Gigantism

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PHAREX MEDICS
Acromegaly and Gigantism Treatment

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Acromegaly and gigantism are caused by tumors in the pituitary gland that lead to too much production of growth hormone in the individual. The goal of gigantism or acromegaly treatment is to remove the tumor and lessen growth hormone levels.

Tumor Removal for Treatment of Gigantism and Acromegaly

When possible, the best treatment for acromegaly is removal of the tumor. A procedure called transsphenoidal microsurgery is the least invasive option. This surgery is performed through the sinus passages, removing or reducing the tumor and relieving the pressure the tumor causes. Cure rates for this surgery depends on the size and location of the tumor. For small tumors, the cure rate is between 80 and 85 percent. Larger tumors have a cure rate of 50 to 60 percent.

In rare cases, acromegaly treatment will require opening a section of the skull to remove the tumor, a surgery known as craniotomy. This is only required if the tumor is not able to be removed through the sinuses.

Medication Therapy for Gigantism and Acromegaly

When patients are not good candidates for surgery, or when the doctor is unable to remove the entire tumor through surgical means, medication may be used to control hormone production. Somatostatin analog injections are one option. These injections cause tumor shrinkage in 30 to 50 percent of patients, and also help with some of the other symptoms of gigantism and acromegaly, like sleep apnea, headache and joint pain.
Sometimes the tumors themselves are not the problem targeted, but rather the effect of high levels of growth hormone on the body. Pegvisomant is a medication that stops the actions of the growth hormone on the body, without actually changing the tumor. Like somatostatin, pegvisomant is an injection.

**Radiation Therapy as Treatment for Gigantism and Acromegaly**

When surgery and medication are not sufficient to shrink tumors or control symptoms, patients may need radiation therapy. Stereotactic radiosurgery aims a focused beam of radiation into the tumor, helping to shrink it and lower growth hormone levels. The treatment does carry risk, but the latest technology ensures that the surrounding brain structures receive minimal radiation during therapy. However, radiation therapy is avoided in children whenever possible, as it can lead to emotional changes, learning disabilities and obesity.

**Prognosis for Treatment**

The prognosis for treatment, again, depends on the size of the tumor and its location. If the tumor is contained within the pituitary gland and the surgeon can remove it all through surgery, then patients have a high chance of seeing improvement of their symptoms.

The speed at which symptoms get better varies as well. Some symptoms will disappear quickly, while others, especially the thick skin on the palms and feet, will take longer to disappear. Some changes, like bone changes or extreme height, may not change at all.

If you or your child have gigantism or acromegaly, treatment is available. Talk to your doctor early about treatment options, before the tumors have a chance to grow beyond the pituitary gland. This gives you the best possible chance of a cure for the condition.
Acromegaly and Gigantism

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1. Introduction
Human growth hormone (GH), a single-chain peptide of 191 amino acids, was isolated from somatotroph cells of the anterior pituitary gland in 1956 and first used therapeutically for treatment of pituitary dwarfism in 1958 (Raben, 1958). Pituitary dwarfism is the classic form of growth hormone deficiency during childhood. Gigantism refers to any standing height more than 2 standard deviations above the mean for the person's sex, age, and Tanner stage. Abnormally high linear growth due to excessive action of insulin-like growth factor-I (IGF-I)/GH causes gigantism while the epiphyseal growth plates are open during childhood, as puberty occurs it is followed by progressive acromegalic changes leading to a picture of a giant with acromegalic features - acromegalic gigantism. When onset disease is after epiphyseal closure, only acromegaly results.

Acromegaly, a somatic growth and proportion disorder first described by Marie in 1886 (Marie, 1886). Elevated levels of growth hormone and IGF-1 are the hallmarks of this syndrome (Melmed, et al., 1983). When Marie first described this syndrome at his patients, pituitary overgrowth is the cause or reflection of the visceromegaly at these patients. In 1909, Harvey Cushing reported the remission of clinical symptoms of acromegaly after partial hypophysectomy, thus indicating the etiology of the disease and its potential treatment as well (Cushing, 1909).

2. Epidemiology
It is a rare condition with a prevalence less than or equal to 70 cases per million and annual incidence of 3 to 4 cases per million (Alexander et al., 1980; Ritchie et al., 1990). Acromegaly occurs with equal frequency in males and females. The mean age at diagnosis is 40-45 years.

3. Pathology, etiology, pathophysiology
GH also called somatotropin is main regulator of normal growth. Its actions responsible for the catching up of normal adult height. The GH gene is located on chromosome 17 (Chen et al., 1989). There are at least three monomeric forms of GH-the predominant physiologic 22 kd form, a less abundant 20 kd form, and a third incompletely characterized form (Lin et al., 1992). The principal GH form in the pituitary is a 191 amino acid, single-chain, 22 kDa protein (22K). It is the product coded for by the GH-N gene (N for normal) and has also
been termed GH-N (Parks, 1989). A second product arising from the same gene is the 20,000 dalton GH variant (20K) (Lewis et al., 1978). This protein is identical to 22K, except for an internal 15 amino acid deletion (residues 32-46). 20K GH is the result of an alternatively spliced GH pre-mRNA where part of exon 3 is spliced out (DeNoto et al., 1981). Importance of this heterogeneity is unknown. Both forms of hormone are secreted and have similar growth promoting activity, although metabolic effects of the 20K form are reduced. 20K has decreased insulin-like and perhaps slightly decreased diabetogenic activity compared to 22K (Baumann et al., 1994).

Once secreted from the pituitary, a substantial proportion of GH circulates bound to GH-binding protein (GHBP) (Baumann et al., 1986; Herington et al., 1986; Leung et al., 1987). There are two forms of GHBP, a low-affinity variety and a high-affinity form. GHBP comprises the extracellular domain of the GH receptor (Leung et al., 1987) which is located in peripheral tissues and mediates the effects of GH on target organs. The GH binding protein and GH receptor are products of the same gene. GHBP is produced by proteolytic cleavage of the receptor at the outer surface of target cells (Harrison et al., 1995). GH binding protein prolongs its half-life and regulates changes in free hormone concentration. Free portion can cross capillary membranes and perform its actions.

GH elicits intracellular signaling through a peripheral receptor and initiates a phosphorylation cascade involving the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway (Carter-Su et al., 1996). Liver contains most abundant receptors for GH. When GH receptor activated this causes rapid JAK2 tyrosine kinase activation, leading to phosphorylation of intracellular signaling molecule including the STATs. Phosphorylated STAT proteins are directly translocated to the cell nucleus, where they elicit GH-specific target gene expression by binding to nuclear DNA (Xu et al., 1996).

Growth hormone induces hepatic production of IGF-I responsible of many of its growth-promoting effects. Local production of IGF-I acting either in a paracrine or autocrine manner also has important biological effects, predominant of which is stimulating cell proliferation and inhibiting apoptosis (Le Roith et al., 2001).

Secretion of GH from the pituitary is pulsatile. An average half-life is 10-20 minutes, it is metabolized through the kidneys, liver, or target tissues (Casanueva, 1992). In children and young adults, maximal GH secretion occurs within 1 hour after the onset of deep sleep (stage III or IV) (Finkelstein et al., 1972; Mendelson, 1982; Takahashi et al., 1968). Two hypothalamic hormones regulate GH secretion; Growth hormone releasing hormone (GHRH) provides the primary drive for GH synthesis and secretion by inducing GH gene transcription and hormone release and does not induce other anterior pituitary hormones (Barinaga et al., 1983; Thorner et al., 1984). GHRH is needed for normal pulsatile GH secretion (Painson et al., 1991; Wehrenberg et al., 1982). SRIF powerfully antagonizes the mitogenic effect of GHRH on somatotrophs, but does not inhibit GH synthesis (Billestrup et al., 1986), suppresses GH secretion mainly by high-affinity binding to SST₁₂ and SST₅ receptor subtypes expressed on somatotrophs (Shimon, 1997). It is thought to be interaction between these two hypothalamic hormone plays a role in pulsatile GH secretion.

Ghrelin is another peptide of a primarily gastric origin, although ghrelin mRNA had been found in the hypothalamus playing a role in secretion of GH (Mozid et al., 2003). Synthetic analogues of ghrelin (GHS) had been produced as early as 25 years ago. Acute administration of GHS produces an immediate and massive release of GH. Co-administration of GHS and GH-RH results in powerful GH rise that is greater than the effect
of either peptide administered alone (Bowers et al., 1991). GHS potentiate GH release in response to a maximum stimulating dose of exogenous GHRH (Penalva et al., 1993) and after a saturating dose of GHRH, although subsequent GHRH administration is ineffective, GHS remain fully effective (Jaffe et al., 1993).

Stressful changes in the internal and external environments can produce brief episodes of hormone secretion. Hypoglycemia leads to acute GH secretion, which is the basis for the insulin-induced hypoglycemia test, a gold standard evaluation of pituitary function (Gharib et al., 2003). In man, hyperglycemia causes transient GH suppression for 1 to 3 hours, followed by GH rise 3 to 5 hours after oral glucose administration (Roth et al., 1963). Elevation of free fatty acid levels is a strong inhibitor of GH release in normal humans (Imaki et al., 1985).

Secretory episodes are induced by an increase in certain amino acids, particularly arginine and leucine. Neuropeptides, neurotransmitters, and opioids act on the hypothalamus by affecting GHRH and SRIF release. Three hours after acute glucocorticoid administration, GH levels rise and remain elevated for 2 hours. Glucocorticoids administered to normal subjects dose-dependently inhibit GHRH-simulated GH secretion, similar to that seen in Cushing’s syndrome (Casanueva et al., 1990). While acute glucocorticoid administration stimulates GH secretion, chronic steroid treatment inhibits GH.

Activation of the gonadal system during puberty is accompanied by increased GH and IGF-1 concentrations (Veldhuis et al., 2006; Giordano et al., 2005). Estrogen stimulates GH secretory rates, and testosterone increases GH secretory mass per pulse, with resultant IGF-I induction (Giustina & Veldhuis, 1998).

Chronic malnutrition and prolonged fasting are associated with elevated GH pulse frequency and amplitude (Ho et al., 1988). The maximal GH levels occur within minutes of the onset of slow wave sleep (Holl et al., 1991). Emotional deprivation is associated with suppressed GH secretion and attenuated GH responses to provocative stimuli occur in endogenous depression (Sachar et al., 1972). Exercise and physical stress, including trauma, hypovolemic shock, sepsis increase GH levels (Vigas et al., 1977).

Thyroid disorders also affect GH secretion. Some studies have reported several alterations of the GH/IGF axis and their binding proteins in hypothyroidism. The main alterations reported in untreated adult hypothyroid patients have been low serum concentrations of IGF-1 and IGFBP-3 that increase significantly with restoration of euthyroidism (Miell et al., 1993; Valcavi et al., 1987).

In hypothyroidism, GH pulsatility is decreased and GH responses to a number of secretagogues are attenuated (Valcavi et al., 1992). Fasting serum IGF-1 levels were found significantly lower in the subclinical hypothyroid and with levothyroxine treatment IGF-1 concentrations were significantly increased in subclinical hypothyroid subjects (Akin et al., 2008). Also in hyperthyroidism GH responses to GHRH was found to be decreased whereas serum IGF-1 levels were increased (Valcavi et al., 1993). It could be expected to be decreased due to decreased pituitary GH contents as a result of permanent somatotrophic cell stimulation. At another study, hyperthyroid men is marked by a higher frequency of spontaneous GH secretory bursts, a higher rate of maximal GH secretion attained per burst, and a larger mass of GH released per burst (Iranmanesh et al., 1990). Effects of hyperthyroidism on GH/IGF-1 axis are still controversial. GH–IGF axis was not affected in patients with subclinical hyperthyroidism (Akin et al., 2009).

GHRH have other actions which serve to feed back for GH secretory axis. GHRH stimulates SRIF secretion and inhibits further GHRH secretion in vitro (Aguila et al., 1985). SRIF
inhibits its own secretion in vitro (Peterfreund & Vale, 1984). GH and IGF-I feed back to modulate the GH axis at several levels. IGF-I acts directly on the pituitary to inhibit basal and GHFRH-induced GH secretion and also to suppress GH gene expression (Berelowitz et al., 1981; Ceda et al., 1987; Ceda et al., 1985, Yamashita & Melmed, 1986; Yamashita et al., 1986). IGF-I also seems to have a direct hypothalamic effect, increasing SRIF secretion (Berelowitz et al., 1981).

A benign somatotroph adenoma of the pituitary is the most common cause of acromegaly. Whether intracellular defects or excessive trophic influences from outside causes pituitary tumor need to be discussed. Growth hormone-releasing hormone has trophic activity in the human pituitary (Thorner et al., 1982) and in addition to a case report of diffuse somatotroph hyperplasia in a patient with a growth hormone-releasing hormone-producing bronchial carcinoid (Ezzat et al., 1994). There are several cases of true somatotroph adenoma formation in patients with growth hormone-releasing hormone-producing hypothalamic gangliocytomas (Asa et al., 1984; Bevan et al., 1989). The clonality of a cellular expansion is a secure archaeologic tool capable of distinguishing an irreversible and potentially inexorably progressive process induced by an intracellular insult or insults from a relatively excessive but possibly reversible or self-limiting trophic response to stromal or microenvironmental signals (Levy, 2000; Levy, 2001). The finding of monoclonality in pituitary adenomas is thought to be an evidence for the neoplastic origin of these lesions. Proto-oncogene activation is also a critical prerequisite for pituitary tumor formation.

Pituitary carcinomas are another exceedingly rare cause of acromegaly. Infrequently acromegaly occurs as a result of a hypothalamic tumor secreting GHFRH, ectopic secretion of GHRH from a peripheral neuroendocrine tumour (Thorner et al., 1984) or from excessive hypothalamic GHRH secretion (Asa et al., 1984).

Several genetic disorders including multiple endocrine neoplasia type 1 (MEN1) syndrome, McCune Albright syndrome, familial acromegaly and Carney’s syndrome are also characterized with growth hormone excess. Postzygotic GNAS mutations result in a mosaic pattern of organ specificity with clinical features of McCune-Albright syndrome (OMIM 174800), including pigmented skin lesions and polyostotic fibrous dysplasia, and endocrine dysfunction including precocious puberty, thyrotoxicosis, and GH and ACTH hypersecretion (Weinstein, 1991).

4. Clinical features of acromegaly

The clinical features of acromegaly are depend on high serum concentrations of both GH and IGF-I (Melmed, 2006). The effect of hypersomatropism on tissue growth and metabolic function evolves slowly. 10 or more years may elapse from disease onset until diagnosis of the disease (Colao et al., 2004).

Disease can be manifested also with signs and symptoms of pituitary mass. Any pituitary adenoma can cause headaches commonly retro-orbital. Another common symptom caused by the size and location of the tumor is decreased vision. This usually presents as temporal visual field defects. It is caused by the tumor growing upward out of the sella and pressing on the optic chiasm. Other findings include diplopia, ptosis, ophthalmoplegia as a result of extension into the cavernous sinus and compression of the cranial nerves. Sudden loss of vision secondary to apoplexy within the pituitary adenoma may occur. Aggressive tumors can invade the roof of the palate and cause nasopharyngeal obstruction, infection and CSF leakage. Parinaud syndrome is caused by ectopic pinealomas most often accompanied with paralysis of
upward conjugate gaze. As pituitary tumors grow, they compress the pituitary gland, pituitary stalk and hypothalamus and interfere with normal pituitary hormone production. This results in partial or complete anterior pituitary hormone deficiency. Hypothyroidism symptoms, failure to lactate, decreased libido, infertility or oligo/amenorrhea, sense of not well being are common symptoms of hypopituitarism. Stalk compression leads to hyperprolactinemia. GH-secreting pituitary adenomas may also cosecrete prolactin.

All patients with acromegaly have acral and soft tissue overgrowth, although the extent of the overgrowth varies. Soft tissue findings are macroglossia, large fleshy lips and nose, deepening of the voice, paresthesias of the hands, thickened skin, skin tags, coarsened body hair. Skin tags are common and may be markers for the adenomatous colonic polyps (Leavitt et al., 1983). These soft tissue changes may be attributed to glycosaminoglycan deposition and increased connective tissue collagen production (Verde et al., 1986). Hair growth increases and some women have hirsutism 56 percent in one series (Kaltsas et al., 1999). Acromegalic patients may have a greater incidence of neuropathies because of compression of nerves by adjacent fibrous tissue and endoneural fibrous proliferation. The size and function of sebaceous and sweat glands increase complain of excessive perspiration and body odor. The heart, liver, kidneys, spleen, thyroid, parathyroid glands, and pancreas are larger than normal.

Thyroid dysfunction in acromegaly may be caused by diffuse or nodular toxic or nontoxic goiter or Graves' disease, especially because IGF-I is a major determinant of thyroid cell growth (Kasagi, et al., 1999). As it can be a part of a MEN1 syndrome, hypercalcemia can also be seen.

In the absence of GH there is severe atrophy of the epiphyseal plates, which become narrow as proliferation of cartilage progenitor cells slows markedly.

Conversely, after GH is given to a hypopituitary subject, resumption of cellular proliferation causes columns of chondrocytes to elongate and epiphyseal plates to widen. Synovial tissue and cartilage enlarge, causing hypertrophic arthropathy of the knees, ankles, hips, spine and other joints (Biermasz et al., 2005). Local periarticular fibrous tissue thickening can cause joint stiffening, deformities, and nerve entrapment. Chondrocyte proliferation with increased joint space, ulcerations and fissures of weight-bearing cartilage areas, often accompanied by new bone formation. Chronic osteoarthritis causes narrowed and deformed joint space, osteophyte formation, subchondral cysts, and lax periarticular ligaments with ossification (Dons et al., 1988; 75 Lieberman et al., 1992). When excess GH secretion begins before the epiphyses of the long bones are fused, linear growth does increase; the result is pituitary gigantism. Skeletal overgrowth owing to periosteal new bone formation in response to IGF-1 (McCarthy, et al., 1989). Subtle skeletal and acral overgrowth and soft tissue enlargement causes increased shoe and ring size. Mandibular overgrowth with prognathism, maxillary widening, teeth separation, jaw malocclusion other skeletal manifestations of the acromegaly. Prognathism, thick lips, macroglossia, and hypertrophied nasal structures can obstruct airways (Rosenow et al., 1996; Grunstein et al., 1994). This result in obstructive sleep apnea syndrome. Sleep apnea may also be central in origin and associated with higher GH and IGF-I levels (Grunstein et al., 1994).

Untreated acromegaly results in premature mortality, most commonly from cardiovascular disease (Ritchie et al., 1990; Wright et al., 1970; Etxabe et al., 1993; Rajasoorya et al., 1994; Orme et al., 1998). Asymmetric septal hypertrophy, left ventricular hypertrophy, cardiomegaly and cardiac failure develop; effective treatment reducing growth hormone and IGF-I serum levels improves cardiac function (Colao et al., 1999). Heart failure occurs in
3 to 10 percent of patients (Damjanovic et al., 2002; Bihan et al., 2004). An increased prevalence of valvular heart disease has also been reported. Arterial blood pressure (systolic and diastolic) is higher with loss of normal daily circadian variability (Terzolo et al., 1999). Hypertension was reported in approximately one third of patients who had acromegaly (Pietrobelli et al., 2001; Minniti et al., 1998). Insulin resistance and diabetes mellitus occur as a result of direct anti-insulin effects of GH (Coculescu et al., 2007; Kasayama et al., 2000). Several benign and malignant neoplasms, especially in the gastrointestinal tract, have been reported in association with acromegaly (Cheung et al., 1997; Ron et al., 1991), particularly colorectal tubular adenomas and carcinoma (Jenkins et al., 2001; Jenkins, 2006). It is related to disease activity with patients with elevated serum growth hormone and IGF-I levels being particularly prone to developing colonic adenomas (Jenkins et al., 2000). A compelling cause-and-effect relationship of acromegaly with cancer has not been established (Delhongne et al., 1995; Ladas et al., 1994). A recent controlled study in 161 patients revealed no increase in polyp incidence in acromegaly (Renehan et al., 2000). Analysis of nine retrospective reports (1956-1998) encompassing 21,470 person-years at risk, yielded no significant increased cancer incidence (Melmed et al., 2001).

Whether patients with acromegaly are also prone to other malignancies remains controversial. Certainly there is epidemiological evidence in the general population that serum IGF-I levels in the upper part of the normal range are associated with an increased risk of breast and prostate cancer and some reviews have shown the former to be increased in acromegaly (Renehan et al., 2004; Nabarro, 1987).

5. Molecular pathogenesis of acromegaly

GH elicits intracellular signaling through a peripheral receptor and initiates a phosphorylation cascade involving the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway (Carter-Su et al., 1996). The STAT proteins become phosphorylated and translocate into the cell nucleus. Transcription of target proteins, such as IGF-I evoke pleiotropic cell responses including IGF1 synthesis, glucose metabolism, cell proliferation, and cytoskeletal changes.

STAT5b is the key intracellular molecule required for GH mediation of postnatal growth, adipose tissue function, and sexual dimorphism of hepatic gene expression (Lanning et al., 2006). In humans, STAT mutations result in relative GH insensitivity and growth retardation (Kofoed, 2003).

6. Diagnosis

Normal GH production from the pituitary gland is pulsatile with the maximal production occurring at night. Even though episodic basal growth hormone secretion patterns are sustained in acromegaly, diurnal variation and the sleep-related growth hormone rise are lost (Barkan et al., 1989). Most values of GH fall in the range of 0.1–0.2 μg/L in normal subjects. However there are six to ten secretory bursts during the day when GH reaches values of 5–30 μg/L, which may overlap with values seen in acromegalic patients. Therefore the only value of a random GH measurement is that of excluding acromegaly if it is undetectable. Unlike the largely undetectable nadir GH levels in normal subjects, those with acromegaly sampled over 24 hours contain detectable levels of GH (>2 μg/L) Elevated integrated growth hormone levels during 24-hour sampling of less than 2.5 μg/L
effectively exclude acromegaly (Duncan et al., 1999). The optimal way to assess the overall daily GH production is to obtain a mean GH over 24 h by frequent GH sampling. However, this method is inconvenient both for the patient and the clinician (Cordero et al., 2008).

The current international consensus for the diagnosis of acromegaly (Giustina et al., 2000) recommends a nadir GH of more than 1 μg/L during an OGTT for diagnosis in conjunction with clinical suspicion and high IGF-1 levels. Using more sensitive newer assays, the GH cut-off may be even lower (Freda et al., 2003). There is a need to verify the current guidelines and propose lowering the current cut off for GH nadir (Costas et al., 2002; Serri et al., 2004). The standard OGTT consists of the administration of 75 g of glucose with GH measurements at various time points for up to 120 min. Normal subjects demonstrate a suppression of GH concentration to 2 μg/L or less throughout the 2 hours of testing (Chapman et al., 1994; Hattori et al., 1990). Acromegalic subjects often gives response paradoxically higher GH levels. Clinicians should be aware that the OGTT’s usefulness is limited in high catabolic states, such as stress, hepatic and renal failure, diabetes mellitus, obesity, pregnancy, patients on estrogen replacement or in tall adolescents in whom GH values may be falsely elevated (Duncan et al., 1999; Melmed et al., 2006).

Serum sex and age-matched elevated IGF-1 levels are highly specific for acromegaly in the nonpregnant adult and correlate with clinical disease activity (Clemmons et al., 1979). IGF-1 is an ideal screening test as it has a long half life of 18–20 h and the levels remain stable throughout the day (Giustina et al., 2000). Furthermore IGF-1 correlates with mean GH levels (Barkan et al., 1988) and with clinical features of acromegaly (Clemmons et al., 1979). Even several months after treatment when growth hormone levels are controlled, IGF-1 serum levels may remain persistently high (Drange et al., 1999). Multiple physiologic factors affect IGF-1 levels and need to be taken into account when interpreting the data. IGF-1 is affected by age and gender (Ghigo et al., 1996) with approximately 14% decrease per decade during adult life (Brabant et al., 2003). Again a uniform standard for age range had not been established (Pokrajac et al., 2007) where serum samples with GH and IGF-1 levels close to the current Cortina consensus (Giustina et al., 2000) cutoffs were distributed to different centers to evaluate variability in assay performance. Other problems include the assay susceptibility to interference from binding proteins and the tendency of IGF-1 to plateau at mean GH levels above approximately 20 μg/L (Barkan et al., 1988). The use of exogenous estrogen, malnutrition, liver and renal failure decrease IGF-1 levels (Ho et al., 1922; Freda et al., 2003; Ho et al., 2003). On the other hand, normal pregnancy and adolescence are associated with elevated IGF-1 levels (Duncan et al., 1999).

IGFBP-3 levels are also elevated. However, considerable overlap of these values with those in normal persons, thereby limiting the utility of this measurement.

Magnetic resonance imaging (MRI) of the pituitary gland is the preferred imaging modality for diagnosis in acromegaly. An MRI provides the best assessment of tumor size, location, extent, and relationship to important surrounding structures and is essential for the neurosurgeon to adequately plan surgery and to monitor treatment. If an MRI is not available, a computed tomography (CT) study directed at the pituitary region may be done. Ectopic GHRH producing tumors may arise from bronchial and pancreatic neuroendocrine tumors, pheochromocytomas, pulmonary endocrine carcinomas, or rarely thymic carcinoid (Vieira et al., 2007; Sugihara et al., 2007; Fainstein et al., 2007; Nasr et al., 2006; Bolanowski et al., 2006; Jansson et al., 1998). The measurement of plasma GHRH concentrations can be very helpful in identifying an ectopic source of GHRH in these particular cases. Total body scintigraphy with radiolabeled somatostatin should be performed to localize the tumor and
to demonstrate somatostatin receptor expression by the tumor which may respond favorably to somatostatin analogue therapy (Kwekkeboom et al., 1993; Drange et al., 1998).

7. Differential diagnosis

Exclusion of an abnormality of the somatotrophic axis in a young patient with acromegaloid features should lead the differential diagnosis towards diagnoses such as pachydermoperiostosis (Hambrick et al., 1996; Rimoin, 1965; Harbison et al., 1971) or insulin mediated pseudoacromegaly, a disorder associated with severe insulin resistance (Flier et al., 1993). These nadir entities must be considered at differential diagnosis of acromegaly.

8. Treatment

Treatment should aim at managing the tumor mass and GH hypersecretion to prevent morbidity and increased mortality while preserving normal pituitary function. Complete surgical removal of GH-secreting tumors results in hormonal control of acromegaly and improvement of soft tissue changes. After successful resection, growth hormone levels return to normal within 1 hour, and metabolic dysfunction and soft-tissue swelling quickly resolve. In patients with intrasellar microadenomas, surgical removal provides biochemical control with normalization of IGF-I in 75–95% of patients (De et al., 2003; Ludecke et al., 2006; Nomikos et al., 2005; Kaltzas et al., 2001; Shimon et al., 2001; Beuregard et al., 2003). Transsphenoidal microsurgical adenomectomy approach is used most commonly and, in the hands of experienced neurosurgeons, cures the majority of patients who are harboring a well-circumscribed microadenoma and who have serum GH levels less than 40 μg/L (Gittoes et al., 1999; Shimon et al., 2001; Kreutzer et al., 2001). Control rates are lower in patients with noninvasive macroadenomas but even in these cases surgical removal provides biochemical control with normalization of IGF-I in 40–68% of patients (De et al., 2003; Ludecke et al., 2006; Nomikos et al., 2005; Kaltzas et al., 2001; Shimon et al., 2001; Beuregard et al., 2003). The success of surgery depends on the skill and experience of the surgeon in resecting the entire tumor without damaging normal anterior pituitary tissue. Cranietomy is very rarely indicated in patients with acromegaly.

Post-transsphenoidal surgical mortality is rare and most side effects are transient. Permanent diabetes insipidus, cerebrospinal fluid leak, hemorrhage, and meningitis develop in up to 5% and their frequency correlates with tumor size, invasiveness, and neurosurgical experience (Gittoes et al., 1999). In experienced hands, other complications of transsphenoidal surgery are rare including transient oculomotor palsies, deterioration of vision, carotid artery injury and epistaxis (occurring in less than 1% of patients) (Ludecke & Abbe, 2006; Nomikos et al., 2005).

Dopamine agonists (DAs), somatostatin receptor ligands (SRLs), and a GH receptor antagonist (GHRA) are the drugs classes available for the treatment of acromegaly. SRLs are the first-choice pharmacotherapy for treating patients who have acromegaly. Two formulas are available for treatment of acromegaly octreotide and lanreotide. Somatotroph and thyrotroph cells express mainly two of five SRIF receptors, SSTR2 and SSTR5 that mediate growth hormone and TSH secretion (Shimon & Melmed, 1998; Weckbecker et al., 2003).

Octreotide is a short-acting somatostatin analogue that binds mainly to SSTR2 and to a lesser extent to SSTR5 (Lamberts, 1988). Lanreotid also acts in a same way. Octreotide also exhibits some SST3 affinity (Patel, 1999). Sandostatin LAR (octreotide acetate) is a long-
acting somatostatin analogue (Flogstad et al., 1995; Lancranjan et al., 1999) requiring monthly injections. Starting dose is 20-mg monthly increasing up to 40 mg depending on clinical and biochemical responses. Depot preparation of lanreotide delivered as an aqueous, small-volume mixture (60, 90, or 120 mg) in prefilled syringes for deep subcutaneous administration every 28 days (Biermasz et al., 2005).

Most studies assessing SRLs efficacy in acromegaly define disease control by mean fasting random serum GH levels less than 2.5 \(\mu\)g/L or normalization of age- and gender-matched IGF-1 plasma levels. Treatment with depot form of lanreotide (60 mg every 21 or 28 days) reduced GH less than 2.5 \(\mu\)g/L in 76% of patients (Attanasio et al., 2003; Ambrosio et al., 2002). In another study, monthly injections sandostatin for 9 years reduced integrated serum GH levels to less than 2 \(\mu\)g/L in more than 75% of patients (Cozzi et al., 2006). More than 70% of patients experience improved general well-being, and soft tissue swelling dissipates within several days of treatment (Ezzat, et al., 1992). Headache, a common symptom in acromegaly, usually resolves within minutes of injection (Pascual et al., 1991) reflecting a specific central analgesic effect.

Joint function and crepitus improve, ultrasound shows evidence of bone or cartilage repair, and after several months, sleep apnea improves (Colao et al., 2004). Asymptomatic patients experience a significant decrease of blood pressure, heart rate, and left ventricular (LV) wall thickness (Colao et al., 2000).

SRLs are effective also in reducing tumor size. Significant tumor size decrease has been reported in 52% of patients on primary therapy (Bevan et al., 2005). A critical analysis of 14 studies reported that 37% of patients treated primarily by SRL experience significant tumor shrinkage (Melmed et al., 2005).

In vivo octreoscan imaging visualizing SRIF receptors demonstrates that GH responsiveness directly correlates with the abundance of pituitary receptors, and patients resistant to octreotide do not have visible receptor binding sites (Ur et al., 1992). Efficacy of octreotide action is determined by frequency of drug administration, total daily dose, tumor size, densely granulated tumors (Bhayana et al., 2005) and pretreatment GH levels.

The use of SRLs is most appropriate; as first-line therapy when there is a low probability of a surgical cure (Melmed et al., 2005; Cozzi et al., 2006; Maiza et al., 2007; Mercado et al., 2007; Colao, et al., 2006) after surgery has failed to achieve biochemical control, before surgery to improve severe comorbidities that prevent or could complicate immediate surgery (Carlsen et al., 2008) to provide disease control, or partial control in the time between administration of radiation therapy and the onset of maximum benefit attained from radiation therapy (Melmed et al., 2009). Gastrointestinal symptoms including nausea, mild malabsorption, flatulence, diarrhea or constipation are common mild side effects of SRLs. Multiple small gallstones and gallbladder sludge may occur, occasionally result in cholecystitis. Abnormal glucose metabolism is described with the use of SRLs, as activation of SST2 and SST5 in the pancreatic insulin-secreting beta cells likely inhibits insulin secretion and counter-regulatory hormones, such as glucagon. Mild hyperglycemia and, rarely hypoglycemia (Bruttomesso et al., 2001) manifest mostly in patients who have pre-existing glucose abnormalities. Octreotide can interact with several drugs including cyclosporine. Absorption of oral hypoglycemic agents, \(\beta\)-blockers, calcium channel blockers can be change and dosage titration should be made slowly with SRL at patients using these agents. Asymptomatic sinus bradycardia can also be seen with these drugs.

Only cabergoline has any efficacy in acromegaly, and this is limited monotherapy effective in less than 10% of patients (Bevan et al., 1992; Colao et al., 1997; Abs et al., 1998; Cozzi et al., 1998). Patients with hyperprolactinemia and minimal GH elevation might benefit most from
dopamine agonist treatment. Main usages of DAs are; when the patient prefers oral medication, after surgery in selected patients, such as those with markedly elevated prolactin and/or modestly elevated GH and IGF-I levels (Melmed et al., 2009) as additive therapy to SRL therapy in patients partially responsive to a maximum SRL dose (Wagenaar et al., 1990; Sadoul et al., 1992; Cremonini et al., 1992; Marzullo et al., 1999; Cozzi et al., 2004; Selvarajah et al., 2005). Side effects of DAs include gastrointestinal discomfort, transient nausea and vomiting, nasal congestion, dizziness, postural hypotension, headache, and mood disorders (Colao et al., 1997). It is known that increased incidence of valvular heart disease with high doses of carbegoline.

GH action through the surface membrane GH receptor is mediated by ligand-induced receptor signaling. The postreceptor GH signal is not elicited if the receptor is bound by pegvisomant, a GH-receptor antagonist, which blocks subsequent IGF-I generation (Trainer, et al., 2000). Daily pegvisomant (20 mg) given for 12 weeks, normalized IGF-1 levels in 82% of patients who had acromegaly (Kopchick et al., 2002). The indications for its use are; in patients that have persistently elevated IGF-I levels despite maximal therapy with other treatment modalities, possibly as monotherapy or in combination with a SRL in other patients (Melmed et al., 2009).

Because elevated hepatic transaminases have been reported (Biering et al., 2006) liver enzymes should be measured every 6 months. Serum GH levels are increased as much as 76% over baseline levels and persistent tumor growth is reported (Trainer et al., 2000) even though, in most cases, GH-secreting adenoma volumes do not change (Van der Lely et al., 2001; Barkan et al., 2005). Current recommendations are to perform a pituitary MRI every 6 months in all patients (Melmed et al., 2006).

Primary or adjuvant radiation of GH-secreting tumors may be achieved by conventional external deep X-ray therapy, proton beam, or gamma knife radiation surgery. It is usually reserved for patients who have postoperative persistent or recurrent tumors that are resistant or intolerant to medical treatment may benefit from radiotherapy. After conventional radiation (up to 5000 rads divided in 180-rad fractions over 6 weeks), tumors cease growing and shrink in most of patients (Biermasz et al., 2000). Conventional radiotherapy (conformal fractionated radiotherapy) can lower GH levels and normalize IGF-I in over 60% of patients, but maximum response is achieved 10–15 yr after radiotherapy is administered (Barrande et al., 2000; Jenkins et al., 2006; Minniti et al., 2005). Stereotactic radiosurgery using gamma knife delivers a single tumor-focused radiation fraction. Five-year remission rates with gamma knife radiotherapy in patients with acromegaly (after surgical debulking) range from 29 to 60% (Attanasio et al., 2003; Castinetti et al., 2005; Jezkova et al., 2006; Pollock et al., 2007). After 10 years, about half of all patients receiving radiation therapy have signs of pituitary trophic hormone disruption, and this prevalence increases annually thereafter. Side effects of conventional radiation including hair loss, cranial nerve palsies, tumor necrosis with hemorrhage, and loss of vision or pituitary apoplexy (both rare) have been documented in up to 2% of patients (Van der Lely, 1997). Lethargy, impaired memory, brain tumors at irradiation site and personality changes can also occur.

9. Posttreatment follow-up

GH and IGF-I should be measured to assess the biochemical response to any medical treatment. OGTT and IGF-1 measurement wit clinical examination should be performed at 3–6 months after surgery, and 3-4 months period thereafter. If patient receiving pegvisomant,
monitoring should be made with only IGF-1. OGTT is not helpful in monitoring therapeutic responses while patients are receiving SRL therapy (Arafat et al., 2008; Carmichael et al., 2009). Biochemical control is generally defined as a normal IGF-I for age and gender and age less than 1.0 ng/ml during an OGTT. After biochemical control is achieved, follow up of patients can be made semiannually. With usage of more sensitive GH level less than 0.4 ng/ml thought to be consistent with remission. Pituitary MRI should be performed annually, especially at patients having residual tumor and medical treatment.

Colonoscopy should be performed at three- to four-year intervals in patients over 50 years old and in those with more than three skin tags for early detection and treatment of premalignant colonic polyps (Melmed, 2002). At follow up patients should be evaluated periodically for cardiovascular, skeletal, dental problems.

10. Future prospects of acromegaly

Bogazzi et al. (Bogazzi et al., 2004) reported that thiazolidinedione treatment might slow down the growth of well-established GH-secreting tumors and might effectively reduce the GH hypersecretion. In a study, rosiglitazone, used at maximum approved dosage, did not reduce plasma GH and IGF-1 levels in patients with acromegaly (Bastemir et al., 2007).

In recent years, molecular studies investigated the possible association of gene polymorphisms and susceptibility to diseases. Recently, a polymorphism in the promotor region of the IGF-I gene which is associated with IGF-I serum levels, birthweight and body height in adults has been identified (Vaessen et al., 2001; Rietveld et al., 2004). 194 bp allele (20 CA repeats) of the IGF-I promoter have higher circulating IGF-I levels than others. The patients with 194 bp genotype are the resistant patients with active disease and they required high dose medication responsible from resistance to drugs (Akin et al., 2010). The angiotensinogen MT and AT1R CC1166 genotype carriers may have more risk than other genotypes in the development of hypertension in acromegaly (Turgut, et al., 2011).

11. References


Arafat, AM; Mohlig, M; Weickert, MO; Perschel, FH; Purschwitz, J; Spranger, J; Strasburger, CJ; Schofl, C; Pfieffer, AF. (2008). Growth hormone response during oral glucose tolerance test: the impact of assay method on the estimation of reference values in patients with acromegaly and in healthy controls, and the role of gender, age, and body mass index. J Clin Endocrinol Metab. 93:1254–1262.


Berelowitz, M; Szabo, M; Frohman, LA. (1981). Somatomedin C mediates growth hormone negative feedback by effects on both the hypothalamus and the pituitary. Science. 212:1279-1281.


Bogazzi, F; Ultimieri, F; Raggi, F; Russo, D; Vanacore, R; Guida, C; Cividana, P; Cecchetti, D; Acerbi, G; Brogioni, S; Cosci, C; Gasperi, M; Bartalena, L; Martino, E. (2004). PPAR-gamma inhibits GH synthesis and secretion and increases apoptosis of pituitary GH-secreting adenomas. Eur J Endocrinol. 150: 863–875.


Bowers, CY; Sartor, AO; Reynolds, GA. (1991). On the actions of the growth hormone releasing hexapeptide, GHRP. Endocrinology. 128. 2027-2035.


Carmichael, JD; Bonert, VS; Mirocha, JM; Melmed, S. (2009). The utility of oral glucose tolerance testing for diagnosis and assessment of treatment outcomes in 166 patients with acromegaly J Clin Endocrinol Metab. 94:523–527.


Cedena, GP; Hoffman, AR; Silverberg, GD. (1985). Regulation of growth hormone release from cultured human pituitary adenomas by somatomedins and insulin. J Clin Endocrinol Metab. 60:1204-1209.

Cedena, GP; Davies, RG; Rosenfeld, RG. (1987). The growth hormone (GH)-releasing hormone (GHRH)-GH-somatemedin axis: Evidence for rapid inhibition of GHRH-elicited GH release by insulin-like growth factors I and II. Endocrinology. 120:1658-1662.


Costas, ACF; Rossi, A; Martinelli, CE, Jr; Machado, HR; Moreira, AC. (2002). Assessment of disease activity in treated acromegalic patients using a sensitive GH assay: should we achieve strict normal GH levels for a biochemical cure. J Clin Endocrinol Metab. 87(7):3142–7.


Cozzi, R; Montini, M; Attanasio, R; Albizzi, M; Lasio, G; Lodrini, S; Doneda, P; Cortesi, L; Pagani G. (2006). Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. J Clin Endocrinol Metab.91:1397–1403.


Damjanovic, SS; Neskovic, AN; Petakov, MS; Popovic, V; Vujisic, B; Petrovic, M; Nikolic-Djurovic, M; Simic, M; Pekic, S; Marinkovic, J. (2002). High output heart failure in patients with newly diagnosed acromegaly. Am J Med. 112(8):610-6.

De, P; Rees, DA; Davies, N; John, R; Neal, J; Mills, RG; Vafidis, J; Davies, JS; Scanlon, MF. (2003). Transsphenoidal surgery for acromegaly in Wales: results based on stringent criteria of remission. J Clin Endocrinol Metab. 88:3567–3572.


Flier, JS; Moller, DE; Moses, AC; O'Rahilly, S; Chaiken, RL; Grigorescu, F; Elahi, D; Kahn, BB; Weinreb JE; Eastman R. (1993). Insulin-mediated pseudoacromegaly: clinical and biochemical characterization of a syndrome of selective insulin resistance. J Clin Endocrinol Metab. 76:1533–1541.


Freda, PU; Reyes, CM; Nuruzzaman, AT. (2003). Basal and glucose-suppressed GH levels less than 1 μg/L in newly diagnosed acromegaly. Pituitary. 6:175-180.


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Jenkins, PJ; Frajese, V; Jones, AM; Camacho-Hubner, C; Lowe, DG; Fairclough, PD; Chew, SL; Grossmann, AB; Monson, J & Besser, GM. (2000). IGF-I and the development of colorectal neoplasia in acromegaly. Journal of Clinical Endocrinology and Metabolism. 85:3218-3221.


Kaltasas, GA; Isidori, AM; Florakis, D; Trainer, PJ; Camacho-Hubner, C; Afshar, F; Sabin, I; Jenkins, JP; Chew, SL; Monson, JP; Besser, GM; Grossman, AB. (2001). Predictors of the outcome of surgical treatment in acromegaly and the value of the mean growth hormone day curve in assessing postoperative disease activity. J Clin Endocrinol Metab. 86:1645-1652.

Kasagi, K; Shimatsu, A; Miyamoto, S. (1999). Goiter associated with acromegaly: sonographic and scintigraphic findings of the thyroid gland. Thyroid. 9:791-796.


Ladas, SD; Thalassinos, NC; Ioannides, G; Raptis, SA. (1994). Does acromegaly really predispose to an increased prevalence of gastrointestinal tumours?. Clin Endocrinol (Oxf). 41:597-601.


Ludecke, DK; Abe; T. (2006). Transsphenoidal microsurgery for newly diagnosed acromegaly: a personal view after more than 1,000 operations. Neuroendocrinology. 83:230-239.

Maiza, JC; Vezzosi, D; Matta, M; Donadille, F; Loubes-Lacroix, F; Cournot, M; Bennet, A; Caron, P. (2007). Long-term (up to 18 years) effects on GH/IGF-1 hypersecretion and tumour size of primary somatostatin analogue (SSTa) therapy in patients with GH-secreting pituitary adenoma responsive to SSTa. Clin Endocrinol (Oxf). 67:282-28.

Marzullo, P; Ferone, D; Di Somma, C; Pivonello, R; Filippella, M; Lombardi, G; Colao, A. (1999). Efficacy of combined treatment with lanreotide and cabergoline in selected therapy-resistant acromegalic patients. Pituitary. 1:115-120.


Melmed, S; Casanueva, FF; Cavagnini, F; Chanson, P; Frohman, L; Grossman, A; Ho, K; Kleinberg, D; Lamberts, S; Laws, E; Lombardi, G; Vance, ML; Werder, KV; Wass, J; Giustina, A. (2002). Guidelines for acromegaly management. J Clin Endocrinol Metab. 87(9):4054-8.


Melmed, S; Colao, A; Barkan A; Molitch, M; Grossman, AB; Kleinberg; Clemmons, D; Chanson, P; Laws, E; Schlechte, J; Vance, ML; Ho, K and Giustina, A. (2009). Guidelines for Acromegaly Management: An Update J Clin Endocrinol Metab. 94(5):1509–1517.


Mercado, M; Borges, F; Bouterfa, H; Chang, TC; Chervin A, ; Farrall AJ;; Patocs A; Petersenn S; Podoba, J; Safari, M; Wardlaw, J. (2007). A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. Clin Endocrinol (Oxf). 66:859–868.


Mozid, AM; Tringali, G; Forsling, ML. (2003). Ghrelin is released from rat hypothalamic explants and stimulates corticotrophin releasing hormone and arginine vasopressin. Horm Metab Res. 35. 455-459.


Renehan, AG; Bhaskar, P; Painter, JE. (2000). The prevalence and characteristics of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab. 85:3417-3424.


Rietveld, I; Janssen, JA; van Rossum, EF; Houwing-Duistermaat, JJ; Rivadeneira, F; Hofman, A; Pols, HA; van Duijn, CM; Lamberts, SW. (2004). A polymorphic CA repeat in the IGF-I gene is associated with gender-specific differences in body height, but has no effect on the secular trend in body height. Clin. Endocrinol. (Oxf) 61;195–203


Valcavi, R; Dieguez, C; Preece, M; Taylor, A; Portioli I & Scanlon MF. Effect of thyroxine replacement therapy on plasma insulin like growth factor 1 levels and growth hormone responsiveness to growth hormone releasing hormone in hypothyroid patients. (1987). Clinical Endocrinology. 27:85-90.


Vieira, Neto L; Taboada, GF; Corrêa, LL; Polo, J; Nascimento, AF; Chimelli, L. (2007). Acromegaly secondary to growth hormone releasing hormone secreted by an incidentally discovered pheochromocytoma. Endocrinol Pathol. 18(1):46-52.


Xu, BC; Wang, X; Darus, CJ; Kopchick, JJ. (1996) Growth hormone promotes the association of transcription factor STAT5 with the growth hormone receptor. J Biol Chem. 271:19768-19773.


This book aims to provide readers with a general as well as an advanced overview of the key trends in endocrine disorders. While covering a variety of topics ranging from thyroid carcinogenesis and pituitary adenomas to adrenal tumors and metabolic bone disease, this book also focuses on more specific issues not yet fully elucidated (e.g. the molecular pathways involved in thyrotropin beta gene regulation or monogenic phosphate balance disorders). Readers of different fields and background will have the opportunity to update their knowledge and more importantly to clarify areas of uncertainty and controversies in several topics of endocrine disorders.

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In order to correctly reference this scholarly work, feel free to copy and paste the following:

Gigantism and Acromegaly Due to Xq26 Microduplications and GPR101 Mutation


BACKGROUND
Increased secretion of growth hormone leads to gigantism in children and acromegaly in adults; the genetic causes of gigantism and acromegaly are poorly understood.

METHODS
We performed clinical and genetic studies of samples obtained from 43 patients with gigantism and then sequenced an implicated gene in samples from 248 patients with acromegaly.

RESULTS
We observed microduplication on chromosome Xq26.3 in samples from 13 patients with gigantism; of these samples, 4 were obtained from members of two unrelated kindreds, and 9 were from patients with sporadic cases. All the patients had disease onset during early childhood. Of the patients with gigantism who did not carry an Xq26.3 microduplication, none presented before the age of 5 years. Genomic characterization of the Xq26.3 region suggests that the microduplications are generated during chromosome replication and that they contain four protein-coding genes. Only one of these genes, GPR101, which encodes a G-protein–coupled receptor, was overexpressed in patients’ pituitary lesions. We identified a recurrent GPR101 mutation (p.E308D) in 11 of 248 patients with acromegaly, with the mutation found mostly in tumors. When the mutation was transfected into rat GH3 cells, it led to increased release of growth hormone and proliferation of growth hormone–producing cells.

CONCLUSIONS
We describe a pediatric disorder (which we have termed X-linked acrogigantism [X-LAG]) that is caused by an Xq26.3 genomic duplication and is characterized by early-onset gigantism resulting from an excess of growth hormone. Duplication of GPR101 probably causes X-LAG. We also found a recurrent mutation in GPR101 in some adults with acromegaly. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and others.)
SOMATIC GROWTH IS ORCHESTRATED BY A complex hormonal crosstalk involving the hypothalamus, pituitary, and peripheral tissues. Genetic disorders that affect this network can lead to increased secretion of growth hormone, which results in acromegaly. If the excess in growth hormone occurs before epiphyseal fusion, the result can be gigantism. Nonsyndromic gigantism is most frequently caused by pituitary adenomas occurring as familial isolated pituitary adenomas or sporadically, usually as a result of mutations in the gene encoding aryl hydrocarbon receptor–interacting protein (AIP). Other monogenic diseases can cause gigantism, but most of these conditions develop in adulthood in association with other tumors. In young children, somatic overgrowth that is due to an excess of growth hormone is rare, and the cause is unknown. Other syndromic genetic overgrowth conditions in children, such as the Sotos syndrome and the Simpson–Golabi–Behmel syndrome, are not associated with pituitary abnormalities.

We report a striking phenotype of gigantism that has an onset in early childhood and that is caused by an excess of growth hormone. The disorder is associated with heritable microduplications on chromosome Xq26.3. There are four genes in the duplicated stretch of DNA; one of these, GPR101, encodes an orphan G-protein-coupled receptor and is probably the gene that drives the phenotype in young children and the growth of sporadic growth hormone–producing adenomas in some patients with acromegaly.

METHODS

PATIENTS
We analyzed samples obtained from 43 patients with gigantism who had hypersecretion of growth hormone, evidence of an anterior pituitary lesion on magnetic resonance imaging, a height on country-specific growth charts of either more than the 97th percentile or more than 2 SD above the mean height for age, and negative test results for mutations or deletions in genes associated with pituitary adenomas (Table 1). Details with respect to one family with this syndrome and two patients with sporadic disease have been described previously.

GENETIC ANALYSES
We sequenced the four genes in the duplicated region on chromosome Xq26.3 in 259 germline and tumor DNA samples that were obtained from 248 patients with sporadic acromegaly (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We sequenced GPR101 and performed array comparative genomic hybridization (aCGH) on germline DNA in samples obtained from 13 families with familial isolated pituitary adenomas without AIP mutations. We used quantitative reverse-transcriptase–polymerase-chain-reaction (qRT-PCR) assays to measure the expression levels of duplicated genes in both leukocytes and pituitary tumors. We performed comparative protein-structure modeling on GPR101 using Modeller software, version 9.13. We determined the level of growth hormone and cyclic AMP (cAMP) and the rate of cellular proliferation after transient overexpression of each of the four implicated genes in GH3 cells obtained from rat pituitary tumors.

RESULTS

CLINICAL PRESENTATION
The clinical and biochemical characteristics of the 43 patients who had nonsyndromic gigantism without abnormalities in genes associated with pituitary tumors are presented in Table 1. Genetic analyses delineated two phenotypes: an early-childhood form of gigantism with a typical onset in late infancy (Fig. 1) and a second form with a typical onset in adolescence.

IDENTIFICATION OF Xq26.3 MICRODUPlication
We detected microduplications on chromosome Xq26.3 in samples obtained from patients with the early-childhood form of gigantism (Fig. 2, and Fig. S1, S2, and S3 in the Supplementary Appendix). Nine of the 13 patients with an Xq26.3 microduplication and the 1 probable carrier (an affected mother with gigantism) were female and were of normal size at birth. All the patients grew rapidly during infancy, attaining a median
height score of +3.8 SD at diagnosis (median age, 36 months). At the time of diagnosis, they showed marked overall somatic growth, with elevated weight and an enlarged head circumference (median, 51.2 cm). The onset of accelerated growth and the onset of accelerated weight gain usually coincided but were not always synchronous (Fig. 1, and Fig. S4 in the Supplementary Appendix). As compared with patients who did not have an Xq26.3 microduplication, those with the microduplication had an earlier median age at the onset of abnormal growth (12 months vs. 16 years), an increased acceleration in height, and elevated levels of insulin-like growth factor 1 and prolactin (Table 1). We did not observe precocious puberty in the microduplication carriers.

Levels of peripheral growth hormone–releasing hormone did not suggest ectopic secretion of this hormone, and nuclear imaging scans were negative for other tumors. Of the 13 patients who underwent surgery, 10 had pituitary macroadenomas alone (median maximum diameter, 16 mm), and 3 patients had pituitary hyperplasia, with or without an identified adenoma (Fig. 3H). In all the patients, hormonal control was not achieved with medical therapy alone. Such control required either radical or repeated neurosurgery alone (in 4 patients) or in combination with the administration of the growth hormone receptor antagonist pegvisomant (in 3 patients) or radiotherapy (in 2 patients). Seven patients had permanent hypopituitarism at the time of this study.

The common duplicated genomic segment was approximately 500 kb in length, from position 135,627,637 to 136,118,269 (GRCh37/hg19).

**Table 1. Clinical Characteristics of 43 Patients with Gigantism with and without Xq26.3 Microduplications.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Xq26.3 Microduplication</th>
<th>No Xq26.3 Microduplication</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex — no. (%)</td>
<td>10 (71)</td>
<td>7 (24)</td>
<td>0.007</td>
</tr>
<tr>
<td>Median age at onset of rapid growth (range) — yr</td>
<td>1.0 (0.5 to 2.0)</td>
<td>16.0 (5.0 to 18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median age at diagnosis (range) — yr</td>
<td>3 (1 to 22)</td>
<td>21 (5 to 34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median height at diagnosis (range) — cm</td>
<td>116 (99 to 175)</td>
<td>187 (171 to 209)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median standard-deviation score for height at diagnosis (range)</td>
<td>+3.8 (+1.9 to +7.1)</td>
<td>+3.3 (+2.1 to +5.8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Elevated levels of growth hormone and insulin-like growth factor 1 at diagnosis — no. (%)</td>
<td>14 (100)</td>
<td>29 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>No suppression of growth hormone during oral glucose-tolerance test — no. (%)</td>
<td>14 (100)</td>
<td>29 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Median factor increase in insulin-like growth factor 1 at diagnosis (range) — multiple of ULN</td>
<td>4.4 (2.4 to 5.2)</td>
<td>2.1 (1.4 to 5.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Elevated prolactin level at diagnosis — no. (%)</td>
<td>13 (93)</td>
<td>6 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median maximum tumor diameter (range) — mm</td>
<td>16 (10 to 39)</td>
<td>20 (9 to 41)</td>
<td>0.16</td>
</tr>
<tr>
<td>Adenoma or hyperplasia — no. (%)†</td>
<td>Both adenoma and hyperplasia</td>
<td>2 (14)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Adenoma only</td>
<td>10 (71)</td>
<td>29 (100)</td>
</tr>
<tr>
<td></td>
<td>Hyperplasia only</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Type of syndrome — no. (%)</td>
<td>Sporadic</td>
<td>9 (64)</td>
<td>29 (100)</td>
</tr>
<tr>
<td></td>
<td>Familial</td>
<td>5 (36)‡</td>
<td>0</td>
</tr>
<tr>
<td>Siblings with normal growth — no./total no. (%)</td>
<td>9/11 (82)</td>
<td>29/29 (100)</td>
<td>—</td>
</tr>
</tbody>
</table>

* ULN denotes upper limit of the normal range.
† The presence of hyperplasia or adenoma could not be determined in one patient who did not undergo surgery.
‡ In one patient with the familial syndrome, pituitary gigantism was diagnosed in the mother and son at the same visit, when the son was 8 years of age and the mother was 22 years of age. The mother had tall stature and acromegalic features since childhood for which she had not been referred for medical attention. The clinical data for the mother, for whom DNA was not available, are included.
Birth to 24 months: Boys
Length-for-age and Weight-for-age percentiles

Published by the Centers for Disease Control and Prevention, November 1, 2009


Birth to 24 months: Girls
Length-for-age and Weight-for-age percentiles

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One patient had a complex genomic rearrangement, with two duplicated segments that were separated by a short region of normal genomic sequence. No other patterns of duplication or deletion or homozygosity were shared among the affected patients. One family with familial isolated pituitary adenomas included an affected mother and two affected sons (who have been described previously) with the same Xq26.3 microduplication; the unaffected father did not have the duplication. In another family with this condition, the mother had childhood-onset gigantism and a histologically confirmed pituitary macroadenoma but had died of complications of hypopituitarism. She had two children: the son carried the Xq26.3 microduplication and had childhood-onset gigantism (Patient F2A), and the healthy daughter did not have the duplication. The most parsimonious explanation is that the son inherited the X-linked disease from his carrier mother. Hence, Xq26.3 microduplications can be considered to be a new pathogenic explanation in certain kindreds with familial isolated pituitary adenomas that have acrogigantism without AIP mutations.

Figure 2. Summary of the Genomic Gains on Chromosome Xq26.3.
Shown are 10 different Xq26.3 microduplications, as seen on array comparative genomic hybridization, that were found in 12 patients with familial or sporadic gigantism (with the inheritance pattern indicated at right). Duplicated genomic segments (red) and nonduplicated segments (white) are shown. The genomic coordinates are provided at base-pair resolution on the x axis. The two smallest regions of overlap (SRO), SRO1 and SRO2, are identified, showing the genomic contents in the corresponding regions. The symbols next to the gene names represent the structure of the genes, with vertical lines representing exons and horizontal lines (with or without arrows) representing introns. Adapted from the UCSC Genes track in the UCSC Genome Browser.
Figure 3. Imaging and Histopathological Findings in Patients with Xq26.3 Microduplications.

Panels A through D show progressive changes from normal pituitary tissue (Panel A) to adenoma (Panel D), as indicated by reticulin staining of the pituitary gland in Patient F1C. In Panel A, normal pituitary gives way to the expanded hyperplastic acini (Panel B), and in Panel C, areas of transformation are evident (circled) with enlarged, hyperplastic, confluent acini that are caused by breakdown of reticulin fibers and that lead to adenoma (Panel D) with disruption of the reticulin fiber network. Increased GPR101 expression was observed in five tested patients with Xq26 microduplications, whereas there is little if any expression in normal pituitary tissue or growth hormone–producing tumors without Xq26.3 microduplications or GPR101 defects (see also Fig. S7 in the Supplementary Appendix); an example is shown here (Panels E through G) from Patient S3. When the staining of growth hormone (Panel E) and the staining of GPR101 (Panel F) are merged, GPR101 seems to be expressed in some of the growth hormone–secreting cells (Panel G, arrows) but not in all such cells. Nuclei (blue) were stained with DAPI. Panel H shows a sagittal view of a macroadenoma on magnetic resonance imaging of Patient S5 with the Xq26.3 microduplication.
GIGANTISM AND ACROMEGALY DUE TO Xq26 ABNORMALITIES

FURTHER CHARACTERIZATION OF Xq26.3 MICRODUPPLICATION

Using high-definition analysis of the critical duplicated region, we analyzed 10 distinct genomic duplications in 12 patients, including 4 patients with the familial form of the disease and 8 patients with the sporadic form (Fig. S1 and S3 in the Supplementary Appendix). On genomewide aCGH, these mutations appeared to be simple duplications. However, using high-resolution aCGH, long-range PCR, and Sanger sequencing of the breakpoints, we found various underlying genomic complexities (Fig. S3 in the Supplementary Appendix).

All sporadic Xq26.3 duplications were nonrecurring; the boundaries of the duplicated segment were unique to each patient. On both aCGH and breakpoint PCR assays, samples obtained from unaffected parents and siblings of patients with sporadic disease showed negative results, documenting the microduplication as a new mutation (Fig. S3A and S5A in the Supplementary Appendix). The same duplication was transmitted from an affected mother (Patient F1A) to her affected offspring, Patients F1B and F1C (Fig. 2, and Fig. S3 and S5B in the Supplementary Appendix).

The duplicated genomic regions that were shared by all affected persons consisted of the two smallest regions of overlap (SRO), which were designated as SRO1 and SRO2 (Fig. 2). SRO1 (chromosomal position, 135,627,637 to 135,986,830; hg19) encompassed three genes in the Online Mendelian Inheritance in Man (OMIM) database: CD40LG (OMIM number, 300386), ARHGEF6 (OMIM number, 300267), and RBMX (OMIM number, 300199), whereas SRO2 (chromosomal position, 136,045,310 to 136,118,269; hg19) included GPR101 (OMIM number, 300393) (Fig. 2).

INVESTIGATION OF CANDIDATE GENES

Sequencing of each of the four genes in the 43 patients with gigantism did not reveal any single-nucleotide variants of likely pathogenicity. A quantitative RT-PCR assay of pituitary tumor RNA from 2 patients with Xq26.3 microduplications suggested that CD40LG was not expressed in the pituitary tumors. Neither ARHGEF6 nor RBMX showed up-regulated expression in the pituitary tumors of 2 patients with the duplication (Fig. 4). In contrast, the expression of GPR101 in the pituitaries of the children carrying an Xq26.3 duplication was increased by a factor as high as 1000, as compared with unaffected pituitary tissue and pituitary tumors from persons who tested negative for microduplications (Fig. 4A). This result was confirmed at the protein level by increased immunostaining for GPR101 in pituitary tumors from patients with Xq26.3 duplications (Fig. 3G, and Fig. S7 in the Supplementary Appendix). Experimental overexpression of ARHGEF6, RBMX, and GPR101 alone in the rat GH3 cell line did not significantly increase either cell proliferation or the secretion of growth hormone (Fig. 4D and 4E, and Fig. S8 in the Supplementary Appendix).

Nonmutated GPR101 in combination with ARHGEF6, RBMX, or both modestly increased cell proliferation but not the secretion of growth hormone (Fig. S8 in the Supplementary Appendix).

The X-chromosome–inactivation pattern was random in the female patients with sporadic disease and skewed in Patient F1A, who had familial disease; CpG islands were identified in silico only in RBMX and GPR101 (Fig. S9 and S10 in the Supplementary Appendix).

IDENTIFICATION OF p.E308D MUTATION IN GPR101

In a series of 248 patients with sporadic acromegaly, none carried a microduplication at Xq26.3. However, 11 patients had a c.924G→C substitution (p.E308D) in GPR101, which was not found in 7600 control samples obtained from public databases (Tables S1 and S2 in the Supplementary Appendix). Of the 11 mutation carriers, 3 appeared to carry a constitutive mutation, which was detected in DNA from peripheral-blood mononuclear cells (PBMCs). We detected the mutation in the tumor DNA in the remaining 8 patients (Fig. 5A). In one patient, we determined that the mutation was a de novo somatic mutation — that is, the GPR101 mutation occurred only in the tumor DNA sequence and not in the PBMC sequence (Fig. 5B). None of the 13 families with familial isolated pituitary adenomas carried the p.E308D mutation in GPR101.

GPR101 encodes an orphan G-protein–coupled receptor that is highly expressed in rodent hypothalamus (Fig. S11 and S12 in the Supplementary Appendix) and is predicted to couple to the stimulatory G protein (Gs), a potent activator of adenyl cyclase. A model of human GPR101 in complex with a Gs heterotrimer shows the physical relationship between the p.E308D amino acid change and the activating p.A397K change, a mutation that has been described previously. The two amino acids, which are predicted to be...
Figure 4. Expression of GPR101 in Pituitary Tissue from Children with Xq26.3 Microduplications.

The expression of GPR101 in pituitary tissue from children carrying Xq26.3 microduplications was increased by a factor as high as 1000, as compared with the expression in unaffected pituitary tissue (in five samples [NP1 through NP5] obtained on autopsy) and in pituitary tumors from two patients with sporadic acromegaly (GH1 and GH2) who tested negative for the microduplication (Panel A). These findings, which were obtained on quantitative reverse-transcriptase–polymerase-chain-reaction (qRT-PCR) assay and normalized by a housekeeping gene, contrast with those for two other genes, ARHGEF6 (Panel B) and RBMX (Panel C), in the duplicated stretch of DNA; neither of these two genes showed up-regulated expression. Also shown are cell proliferation (Panel D), growth hormone secretion (Panel E), and activation of DNA sequences called cyclic AMP response elements (CRE) (Panel F) in rat GH3 cells transfected with mutant (p.E308D and p.A397K) and nonmutant GPR101 constructs. Values for cells transfected with empty (control) vector were set at 1. Also shown are values for untreated cells (vehicle) and forskolin (which increases CRE activation). Data are expressed as the mean results of three to five independent experiments, each of which was performed in triplicate. The T bars indicate standard deviations. One asterisk denotes P<0.05, two asterisks P<0.01, and three asterisks P<0.001.
Figure 5. Effect of the p.E308D Mutation in GPR101 in 11 Patients with Sporadic Acromegaly.
Panel A shows the sequence for GPR101 in growth hormone–producing pituitary tumors obtained from patients with sporadic acromegaly, as compared with normal tissue. Panel B shows results for a patient with a somatic mutation, which was determined by the presence of the mutation in the GPR101 sequence of DNA in the tumor sample but not in the sequence in peripheral-blood mononuclear cells. None of the 13 families with familial isolated pituitary adenomas carried the p.E308D mutation in GPR101. Panel C shows a structural model of GPR101 bearing the p.E308D mutation. Residue A397 is located at the cytosolic end of transmembrane (TM) 6 of GPR101. The mutated D308 residue and the nonmutated A397 residue are shown in space-filling representation and colored according to elements, with carbon atoms in gray, oxygen atoms in red, and nitrogen atoms in blue. The backbone of the receptor and the G protein heterotrimer is schematically represented as a ribbon, with the receptor shown with a spectrum of colors that ranges from red at the N-terminal to purple at the C-terminal; the α, β, and γ subunits of the G protein are in gray, blue, and pink, respectively. The cytosolic ends of TM 5 and TM 6 and intracellular loop (IL) 3, which connects them, are indicated by labels. The blue arrows show directions of the β-sheet domains of the β subunit of the G protein.
affected by the mutations, are on the cytosolic side of the receptor (Fig. 5C). The E308 residue is located in the long intracellular loop 3, which connects transmembrane domains 5 and 6.

Overexpression of the p.E308D and p.A397K mutants, but not of nonmutant GPR101, significantly increased cell proliferation and secretion of growth hormone in rat GH3 cells (Fig. 4D and 4E). As in the construct containing the nonmutant receptor, the two mutant constructs resulted in increased cAMP signaling in GH3 cells in an in vitro reporter assay, both at baseline and in the presence of 10 μM forskolin, a direct stimulator of adenylyl cyclase (Fig. 4F).

**DISCUSSION**

Several lines of evidence support the identification of a new pituitary gigantism syndrome in young children carrying microduplications on chromosome Xq26.3, a disorder that is probably caused by GPR101 overexpression. We propose that this syndrome be called X-linked acrogigantism (X-LAG). First, we did not find disruption of Xq26.3 in patients with later-onset gigantism (Table 1). Second, the finding that patients with other conditions had different duplications within the same region narrowed our focus to the smallest region of overlap. A duplication encompassing CD40LG and ARHGEF6 but not RBMX and GPR101 occurred in a family with low birth weight, intellectual disability, and craniofacial abnormalities, which suggests that duplications with the exclusion of RBMX and GPR101 do not lead to gigantism. Third, short stature has been reported in several patients with deletions in this region, which suggests that the absence of these genes may lead to the opposite phenotype (Table S4 in the Supplementary Appendix). Other investigators have described at least 15 additional patients with the same phenotype of early-onset growth who may be good candidates for a diagnosis of X-LAG (Table S3 in the Supplementary Appendix).

The breakpoint features of Xq26.3 duplications suggest that they were generated by means of a replication-based mechanism that underlies the genesis of other copy-number variants (CNVs) and the pathogenesis of other genomic disorders.

The cytogenetic data narrowed the smallest region of overlap to a segment spanning CD40LG, ARHGEF6, RBMX, GPR101, one microRNA (miR-934), and a small nucleolar RNA (SNORD61) of unknown function. We did not detect CD40LG expression in the pituitary tissues from our patients (Fig. 4). Messenger RNA for ARHGEF6 and RBMX was expressed to a similar degree in affected and unaffected tissues from duplication carriers. Of all the genes and the noncoding RNAs in the duplicated segment, only GPR101 had markedly increased expression in the pituitary tumors from the duplication carriers (Fig. 4).

GPR101 is an orphan G-protein–coupled receptor that is strongly expressed in the hypothalamus in rodents (Fig. S11 and S12 in the Supplementary Appendix). It was recently shown that a fragment of the gonadotropin-releasing hormone could be a ligand for this receptor.21 The GPR101 protein may also play a role in hypothalamic control of energy homeostasis.22 The effect of a mutation (p.A397K) that is predicted to activate GPR101 when tested in vitro and in mice supports such a role.15 The pituitary-specific overexpression of GPR101 may be due to a gene-dose effect (as described in many genomic disorders) or to an unknown promoter sequence created by the chromosomal rearrangement, although we did not identify any putative new promoter, or to perturbed chromatin regulation due to the genomic structural alteration from duplication CNVs.

On the basis of our data from transfection experiments, we cannot rule out a modest contribution of RBMX and ARHGEF6 coexpression to cell proliferation. However, unlike GPR101, neither ARHGEF6 nor RBMX was overexpressed in the pituitary tumors from children with microduplications.

Our studies of sporadic acromegaly provide further support for a role of GPR101 in X-LAG. We found a recurrent GPR101 mutation, p.E308D, in 4.4% of DNA in tumor samples and in 1.9% of DNA in PBMC samples obtained from patients with isolated acromegaly. In at least one patient, the mutation was present only in the tumor DNA. We did not identify GPR101 mutations in families with familial isolated pituitary adenomas. A model of human GPR101 in complex with a Gβ heterotrimer showed that both the p.E308D mutation and the previously described p.A397K mutation are on the cytosolic side of the receptor that interacts with heterotrimeric G proteins. Residue E308 is located in a remarkably long intracellular loop, which connects two transmembrane domains. But in the absence of a model template for the GPR101 intracellular loop in which E308 resides, it is difficult to estimate the structural
effect of the p.E308D substitution. However, transfection of a construct expressing GPR101 containing the p.E308D mutation increased proliferation and growth hormone secretion in a rat pituitary cell line. Moreover, we showed that GPR101 can strongly activate the CAMP pathway, for which the mitogenic effects in pituitary somatotropes are well established. These data further support a role for variant GPR101 in sporadic acromegaly.

The mechanism by which mutant GPR101 contributes to increased growth hormone secretion is unclear. Some of the patients with early-onset gigantism whom we evaluated had normal or mildly elevated levels of circulating growth hormone—releasing hormone (but below the threshold required for ectopic tumoral secretion of this hormone), as was previously noted in Family F1. The tumor tissue showed strong expression of the growth hormone—releasing hormone receptor, in contrast to its expression of growth hormone—releasing hormone, which was low or absent (Fig. S15 in the Supplementary Appendix).

In conclusion, our results suggest that Xq26.3 microduplication is associated with a clinical syndrome of early-onset gigantism, which we have termed X-LAG. An increased dose of GPR101 on chromosome Xq26.3 probably causes the disease, and its activation by mutation occurs in patients with sporadic acromegaly. Xq26.3 microduplications may explain other historical cases of gigantism with features that closely resemble those of X-LAG. Our results offer an opportunity to study a new pathway involved in the central regulation of human growth.

Supported by a grant from the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (Z01-HD008920, to Dr. Stratakis), by a grant from the National Human Genome Research Institute (U54HG006542, to Dr. Lupski), by a grant from Fonds d’Investissement de Recherche Scientifique de Centre Hospitalier Universitaire (CHU) de Liège (to Dr. Beckers), by an educational grant from Pfizer Belgium (to Dr. Beckers), and by the Jabbs Foundation (to Dr. Beckers). Computing resources used for the molecular-modeling component of this work were provided by the American University High Performance Computing System, which is funded in part by a grant from the National Science Foundation (BCS-1039497).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their families for their participation in this study; the nursing and other support staff at the NIH Clinical Research Center (CRC), in particular Dr. Edward Oldfield (now at the University of Virginia, Charlottesville) and Dr. Russell Lonser (now at Ohio State University, Columbus) who operated on most of the patients from the NIH who are described in this report; Dr. Phillip Gorden of the National Institute of Diabetes and Digestive and Kidney Diseases for providing a list of patients with acromegaly who have been seen at the NIH CRC during the past 30 years; Dr. Timothy Jones (Department of Pediatric Endocrinology, Princess Margaret Hospital for Children and School of Pediatrics and Child Health, University of Western Australia); Vincent Schram at the Microscopy and Imaging Core of the NICHD; Dr. Charalampos Lyssikatos and Dr. Monalisa Azevedo (Section on Endocrinology and Genetics, NICHD); Ms. Isabelle Besson and Dr. Michèle Bernier (Pathology and Cytology Department, Hôpital Foch, Suresnes, France); Drs. Antonella Forlini, Annalisa Vetro, and Orsetta Zuffardi (Department of Molecular Medicine, University of Pavia, Pavia, Italy); Dr. Anna Spada and Dr. Paolo Beck-Peccoz (Endocrinology and Diabetology Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca’ Granda Ospedale Maggiore Policlinico, Department of Clinical Sciences, University of Milan); Ms. Carine Mottard, Ms. Carine Deusing, Mr. Valery Leduc, and Ms. Nathalie Sacre (Department of Clinical Genetics, CHU de Liege, Liege, Belgium); Ms. Latifa Karim (GIGA-Genomics, Liege, Belgium); Dr. Silvia Paolotto (Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases); Ms. Silke Williams (Laboratory of Pathology, National Cancer Institute); Dr. Jack A. Yanovski (Section on Growth and Obesity, NICHD); Dr. S.J. Levine (Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute); Dr. Say Viengchareun (INSERM Unité 693 Le Kremlin-Bicêtre, France); Dr. Paul Hofman (Liggins Institute, University of Auckland, Auckland, New Zealand); Dr. Stephen Butler (Taranaki District Health Board, New Plymouth, New Zealand); Dr. Yvonne C. Anderson (Liggins Institute, University of Auckland, Auckland, New Zealand, and Taranaki Base Hospital, New Plymouth, New Zealand); Dr. Ian Holdaway (Auckland City Hospital and Greenlane Clinical Centre, Auckland, New Zealand); and Dr. Karen Carpenter (Department of Diagnostic Genomics, PathWest Laboratory Medicine Western Australia, Perth, Australia).

APPENDIX

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REFERENCES

27. de Herder WW. Acromegaly and gigan- tism in the medical literature: case de- scriptions in the era before and the early years after the initial publication of Pierre Marie (1886). Pituitary 2009;12:236-44.
Gigantism and Acromegaly Treatment & Management

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Updated: Jan 06, 2015

Approach Considerations

Most experts define cure, or adequate control, of growth hormone (GH) excess as a glucose-suppressed GH concentration of less than 2 ng/mL, as determined by radioimmunoassay (1 mcg/L by IRMA), and normalization of the serum insulinlike growth factor I (IGF-I) concentration.

However, no single treatment modality consistently achieves control of GH excess. For pituitary adenomas, transsphenoidal surgery is usually considered the first line of treatment, followed by medical therapy for residual disease.[6] Radiation treatment usually is reserved for recalcitrant cases.

Radiotherapy and medical treatment are important because in long-term studies, surgery has been found to cure only approximately 60% of patients with acromegaly.[24] Slow-release formulations of somatostatin are now widely used (including as a primary treatment) and appear to be safe and effective in 50-60% of the patients. A GH-receptor blocking agent, pegvisomant, appears to normalize IGF-I levels in almost all patients.

Guidelines released by the US Endocrine Society in 2014 address important clinical issues regarding the evaluation and management of acromegaly.[25, 26]

Recommendations include the following:

- For most patients with acromegaly, surgical removal of the pituitary gland tumor should be considered the primary treatment
- An imaging study should be performed at least 12 weeks postsurgery to determine whether any residual tumor tissue is present
- Patients should be evaluated for any damage caused by the pituitary tumor and for the development of hypopituitarism
- Medical therapy should be administered only to patients with persistent postoperative disease

The guidelines also address the management of women with acromegaly who are pregnant or trying to conceive.

Pharmacologic Therapy

The goals of medical therapy for GH excess are as follows:

- Remove or shrink the pituitary mass
- Restore GH secretory patterns to normal
- Restore serum total IGF-I and IGF binding protein 3 (IGFBP-3) levels to normal
- Retain normal pituitary secretion of other hormones
- Prevent recurrence of disease

Somatostatin and dopamine analogues and GH receptor antagonists are the mainstays of medical treatment for GH excess and are generally used when primary surgery fails to induce complete remission.

Somatostatin analogues

The most extensively studied and used somatostatin analogue, octreotide, binds to the somatostatin receptor subtypes II and V, inhibiting GH secretion. Octreotide suppresses the serum GH level to less than 2.5 mcg/L in 65% of patients with acromegaly and normalizes circulating IGF-I levels in 70% of patients. Tumor shrinkage, although generally modest, is seen in 20-50% of patients. Consistent GH suppression was achieved with a continuous subcutaneous pump infusion of octreotide in a pubertal boy with pituitary gigantism.

Studies of patients with GH excess for longer than 14 years have demonstrated that the effects of octreotide are well sustained over time. An anaphylactic reaction to octreotide has been described.[27]

Primary treatment with depot octreotide and lanreotide has been found to induce tumor shrinkage in newly diagnosed acromegaly.[6]

Long-acting formulations, including long-acting octreotide, lanreotide, and pasireotide, have been demonstrated to produce consistent GH and IGF-I suppression in patients with acromegaly with once-monthly or biweekly intramuscular depot injections. (Sustained-released preparations have not been formally tested in children with gigantism.)

In 2 Japanese studies, by Shimatsu et al, the sustained-release lanreotide...
Somatuline Depot (or lanreotide Autogel) was found to control elevated GH and IGF-I levels within the first weeks of treatment, as well as over a long-term period of administration. In an open-label, parallel-group, dose-response study, which included 29 patients with acromegaly and 3 with pituitary gigantism, 5 injections of lanreotide Autogel were administered over a 24-week period, in dosages of 60, 90, or 120 mg.[29]

At week 4, serum GH levels of below 2.5 ng/mL and normalized IGF-I levels were found in 41% and 31% of patients, respectively. At week 24, the investigators found that serum GH levels of below 2.5 ng/mL and normalized IGF-I levels had been attained in 53% and 44% of patients, respectively.[28]

In the second investigation, an open-label, long-term study of 30 patients with acromegaly and 2 with pituitary gigantism, lanreotide Autogel injections were administered every 4 weeks for a period of 52 weeks (13 injections). Patients initially received a 90-mg dose, which was subsequently adjusted based on clinical response. At week 52, serum GH levels of below 2.5 ng/mL, and normalized IGF-I levels had been achieved in 47% and 53% of patients, respectively.[28]

Pasireotide’s approval was based on 2 multicenter, phase 3 studies. One in medically naive patients with acromegaly who had prior surgery or in whom surgery was not an option, and the other in patients inadequately controlled on first-generation somatostatin analogs (ie, octreotide, lanreotide). The risk for hyperglycemia needs to be considered with use of pasireotide.[29, 30]

Dopamine-receptor agonists

Dopamine-receptor agonists (eg, bromocriptine, cabergoline) bind to pituitary dopamine type 2 (D2) receptors and suppress GH secretion, although their precise mechanism of action remains unclear.

Prolactin levels are often adequately suppressed with these agents. However, circulating GH and IGF-I levels rarely normalize with this therapy. Less than 20% of patients achieve GH levels of less than 5 ng/mL, and less than 10% achieve normal IGF-I levels. Tumor shrinkage occurs in a few patients.

Dopamine-receptor agonists are generally used as adjuvant medical treatments for GH excess, and their effectiveness may be added to that of octreotide.

Although long-acting formulations are available, no data about the long-term control of GH and IGF-I with these agents are available.

Bromocriptine

Bromocriptine has an adjunctive role in the treatment of patients with GH excess who fail to achieve a cure by surgical treatment or who are to be treated with radiation. It has limited effectiveness, however, reducing the circulating GH level to less than 5 ng/mL in only 20% of patients with acromegaly and normalizing IGF-I concentration in only 10% of these patients. Shrinkage in tumor size also occurs, albeit in fewer than 20% of patients. Patients in whom prolactin is elevated are more likely to have a favorable response to bromocriptine.

Cabergoline

Cabergoline, another dopamine-receptor agonist, is somewhat more effective than bromocriptine in reducing GH levels, with response rates of 46%. A meta-analysis found that cabergoline used as single-agent therapy in patients with acromegaly normalized IGF-I levels in one third of patients. In those cases in which a somatostatin analogue has failed to control acromegaly, cabergoline adjunction normalized IGF-I levels in about 50% of cases.

GH-receptor antagonists

Tests of pegvisomant (Somavert), a novel hepatic GH-receptor antagonist, demonstrated effective suppression of GH and IGF-I levels in patients with acromegaly due to pituitary tumors or ectopic GHRH hypersecretion.

Normalization of IGF-I levels occurs in as many as 90% of patients treated daily with this drug for 3 months.

In the interim analysis of ACROSTUDY, a global noninterventional surveillance study of 1288 patients with acromegaly treated with pegvisomant for a mean period of 3.7 years (2.1- to mean follow-up), 63.2% of subjects had normal IGF-I levels at a mean dose of 18 mg/day. The reported incidence of transaminitis, lipodystrophy, and increase in pituitary tumor size was low.[32]

Combination therapy with pegvisomant and cabergoline or somatostatin analogues is also being investigated for efficacy.[33]

Pegvisomant has not been formally tested in children; however, a case study described normalization of IGF-I in a 12-year-old girl with pituitary gigantism treated with pegvisomant 20 mg/day.[34]

Radiation Therapy

In general, radiation therapy is recommended if GH hypersecretion is not normalized with surgery. Radiation prevents further growth of the tumor in more
than 99% of patients after surgical resection.

However, radiation treatment takes to years reduce/normalize GH/IGF-I levels.\textsuperscript{[35]} About 60% of patients have a GH concentration of less than 5 ng/mL 10 years after radiotherapy.

Hypopituitarism is a predictable outcome of radiation treatment, occurring in 40-50% of patients within 10 years after irradiation. Some studies suggest that radiation is associated with the development of secondary tumors.

Newer modalities (eg, stereotactic fractionated radiotherapy, proton beam therapy) may have the advantage of a better target dose-conformation, but long-term outcome data are lacking at this time.\textsuperscript{[36]}

Stereotactic gamma-knife radiosurgery for recurrent or residual pituitary adenomas, when combined with microsurgery, is often effective in controlling pituitary adenoma growth and hormone hypersecretion.\textsuperscript{[37]} Results are influenced by many factors, including adenoma histology, adenoma volume, and radiation dose.

**Transsphenoidal Surgery**

The primary goal of surgery is to normalize GH levels. For well-circumscribed pituitary adenomas, transsphenoidal surgery to completely remove the tumor is the treatment of choice, and it may be curative. The procedure can also rapidly improve symptoms caused by mass effect of the pituitary tumor. The following should be kept in mind concerning surgical treatment:

- The likelihood of a surgical cure greatly depends on the surgeons’ expertise and on the size and extension of the mass
- Intraoperative GH measurements can improve the results of tumor resection
- Transsphenoidal surgery to resect tumors is as safe in children as it is in adults
- A transcranial approach is sometimes necessary

As determined by using the GH assays available to date, GH levels should be normalized (< 1 ng/mL for ≥50% of the points measured during the day) in all patients. Because this change is impractical to test, however, GH levels (< 1 ng/mL within 2 h after a glucose load) and serum IGF-I levels (within 2 standard deviations of the reference range adjusted for age, sex, and Tanner stage) are the best measures of a biochemical cure.

A remission rate of 80-85% can be expected for microadenomas and 50-65% for macroadenomas.

The postoperative GH concentration may predict remission rates. According to the results of one study, a postoperative GH concentration of less than 3 ng/dL was associated with a 90% remission rate, which declined to 5% in patients with a postoperative GH concentration of greater than 5 ng/dL.

A significant proportion of acromegalic patients who have undergone surgery have been found to have a change in biochemical status upon long-term follow-up. Most of these changes have occurred within the first postoperative year and were more likely to occur if the initial GH postglucose and IGF-I levels were discordant.\textsuperscript{[38]}

If surgery does not normalize GH secretion, options include pituitary radiation and medical therapy.

**Long-Term Monitoring**

All patients with a history of GH excess require periodic, lifelong evaluation. In one series, the long-term recurrence rate for GH-secreting adenomas in children was 13.3% after surgery.\textsuperscript{[39]}

IGF-I levels appear to correlate better with clinical activity than do GH levels and should therefore be monitored.

Patients should also be evaluated for severe GH deficiency, which may occur in more than half of all patients treated for acromegaly (even those who have been cured by surgery alone).\textsuperscript{[40]}

Because an association exists between acromegaly and regurgitant valvular heart disease, patients with acromegaly require adequate cardiac evaluation and follow-up to establish whether valvular disease is present and, if so, to determine the extent and progression of valvular involvement.\textsuperscript{[41]}

**Medication**

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References


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Gigantism and Acromegaly

- Author: Alicia Diaz-Thomas, MD, MPH; Chief Editor: Stephen Kemp, MD, PhD  more...

Updated: Jan 06, 2015

Practice Essentials

Gigantism refers to abnormally high linear growth (see the image below) due to excessive action of insulinlike growth factor I (IGF-I) while the epiphyseal growth plates are open during childhood. Acromegaly is the same disorder of IGF-I excess but occurs after the growth plate cartilage fuses in adulthood.

Image shows a coauthor of this article with a statue of Robert Wadlow, who was called the Alton giant. The tallest person on record, he was 8 feet 11 inches tall at the time of his death.

In acromegaly, a severe disease that is often diagnosed late, morbidity and mortality rates are high, particularly as a result of associated cardiovascular, cerebrovascular, and respiratory disorders and malignancies.\(^1\)

Essential update: Researchers identify new gene that may play a part in growth disorders

Researchers have identified a gene on the X chromosome, GPR101, which was overexpressed 1000-fold more than normal in a genetic study of 43 patients affected by sporadic or inherited gigantism that manifested during childhood or adolescence. This duplication was not evident in patients who began abnormal growth at age 9 or 10, but only in those who started to grow excessively before the age of 3. In a separate analysis of 248 patients with sporadic acromegaly, a mutation in the GPR101 gene was found in about 4% of cases.\(^2, 3\)

The GPR101 gene may be a target for the treatment of growth disorders.

Signs and symptoms

Gigantism

The presentation of patients with gigantism is usually dramatic, unlike the insidious onset of acromegaly in adults. Manifestations include the following:

- Tall stature
- Mild to moderate obesity (common)
- Macrocephaly (may precede linear growth)
- Headaches
- Visual changes
- Hypopituitarism
- Soft tissue hypertrophy
- Exaggerated growth of the hands and feet, with thick fingers and toes
- Coarse facial features
- Frontal bossing
- Prognathism
- Hyperhidrosis
- Osteoarthritis (a late feature of IGF-I excess)
- Peripheral neuropathies (eg, carpal tunnel syndrome)

http://emedicine.medscape.com/article/925446-overview
• Cardiovascular disease
• Benign tumors
• Endocrinopathies

Gigantism

Signs and symptoms of gigantism include the following:
• Excess growth in childhood
• Enlargement of the lower lip and nose
• Noticeably large pores
• Thick and edematous eyelids
• Enlargement of the lower lip and nose (the nose takes on a triangular configuration)
• Wide spacing of the teeth and prognathism
• Cutis verticis gyrata (ie, furrows resembling gyr of the scalp) [4]
• Small sessile and pedunculated fibromas (ie, skin tags)
• Hypertrichosis
• Oily skin (acne is not common)
• Hyperpigmentation (40% of patients)
• Acanthosis nigricans (a small percentage of patients)
• Excessive eccrine and apocrine sweating
• Breast tissue becoming atrophic; galeactornea
• High blood pressure
• Mitral valvular regurgitation
• Mild hirsutism (in women)

Diagnosis

Laboratory studies used in the diagnosis of growth hormone (GH)/IGF-I excess include the following:
• Oral glucose: To determine the extent to which the patient can suppress GH concentration after the consumption of oral glucose
• GH: Clearly elevated GH levels (>10 ng/mL) after oral glucose, combined with the clinical picture, secure the diagnosis of acromegaly
• IGF-I: Elevated IGF-I values in a patient whose symptoms prompt appropriate clinical suspicion almost always indicate GH excess

Imaging studies include the following:
• Magnetic resonance imaging (MRI): To image pituitary adenomas
• Computed tomography (CT) scanning: To evaluate the patient for pancreatic, adrenal, and ovarian tumors secreting GH/GHRH; use chest CT scans to evaluate for bronchogenic carcinoma secreting GH/GHRH
• Radiography: To demonstrate skeletal manifestations of GH/IGF-I excess

Management

No single treatment modality consistently achieves control of GH excess. For pituitary adenomas, transsphenoidal surgery is usually considered the first line of treatment, followed by medical therapy for residual disease. [6] Radiation treatment usually is reserved for recalcitrant cases.

Somatostatin and dopamine analogues and GH receptor antagonists are the mainstays of medical treatment for GH excess and are generally used when primary surgery fails to induce complete remission.

Primary treatment with the somatostatin analogues depot octreotide and lanreotide has been found to induce tumor shrinkage in newly diagnosed acromegaly. [8] Dopamine-receptor agonists are generally used as adjuvant medical treatments for GH excess, and their effectiveness may be added to that of octreotide.

Radiation therapy is also generally recommended if GH hypersecretion is not normalized with surgery.

Background

Gigantism refers to abnormally high linear growth due to excessive action of insulin-like growth factor I (IGF-I) while the epiphyseal growth plates are open during childhood. Acromegaly is the same disorder of IGF-I excess but occurs after the growth plate cartilage fuses in adulthood. (See Pathophysiology and Etiology.)

Gigantism

Gigantism is a nonspecific term that refers to any standing height more than 2 standard deviations above the mean for the person’s sex, age, and Tanner stage (ie., height Z score >+2). These disorders are placed along a spectrum of IGF-I hypersecretion, wherein the developmental stage when such excess originates determines the principal manifestations. The onset of IGF-I hypersecretion in childhood or late adolescence results in tall stature (see the image below). (See Clinical Presentation and Workup.)
Scientific breakthroughs in the molecular, genetic, and hormonal basis of growth hormone (GH) excess have provided important insights into the pathogenesis, prognosis, and treatment of this exceedingly rare disease. (See Prognosis, Treatment, and Medication.)

Acromegaly

Acromegaly is a rare, insidious, and potentially life-threatening condition for which there is good, albeit incomplete, treatment that can give the patient additional years of high-quality life. (See Prognosis, Treatment, and Medication.)

Symptoms develop insidiously, taking from years to decades to become apparent. The mean duration from symptom onset to diagnosis is 5-15 years, with a mean delay of 8.7 years. Excess GH produces a myriad of signs and symptoms and significantly increases morbidity and mortality rates. Additionally, the mass effect of the pituitary tumor itself can cause symptoms. Annual new patient incidence is estimated to be 3-4 cases per million population per year. The mean age at diagnosis is 40 years in males and 45 years in females. (See Presentation.)

Growth hormone and insulinlike growth factor

GH is necessary for normal linear growth. Its secretion from the pituitary gland is controlled by combined hypothalamic regulation, with secretion being stimulated by GHRH and inhibited by somatostatin (also called GH release-inhibiting hormone). Several tissues, including the endocrine pancreas, produce somatostatin in response to GH. (See Pathophysiology and Etiology.)

GH acts indirectly, by stimulating the formation of IGF hormones (also called somatomedins). IGF-I (somatotedin C), the most important IGF in postnatal growth, is produced in the liver, chondrocytes, kidneys, muscles, pituitary gland, and gastrointestinal tract.

Once released into the circulation, GH stimulates the production of IGF-I. The main source of circulating IGF-I is the liver, though it is produced in many other tissues. IGF-I is the primary mediator of the growth-promoting effects of GH.

It is characterized by increased and unregulated GH production, usually caused by a GH-secreting pituitary tumor (somatotroph tumor). Other causes of increased and unregulated GH production, all very rare, include increased GH-releasing hormone (GHRH) from hypothalamic tumors; ectopic GHRH from nonendocrine tumors; and ectopic GH secretion by nonendocrine tumors.

Pathophysiology and Etiology

Causes of excess IGF-I action can be divided into the following 3 categories:

- Release of primary GH excess from the pituitary
- Increased GHRH secretion or hypothalamic dysregulation
- Hypothetically, the excessive production of IGF-binding protein, which prolongs the half-life of circulating IGF-I

By far, most people with gigantism or acromegaly have GH-secreting pituitary adenomas or hyperplasia. Other causes of increased and unregulated GH production, all very rare, include increased GHRH from hypothalamic tumors; ectopic GHRH from nonendocrine tumors; and ectopic GH secretion by nonendocrine tumors.

Although gigantism is typically an isolated disorder, rare cases occur as a feature of other conditions, such as the following:

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3/11
Approximately 20% of patients with gigantism have McCune-Albright syndrome (the triad of precocious puberty, café au lait spots, fibrous dysplasia) and may have either pituitary hyperplasia or adenomas. (See the image below.)

A 12-year-old boy with McCune-Albright syndrome. His growth-hormone excess manifested as tall stature, coarse facial features, and macrocephaly.

More than 95% of acromegaly cases are caused by a pituitary adenoma that secretes excess amounts of GH. Histopathologically, tumors include acidophil adenomas, densely granulated GH adenomas, sparsely granulated GH adenomas, somatomammotropic adenomas, and plurihormonal adenomas.

Ectopic production of GH and GHRH by malignant tumors accounts for other causes of IGF-I excess. (Ectopic GHRH-producing tumors, usually seen in the lung or pancreas, may occasionally be evident elsewhere, such as in the duodenum as a neuroendocrine carcinoma.)

Of these tumors, up to 40% have a mutation involving the alpha subunit of the stimulatory guanosine triphosphate (GTP)-binding protein. In the presence of a mutation, persistent elevation of cyclic adenosine monophosphate (cAMP) in the somatotrophs results in excessive GH secretion.

The pathologic effects of GH excess include acral overgrowth, insulin antagonism, nitrogen retention, increased risk of colon polyps/tumors, and acral overgrowth (ie, macroglossia; enlargement of the facial bone structure, as well as of the hands and feet; and visceral overgrowth, including macroglossia and enlargement of the heart muscle, thyroid, liver, and kidney).

Pathologic studies on acromegalic hearts have shown extensive interstitial fibrosis, suggesting the existence of a specific acromegalic cardiomyopathy.

GH/IGF-I excess

Despite diverse pathophysiologic mechanisms, the final common abnormality in gigantism and acromegaly is IGF-I excess. Elevated tissue levels of free IGF-I, which is produced primarily in hepatocytes in response to excess GH, mediate most, if not all, growth-related outcomes in gigantism. Transgenic mice that overexpressed GH, GHRH, or IGF-I were found to have dramatically accelerated somatic growth compared with control litter mates.

One acromegalic patient had low serum GH levels and elevated serum total IGF-I levels; this finding implicates IGF-I as the key pathologic factor in this disease. Serum levels of IGF-I are consistently elevated in patients with acromegaly and, therefore, are used to monitor treatment success. The conditions described below can cause IGF-I oversecretion.

Primary pituitary GH excess

In most individuals with GH excess, the underlying anomaly is a benign pituitary tumor composed of somatotrophs (GH-secreting cells) or mammosomatotrophs (GH-secreting and prolactin-secreting cells) in the form of a pituitary microadenoma (<1 cm) or macroadenoma (>1 cm). The adenomas are most characteristically well-demarcated and confined to the anterior lobe of the pituitary gland. In some people with GH excess, the tumor spreads outside the sella, invading the sphenoid bone, optic nerves, and brain. GH-secreting tumors are more likely to be locally invasive or aggressive in pediatric patients than in adults.
G proteins play an integral role in postligand signal transduction in many endocrine cells by stimulating adenyl cyclase, resulting in an accumulation of cyclic adenosine monophosphate (cAMP) and subsequent gene transcription. About 20% of patients with gigantism have McCune-Albright syndrome and pituitary hyperplasia or adenomas.

Activating mutations of the stimulatory Gsa protein have been found in the pituitary lesions in McCune-Albright syndrome and are believed to cause the other glandular adenomas observed. Point mutations found in several tissues affected in McCune-Albright syndrome involve a single amino-acid substitution in codon 201 (exon 8) or 227 (exon 9) of the gene for Gsa. Somatic point mutations have been identified in the somatotrophs of less than 40% of sporadic GH-secreting pituitary adenomas. The resulting oncogene (gsp) is thought to induce tumorigenesis by persistently activating adenyl cyclase, with subsequent GH hypersecretion.

Loss of band 11q13 heterozygosity

Loss of heterozygosity at the site of a putative tumor-suppressor gene on band 11q13 was first identified in tumors from patients with MEN type I and GH excess. Loss of heterozygosity at band 11q13 has also been observed in all types of sporadically occurring pituitary adenomas. It is associated with an increased propensity for tumoral invasiveness and biologic activity.

Isolated familial somatotropinoma, a rare disease, refers to the occurrence of 2 or more cases of acromegaly or gigantism in a family in whom the features of Carney complex or MEN type 1 are absent. It appears to be inherited as an autosomal dominant disease with incomplete penetrance. Although an association exists between isolated familial somatotropinoma and loss of heterozygosity on 11q13, the responsible gene remains unknown.

Abnormality at Carney loci on chromosomes 2 and 17

The Carney complex, which is characterized by myxomas, endocrine tumors, and spotty pigmentation, is transmitted as an autosomal dominant trait. About 8% of affected individuals have GH-producing pituitary adenomas. The causative gene for this disease was mapped to bands 2p16 and 17q22-24. Germline mutations in PRKAR1A (which encodes for the protein kinase A type I-alpha regulatory subunit, an apparent tumor-suppressor gene on chromosome arm 17q) were detected in several families with Carney complex.

Secondary GH excess

Causes of secondary GH excess include increased secretion of GHRH due to an intracranial or ectopic source and dysregulation of the hypothalamic-pituitary-GH axis.

GHRH excess

Hypothalamic GHRH excess is postulated as a cause for gigantism, possibly secondary to an activating mutation in hypothalamic GHRH neurons. Excess GHRH secretion may be due to an intracranial or ectopic tumor. Several well-documented incidents of hypothalamic GHRH excess demonstrated intracranial gangliocytomas associated with gigantism or acromegaly.

Ectopic GHRH-secreting tumors have included carcinoid, pancreatic islet-cell, and bronchial neoplasms. Prolonged tumor secretion of GHRH leads to pituitary hyperplasia, with or without adenomatous transformation, that increases levels of GH and other adenohypophysal peptides.

Disruption of somatostatin tone

Tumoral infiltration into somatostatinergic pathways are hypothesized to be the basis for GH excess in rare incidents of gigantism associated with neurofibromatosis and optic glioma or astrocytomas.

Epidemiology

Occurrence in the United States

Gigantism is extremely rare, with approximately 100 reported cases to date. Acromegaly is more common than gigantism, with an incidence of 3-4 cases per million people per year and a prevalence of 40-70 cases per million population.

Age-related demographics

Gigantism may begin at any age before epiphyseal fusion. The mean age for onset of acromegaly is in the third decade of life; the delay from the insidious onset of symptoms to diagnosis is 5-15 years, with a mean delay of 8.7 years. The mean age at diagnosis for acromegaly is 40 years in males and 45 years in females.

Prognosis

Because of the small number of people with gigantism, mortality and morbidity rates for this disease during childhood are unknown.
In acromegaly, a severe disease that is often diagnosed late, morbidity and mortality rates are high, particularly as a result of associated cardiovascular, cerebrovascular, and disorders and malignancies.\[1\]

Because IGF-I is a general growth factor, somatic hypertrophy in acromegaly occurs across all organ systems. Associated complications include the following\[12\]:

- Acromegalic heart
- Increased muscle and soft tissue mass
- Increased kidney size
- Articular overgrowth of synovial tissue and hypertrophic arthropathy
- Joint symptoms, back pain, and kyphosis: Common presenting features
- Thick skin
- Hyperhidrosis (often malodorus)
- Carpal tunnel syndrome and other entrapment syndromes
- Macroglossia: May result in sleep apnea
- Cerebral aneurysm and increased risk of cerebrovascular accident: Less common \[13\]

Early diagnosis of acromegaly, however, results in early transsphenoidal pituitary microsurgery, and currently, patients are more likely to be cured than in the past.

Reversal of excessive GH produces the following:

- Decreased soft tissue swelling
- Diminished sweating
- Restoration of normal glucose tolerance

No studies have established, however, that the treatment of acromegaly leads to a reduction in morbidity and mortality rates, although successful treatment, with normalization of IGF-I levels, may be associated with a return to normal life expectancy.

Remission depends on the initial size of the tumor, the patient’s GH level, and the skill of the neurosurgeon. Remission rates of 80-85% and 50-65% can be expected for microadenomas and macroadenomas, respectively.

The postoperative GH concentration may predict remission rates. According to the results of one study, a postoperative GH concentration of less than 3 ng/dL was associated with a 90% remission rate, which declined to 5% in patients with a postoperative GH concentration of greater than 5 ng/dL.

Metabolic and endocrine complications

Diabetes mellitus occurs in 10-20% of patients with acromegaly. A 2009 study suggests that in patients with acromegaly, insulin resistance and hyperinsulinemia are positively correlated with the level of disease activity.\[14\] Hypertriglyceridemia is found in 19-44% of patients. Multinodular goiter also is often present in acromegaly.

Hypopituitarism may develop in patients with acromegaly, as a result of the pituitary mass or as a complication of surgery or radiation therapy. Treat pituitary failure with appropriate hormone-replacement therapy.

Respiratory complications

In acromegaly, respiratory complications occur as follows:

- Increased lung capacity: 81% of men and 56% of women
- Small airway narrowing: 36% of patients
- Upper airway narrowing: 26% of patients
- Acute dyspnea and stridor
- Sleep apnea: As a significant cause of morbidity, sleep apnea may be both obstructive and central; curing acromegaly does not necessarily correct the disorder

Cardiovascular complications

A study by Berg et al found an increased prevalence of cardiovascular risk factors in patients with acromegaly compared with controls.\[1\] Cardiovascular complications include the following:

- Hypertension
- Acromegalic cardiomyopathy (with dysfunction and arrhythmias)
- Left ventricular hypertrophy
- Increased left ventricular mass

Disorders of calcium and bone metabolism

The following calcium and bone metabolism disorders can be found in acromegaly:

- Hypercalciuria
- Hypophosphatemia
- Urolithiasis

Neuromuscular complications

In acromegaly, these include the following:

http://emedicine.medscape.com/article/925446-overview
• Weakness (although with muscular appearance)
• Nerve root compression
• Radiculopathy
• Spinal stenosis
• Carpal tunnel syndrome

Cancer risks

Patients with acromegaly may be at increased risk for colorectal cancer and premalignant adenomatous polyps. Most studies suggest that as many as 30% of patients may have a premalignant colon polyp at diagnosis and that as many as 5% may have a colonic malignancy. In studies, polyps were generally multiple and proximal to the splenic flexure, making them less likely to be discovered during sigmoidoscopy. However, the long-term effect of colonic lesions on morbidity and mortality has not been established.

Patients with acromegaly may also have an increased risk of developing breast and prostate tumors, although no clear evidence supports this; the risk of thyroid cancer is increased in males. However, the prevalence of cancers in patients with acromegaly remains controversial, although patients might be advised to undergo screening colonoscopy and thyroid ultrasonography.

Mortality

For individuals with acromegaly, the mortality rate is 2-3 times that of the general population, with cardiovascular and respiratory complications being the most frequent causes of death. Transgenic mouse models of acromegaly demonstrate cardiac and vascular hypertrophy but normal function, raising the concern that hypertrophic cardiomyopathy may contribute to the increased mortality.

A study by Bates et al suggested that the extent of a patient’s GH excess impacts mortality. The investigators found that acromegaly patients with a GH concentration of greater than 10 ng/mL had double the expected mortality rate, whereas patients with a GH concentration of less than 5 ng/mL approached normal mortality. These results underscore the necessity to reduce GH and IGF-I concentration in patients with acromegaly.

Researchers disagree on whether malignancy is a significant cause of increased mortality in acromegaly. Although benign tumors (including uterine myomas, prostatic hypertrophy, and skin tags) are frequently encountered in acromegaly, documentation for overall prevalence of malignancies in patients with acromegaly remains controversial.

Patient Education

Refer patients to the Hormone Health Foundation for additional information.

For patient education information, the Thyroid & Metabolism Center, as well as, Acromegaly, Acromegaly FAQs, and Understanding Acromegaly Medications.

Clinical Presentation

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Disclosure: Nothing to disclose.

References


Once it has left the blood to migrate into tissue, a neutrophil has been generally believed to choose or to be forced to undergo three possible, eventually fatal, fates: necrosis, apoptosis, or NETosis [1]. The paper by Dyugovskaya et al. [2], in this issue of JLB, points to the existence of a possible fourth fate represented by the formation of long-lived giant neutrophils that grow in size by internalizing cell debris that has arisen from dying neutrophils. This form of gigantism is profoundly different from that characterized in cells of the monocyte/macrophage lineage. In fact, classical giant cells, such as Langerhans cells and other macrophage-derived giant cells, in tuberculosis and other infectious, or sterile granuloma or bone-resorbing osteoclasts arise via cell–cell fusion and the consequent formation of multinucleated heterokaryons [3]. Interestingly, in mixed neutrophil/monocyte cocultures, which Dyugovskaya et al. [2] examined to exclude that the “giant neutrophil” could actually be derived from monocytes internalizing neutrophil debris, formation of true giant neutrophils was reduced. This finding suggests that in conditions in which the monocyte/macrophage-mediated resolution phase of inflammation is reduced, neutrophils play a role of getting rid of cell debris. Alternatively, one could envision that in certain inflammatory environments, the permanence of this giant neutrophil, which is eventually able to discharge granule constituents and ROS, may contribute to long-lasting inflammation and tissue damage.

A provisional suggestion to favor the view of the giant neutrophil as a new scavenging cell involved in resolution of inflammation comes from the evidence that this cell contains several vacuoles coated with the autophagy protein LC3B. Dyugovskaya et al. [2] provide a direct link between formation of giant neutrophils and autophagy by showing that two specific autophagy inhibitors abolish giant neutrophil formation. Accumulating evidence points to an important role of autophagy in innate-immunity cell responses and development of inflammation [4]. Double-membrane autophagosomes can directly mediate sequestration of intracellular microorganisms, but autophagy proteins, including those of the LC3 group, act by enhancing the maturation of conventional membrane-derived phagosomes. In this scenario, it is not surprising that giant neutrophils contain several LC3B-coated vacuoles filled with cell debris derived.

Abbreviation: ROS—reactive oxygen species

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from apoptotic neutrophils. Yet, to be discovered are the mechanisms inducing a high expression of LC3B, which Dyugovskaya et al. [2] show to be weakly expressed by neutrophils. Importantly, genetic and functional studies identified autophagy as a mechanism of dampening of the inflammatory response, which occurs via inhibition of inflammasome activation and IL-1β secretion (see ref. [4] for review). Those findings encourage future studies to address the expression of other autophagy proteins and inflammasome activation in giant neutrophils—a goal that is hampered by the actual limit in obtaining a number of pure giant neutrophils suitable for biochemical assays. Scientists interested in neutrophil biology can now face a new aspect of this cell behavior that brings further evidence to emphasize its impressive plasticity.

REFERENCES

KEY WORDS: giant cell · apoptosis
Paper

Hereditary Gigantism – the biblical giant Goliath and his brothers

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Accepted 12 March 2014

ABSTRACT:
The biblical giant Goliath has an identifiable family tree suggestive of autosomal dominant inheritance. We suggest that he had a hereditary pituitary disorder possibly due to the AIP gene, causing early onset and familial acromegaly or gigantism. We comment on the evidence within the scriptures for his other relatives including a relative with six digits and speculate on possible causes of the six digits. Recognition of a hereditary pituitary disorder in the biblical Goliath and his family sheds additional information on his and other family members’ battles with David and his relatives.

INTRODUCTION
Giants have been around since time began; they are first described in the Bible in the book of Genesis (6:1-4)1. Originally, giants appear to have been regarded positively, often considered as heroes, particularly by the non-Hebrew population. After the great Flood, giants remained present in the scriptural texts, but their good reputation had waned in the eyes of the Hebrews, and they often tended to be seen as the enemy, often fighting in armies. Giants lived together as a number of separate races, before and after the Flood. The exact relations between different families of giants are a little unclear. For example, the Nephilim (Numbers 13:32-33), appear to be present before and after the Flood. The Emites, the Ammonites (or Anakites) and the Rephaim (Deuteronomy 2:10-11), existed after the Flood and appear to be separate entities although the chronicler often uses the phrase ‘like’ suggesting they had a similar phenotype. The Anakim seem to be derived from the Nephilim. The Rephaim although similar to the Nephilim, appear to be distinct from them with respect to family lineage. Deuteronomy 2.21 states the Rephaim were largely subdued by the Ammonites which ‘dwelt in their stead’ One of the most prominent Rephaim was Og, King of Bashan, who slept in ‘a bedstead of iron; nine cubits was the length, and four cubits the breadth of it’ (Deuteronomy 3:11). A cubit was the distance from the elbow to the fingertips. He appears to be one of the last survivors of the Rephaim. A race of giants implies a hereditary element and the origins of some names may indicate the genetic pathway involved. The Hebrew word anaq may mean necklace (Proverbs 1:9), or possibly goitre. This could suggest hyperthyroidism, possibly due to underlying pituitary gland, or other endocrine, dysfunction.

A FAMILIAL ASPECT TO GOLIATH’S GIGANTISM.
Goliath, the Gittite, is the most well known giant in the Bible. He is described as ‘a champion out of the camp of the Philistines, whose height was six cubits and a span’ (Samuel 17:4). From Samuel and Chronicles (table 1), we have drawn Goliath’s pedigree (figure 1). A literal interpretation of the verses suggests that his brother and three sons were also of giant stature. The name of Goliath’s third son does not appear in the Bible, so we have named him Exadactylus as it was said that ‘he had on every hand six fingers, and on every foot six toes’ (Samuel 21:20-21). Goliath’s family tree is suggestive...
Gigantism results when a growth hormone-secreting pituitary adenoma is present before epiphysial fusion. Pituitary adenomas can be present in a number of genetic conditions, such as multiple endocrine neoplasia type 1, Carney complex, and Familial Isolated Pituitary Adenoma (FIPA). FIPA is an autosomal dominant condition with incomplete penetrance, caused by germline mutations of the aryl hydrocarbon receptor interacting protein (AIP) gene. Patients with AIP mutations have an earlier mean age at diagnosis than AIP mutation-negative patients. The age of Goliath is not clear, but early onset of pituitary tumours is typical of hereditary gigantism and limitation of lateral vision is common. Goliath himself had a shield bearer precede him, possibly to indicate to Goliath the direction of the approaching foe.

Polydactyly has not been described in association with FIPA. The AIP gene lies on chromosome 11q13.3. The Bardet-Biedl gene, BBS1, is located close by on chromosome 11q13.2. Bardet-Biedl syndrome type 1 is characterized by rod-cone dystrophy, truncal obesity, cognitive impairment and postaxial polydactyly. The protein encoded by BBS1 is thought to play a role in limb development. It is unlikely that Goliath’s family had FIPA caused by a microdeletion which also involved BBS1, as the genetic distance between the BBS1 and AIP genes is separated by a 1 Mb gene-packed region. Such a gap makes an inherited contiguous gene syndrome unlikely as there would have been too many other features. Very rarely BBS1 patients have symmetric exadactyly; most commonly it is present in one or two extremities, upper and lower - not in all four. We are not given much other detail about Exadactylus so a new BBS1 mutation due to some complex rearrangement is unlikely – a new mutation in an autosomal dominant polydactyly gene might explain his symmetrical phenotype. If he had pituitary disease and six digits – he may have looked an intimidating foe - but he may not have been a great warrior in action.

Interestingly, the book of Samuel refers to five stones that David carefully selected for his sling from the nearby stream, and further reading of the surrounding passages shows that David’s relatives were all involved in the deaths of the other giants in Goliath’s family. There can be other interpretations for this and various types of symbolism, but it appears likely that several giants may have been from Goliath’s family, further suggesting autosomal dominant inheritance. The reverse also almost happened - Ishbibenob, Goliath’s son, is credited with almost killing David until the swift intervention of David’s nephew Abishai (2 Samuel 21.16), so clearly intellect or agility was not deficient in some of the giants, and myopathy seen in some cases of pituitary disease in later life, not a direct issue in the younger giants.

The giants from Gath were present after the Flood. One possible answer to the often raised question of why the Nephlim giants, present before the Flood were not eradicated by it, could be that new mutations in the AIP gene (or other genes) caused new families of giants to appear. There is no evidence in the Bible to suggest that the Nephlim, Rephaim or Anakim were directly related but they may have had some relations and intertwined lineage. If Goliath was the son of Rapha – he is likely to be descended from the Rephaim, but being brought up in Gath, an ancient stronghold of the Anakim, could suggest he may also have had some Anakim relatives, making his champion status even more significant in the ancient world.

Families of giants have been described in the medical literature, but this may be one of the oldest and most famous examples to be documented. Perusal of the archaeological literature of that period gives evidence of giants being excavated but numerous fakes exist. Technology now exists to extract DNA from giant skeletons, and if any new excavations in the Middle East unearth a skeleton suggestive of Goliath, or of Og or similar biblical giants, more proof may be obtained by careful DNA analysis and it may be possible
in the future to delineate the exact relations between different giant lineages in the bible, and dissect them further.

In conclusion, Goliath may have had an AIP mutation causing early onset autosomal dominant pituitary gigantism and one of his sons may have had a syndrome involving both AIP and BBS1, which could some way account for the physical characteristics of his family and their good success rate on the battle field until they met David.

Acknowledgements.

We thank the reviewers for their helpful comments, particularly the theological reviewer who carefully checked our statements on the Biblical giants for accuracy and who provided very helpful comments including original Hebrew text, which has helped us clarify the scriptural texts for UMJ readers.

The authors have no conflict of interest.

REFERENCES

Pituitary
Gigantism

Dan Chandler, Matt Packard & Spencer P.S.
The Pituitary Gland

- Endocrine glands – specialized secretory tissue that effect growth, development, metabolism, etc.
- All endocrine glands under hormonal control of the pituitary – the “master” gland
The Pituitary Gland

- Ventral to the hypothalamus in the brain
- Separated into two lobes – anterior and posterior
- Posterior is extension of the hypothalamus of the brain, anterior is true glandular tissue
Growth Hormone Releasing Hormone

- Pituitary regulates endocrine function by secreting hormones from neurons into vasculature
- Anterior neurons synapse on capillaries that target endocrine cells in the gland itself
- Posterior neurons synapse on capillaries that carry hormone to much more distant targets
- GHRH stimulates release of growth hormone from anterior pituitary
Growth Hormone

- Growth hormone required for proper growth and development
- Directly effects fat metabolism
- Indirectly effects bone growth
- Pituitary gigantism caused by excess secretion of GH prior to closure of epiphyseal growth plates in long bone – must occur before onset of puberty
- Excess secretion after puberty causes acromegaly
Hypersecretion of GH

- Gigantism caused by excess circulating levels of GH
- Commonly caused by pituitary tumors that secrete a mutant protein that eliminates need for GHRH
- Tumors block gonadotropin release – responsible for sexual development – may cause amenorrhea in women and impotence in men
Epiphyseal Growth Plates

- Area in long bones responsible for creating new bone during growth
- Multiple layers in the plates responsible for bone growth
- Open only before puberty, excess GH after causes thickening of bone
Growth Plates and Chondrocytes

- Before onset of puberty, cells in first layer of growth plate differentiate to chondrocytes – cartilage producing cells.
- Second layer of plate composed of chondrocytes, responsive to GH – stimulates mitosis.
- After chondrocytes mature, deposit calcium into bone matrix to help form new bone.
Effects of Growth Hormone

- calcium deposited into bone matrix, osteoblasts (bone building cells) use calcium to form new tissue in long bone
- excess calcium converted into connective tissue, bones elongate
- GH activates insulin-like growth factor (IGF1) – causes growth of muscle to keep up with bone growth
A 12 year old boy, 6’5”, with his mother, and his hand (left) in comparison with that of a grown man, 6’1”

All long bones in the body effected before closure of epiphyseal growth plates
Some General Facts

- About 3 people in 1 million have pituitary gigantism
- 100 cases to date in United States
- 2 – 3 times higher mortality rate in comparison to general population
- No racial predilection
- Males and females affected equally
- Not a genetic disorder
Medical Side Effects

- Life span is generally reduced significantly due to medical complications, ex. heart failure, respiratory problems and skeletal/muscular problems
- Tall stature, enlarged hands/feet, coarse facial features, excessive sweating, osteoarthritis, carpal tunnel syndrome, cardiovascular diseases, benign tumor growth, diabetes, varying levels of obesity and sleep apnea, deepening of voice
- Tumor in pituitary can cause chronic headache and visual impairment due to proximity of gland to optic chiasm
Testing and Diagnosis

- Not a heritable genetic disorder, no prenatal testing
- Initially growth is not necessarily exaggerated; with time becomes much more apparent
- Blood work possible to test circulating levels of GH and IGF1
- Computed tomography and magnetic resonance imaging available to look for pituitary tumors
Treatment

- Disorder is developmental in nature; treatment difficult because GH continually surges from pituitary, increasing body size
- Pituitary tumor (adenoma) can be removed with surgery depending on its size to stop release of GH
- Drugs: octreotide, bromocriptine block GH effects
- Radiation can be used to treat tumor
Living with Gigantism

- Gigantism and acromegaly generally have outward negative effects that can be treated medically, i.e. sleep disturbances, joint pain, cardiovascular issues, etc.
- Surgery is oftentimes ineffective due to complex nature of endocrine system, very stressful – gigantism very traumatic emotionally
- Causes general tiredness, muscular weakness, impotence
- Generally, life with gigantism becomes more difficult, however, several famous cases exist to demonstrate possibility of more positive, happier life
Robert Pershing Wadlow

- Robert Wadlow – “The Alton Giant”
- Tallest man ever at 8’11”, suffered from the disorder
- Born normal weight and size but 30lbs at 6 months of age
The Alton Giant

- No treatment in 1920’s for overactive pituitary
- Maintained normal lifestyle, participated as a boy scout, collected stamps and enjoyed photography
- Shoes cost $100 (specially made)
- Worked for international shoe company as an attraction, went on nationwide tour in U.S. in exchange for free shoes for life

<table>
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<td>6' 5&quot;</td>
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<td>30 1</td>
<td>374</td>
<td>39 1</td>
<td>48 8</td>
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The Alton Giant

- Died at 22 during tour due to severe infections on feet due to blisters – very little sensation in feet
- 1985 – bronze statue dedicated to his memory at University of Southern Illinois School of Dentistry
- After death, family destroyed personal belongings so they wouldn’t be exploited as freak show memorabilia
Andre The Giant

- 7’4”, 500lbs
- Wrestled in WWF and many other leagues, won multiple titles including heavy weight and tag team belts
- Offered position on Redskins, turned it down to wrestle
- Had a role in *The Princess Bride* as a giant
- Disabled later in life due to joint pains and cardiovascular complications
Andre the Giant

- Broke ankle stepping out of bed, confined to wheelchair when not in front of camera
- Died in 1993 by congestive heart failure in his sleep
- Autopsy showed his heart was abnormally large – size of two fists
Matthew McGrory

- Holds Guinness Book of World Records title for largest feet on living man – size 29 ½
- 15lbs at birth
- 7’6” tall, 330lbs
- Also worked for Dr. Scholl’s on promotional tours, appeared occasionally on Howard Stern Show under alias “Bigfoot”
- Educated as lawyer, became actor
Matthew McGrory

- Had roles in *Big Fish*, *House of 1000 Corpses*, *The Devil’s Rejects*, *Bubble Boy*, *Men in Black II*, and *Constantine*
- Working on tribute film to Andre the Giant, died due to heart failure during filming this past August
- Described desire to “walk down the street and not have people stare”
Giants as Freaks?

- Very obvious strange outward appearance – much larger and more pronounced features than normal people
- Can be considered more exotic or wonders than monsters – not looked down upon (literally) or outcast by society
- Oftentimes project selves as “freaks” for personal benefit
- Can still be productive in society and lead happy lives
References

- http://www.merck.com/mrkshared/mmanual/section2/chapter7/7b.jsp
- http://www.abcbodybuilding.com/magazine03/glands.jpg
- http://www.rickrichards.com/chakras/Chakras1c.html
- http://www.endotext.org/pediatrics/pediatrics1b/pediatrics1b.htm
- http://endocrine-disorders.health-cares.net/gigantism.php
- http://buffaloneuro.com/pittumo/ENDOPI.HTM
- http://www.dental.mu.edu/oralpath/lesions/Gigantism/gigantism.htm
- http://www.altonweb.com/history/wadlow/
- http://www.cladonia.co.uk/acromegaly/images_large/postcard-01.jpg
- http://www.cladonia.co.uk/acromegaly/images_large/chalk-1857-01.jpg
Surgical Treatment Of Segmental Giantism Of The Foot
Edward T. Haslam, M.D.

My purpose in this article is to present an example of the operative technique we have found useful in a few patients with giantism or congenital hypertrophy limited to one or more rays of the foot, not associated with demonstrable neurofibromatosis, arteriovenous fistulae, or hemangiomatosis. In these patients the remainder of the extremity has been essentially normal, the reason for treatment being that the foot could not be fitted with a shoe. The case described here is merely an example, since none of the several patients whom I have seen with these conditions have had identical deformities.

The patient (G.C.) was admitted to Charity Hospital in New Orleans on April 3, 1964, at 22 months of age with the complaint of enlargement of the right foot, which prevented satisfactory shoe fitting. He had been delivered at home after an uncomplicated pregnancy with no history of maternal illness or ingestion of any medications, and was normal at birth except for enlargement of the third, fourth, and fifth toes and a moderate deformity of the second toe of the right foot. Three siblings were normal, and as far as was known, no other members of the family had experienced similar deformities. The patient had been healthy since birth, had walked at nine months of age, and otherwise exhibited normal development.

Physical examination revealed only that the right foot was grossly larger than the left, due partially to hypertrophy of the third, fourth, and fifth toes and partially to hypertrophy of the subcutaneous tissue corresponding to these three rays. These toes were functionless (Fig. 1), since the thickened plantar fat pad prevented them from coming into contact with the ground, and the second toe was functionless because of its extended position.

X-rays of the right foot (Fig. 2) confirmed the hypertrophy and deformity evident on examination. X-rays of the left foot (Fig. 3) revealed that it was normal.

Figure 1. Patient’s feet at initial examination, with right foot grossly larger than the left.
Procedure

On April 8, 1964, under general anesthesia and with the use of a pneumatic tourniquet, the third, fourth, and fifth toes were amputated, and the third metatarsal and excess skin and fat were removed. Outline for the tentative incisions were marked with methylene blue (Fig. 4 and 5). Additional plantar skin was removed just proximal to the second toe to correct the dorsiflexion deformity exhibited. Fig. 6 shows, the appearance of the foot after ablation of the lateral three toes and the third metatarsal shaft with appropriate defatting, A capsulotomy at the bases of the second and fourth metatarsals was carried out to allow partial obliteration of the dead space resulting from disarticulation and removal of the third metatarsal. The transverse intermetatarsal ligament was sutured with chromic catgut, the
subcutaneous fascia was similarly closed, and the skin was closed with interrupted sutures of No.0000 silk (Fig. 7 and Fig. 8).

Figures 4 and 5. Outline for tentative incision marked in methylene blue prior to amputation.

Figure 6. Appearance of foot after ablation of three lateral toes and the third metatarsal shaft with appropriate defatting.
Figures 7. Postoperative views of foot.
In keeping with our usual practice, we planned our operative incision to allow generous skin coverage and then removed any skin found to be superfluous. In defatting the sole of the foot, attention was given to preservation of blood supply. As visible arteries and veins were encountered, they were ligated and tied, and the circulation returned promptly to the first and second toes after the tourniquet was removed. No drains were used, and a posterior plaster splint was applied over a pressure dressing.

The patient's postoperative course was uneventful, and the sutures were removed on the 18th day following the operation. A small-sized area of the skin slough was present just lateral to the second toe, but this healed within four weeks postoperatively. X-rays taken five weeks postoperatively revealed that the condition of the foot was satisfactory (Fig. 9). The patient was fitted with mismated surgical shoes because of the swelling, and weight bearing was resumed.
He has been seen periodically from time to time, and when last seen in February 1966 had no complaints, was doing well, and was wearing mismated regular shoes. Unfortunately we have not been able to obtain current photographs of this patient. His gait is normal.

**Discussion**

Satisfactory management of this condition involves an analysis of each individual case and modification of some basic principles of foot surgery. This applies particularly to the longitudinal plantar incision, which is necessary if an adequate amount of fat is to be removed and the width of the foot reduced to approximately the same size as the other. It is often impossible to match the foot sizes exactly, but this should be the surgeon's goal. The removal of the three lateral toes in this case did not impair function, since the toes were functionless anyway. Postoperatively the second toe was in a position to touch the floor and function, whereas preoperatively it was not. Therefore, although the surgery was ablative and destructive in one sense, it was really reconstructive in another.

This patient was operated on at 22 months of age, which was when we first encountered him. However, such surgery, in the absence of contraindications, would probably be better done at about the time that the child is establishing gait, when he is too young to be the object of his playmates' ridicule.

In addition to the case described, our experience has included a similar one involving the second, third, and fourth rays. This patient was treated by amputation of these toes and resection of the third metatarsal. A third patient had gross hypertrophy of the second ray and less marked hypertrophy of the third ray.

We are planning to review these cases after they have achieved skeletal maturity and hope to submit a more detailed report at that time. To date we have not found it necessary to do epiphyseal arrests to control leg length discrepancy in such patients, but the possibility should be kept in mind.

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Source: Journal of the Association of Children's Prosthetic-Orthotic Clinics 1966; Vol 5, Num 9, p 1
The asymmetric limb (gigantism): diagnostic approach
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Andrea Gallo H.1
Gabriel Daza C.2
MÃ­nica Tafur A.2
Oscar Rivero2
Gustavo Triana2

Summary:
Diseases that present with asymmetric development of one of the extremities are unusual entities and are considered a diagnostic challenge for radiologists. Within these group of entities, we could find Proteus syndrome, Maffucci syndrome, Klippel-Trenaunay-Weber syndrome and lipomatous macrodystrophy. It is important to recognize radiological findings of the diseases that are characterized by gigantism in order to achieve an accurate diagnosis.

Key Words (MeSH)
Gigantism
Extremity
Proteus
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Introduction
There are diseases that cause overgrowth of an extremity or extremities, or parts of it, with the consequent asymmetry in the size of the extremities, and that do not constitute congenital malformations, but abnormalities that are developed during lifetime. Frequently we face the challenge of evaluating studies of patients with clear limb asymmetry, with excessive growth in some of their extremities, global or focal, associated with or without alteration in the morphology of soft tissues. Differential diagnosis is not broad, clinical history, physical examination and evaluation of comparative images are essential elements, in most cases it is possible to reach an adequate diagnosis.

Maffucci Syndrome
Maffucci syndrome is an unusual condition, not inherited (1). It is a congenital mesodermal dysplasia (2), characterized by multiple enchondroma associated with cavernous hemangiomas, lymphangiomas are less often found in the soft tissues (3,4).
Enchondromas are benign cartilaginous tumors that can occur in any bone but most commonly occur in phalanges and long bones (2). In 25% of cases, symptoms appear during childhood or during the first year of life, in 45% the beginning of symptoms occur before the age of 6 years, and in 78% before puberty (1). The bone and vascular lesions in the extremities are usually asymmetrical in distribution, with a unilateral compromise in 50% of patients. Hemangiomas are located in the subcutaneous tissue and are seen as bluish nodules, although there may also be visceral and mucous involvement. Bony lesions have a predilection for the tubular bones, with greater compromise in metacarpals and phalanges of hands. Enchondromas can also be found in the bones of the foot, tibia, fibula, radius and ulna. They might present with painless swelling or pathological fractures in 26% of cases (2,3). The prevalence of malignancy in the literature varies from 23% to 100%, where chondrosarcoma is the most common tumor, with an incidence of 51% in patients with Maffucci syndrome (5). Other malignancies (1) as fibrosarcoma, hemangioendothelioma, hemangiosarcoma or lymphangiosarcoma could be found. Maffucci syndrome is also associated with tumors in other organs such as CNS, gastrointestinal tract, pancreas and ovary (3,4). Radiographically, the abnormalities are more evident in the hands and feet (2), and appear as radiolucent lesions with well defined borders, with expansive remodeling of bone, cortical thinning and endosteal scalloping. In some cases it can be seen chondroid matrix mineralization in arcs and rings. These changes cause bone deformity. In the soft tissues are evident phleboliths and “popcorn” calcifications (1,3,6) (Figures. 1a, 1b). Magnetic resonance imaging (MRI) is useful for diagnosis and location of deep hemangiomas (2,5,7). Maffucci syndrome treatment is largely symptomatic and patients should be followed periodically to detect malignant transformation. In some cases surgical management is indicated to correct the bone and soft tissue deformities especially if there is
functional impairment of the extremity or for cosmetic reasons (1.8).

Klippel-Trenaunay-Weber syndrome

Described by Klippel and Trenaunay in 1900, it is considered a rare entity characterized by combined capillary, vein and lymphatic malformations, and congenital hypertrophy of a lower extremity (9). It occurs in 1 in 20000-40000 live births, and there are no gender differences (10-13).

Parkes-Weber syndrome, which consists of varicose vein dilatation and multiple congenital arteriovenous fistulas with secondary outgrowth of the limb that occurs until epiphyseal closure is a similar condition. Klippel-Trenaunay-Weber syndrome etiology is unclear. There are three origin theories. Staple and Bliznak propose damage to the sympathetic ganglion or the lateral intermediate tract dilatation leading to microscopic arteriovenous anastomoses, resulting in venous abnormalities (15). Servelle suggests that blockage of the venous flow secondary to deep venous abnormalities causes, venous hypertension and varicose dilatations. Baskerville suggests that due to a mesodermal defect abnormal vascular communications occur (9,10,16).

Venous malformations or varicose dilations occur in 72% of cases, and often the abnormal venous flow is caused by persistent embryonic veins, agenesis, hypoplasia, valvular incompetence, or aneurysms of deep veins, and they occur in the superficial, deep and perforator venous systems (2.17 to 19). These vascular malformations are slow flowing, because there are no arterial compromise, associated lymphatic compromise, turns the skin blue or purple (Figures. 2a, 2b) (13,20,21). Hypertrophy of the extremity is due to the vascular malformations described and the increased volume of the soft tissues and bone, usually in an asymmetric configuration, it occurs in 95% of the cases.

Proteus Syndrome

It was described by Cohen and Hayden in the year of 1979. The name comes from
the Greek God Proteus who had the ability to change shape, and was proposed by Wiedemann in 1983 (3335). It is an entity of unknown cause, although it is believed that is caused by a somatic gene mutation, which has not been identified. It is a rare hamartomatous condition, characterized by a broad spectrum of malformations. Focal overgrowth of tissues derived from all three germ layers is found, it is a multisystemic disease with a great clinical diversity (3638).

In general, it is not apparent at birth, it develops in childhood and early adolescence after this time disease stabilizes. It has general and specific clinical diagnostic criteria.

**General Clinical criterion:**
- Random distribution in the body
- Progressive course of lesions
- Sporadic Occurrence.

**Specific clinical criterion:**
- **Category A:** Cerebriform connective tissue nevus (pathognomonic but uncommon) (35.39).
- **Category B:** Linear squamous cell nevus, disproportionate, asymmetric overgrowth (compromise of one or more limbs, skull and vertebrae) (Figure. 3a), specific tumors (bilateral ovarian cystadenoma and monomorphic adenoma before or during the second decade), hemimegalencephaly, splenomegaly and fatty infiltration of the parotid gland, usually, in the right side, rarely occur. Increased subcutaneous fat and muscle pseudohypertrophy on the affected side of face is observed (35.39).
- **Category C:** Adipose tissue compromise: Lipoma or regional absence of fat, vascular malformations, lung cysts and facial phenotype (may not be present: dolichocephaly, long face, mild ptosis, low nasal bridge, wide or inverted nostrils, mouth open at rest) (35.39).

Diagnosis is made if one of the signs of A category two of the B category or 3 three in the C category is present. (35.39). In plain films osteoporosis or hyperostosis is evident; macrodactyly (Figures. 3b, 3c) clinodactyly, polydactyly and syndactyly are occasionally found. In addition, malformed vertebral bodies and asymmetric cranial vault...
thickening can be observed (35). Computed tomography (CT) and MRI shows diffuse asymmetric hypertrophy of soft tissues, muscle and adipose tissue (Figures. 3d3f), sometimes associated with lymphatic, capillary and venous malformations, (35). Visceral compromise is less common than musculoskeletal and soft tissue abnormalities, splenomegaly, asymmetric megalencephaly white matter abnormalities and nephromegalia could occur. Cases of pulmonary embolism and pulmonary cystic changes has been described (34, 40, 41).

6 Lipomatous Macrodistrophy
This rare disease is characterized by overgrowth of all mesenchymal elements surrounding the toes or fingers, associated or not to macrodactyly (42-44). It is a nonhereditary disease that can manifest in two ways: The first way of presentation is detectable from birth (static form), asymmetry of the fingers of the affected limb, which grows synchronously with the rest of the body is evident (43). The second way of presentation (progressive form) is detected in older age patients disproportionate and progressive growth of the affected part is found (45). Generally growth stops at puberty, the lateral aspect of the upper extremity is usually affected (finding described by Golding in 1960) and the medial aspect of the lower extremity (finding described by Feriz 1925) (43, 46). It equally affects both genders unilaterally, lower limb compromise is predominant; second and third toes are more often involved (46). The etiology of this disease is unknown, it is suspected that alterations may be linked to changes in uteru with growth factor or fetal circulation changes. Another theory relates to lipomatous degeneration (46, 47). Histology shows proliferation of a fibrous network and fat that normally surrounds the bones, tendons, muscles and nerves, especially in the palmar or plantar aspect of the affected limb, resulting in extra deposit of bone material in the fingers, at the endosteum and periostium with subsequent overgrowth, this results in aesthetic deformity and
functional impairment. (47,48). Median and planter nerve compromise produce compression neuropathy. Plain radiography demonstrates focal macrodactyly secondary to increase in thickness and length of the metacarpals or metatarsals and their phalanges, as well as thickening of the soft tissues that surround them (Figures.4a, 4b) (44). It is common to find degenerative changes in juxta articular regions, probably by an alteration of the normal biomechanics of the limb, which leads to formation of osteophytes, subchondral cysts, joint space narrowing and subluxation, predominantly compromising the ulnar aspect of (hands) or the lateral aspect of foot) (Figures. 4c, 4d). Soft tissues show normal fat tissue lucency (46,47). CT shows negative attenuation coefficients in tissues surrounding bony structures (44.49). Due to increased fibrofatty tissue on fat saturation sequences, MRI could confirm the lipid nature of the tissue surrounding the affected fingers, and at the same time, could evaluate the bone marrow infiltration of the phalanges, which shows high signal intensity in sequences with T1 and T2 information, and decreased signal intensity on STIR (short time inversion recovery) or FATSAT (fat saturation) sequences. Fibrous tissue has low signal intensity on all sequences (Figures.4e, 4f) (43.50).

Conclusion

Conditions that produce asymmetry in the growth of the extremities are rare entities associated with a variety of clinical and imaging findings, which allow differentiation between them. It is therefore important to recognize particular imaging findings of these group of diseases that are characterized by gigantism, to achieve an accurate diagnosis.

References

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3. Zwenneke Flach H, Ginai AZ, Wolter Oosterhuis J. Best cases from the AFIP.


49. Aisen AM, Martel W, Braunstein EM, McMillin KI, Phillips WA, Kling TF. MRI and
CT evaluation of primary bone and soft tissue tumors. AJR. 1986;146(4):74956.
50. Cohen JM, Weinreb JC, Redman HC. Arteriovenous malformations of the extremities:
Figures
Figs. 1a, 1b. Maffucci syndrome. Radiographs of upper limbs in two patients.
Maffucci syndrome, popcorn vascular calcifications are evident in the soft tissues.
Enchondroma in the fourth and fifth finger in the first patient.
Figs. 2a, 2b. Klippel-Trenaunay-Weber syndrome.
Clinical photographs of two patients, the lower limb edema, venous congestion and echymotic vascular markings on the skin.
Figs. 2c, 2d. Klippel-Trenaunay-Weber syndrome.
Radiography of the foot and right leg
Venography of a different patient, there is asymmetric enlargement of the first finger and absence of the deep venous system, with a large draining superficial vein.
Figs. 2e, 2f, 2g. Klippel-Trenaunay-Weber syndrome.
Venography, coronal and axial
MR images of a patient with multiple serpintiginos tubular images corresponding to superficial venous dilatations.
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Fig. 3a. Proteus Syndrome. Clinical photograph of a patient with Proteus syndrome, which shows exaggerated increase in size of the second finger of right hand.
Figs. 3b, 3c. Radiographs of hands and feet of another patient who presented macrodactyly of the third finger and third toe of the right foot. Figures. 3d, 3e, 3f. Coronal gradient echo
MR images, DP and 3D reconstruction in a patient with amputation of the fourth finger, macrodactyly and subluxation of the distal interphalangeal joint of the third finger, with ulceration of the dorsal region and a fluid collection due to repetitive trauma in that location.
Fig. 4a.
Lipomatous Macrodistrophi . Radiographs of patient with macrodactyly, asymmetrical third and fourth fingers of the feet with prominence of the soft tissues.
Fig. 4b. Lipomatous macrodystrophy detected from birth affecting the first finger.
Figs. 4 (cd). Same patient. Significant degenerative changes in the distal interphalangeal
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and third
fingers. (E) T1 MR images (same patient), shows signal intensity similar to
subcutaneous
fat in the tissues surrounding macrodactyly of the fourth and fifth toes. signal
intensity of
the bony structures is slightly lower than in normal bone.
Fig. 4f. fat saturation sequence in the same patient, homogeneous decrease of
signal
intensity of bone marrow and soft tissues confirming its fatty nature.
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Received for evaluation: September 12th, 2009
Accepted for publication: November 18th, 2009
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Figs. 1a, 1b. Síndrome de Maffucci. Radiografías de miembros superiores en dos pacientes con síndrome de Maffucci, donde son evidentes las calcificaciones vasculares en forma de palomitas de maíz en los tejidos blandos. Encondromas en los dedos cuarto y quinto en el primer paciente.
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Figs. 2e, 2f, 2g. Síndrome de Klippel-Trenaunay-Weber. Veneografía e imágenes de RM en los planos coronal y axial, de un paciente con múltiples imágenes tubulares serpiginosas que corresponden a dilataciones venosas superficiales.

Fig. 3a. Síndrome de Proteus. Fotografía clínica de un paciente con síndrome de Proteus, que demuestra incremento exagerado en el tamaño del segundo dedo de la mano derecha.

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Fig. 4a. Macrodistrofia lipomatosa. Radiografías de paciente con macrodistrofia lipomatosa, donde se evidencia macrodactilia asimétrica de los dedos tercero y cuarto de los pies, con prominencia de los soles blando.

Fig. 4b. Macrodistrofia lipomatosa que afecta el primer dedo, lo cual es perceptible desde el nacimiento.
Figs. 4(c-d). El mismo paciente. Importante cambio de tipo degenerativo en las articulaciones interfalángicas distales: la fusión de los dedos cuarto y quinto, y la ausencia de falanges en los dedos segundo y tercero. (e) Resonancia magnética en secuencia T1 (del mismo paciente), que muestra intensidad de señal similar a la de la grasa subcutánea, en los tejidos que rodean la macrodacilita de los dedos cuarto y quinto. Obsérvese que la intensidad de señal de las estructuras óseas es discretamente menor a la de las muces normales.
Fig. 4f. Secuencia con saturación grasa en el mismo paciente, donde es posible evidenciar la disminución homogénea de la intensidad de señal de la medula ósea y de los tejidos blandos, lo cual confirma su naturaleza grasa.