellitus, hyperinsulinemia, and hypertriglyceridemia may confer an increased risk of coronary artery disease in acromegaly; however, decreased visceral adiposity in acromegaly may tend to decrease cardiovascular risk. Studies investigating coronary artery disease in acromegaly are limited. Using autopsy data,

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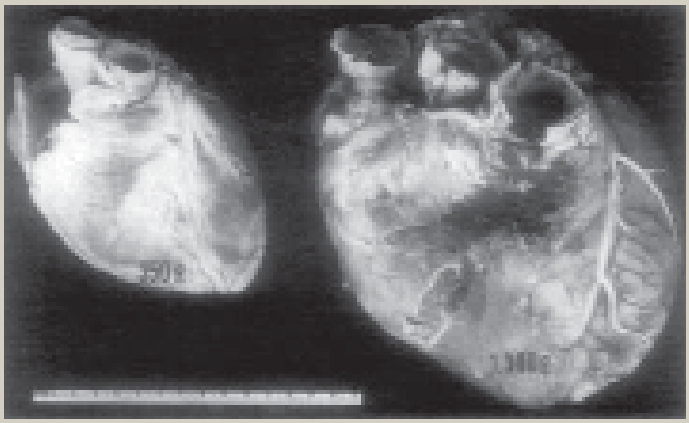

Figure 1

Comparison of a normal sized heart (on the left) with an acromegalic heart (on the right). Reprinted from American Heart Journal (9) with permission from Elsevier.

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coronary artery disease was not observed more in acromegaly than expected (9). Recently, a study using cardiac calcifications detected by computed tomography integrated with evaluation of the Framingham risk score showed that 41% of acromegalic patients are at risk for coronary atherosclerosis, even though overall myocardial infarction rate was not increased above that of the general population (12). Cardiovascular risk markers including triglycerides, lipoprotein (a), apolipoprotein A-1, apolipoprotein-E, fibrinogen, plasminogen activator inhibitor activity are increased in acromegaly (13,14). On the other hand, C-reactive protein (CRP) is lower in acromegaly compared to healthy controls, while insulin levels are higher (15). With administration of the GH-antagonist, pegvisomant, CRP levels increase in acromegalic patients (15). The clinical significance of these cardiovascular risk marker changes remains to be determined.

Fortunately, treatment of acromegaly with normalization of GH and IGF-I levels can improve many of the acromegaly-associated cardiac disorders and also decrease the mortality rate.

Other manifestations of acromegaly including diabetes mellitus and central sleep apnea also have cardiovascular consequences. The insulin-antagonistic action of GH can lead to insulin resistance and diabetes mellitus in acromegaly. Diabetes mellitus is a well-established cause of cardiovascular pathology including coronary artery disease and diabetic cardiomyopathy. Insulin resistance is associated with endothelial dysfunction (16). Maison and colleagues previously reported impaired endothelial function in acromegalic patients (17). Brevetti and colleagues also found significantly lower flow-mediated vasodilation of the brachial artery in acromegalic patients compared to risk-factor-matched controls (18). It is unclear to what degree insulin resistance or GH and IGF-I excess contribute to the endothelial dysfunction observed in acromegaly. Central sleep apnea is a common manifestation of acromegaly (19). Sleep apnea may predispose patients to increased cardiorespiratory deaths, cardiac events, and hypertension.

Sudden cardiac death can occur in acromegaly and ventricular arrhythmias are a potential cause (20). Kahaly and colleagues found that 48% of acromegalic patients had more frequent and complex ventricular arrhythmias on holter monitoring compared to 12% of controls. Ventricular arrhythmias correlated with LV mass and duration of acromegaly (21). The American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines 2006 recommend that management of ventricular arrhythmias should address the underlying endocrinopathy and any electrolyte imbalances and that persistent life-threatening arrhythmias need to be treated with the use of ICD and pacemakers (22). Baseline corrected QT interval duration has also been found to be significantly longer in patients with acromegaly and is a known risk factor for life-threatening arrhythmias (23). Treatment with somatostatin analogues has been shown to improve QT interval duration in patients with acromegaly (23).

Several longitudinal studies have demonstrated that normalization of GH and IGF-I levels can improve cardiac function and decrease mortality, thus underscoring the importance of appropriate treatment of acromegaly. Many of the cardiovascular changes in acromegaly are reversible, especially in those with shorter disease duration. Somatostatin analogues including octreotide and lanreotide decrease ventricular hypertrophy and improve arrhythmia profile (24,25,26). Surgical treatment has also been shown to improve cardiac function and mortality (27,6). Valvular heart disease, on the other hand, does not appear to reverse with treatment of acromegaly and, therefore, early diagnosis of acromegaly may prevent development of potentially irreversible abnormalities.

In conclusion, patients with acromegaly are predisposed to developing cardiac diseases that lead to decreased life expectancy. Fortunately, treatment of acromegaly with normalization of GH and IGF-I levels can improve many of the acromegaly-associated cardiac disorders and also decrease the mortality rate. Assessments for functional, valvular, ischemic, and electrophysiologic cardiac abnormalities as well as other manifestations of acromegaly known to increase cardiovascular risk such as hypertension, diabetes mellitus and sleep apnea are appropriate to consider in the clinical care of acromegalic patients.

Clinical studies are available for patients with acromegaly

(see last page for contact information)

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Endocrine and Sleep Interactions

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There is a complex interaction between sleep and neuroendocrine hormones. Endocrine disorders can lead to sleep disturbance and conversely, altered sleep patterns can affect normal hormonal secretion profiles. The hypothalamus and the sympathetic nervous system have been most carefully studied for their contribution to normal and pathologic sleep. Two of the hypothalamic hormones that have been implicated as important in the regulation of sleep are growth hormone releasing hormone (GHRH) and corticotrophin releasing hormone (CRH). GHRH and CRH likely have direct neuronal effects that influence sleep as well as secondary effects mediated by the pituitary hormones that they stimulate, namely growth hormone and adrenocorticotropic hormone (ACTH) leading to cortisol release, respectively. Infusion studies in humans have been performed to determine effects on sleep and these studies have indicated that there are sexually dimorphic effects of these hormones. GHRH infusion in men increases slow wave (non-REM) sleep and decreases cortisol, leading to a sleep promoting effect. However, in women GHRH impairs sleep. CRH in both men and women promotes wakefulness.

GH and Sleep GH is secreted in a pulsatile fashion and also shows a sexually dimorphic pattern. Men generally have a single large peak during the early portion of sleep; whereas women have multiple peaks during the day and night and frequently have a burst prior to sleep initiation. The majority of daily GH is secreted during sleep and this higher level of GH secretion is dependent on sleep. With acute total sleep deprivation, nocturnal GH secretion decreases by 50 to 75%. Sleep deprivation promotes sleep and this may be caused by a rise in GHRH levels leading to recovery sleep. During recovery sleep, there is an increased amount of GH released. In states of GH excess, such as acromegaly or high dose GH treatment, there is a decrease in non-REM sleep, potentially by decreasing GHRH or increasing somatostatin.

Cortisol and Sleep Cortisol is secreted in response to CRH and ACTH in a circadian fashion with control by the suprachiasmatic nucleus of the hypothalamus. Cortisol levels are at their lowest around midnight and gradually increase to a peak before 9AM. During the early sleep period, hypothalamic-pituitary-adrenal (HPA) axis activity is suppressed. Acute and partial sleep loss lead to an increase in cortisol levels, due to a decreased rate of cortisol decline in the afternoon and early evening. Decreased sleep or altered sleep patterns, such as night shift work, may have an effect on the measurements used to screen for Cushing's syndrome. While no standards have been established for testing in these individuals, the possibility of a pseudo-Cushing's state should be considered.

The effect of cortisol on sleep is dose-dependent and may be due to the differential affinity of cortisol at mineralocorticoid versus glucocorticoid receptors. Cortisol is a high-affinity ligand at mineralocorticoid receptors. In some tissues, such as kidney, cortisol is rapidly inactivated to cortisone by local 11-ß-hydroxysteroid dehydrogenase-2 (11-ß-HSD-2). However, in other tissues such as brain, decreased 11-ß-HSD-2 expression and increased 11-ß-HSD-1 expression increase the local cortisol concentration. As cortisol has higher affinity at mineralocorticoid than glucocorticoid receptors, it exerts mineralocorticoid effects at low concentrations and glucocorticoid effects at higher concentrations. Thus the slow wave sleep promoting effect of mineralocorticoid receptor activation occurs with low dose cortisol. The mechanism for sleep promotion may be by mineralocorticoid-mediated inhibition of CRH release. As cortisol levels rise overnight, there is a shift toward increased wakefulness. Higher doses of cortisol activate the glucocorticoid receptors and thus wakefulness and this may also explain the adverse sleep patterns of Cushing's syndrome, a state of high cortisol concentration.

Metabolic Consequence of Altered Sleep While it is believed that young adults require approximately eight to nine hours of sleep, many obtain only five to six hours through self-imposed sleep restriction. Studies have shown that sleep deprivation leads to detrimental glucose dynamics. This may be due to a direct effect on glucose regulation or promotion of obesity. Partial sleep restriction (four hours per night for five or six nights) decreases glucose tolerance and insulin secretion. Contributors to this effect may include an increase in the counter-regulatory hormones that control glucose dynamics, including increased sympathetic nervous system activity and increased cortisol levels. Interestingly, studies of individuals who have restricted their sleep to less than 6.5 hours per night for at least six months have normal glucose tolerance but significantly higher insulin levels, suggesting a chronic adaptation with worsened insulin sensitivity. The alteration in insulin dynamics may be exacerbated by changes in hormones that affect appetite and thus weight. Sleep deprivation leads to decreased leptin levels and increased ghrelin levels. As leptin is anorexigenic and ghrelin orexigenic, this may underlie the increased appetite that is associated with sleep deprivation.

Pathologic Sleep States Certain primary endocrine disorders have been associated with dysregulated sleep, including acromegaly with sleep apnea and Cushing's syndrome with sleep disturbance. Additionally, several other medical conditions have been linked with altered cortisol dynamics. Chronic insomnia may represent a state of HPA axis arousal with preserved circadian rhythm, but blunted decline in cortisol in the afternoon and early evening. It has been postulated that this increased cortisol contributes to the long sleep latency and frequent awakenings of insomnia. Depression is a disorder that has been associated with increased cortisol levels and decreased sleep. The cause and effect relationship between HPA axis activation and depression is unknown. CRH receptor antagonists are currently being explored as a therapeutic for insomnia and depression. Treatment of insomnia with medications such mirtazapine, trazodone, and benzodiazepines has been associated with a decline in cortisol levels.

While there is a strong association between obesity and insulin resistance, sleep apnea worsens insulin resistance independent of an individual's body mass index. Several mechanisms have been proposed for the negative metabolic effect of sleep apnea, including sympathetic nervous system activation, HPA axis stimulation,

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Sleep Interactions...*continued from page 3*

and inflammatory cytokine release. The standard treatment for sleep apnea, continuous positive airway pressure (CPAP), has shown mixed results in its ability to improve metabolic parameters. Some studies suggest that obesity is the primary determinant of the metabolic dysfunction and correction of the sleep disordered breathing cannot overcome the negative metabolic impact of obesity; whereas individuals of lower weight are more likely to respond to sleep apnea treatment with improvements in insulin sensitivity. Sleep apnea has also been associated with low growth hormone and IGF-I levels and CPAP has been shown to increase these levels. The consequence of this metabolic derangement is yet to be determined.

Conclusion It has been established that hormones such as GH and cortisol are secreted with a circadian rhythm. New research suggests that sleep itself may impact these secretion profiles. Sleep disruption has become a common condition for many individuals, thus understanding the resulting hormonal changes is imperative. As alterations in growth hormone and cortisol have been linked to metabolic derangements such as impaired glucose tolerance and increased cardiovascular risk, efforts to promote normal sleep patterns may improve this risk profile.

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Insulin-like Growth Factor I Deficiency

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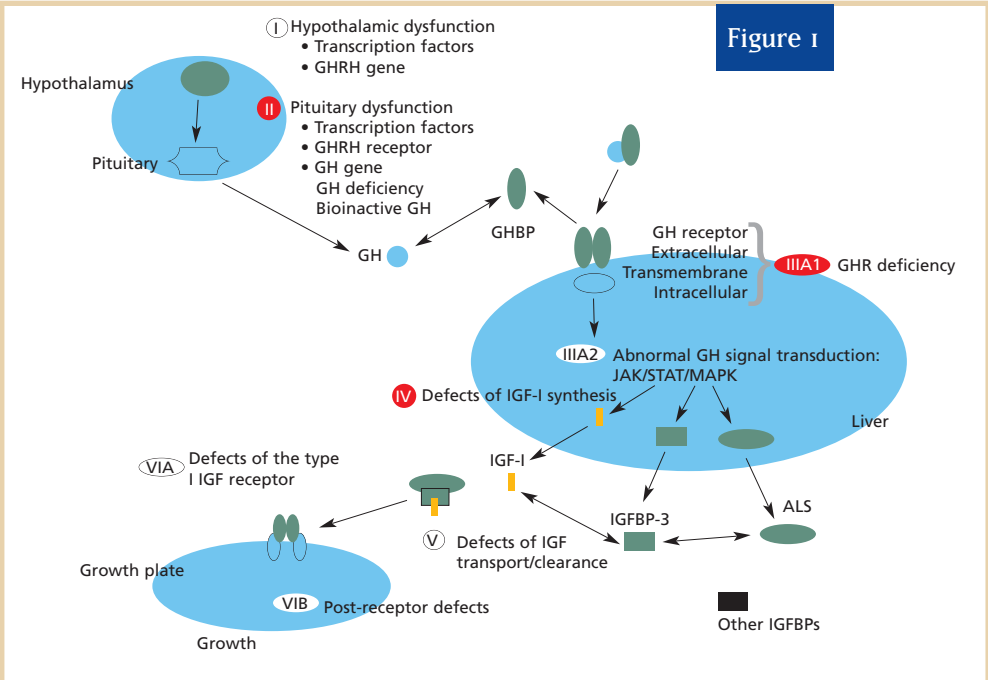
Rapid strides have been made in the last several years in the field of human growth disorders. Even as newer molecular defects are being identified along the somatotropic axis (Figure 1), animal models are emerging to contribute a better understanding of the human disorders (1). Paramount to these growth models, human and animals alike, is a decline in circulating insulin-like growth factor I (IGF-I) levels, either as a consequence of decreased growth hormone (GH) action or as a direct result of decreased IGF-I production in the liver and other tissues. Insulin-like growth factor I, formerly known as "somatomedin-C", is a vital mediator of the anabolic and growth promoting effects of GH. Growth hormone acts directly and indirectly by inducing IGF-I production locally in the bone and in the liver, the major source of IGF-I in the circulation. IGF-I also has paracrine effects in many tissues including bone. Receptors for IGF-I are present in virtually all cells of connective tissues. The majority of naturally circulating IGF-I exists in the form of a ternary complex consisting of equimolar amounts of IGF-I, IGFBP-3, and Acid Labile Subunit (ALS). IGFBP-3 binds IGF-I and ALS to regulate IGF-I bioavailability and biodistribution. IGF-I carried within the ternary complex has a half-life of more than 12 hours. Levels of IGF-I parallel GH levels during childhood, through adolescence into adulthood. Growth hormone, and thereby IGF-I levels decline with increasing age, beginning in young adulthood. Levels of IGF-I must therefore to be interpreted based on normal values for age (2) (Figure 2). Unlike the pulsatile pattern of GH, IGF-I levels are constant through the day. The age and sex-related reference range (mean ± 2 SD) based on a recent European study by Brabant *et al.* is shown from birth to age 80 in Figure 2 (3).

Classification of IGF-I deficiency remains a controversy. One useful classification scheme is shown in Table 1 (14).



The hypothalamic-pituitary-IGF axis: sites of established and hypothetical defects. The established defects are shown as Roman numerals in the red-shaded circles or ovals, and the hypothetical defects are shown in the white circles or ovals. ALS, acid-labile subunit; GH, growth hormone; GHBP, GH-binding protein; GHRH, GH-releasing hormone; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; STAT, signal transducer and activator of transcription. Reprinted from Trends in Endocrinology and Metabolism (13) with permission from Elsevier.

This divides disorders into being due to GH deficiency (either congenital or acquired) or due to resistance/insensitivity to GH (either inherited or acquired). IGF-I deficiency from secondary causes of GH insensitivity (GHI) account for many IGF-I deficient patients, such as those with critical illness, malnutrition, chronic renal or liver disease, HIV/AIDS and other systemic disorders.

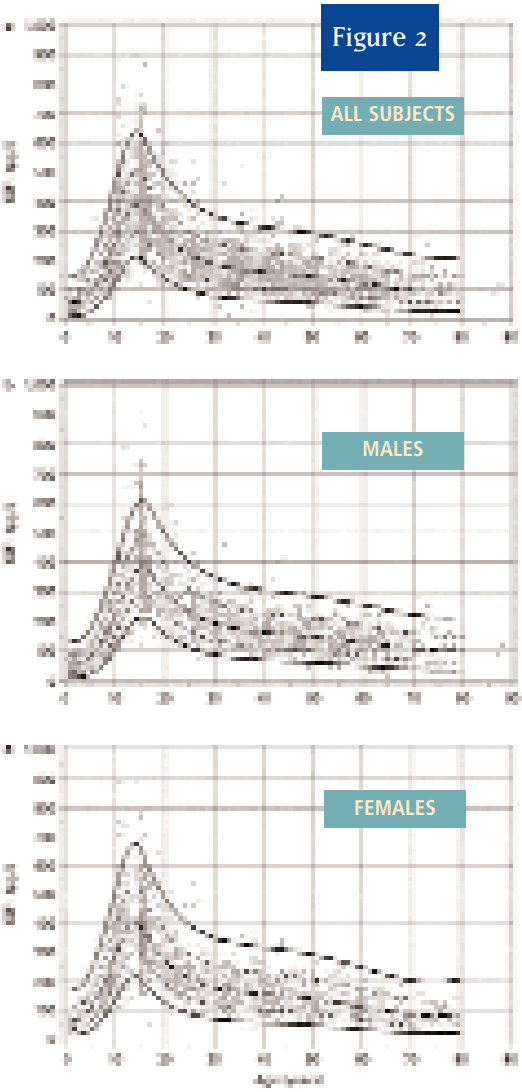
Clinical Features A deficiency of IGF-I, whether from a defect in synthesis or from insensitivity to GH, is associated with profound effects on many organ systems.

IGF-I deficiency states, which may be due to hypothalamic, pituitary, or hepatic origin, share a common phenotype because of the role of IGF-I in mediating most of the anabolic and growth-promoting actions of GH. The ability of IGF-I therapy to treat growth disorders in children with mutations of the GH receptor gene supports this further. The cardinal clinical feature of IGF-I deficiency in childhood is growth failure. Intrauterine growth is not markedly affected, although birth weight and length may be marginally subnormal. However, postnatal linear growth failure is always seen, with a severe and rapid decline in growth velocity. Growth failure typically occurs in the first few months of life, with lengths up to 3 to 4 SD below the mean. By 6 to 12 months, growth can slow down and the growth curves may dip 3 to 4 SD below the mean.

Skeletal and muscular systems are not fully developed, and osteopenia is characteristic. Prolactin deficiency is independently associated with reduced IGF-I status in severely GH-deficient adults (5). Patients with IGF-I deficiency secondary to GHI (Laron syndrome) have additional features such as dysmorphism, reproductive and musculoskeletal abnormalities (6).

Insulin-like growth factor I deficiency has many long-term effects in addition to short stature. It increases the risk of diabetes, cardiovascular disease, and low bone mineral density (7). In a study by Juul *et al.* (8), individuals without ischemic heart disease, but with low circulating IGF-I levels and high IGFBP-3 levels were shown to have significantly increased risk of developing ischemic heart disease during a 15-year follow-up period, suggesting a possible role for IGF-I in the pathogenesis of cardiac ischemia. Some data suggest that, in addition to GnRH and gonadotropins, GH/IGF-I influences the pituitary and gonadal functions in animals and humans (9,10).

Figure 2



Serum-IGF-I as a function of age. The figure gives the individual values of the 3,961 healthy subjects (2,201 males, 1,760 females) as well as the curves for the fitted mean, ±1 SD and ±2 SD functions given by [f(age) ± kSD)] $^{2.5}$ k = 0, 1, 2. (a all subjects; b males; c females). Reprinted from Hormone Research (3) with permission from S Karger AG.

Table 1

IGF-I deficiency

Low GH

GH deficiency
- Congenital - Mutations of PIT 1, PROP 1 , HESX1, LHX4, RIEG
- Acquired
  - Trauma
  - Tumor / cyst
  - Inflammatory conditions like sarcoid, TB, etc.
  - Surgery
  - Radiation

Normal or high GH

Primary GH insensitivity (hereditary defects)
- GH receptor defect (may be +/- for GH-binding protein)
  - Extracellular mutation
  - Cytoplasmic mutation
  - Intracellular mutation
- GH signal transduction defect (distal to cytoplasmic domain of GH receptor)
- Insulin-like growth factor I (IGF-I) synthetic defect
- (IGF-I gene deletion)
- IGF-I transport defect
- Bioinactive GH molecule

Secondary GH insensitivity (acquired defects)
- Circulating antibodies to GH that inhibit GH action
- Antibodies to the GH receptor
- Medical conditions
  - Acute and chronic malnutrition
  - Chronic liver disease
  - Crohn's disease
  - Celiac disease
  - Chronic renal disease
  - Chronic anemias (like sickle cell disease / thalassemia)
  - Poorly controlled diabetes mellitus
  - Cystic fibrosis
  - HIV/AIDS
  - Hypothyroidism

Proposed classification of IGF-I deficiency. Adapted from Williams Textbook of Endocrinology (14) with permission from Elsevier.

Diagnosis Low levels of IGF-I are suggestive but are not diagnostic of IGF-I deficiency. Levels are to be interpreted with regard to age and gender. Patients with insensitivity to GH typically have low serum levels of IGF-I, IGFBP-3, ALS, and GHBP. IGF-I generation tests help in differentiating GHI from other disorders characterized by low serum IGF-I.

Several caveats relate to the use of IGF-I as a diagnostic test. First of all, measured IGF-I reflects only the "endocrine" IGF-I while the "paracrine" IGF-I which perhaps may be more important for growth, is not

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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.

SUBJECTS	STUDIES	CONTACT 617-726-3870
Newly diagnosed acromegaly	• Evaluating preoperative medical treatments	Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller
Cushing's Syndrome	• Evaluating a potential new medical therapy (Anticipated Start: Fall 2007)	Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller
Patients with active acromegaly	• Body composition and cardiovascular evaluation	Dr. Anne Klibanski Dr. Tamara Wexler
Patients with history of cured acromegaly with or without hypopituitarism	• Body composition and cardiovascular evaluation • GH replacement study in patients with GH deficiency	Dr. Anne Klibanski Dr. Tamara Wexler
Adolescent girls with anorexia nervosa	• Evaluating bone density and the effects of estrogen replacement • Newer therapeutic possibilities	Dr. Anne Klibanski Dr. Madhu Misra
Healthy adolescent girls and boys	• To determine extent of growth hormone suppression following an oral glucose load	Dr. Anne Klibanski Dr. Madhu Misra
Healthy and overweight adolescent girls, ages 12-18	• Investigating body weight in relation to GH and ghrelin secretion in adolescents	Dr. Anne Klibanski Dr. Madhu Misra
Women and adolescent girls with anorexia nervosa	• Investigating effects of rhGH on bone metabolism	Dr. Anne Klibanski Dr. Madhu Misra Dr. Rajani Prabhakaran
Women with anorexia nervosa	• New therapies	Dr. Karen K. Miller Dr. Anne Klibanski
Women and men, ages 18-45	• Investigating body weight and GH secretion • GH treatment in abdominal obesity	Dr. Andrea Utz Dr. Karen K. Miller
Healthy women, ages 18-45	• Investigating the link between cortisol regulation and bone density	Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski
Women with irregular menstrual periods (hypothalamic amenorrhea), ages 18-45	• Investigating the link between cortisol regulation and bone density	Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski
Men and women with the Metabolic Syndrome (obesity and insulin resistance)	• Evaluating effects of TNF-alpha neutralization, to reduce inflammation	Dr. Steven Grinspoon Dr. Stine Johnsen
HIV positive men and women with fat redistribution	• Assessment of coronary artery calcification • Lifestyle modification strategies, including exercise and insulin sensitization	Dr. Steven Grinspoon Dr. Janet Lo Katie Fitch, ANP
HIV positive men and women with fat redistribution	• Use of GHRH, a growth hormone secretagogue, to increase endogenous GH levels, improve fat distribution and lipid profile • Among patients with reduced GH response to standard GH secretion testing, use of low dose GH as above	Dr. Steven Grinspoon Dr. Janet Lo Jim Liebau, ANP

IGF-I...*continued from page 5*

measured in serum assays. IGF-I levels are particularly low in early childhood (<5 years of age) and in those who are older than 60 years of age; this makes it more difficult to distinguish between normal and abnormal levels of IGF-I and renders the test less useful in these age groups. Besides varying widely with age and gender, IGF-I levels may have more biologic variability than is appreciated commonly and may vary as much as 5% to 37% even in the same individual on two different days (11). Issues with IGF-I assay availability and quality may also pose challenges in the diagnosis.

Treatment GH replacement is used to treat conditions of IGF deficiency resulting from GH deficiency. In acquired GH resistance, identification and treatment of the underlying condition is the definitive treatment. It has been shown that insensitivity to GH can be overcome in select conditions such as chronic renal failure and chronic liver disease, by the use of supraphysiologic doses of GH. Catabolic conditions such as HIV have shown mixed results in research studies, and further data are needed.

Insulin-like growth factor 1 is now available for the treatment of short stature. It is the drug of choice in the treatment of GHI. Long-term studies have shown a decrease in the response from the initial robust increase in growth rate with IGF-I treatment after the first year (12), and children subsequently grew at approximately normal rates. The GHI children from this study may not achieve adult heights in the normal range, unlike their GH deficient counterparts on GH replacement. This might be related to lack of a paracrine IGF-I effect, a more rapid clearance due to lack of binding proteins, or perhaps due to lack of direct effects of GH. Hypoglycemia can occur in the early part of treatment especially in the younger patients, although this lessens with continuation of treatment. Other side effects with IGF-I reported in these studies included headache, convulsions, urolithiasis, and papilledema (possibility of pseudotumour cerebri) that resolved

spontaneously without discontinuation of treatment. The short half life, perhaps from an unaltered IGFBP milieu, renders twice daily dosing a necessity.

Summary It is increasingly recognized that disorders of growth may occur at many points along the hypothalamic-pituitary-hepatic pathway leading to IGF-I production and growth. For true lack of GH, replacement has been effective and IGF-I is now available for GHI (Laron's). Further research is needed to define the role of these hormones in treating the spectrum of IGF-I disorders.

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Physicians' Pituitary Information Service

Physicians with questions may contact:
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617-726-3965 or 1-888-429-6863
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Andrea L. Utz, M.D., Ph.D.

Neurology:
Thomas N. Byrne, M.D.

Neurosurgery:
Robert L. Martuza, M.D.
Chief, Neurosurgical Service
Brooke Swearingen, M.D.
Nicholas T. Zervas, M.D.

Radiation Oncology:
Jay S. Loeffler, M.D.
Chief, Radiation Oncology
Helen A. Shih, M.D.

Psychiatry:
George Papakostas, M.D.

Pediatric Endocrinology
Madhusmita Misra, M.D., M.P.H.

SERVICES AVAILABLE

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.

Neuroendocrine Clinical Conference A weekly interdisciplinary conference is held to discuss all 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.

Physicians' Pituitary Information Service Physicians with questions about pituitary disorders may contact Dr. Biller or Dr. Klibanski at (617) 726-3965 within the Boston area or toll free at (888) 429-6863, or e-mail to pituitary.info@partners.org.

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

PARTNERS HEALTHCARE
MASSACHUSETTS GENERAL HOSPITAL
A HARVARD MEDICAL SCHOOL TEACHING AFFILIATE

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