Gigantism

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ABSTRACT

Gigantism is a non-specific term that denotes excessive growth in a pediatric patient. This may rarely result from an over production of growth hormone (GH), which is often termed *pituitary gigantism*, or it may arise from an overgrowth syndrome. Pituitary gigantism can present as early as during infancy or not until adolescence and may be congenital or acquired. Likewise, it may occur as a sporadic condition or in the context of a well described syndrome in which hypersecretion of GH is a potential feature. Conditions in which GH excess occurs include Neurofibromatosis Type 1, McCune-Albright syndrome, Multiple Endocrine Neoplasia Type 1, Carney Complex, Isolated Familial Somatotropinomas and X-Linked Acrogigantism. Therapeutic modalities for the treatment of pituitary gigantism are the same as those for acromegaly and include surgery, medication and radiation. The second major category of gigantism is that which is due to the presence of an overgrowth syndrome. Some of the most notorious overgrowth syndromes are Sotos syndrome, Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome and Weaver syndrome. Great strides have been made in identification of the molecular genetic basis for both pituitary gigantism and overgrowth syndromes, affording novel insights into the mechanisms underlying normal and abnormal growth. Etiologies, phenotypic features, and diagnostic and treatment considerations pertaining to the most common forms of gigantism are reviewed. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

Gigantism refers to a condition characterized by extreme physical size and stature. By definition, this originates during infancy, childhood or adolescence, while epiphyseal growth plates remain open. Although often used to specifically denote growth hormone excess, the term gigantism is also applied to a number of non-hormonally mediated overgrowth conditions in children (1). All forms of gigantism are extremely rare and have in common a complex pathophysiologic origin and extraordinary clinical manifestations. Although many aspects of overgrowth disorders remain to be elucidated, insights into the molecular genetic basis of several forms of gigantism have contributed greatly to our understanding of specific mediators of growth and cellular function.

GROWTH HORMONE EXCESS

The association between gigantism and growth hormone (GH) excess was recognized as early as the 1800's, when it was noted that pituitary giants invariably developed features of acromegaly, which refers to progressive enlargement of the head, face, hands and feet (2). The major difference between these two conditions is that gigantism results from excessive GH production during the period of active growth and acromegaly results from GH excess ensuing after epiphyseal fusion has occurred. A further distinction relates to the overall incidence of these disorders. While acromegaly is

uncommon, occurring at an estimated worldwide annual rate of 2.8-4 cases per million (3), GH excess during childhood and adolescence is extremely rare, with an estimated incidence of 8 per million person-years and the total number of reported cases thus far numbering only in the hundreds. Despite these disparities, some degree of clinical overlap has been suggested by the observation that 10% of acromegalics have tall stature(4), indicating that the onset of GH excess pre-dates epiphyseal fusion in many patients. GH hypersecretion may occur sporadically or may exist within a constellation of abnormalities in the setting of several well-recognized syndromes. Conversely, a genetic predilection to only the development of GH-secreting pituitary adenomas may be present, as is the case in kindreds with isolated familial somatotropinomas. In recent years there has been increased recognition of the underlying molecular genetic abnormalities that lead to pituitary gigantism, one of which can be identified in approximately 50% of cases (5).Regardless of the underlying etiology, the clinical manifestations of GH hypersecretion in childhood are indistinguishable and the initial diagnostic evaluation is standardized. The various categories and sources of GH excess along with their associated genetic abnormalities, if known, are summarized in Table I and will be discussed individually.

Table 1: Etiologies of Growth Hormone Excess

Sporadic		**Syndromic/Familial**	
Disorder	**Source of GH**	**Disorder**	**Source or Genetic Mutation**
Hypothalamic/Pituitary GH excess	Congenital GHRH excess (postulated)	Neurofibromatosis-1	Tumor infiltration into somatostatinergic
	Pituitary somatotroph or mammosomatotroph adenoma	McCune-Albright syndrome	Activating mutation of Gsα
	Pituitary hyperplasia	Multiple endocrine neoplasia Type-1 and Multiple endocrine	Defect in tumor suppression from mutations in menin and CDKN1 genes
	Hypothalamic gangliocytoma/neurocytoma	Carney complex	• Abnormality at 2p16 • Mutations in PRKAR1A at 17q22-24
		3PA association	Succinate dehydrogenase defects

Ectopic GH excess	• GHRH or GH production by bronchial, carcinoid or pancreatic neoplasm Ectopic pituitary adenoma	• Familial somatotrophinomas • X-LAG syndrome	• Mutation in acyl hydrocarbon receptor geneat 11q13.3 • Abnormality at 2p12-6 • Xq26.3 • duplications
GH-growth hormone, GHRH-growth hormone-releasing hormone, PRKARIA-protein kinase A regulatory subunit 1			

SPORADIC FORMS OF GROWTH HORMONE EXCESS

Sporadic GH excess may arise from CNS pathology or, rarely, from ectopic GH production. Traditionally, the term “primary growth hormone excess” has been used to differentiate an intrinsic pituitary source of GH from other causes, including hypothalamic abnormalities. In actuality, it may be difficult to clearly distinguish the role of the pituitary from the hypothalamus, particularly in cases of early childhood GH excess, as discussed below.

Hypothalamic-Pituitary Growth Hormone Excess

Unlike in acromegalic adults, in whom discreet pituitary adenomas are present in the overwhelming majority of patients (6), a number of different histopathologic mechanisms underlying childhood GH hypersecretion have been suggested or observed. These relate to the concept that childhood GH excess represents a distinct entity, with different characteristics in terms of pituitary morphology and function. Supporting this view have been reports of diffuse pituitary hyperplasia in the setting of early-onset gigantism, in which congenital growth hormone releasing-hormone (GHRH) excess has been proposed as the inciting cause (7;8). Additionally, the nearly ubiquitous finding of combined GH and prolactin over-secretion in nearly all cases of early childhood gigantism, a feature not universally present in acromegaly, suggests that a separate pathologic process may be involved. This dual hormonal secretion has been attributed to the presence of mammosomatotrophs (9;10), which are rare in adulthood but predominate in fetal life. Even in cases of apparent pituitary microadenomas or macroadenomas arising during early childhood, this unique biochemical feature has been present (11;12). In contrast, prolactin levels are usually normal in cases of pituitary GH-secreting adenomas originating during adolescence, which may be thought of as existing within the spectrum of adult GH hypersecretion. Interestingly, a reversible transformation of pituitary somatotrophs into bihormonal mammosomatotrophs under the influence of ectopic overproduction of GHRH has been observed, lending additional support to the concept that hypothalamic GHRH excess may play a pivotal role in the genesis of early-onset gigantism (13). Although the etiology of sporadic gigantism is often unknown, a number of germline and somatic mutations in genes associated with syndromic and familial GH hypersecretion have been reported in children and adolescents with pituitary gigantism (13;14).

An additional cause of sporadic GH excess linked to CNS pathology is that which occurs in the setting of a hypothalamic gangliocytoma or neurocytoma. These rare tumors, comprised of large hypothalamic-like ganglion cells, have been demonstrated to produce GHRH (15;16) and to be found in close proximity to pituitary growth hormone-secreting adenomas (17). Normalization of serum growth hormone levels following resection of the hypothalamic tumor in some patients has

further supported a central role for abnormal GHRH secretion in the development of gigantism or acromegaly in these cases (18).

Ectopic Growth Hormone Excess

Ectopic GH hypersecretion is a rare but important cause of acromegaly in adults, thought to represent less than 1% of all cases (19;20). In this condition, a paraneoplastic elaboration of GHRH or uncommonly GH (21) occurs, with neuroendocrine tumors being the most common source (22). Specific lesions notorious for this capability include bronchial carcinoid and pancreatic neoplasms (23;24). Extra pituitary GH excess has also been reported in the setting of an ectopic pituitary adenoma located within the sphenoid sinus or clivus (25;26), and in association with an empty sella (27). To our knowledge, an ectopic source of GHRH or GH leading to gigantism in a child has never been described.

SYNDROMIC AND FAMILIAL FORMS OF GROWTH HORMONE EXCESS

A second major category of childhood GH hypersecretion is that which occurs in the setting of a well-recognized syndrome. In these cases, gigantism may be the sole presenting feature of the syndrome or it may be detected during on-going clinical follow-up for other endocrine or non-endocrine problems. Alternatively, biochemical evidence of sub-clinical GH excess may be revealed through routine surveillance in a child known to be at risk for the development of gigantism. As is the case in sporadic GH hypersecretion, a variety of different morphologic abnormalities involving the pituitary gland may be found. Paracrine pituitary GHRH secretion has also been implicated by the discovery of GHRH expression from clusters of cells in the hyperplastic pituitaries of two boys from a family with hereditary early-onset gigantism (28). Syndromes that are associated with the development of childhood GH excess are reviewed below. Table 2 outlines the characteristics of the GH excess and other clinical features in these disorders.

Table 2: Clinical Characteristics in Syndromes Associated with Growth Hormone Excess

Disorder	Mode of Inheritance	Clinical Features	Frequenc of Gigantism	Age of Onset of gigantism	Pituitary Morphology	Screening recommendations
Neurofibromatosis -1	Autosomal Dominant or Sporadic	• Optic gliomas • Café au lait skin pigmentation	Extremely rare	6 months on	Optic pathway tumor with normal to small pituitary	Not routine
McCune-Albright Syndrome	Sporadic	• Precocious Puberty • Café au lait skin pigmentation • Fibrous bone dysplasia • Multiple endocrinopathies	15-20%	Early childhood on	Pituitary adenomas or diffuse pituitary hyperplasia or no visible abnormality	Annually

Multiple Endocrine Neoplasia Type 1	Autosomal Dominant or Sporadic	Pituitary, pancreatic and parathyroid adenomas	10-60%	10% by age 40 but has occurred as early as age 5	Pituitary adenoma	Annually beginning at age 5
Multiple Endocrine Neoplasia Type 4	Autosomal Dominant or Sporadic	Pituitary, pancreatic and parathyroid adenomas	Unknown	Unknown	Pituitary adenoma	Not established
Carney Complex	Autosomal Dominant or Sporadic	• Multiple endocrine tumors • Skin lentigines • Cardiac myxomas • Neural	10%	Usually 3rd & 4th decade	Pituitary adenoma or pituitary hyperplasia	Annually beginning post pubertally
3PA Association	Autosomal Dominant or Sporadic	Pheochromocytom paraganglioma, pituitary adenoma	Unknown	Usually 3rd & 4th decade	Pituitary adenoma with intracytoplasmic vacuoles	As clinically indicated in unaffected family members
Isolated Familial Somatotropinomas	Autosomal Dominant or Sporadic	Isolated GH-secreting pituitary adenomas	100%	Before 3rd decade and as early as age 5	Pituitary adenoma	As clinically indicated in unaffected family members
X-linked Acrogigantism	Sporadic or X-linked	Isolated GH excess	100%	Early childhood with onset in late infancy or onset during adolescence	Pituitary adenoma or pituitary hyperplasia or both	As clinically indicated in unaffected family members

Neurofibromatosis-1 (NF-1)

Beginning in the 1970's, several reports of gigantism occurring in young children with NF-1 have appeared in the medical literature (29). In these cases, excessive somatic growth has been noted as early as 6 months of life (30). Neuroimaging in these patients typically reveals an optic glioma (31), usually with infiltration into the medial temporal lobe. However, growth hormone excess has frequently been reported to be a transient phenomenon in children with NF-1, raising questions as to the necessity of treatment (32;33). A number of investigations aimed at identifying the precise etiology of the gigantism in these children have been conducted. In all cases in which tumor tissue has been available, immunostaining for GH, GHRH and somatostatin has been uniformly negative (34;35).

This, in conjunction with the known temporal lobe location of somatostatin-producing neurons, led to the hypothesis that GH excess in these patients was the result of a hypothalamic regulatory defect. Specifically, tumor infiltration of somatostatinergic pathways would presumably result in reduced somatostatin tone leading to overproduction of GHRH-mediated pituitary GH. Despite this plausible explanation, arginine-induced GH stimulation in a patient with gigantism in the setting of NF-1 was normal, contrary to the expected lack of response to arginine, which is believed to act through somatostatin inhibition (36). Thus, the precise pathogenesis of gigantism in NF-1 remains unclear. Little information is available regarding the overall incidence of GH hypersecretion in patients with NF-1 and optic gliomas, although studies have suggested that it may occur in over 10% of affected patients, some of whom have concurrent central precocious puberty (37). Interestingly, growth hormone excess has also been reported in children with sporadic optic pathway tumors without associated NF-1 (38) Figure 1 demonstrates the café-au-lait pigmentation and linear growth acceleration observed in a young boy with NF-1 and gigantism.

Figure 1a: Growth Acceleration.

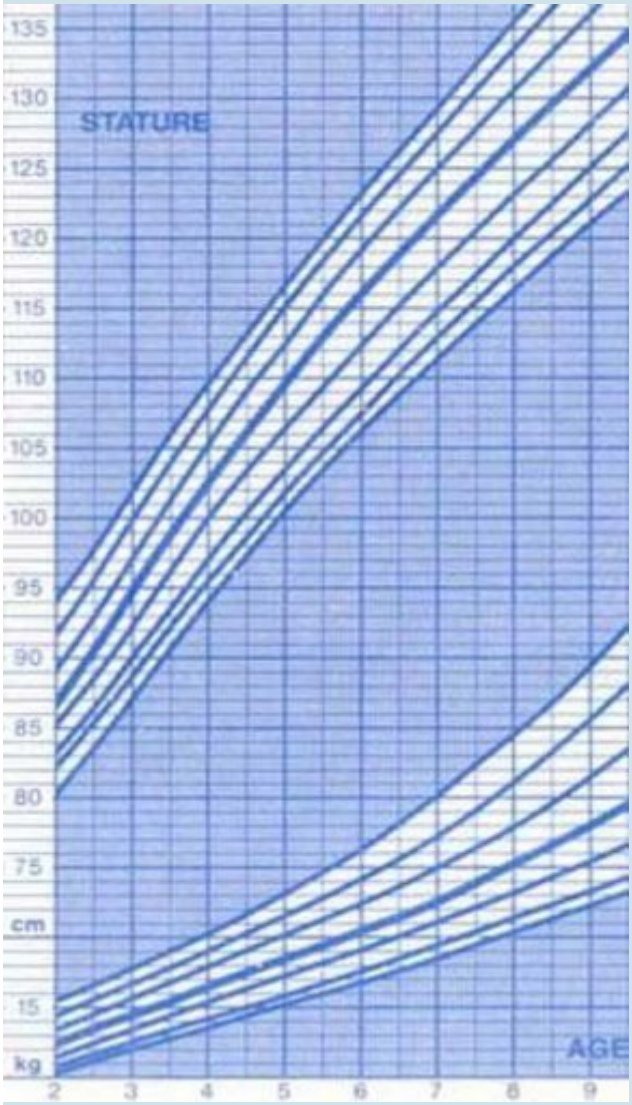
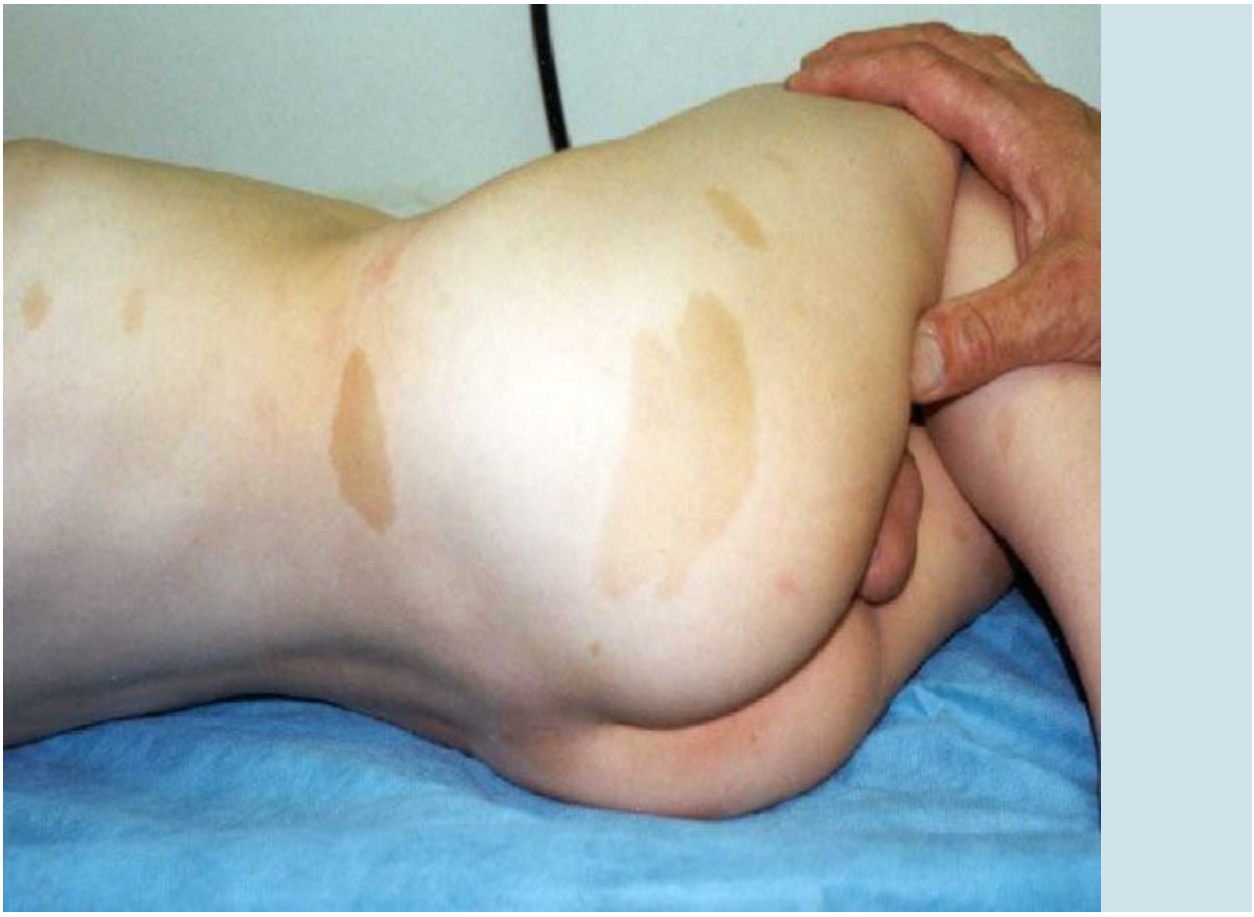


Figure 1b: Characteristic "coast of California" café au lait macules in a child with neurofibromatosis and gigantism.



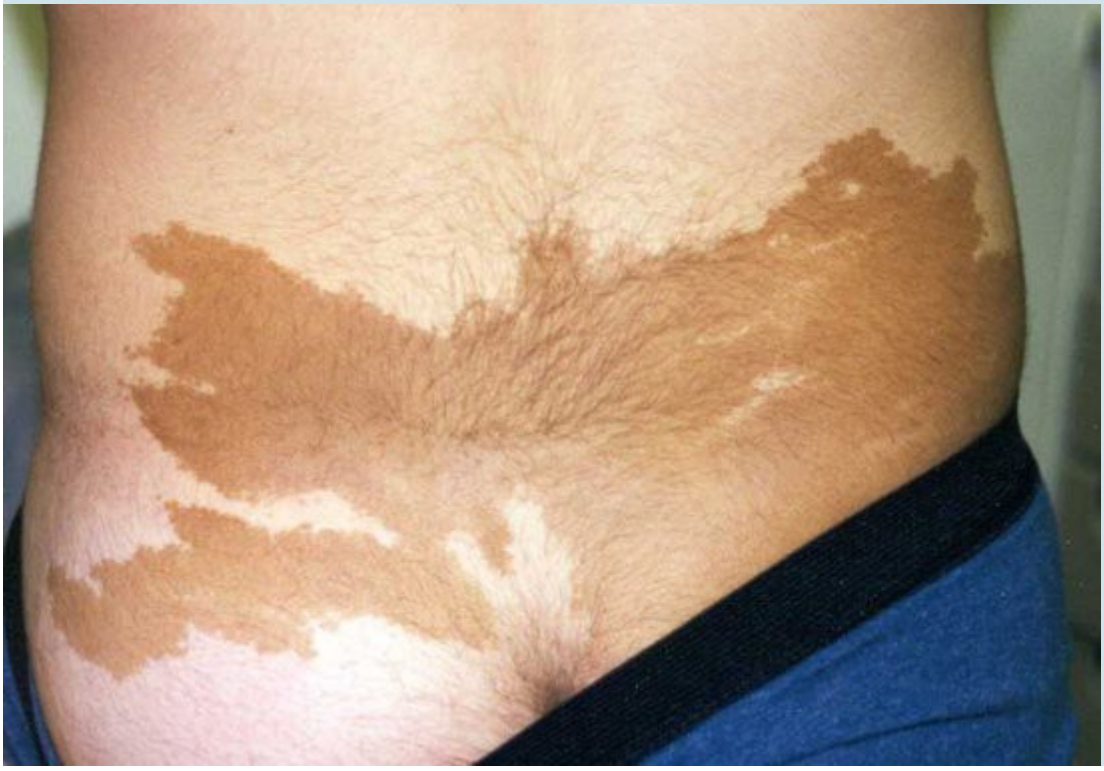
McCune-Albright syndrome (MAS)

MAS is a complex and heterogenous disorder in which GH excess may arise in conjunction with additional endocrinopathies and other abnormalities. In the classic form, MAS results in the triad of precocious puberty, café-au-lait skin pigmentation, and fibrous dysplasia of bone. It has long been recognized, however, that individuals with MAS have a propensity to develop a number of endocrine problems, including gigantism or acromegaly from excessive growth hormone secretion (39).

Elucidation of the molecular genetic defect in MAS in the early 1990's (40) illuminated the underlying mechanism through which abnormal hormone secretion occurs in this condition. Activating mutations of Gsα, the stimulatory subunit of the heterotrimeric G-protein complex involved in intracellular signaling, have now been shown to form the basis for nearly all of the clinical manifestations of MAS(41). These mutations, which typically involve substitution of arginine at the 201 position with cysteine or histidine, result in unregulated signal transduction leading to increased intracellular cAMP accumulation and downstream gene transcription. The precise timing of the mutation during embryologic life, which occurs in a post-zygotic cell line, will ultimately determine the extent of abnormal cells and severity of the resultant clinical phenotype. The incidence of GH excess in classic MAS has generally been reported to be 15-21% (42;43) and may be more common in males (Yao Y 2017). However, enhanced recognition of the frequency of atypical or forme fruste variants of MAS have the potential to result in an increase of this estimated frequency. Indeed, a number of historical reports of extreme gigantism where fibrous bone dysplasia was also present strongly suggest a diagnosis of MAS in these individuals, a

hypothesis confirmed by molecular genetic analysis in at least one case (44;45). Subclinical growth hormone excess has also been reported in MAS, in which the only clinical manifestation may be the presence of normal stature (rather than short stature) in the context of a history of untreated precocious puberty. Additional phenotypic features in this subgroup of patients with MAS include a higher incidence of vision and hearing deficits, TRH responsiveness, and hyperprolactinemia (46). Growth hormone excess in MAS is typically accompanied by skull base fibrous dysplasia and is notorious for being associated with increased craniofacial morbidity and macrocephaly (47). However, early diagnosis and treatment has been found to decrease the risk of optic neuropathy in these patients (48). A variety of pituitary morphologic abnormalities have been noted in MAS patients with GH hypersecretion (49), ranging from discrete pituitary adenomas (50;51) to diffuse pituitary hyperplasia (7), to no discernible radiographic abnormality (52). Of note is the fact that the identical Gsα mutation found in MAS has also been implicated in the pathogenesis of sporadic GH-secreting pituitary adenomas, where it results in formation of the *gsp* oncogene. Up to 40% of somatotroph adenomas in adults have been demonstrated to contain either an Arg201 activating mutation, or a related point substitution of glutamine at position 227(53). Interestingly, these sporadic tumors as well as those from patients with MAS and acromegaly display the Gsα mutation exclusively from the maternal allele, providing evidence that the GNAS1 gene is subject to imprinting(54). Figure 2 demonstrates an area of classic café au lait skin pigmentation in a patient with MAS.

Figure 2: Café au lait pigmentation in the typical "coast of Maine" configuration in an individual with McCune-Albright syndrome.



Multiple Endocrine Neoplasia-Type I (MEN-1)

MEN-1 is one of a number of familial cancer syndromes characterized by autosomal dominant inheritance and multi-endocrine gland involvement. Although significant clinical heterogeneity

exists in terms of specific tumor combinations, the most frequent manifestations of MEN-1 are parathyroid, pancreatic, and pituitary adenomas (55). The gene for MEN-1, which had previously been mapped to chromosomal locus 11q13, has been cloned and demonstrated to encode for a 610 amino acid nuclear protein designated *menin* (56). Many different molecular genetic abnormalities within the menin gene have been identified in kindreds with MEN-1, including nonsense, missense, deletion, insertion and donor-splice mutations(57). Unfortunately, genotype/phenotype correlations have not been observed. In all cases of MEN-1, the development of neoplasia is thought to arise from a defect in normal tumor suppression via a 2-hit hypothesis. The first hit represents inheritance of a germline MEN-1 mutation, leading to a heterozygous loss of the menin gene in every cell (58). As menin is believed to function as a tumor suppressor protein, the second hit involves a somatic MEN-1 mutation in one cell, with subsequent abnormal cellular transformation and clonal expansion. Indeed, somatic biallelic MEN-1 mutations have been demonstrated to be present in at least 15% of sporadic pituitary adenomas, including somatotroph tumors (59). Anterior pituitary adenomas in individuals with known MEN-1 have a reported prevalence of 10-60% and are thought to represent the first clinical manifestation of the disease in up to 25% of sporadic cases (60). Of these, the majority are prolactinomas, with GH-secreting adenomas developing in approximately 10% of individuals with MEN-1 by age 40. The youngest reported case of gigantism in MEN-1 occurred in a 5-year-old boy, who presented with growth acceleration and a GH-secreting mammosomatotroph pituitary adenoma in the context of a known family history of MEN-1 (61). Molecular genetic analysis confirmed the germline and tumor tissue MEN-1 mutations but failed to reveal an etiology for the accelerated presentation in this case. Nonetheless, current recommendations include screening for anterior pituitary hormone excess beginning at age 5 in all individuals with MEN-1, as well as ascertaining MEN-1 carrier status by germline mutation testing in a number of clinical situations (62). Interestingly, GH excess due to ectopic elaboration of GHRH from a pancreatic neuroendocrine tumor has also been reported in several individuals with MEN-1 (63).

Multiple Endocrine Neoplasia-Type 4 (MEN-4)

MEN-4 is a recently recognized entity that is caused by germline mutations in the CDKN1B gene which encodes the putative tumor suppressor p27Kip1 (64). Affected patients are typically heterozygous for mutations in CDKN1B and exhibit a phenotype similar to that seen in MEN-1. Because the number of individuals who have been diagnosed with MEN-4 is low, screening protocols for patients and their family members have not yet been established (65).

Carney Complex (CNC)

Initially described in 1985 (66), CNC is a rare autosomal dominant disorder in which the cardinal features include multiple endocrine tumors, skin lentigines (spotty pigmentation), cardiac myxomas and neural sheath tumors. The condition shares characteristics with several other syndromes, including MEN-1 (multiple endocrine tumors), MAS (endocrine hyperfunction and skin pigmentation) and Peutz-Jeghers (mucosal lentiginoses and gonadal tumors). It has now been demonstrated, however, to have a unique clinical and molecular genetic identity. Two distinct genetic abnormalities have been implicated in the pathogenesis of CNC. The first consists of a locus on 2p16(67), although a specific candidate gene within this region has not been identified. Additionally, mutations in the gene encoding for the protein kinase A regulatory subunit (1α) (PRKAR1A) at 17q22-24 have been demonstrated in 35-44% of both familial and sporadic cases of CNC(68). This protein, which is intricately involved in endocrine cell signaling pathways, is

thought to function as a tumor suppressor gene. Supporting this theory has been the observation that tumors from patients with CNC (in which diminished levels of PRKAR1A are present) exhibit a 2-fold increase in cAMP responsiveness compared with control tumors (69).The identical mutation has also been found in some sporadic endocrine tumors. As with MEN-1, a germline mutation is thought to be the inciting event for eventual development of the disease. The clinical presentation of CNC is extremely heterogeneous, as is the age at diagnosis. The development of GH excess is rare, occurring usually during the 3rd and 4th decades of life and typically found in only 10% of patients at the time of presentation (70). Thus, annual screening for GH hypersecretion is recommended only in post pubertal patients. As in cases of gigantism/acromegaly in the setting of MAS, diffuse pituitary hyperplasia (71) and concomitant hyperprolactinemia (72) are frequently seen in individuals with CNC and GH excess.

3PA Association

The constellation of paraganglioma, pheochromocytoma and pituitary adenoma is termed 3PA Association and has been shown to be due to germline mutations in a variety of subunits of succinate dehydrogenase (65;73). Growth hormone excess typically occurs in the 3rd and 4th decades of life (74). To date, no pediatric patients with gigantism in the setting of the 3PA phenotype have been reported.

Familial Somatotropinomas

It has long been recognized that isolated pituitary gigantism or acromegaly may occur in a familial pattern. This phenomenon, termed “Familial Isolated Pituitary Adenomas” (FIPA), is defined as the development of GH hypersecretion in two or more members of a family that does not exhibit features of MEN-1 or CNC. At least 46 different affected kindreds have been reported (75). Unlike in MEN-1 and CC, GH excess tends to arise fairly early in life, with 70% of those with the disorder diagnosed before the 3rd decade. Early childhood gigantism in this setting has also occurred, involving sisters with abnormal linear growth since age 5 (76) and a more virulent course than is seen in sporadic somatotropinomas has been suggested by a case series (77). Once assumed to represent a variant of MEN-1, mutations within the menin gene as the etiology for IFS were conclusively excluded (78;79). However, the precise molecular genetic basis for the development of pituitary GH-secreting adenomas in the majority of affected families has eluded detection. Initial investigation revealed loss of heterozygosity and linkage to a 9.7 Mb region of 11q13, suggesting the presence of an additional putative tumor suppressor gene in this region, distinct from that involved in MEN-1. Subsequent studies identified inactivating mutations in the gene encoding aryl hydrocarbon receptor interacting protein (*AIP*) at 11q13.3 in 15%-25% of families with FIPA (80-82) making it the most common genetic defect found in these kindreds . Although the mechanism by which these mutations cause pituitary adenomas is unknown, the resulting phenotype is characterized by early-onset and aggressive disease. In an amazing case of medical sleuthing, a germline AIP mutation identified in DNA from the preserved teeth of an 18th century Irish giant was found to be an exact match for the mutation harbored by four contemporary Irish families with FIPA, indicating a common ancestor dating back more than 50 generations ago (83)! Interestingly, a second potential locus for FIPA has mapped to 2p12-16, very close to the region implicated in a number of kindreds with CNC (84). Additional molecular genetic analysis performed in these patients has included a search for germline mutations within the GHRH receptor gene, Gsα and Gi2α genes, all of which were normal. Similar to observations in MEN-1, patients with FIPA have discreet pituitary adenomas, the majority of which are comprised solely of

somatotrophs (75). However, prolactinomas, gonadotropinomas and silent pituitary adenomas may all be seen in different members of the same kindred (85;86) . Macroadenomas with invasion into the cavernous sinus are common in the setting of FIPA, and treatment is notoriously difficult (86).

X-Linked Acrogigantism

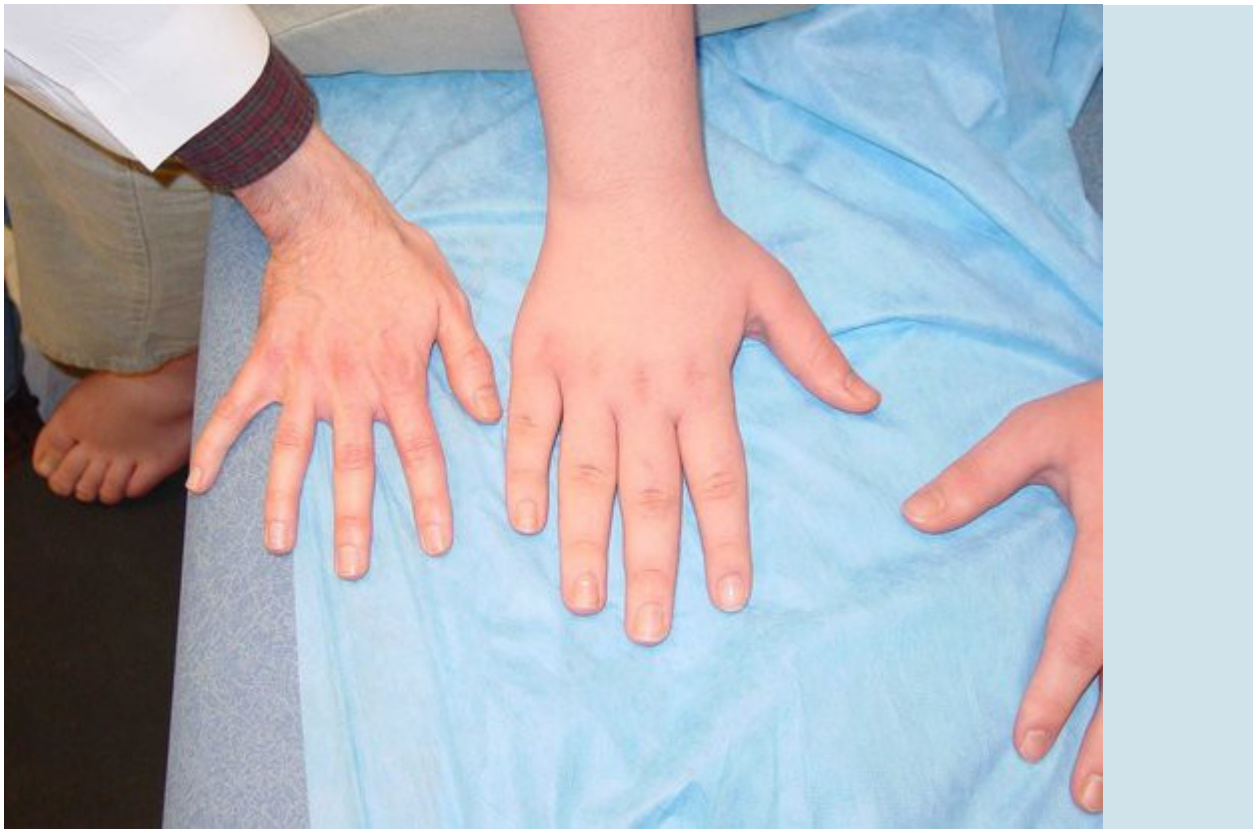
An additional cause of familial gigantism and acromegaly has been linked to microduplication of Xq26.3 and termed X-linked acrogigantism (X-LAG). This genomic duplication was initially identified in 14 patients with gigantism and is associated with both sporadic and familial cases (87;88). Of the four genes contained in the duplicated region, the growth hormone excess appears to result from an abnormality of *GPR101,* a gene that encodes for an orphan G-protein coupled receptor. This gene is markedly over-expressed in pituitary tissue from affected patients. Functional studies suggest a proliferative role for mutant *GPR101*, although the precise mechanism for how this aberration contributes to GH hypersecretion is not yet clear. The condition can result from either germline or somatic duplications in *GPR101* and has a female predominance (89;90). Mosaicism for *GPR101* duplication resulting in X-LAG has also been reported in sporadic cases involving boys (91). Patients harboring the Xq26.3 microduplication exhibit a distinct phenotype characterized by strikingly early gigantism with a median age of onset of 12 months. In addition to hypersecretion of GH, elevated circulating GHRH and prolactin have also been noted (92). Both pituitary adenomas and pituitary hyperplasia have been seen among cases testing positive for X-LAG. This discovery highlights new biological processes that will undoubtedly lead to novel insights regarding the central regulation of human growth.

CLINICAL AND BIOCHEMICAL FEATURES OF GIGANTISM

As would be predicted, linear growth acceleration is the cardinal feature of excessive GH production in a child or adolescent. Based on numerous case reports, however, it is clear that the excessive linear growth observed in young children with gigantism may be accompanied or even preceded by macrocephaly and or obesity (9;11). In a large international study of patients with pituitary gigantism, the median onset of rapid growth was 13 years and occurred earlier in girls than in boys (93). Additional clinical features frequently encountered include frontal bossing, broad nasal bridge, prognathism, excessive sweating, voracious appetite, coarse facial features and enlargement of the hands and feet. Bone age radiographs in these patients have variably been reported to be normal or advanced, even in the complete absence of sex steroid production. Figure 3 demonstrates the prognathism, coarse facial features and typical tall stature seen in a 12-year-old boy with gigantism, and Figure 4 illustrates enlargement of the hands in this same patient.

Figure 3: Twelve-year-old boy with pituitary gigantism measuring 6'5" with his mother. Note the coarse facial features and prominent jaw.

Figure 4: Enlarged hand of the same patient in comparison with the hand of an adult male with a height of 6'1". The patient's middle digit has a circumference of 9 centimeters.



The most consistent biochemical abnormality observed in patients with gigantism is an elevated IGF-1, which is known to exhibit an excellent correlation with 24-hour GH secretion (94). As previously mentioned, hyperprolactinemia is extremely common in early-onset GH hypersecretion. Depending on the individual situation, the additional pituitary screening evaluation may be normal, indicative of hypopituitarism or central precocious puberty. Concurrent endocrinopathies may also be present, particularly in patients with syndromes such as MAS or MEN-1. Rarely, alterations in glucose tolerance brought about by GH excess may result in the development of overt diabetes, leading to transient diabetic ketoacidosis (95-97) which may even be the presenting feature in rare instances (98). An additional physiologic effect of GH excess that may have clinical significance is that of increased erythropoiesis, as demonstrated by a case of acromegaly-induced polycythemia vera that resolved following surgical resection of the GH-secreting adenoma(99).. The importance of GH in the regulation of red blood cell production has further been supported by the observation that pre-treatment hemoglobin concentrations in children with idiopathic growth hormone deficiency are lower than controls (100)

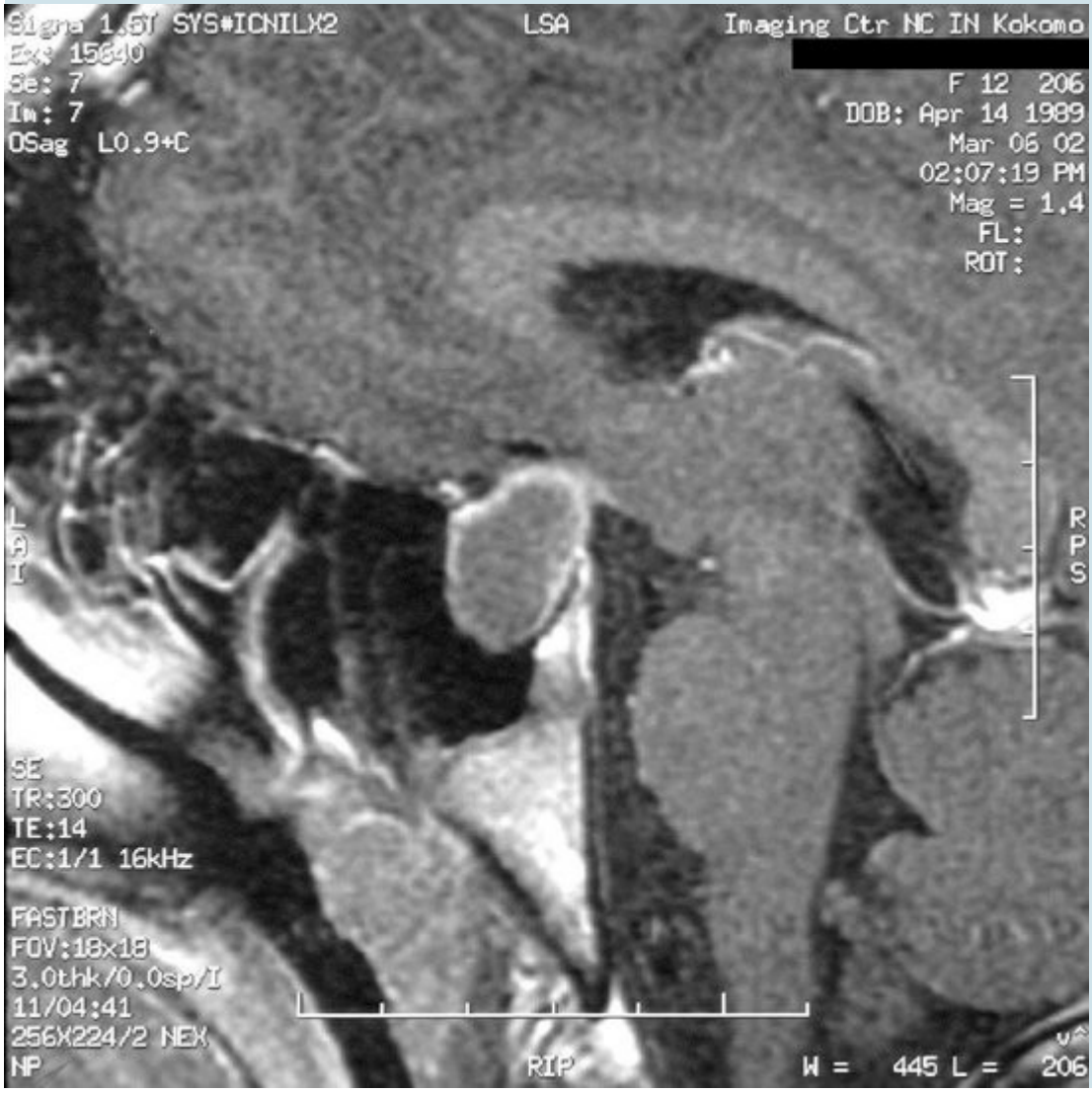
DIAGNOSTIC EVALUATION OF GH EXCESS

The gold standard for making the diagnosis of GH excess relies on the inability to suppress serum GH to an appropriate level following an oral glucose load. While the OGTT has been the diagnostic test of choice for many years, numeric guidelines for the expected degree of suppression in a normal individual have steadily decreased. This trend is the direct result of newer assays with an improved threshold of sensitivity for detection (101). A normal response to a standardized glucose bolus (1.75 gm/kg up to 75 grams) utilizing the newer IRMA/ICMA assays is considered to be a GH level below 1 ng/ml (102). However, given the observation that biochemical recurrence of GH excess may be detected in patients with a GH nadir less than 1 ng/dl, and that healthy subjects nearly always suppress to below 0.14 ng/ml, some investigators have suggested that this cut-off is

too liberal (103). Typically, the nadir in serum GH is expected to occur within the first 2 hours of the test. Along with a lack of suppression following oral glucose, individuals with GH hypersecretion characteristically exhibit a paradoxical response to other forms of hypothalamic-pituitary stimulation testing.

Occasionally, 24 hour integrated GH assessment may be helpful in cases in which an equivocal response to OGTT is seen (104). Despite the development of highly sensitive GH assays, generalizability of results across institutions or regions is hampered by significant heterogeneity in the availability of reference preparations and methods used by specific laboratories (105). Depending on the individual circumstance, measurement of peripheral GHRH may also be indicated to investigate the possibility of ectopic GHRH secretion. Once biochemical evidence of GH excess has been demonstrated, MRI scanning of the H-P region is obviously the next step. Figure 5 illustrates the typical appearance of a GH-secreting pituitary macroadenoma in an adolescent with gigantism.

Figure 5: Pituitary somatotroph macroadenoma in an adolescent with gigantism.



A potential pitfall in the evaluation of gigantism in adolescents is the fact that significant elevations of IGF-1 may be present during normal puberty (106). Moreover, growth hormone response to an oral glucose load in normal children has been found to be gender and pubertal-stage specific, with the

highest nadir GH occurring in Tanner stage 2-3 girls (107). The effect of sex steroids on IGF-1 and GH suppression must also be taken into account when a diagnosis of gigantism is being considered in a child with concurrent precocious puberty, as may be the case in NF-1 or MAS. Adding to the possible diagnostic ambiguity is the fact that a significant percentage of normal tall adolescents fail to suppress serum GH in response to oral glucose testing (108). Therefore, both screening and definitive testing for GH excess should be performed in the context of clinical suspicion, and IGF-1 levels interpreted according to age and pubertal stage-adjusted normal ranges.

TREATMENT

No large-scale studies evaluating various therapeutic approaches to the treatment of GH excess in pediatric patients are available. Therefore, the optimal treatment of gigantism has traditionally been extrapolated from the adult literature as well as case reports or small series involving children. As is the case in adults, the three separate modalities available for the treatment of children and adolescents with GH hypersecretion are surgery, radiation and medical therapy. Of these, the greatest recent advances by far have occurred in the realm of pharmacologic agents, resulting in an exciting armamentarium of drugs promising truly enhanced efficacy and excellent safety. Regardless of the individual treatment strategy, the goals of therapy remain the same, namely the restoration of GH and IGF-1 levels to normal ranges (109). Of all parameters investigated, GH levels themselves appear to correlate most with overall morbidity and mortality in acromegaly (110). Table 3 summarizes the current therapeutic options as they pertain to pediatric patients, each of which is discussed below.

Table 3: Therapeutic Modalities in GH Excess and Experience with Use in Pediatric Patients.

Modality	Specific Options	Current Indications	Pediatric Experience
Surgery	Transphenoidal resection	Pituitary microadenoma or	Performed safely in children as young as 2 years old
Radiation	Conventional radiation	Adjuvant to surgical or medical therapy	Typically avoided if at all possible, but has been used as adjuvant therapy
	Stereotactic radiosurgery, ex: gamma knife	Adjuvant therapy in patients with residual GH hypersecretion	No experience with use in children
Medical Therapy	Somatostatin analogues • Octreotide (Sandostatin) • Lanreotide	• Primary therapy in cases of diffuse pituitary hyperplasia or severe bone disease • Adjuvant to surgery or radiation	Used safely in children with both sporadic and syndromic gigantism for extended periods of time alone and in combination with dopamine analogues

	Depot somatostatin analogues • Sandostatin LAR SR-lanreotide	Same as above	Safety and efficacy appear comparable to non-depot preparations
	Dopamine agonists • Bromocriptine Cabergoline	• Adjuvant to somatostatin analogues and other therapies Particularly useful when concurrent hyperprolactinemia is present	Used safely in children in combination with somatostatin analogues
	GH receptor antagonists Pegvisomant	Particularly useful for treatment of refractory disease	Has been used alone and in combination with somatostatin analogues Preliminary experience in children appears promising

Surgery

Transphenoidal resection is the treatment of choice for discreet pituitary microadenomas or macroadenomas (111), with the objective being the preservation of pituitary function in association with cure of the GH excess. Not surprisingly, individual surgeon expertise has a significant impact on the likelihood of success (112), which is exemplified by a rapid normalization of serum GH levels (often within one hour) and response to OGTT. However, while surgery cures the majority of patients with microadenomas, less than 50% of patients with macroadenomas experience this optimal outcome (113;114). Moreover, extended post-operative follow-up has revealed a gradual return of GH excess over time in a substantial number of patients in whom the disease was previously deemed to be well controlled (115;116). Experience with surgical treatment of gigantism in children and adolescents has been comparable to that observed in adults (117;118), and it has been employed safely in patients as young as 24 months (12). Although further investigation is needed, a potential role for pre-operative medical therapy has been suggested by studies indicating higher surgical remission rates and lower anesthesia risk following a several month course of a somatostatin analogue (119).

Radiation

Although traditionally included as a therapeutic option, significant problems exist with the use of conventional radiotherapy in gigantism or acromegaly. These include a low level of efficacy, delayed normalization of GH levels, and a high incidence of hypopituitarism. In the setting of MAS, radiation therapy for GH hypersecretion may contribute to malignant transformation of dysplastic bone tissue (120).. Additional concerns particularly relevant to children include potential neurocognitive effects and the possible development of hypothalamic obesity, both of which have been linked to cranial irradiation in pediatric patients (120;121). Therefore, radiation therapy would be considered a last resort for the treatment of childhood GH hypersecretion. Improved precision and safety is observed with use of stereotactic radiosurgery in the form of the gamma knife technique, which has been successfully employed as adjuvant therapy in adults with acromegaly (120;122-124).

Medical Therapy

Although most commonly considered adjunctive to surgery or radiation, a primary role for medical therapy has always existed for those patients with diffuse pituitary hyperplasia or severe bony deformities precluding a surgical approach. As tremendous improvements in the pharmacologic agents available for use in GH excess continues to evolve (125), the number of patients offered medical therapy as first-line treatment will surely expand. The three currently existing classes of drugs for suppression of GH and IGF-1 levels are reviewed below.

SOMATOSTATIN ANALOGUES

Ever since their development in the mid-1980's, long acting analogues of somatostatin have held a pivotal place in the medical treatment of GH excess. These agents exert their effect through selective binding to somatostatin receptors within somatotroph adenomas (126). By far the greatest experience in the United States has been with octreotide, which is typically administered subcutaneously in three divided doses. Short-term administration of octreotide results in a decrease in GH levels within one hour in > 90% of patients with acromegaly (127), while sustained use

normalizes GH and IGF-1 levels in up to 65% of patients (128). Experience with the use of octreotide in children has been similarly favorable, where it has been beneficial in the treatment of sporadic as well as syndromic gigantism (129;130). Continuous subcutaneous infusion of octreotide has also resulted in superior efficacy in controlling GH hypersecretion in a pubertal patient (131).Long-acting depot preparations of octreotide in the form of Sandostatin LAR and SR-lanreotide are also available, in which a slow release of drug is achieved through degradation of a polymer in which microspheres are encapsulated (132). This allows for monthly IM administration, resulting in a safety and efficacy profile that is comparable to or improved in contrast to traditional dosing (133). Both slow-release preparations have also been used in the treatment of ectopic forms of GH excess (134) and in MAS associated gigantism (135-137), and have been noted to have equivalent safety and efficacy (138). The development of novel somatostatin analogues has the potential to improve efficacy over existing compounds (139). The major side effect of all the somatostatin analogues is a significantly increased risk of biliary sludge and gallstones after sustained use, necessitating periodic ultrasound examinations in patients treated long-term (140).

DOPAMINE AGONISTS

Although rarely effective alone, dopamine agonists have a valuable role as adjunctive agents in the treatment of GH excess. Due to their suppressive effects on prolactin, these drugs are particularly advantageous when hyperprolactinemia is present, as is often the case in childhood-onset gigantism. Both bromocriptine and the more potent dopamine agonists such as cabergoline have been administered to children in combination with octreotide long-term with no apparent adverse effects (136).

GH RECEPTOR ANTAGONISTS

The latest development in the realm of medical therapy has been the emergence of pegvisomant, a genetically engineered human GH analogue that acts as a highly selective GH antagonist (141). This is achieved through alterations in affinity binding of pegvisomant compared to the native GH molecule (129), resulting in prevention of the normal extracellular dimerization of the growth hormone receptor. Administration of pegvisomant long-term to adults with acromegaly has been shown to result in normalization of serum IGF-1 levels in 97% of patients (142). Despite these extremely promising results, the implications of the nearly ubiquitous elevations in serum GH levels observed in conjunction with pegvisomant treatment initially created some concerns. Although early reports recounted an increase in tumor volume and abnormal liver enzymes in association with pegvisomant use (143;144), long-term follow has demonstrated that these complications are rare and that efficacy is very good (145;146). Combination therapy using pegvisomant along with a dopamine agonist or somatostatin analogue also appears promising (145). Thus far, preliminary experience with the use of pegvisomant alone or in combination with a somatostatin analogue for the treatment of gigantism in children also appears favorable (147). This approach resulted in successful normalization of IGFI levels in a 4 year old with NF-1 (148), a 12 year old with MAS (149), and a couple of children with persistent GH hypersecretion following surgical removal of a pituitary adenoma who had failed a somatostatin analogue (150; 151). Even more reassuring is a report of long-term (up to 3.5 years) treatment using pegvisomant in 3 children with gigantism, all of whom experienced a decline in growth velocity and resolution of acromegalic features (152).

Treatment of Tall Stature

Depending on the absolute height and the degree of growth potential remaining, one of the goals in the treatment of gigantism may be prevention of further linear growth. When this is the case, acceleration of epiphyseal fusion can be achieved with exogenous sex steroids (153). Short-term administration of both high dose testosterone and estrogen have been utilized for this purpose in children with gigantism, resulting in significant improvements in terms of adult height (154;155). However, such an approach would require great caution given reports of subfertility in women who were treated with high dose estrogen during adolescence with the goal of attenuating growth in the setting of constitutional tall stature (156;157).

OVERGROWTH SYNDROMES

The overgrowth syndromes comprise a diverse group of conditions with unique clinical, behavioral and molecular genetic features. While considerable overlap in presentation sometimes exists (158), advances in identification of the precise etiology of specific overgrowth disorders continues to improve the clinician's ability to make an accurate diagnosis. In this chapter, only the most common syndromes characterized by generalized somatic overgrowth will be reviewed, with specific aspects pertaining to each disorder summarized in Table 4. Additional syndromes in which tall stature (such as Marfan syndrome) or obesity (such as Prader-Willi syndrome) are the predominant features will be discussed elsewhere.

Table 4: Comparison of Overgrowth Syndromes

Syndrome	Clinical Features	Mode of Inheritance	Etiology
Sotos syndrome	• Prenatal overgrowth with early transient growth acceleration • Macrocephaly, hypertelorism, prominent forehead, pointed chin • Speech and language delay • clumsiness	• Sporadic • Rare familial cases	• Mutations within the NSD1 gene in 90% of cases

Beckwith-Wiedemann syndrome	• Prenatal and postnatal overgrowth • Macroglossia, abdominal wall defects, ear creases, visceromegaly • Neonatal hypoglycemia • Increased incidence of embryonal tumors	• Sporadic • Rare familial cases	• Abnormal imprinting in growth regulatory genes at 11p15 including IGF-2
Simpson-Golabi-Behmel syndrome	• Prenatal and postnatal overgrowth • Macroglossia, skeletal/hand anomalies, supernumerary nipples, visceromegaly, cardiac abnormalities • Increased incidence of embryonal tumors	• X-linked • Sporadic	• Mutations within the GPC3 gene at Xq26
Weaver syndrome	• Prenatal or postnatal overgrowth • Macrocephaly, hypertelorism, large ears, micrognathia • Advanced skeletal maturation	• Autosomal dominant • Sporadic	• Mutations within EZH2
NSD1-nuclear receptor binding SET domain-containing protein 1, GPG3-glypican 3			

Sotos Syndrome

Sotos syndrome, also known as cerebral gigantism, was first described in 1964 (159). Since then, several hundred cases have been reported. Cardinal features of the disorder include early onset overgrowth, a characteristic facial configuration and stereotypical behavioral profile. The overgrowth in Sotos syndrome is of prenatal onset, with length being the most significantly affected parameter. After birth, acceleration of all growth parameters ensues, with OFC measuring above the 97th percentile in nearly all affected infants by 12 months of age (160). Although the growth velocity slows by age 3 or 4, height invariably remains above the normal range throughout childhood, typically in association with somewhat lower weight percentiles. In contrast, adult stature in Sotos

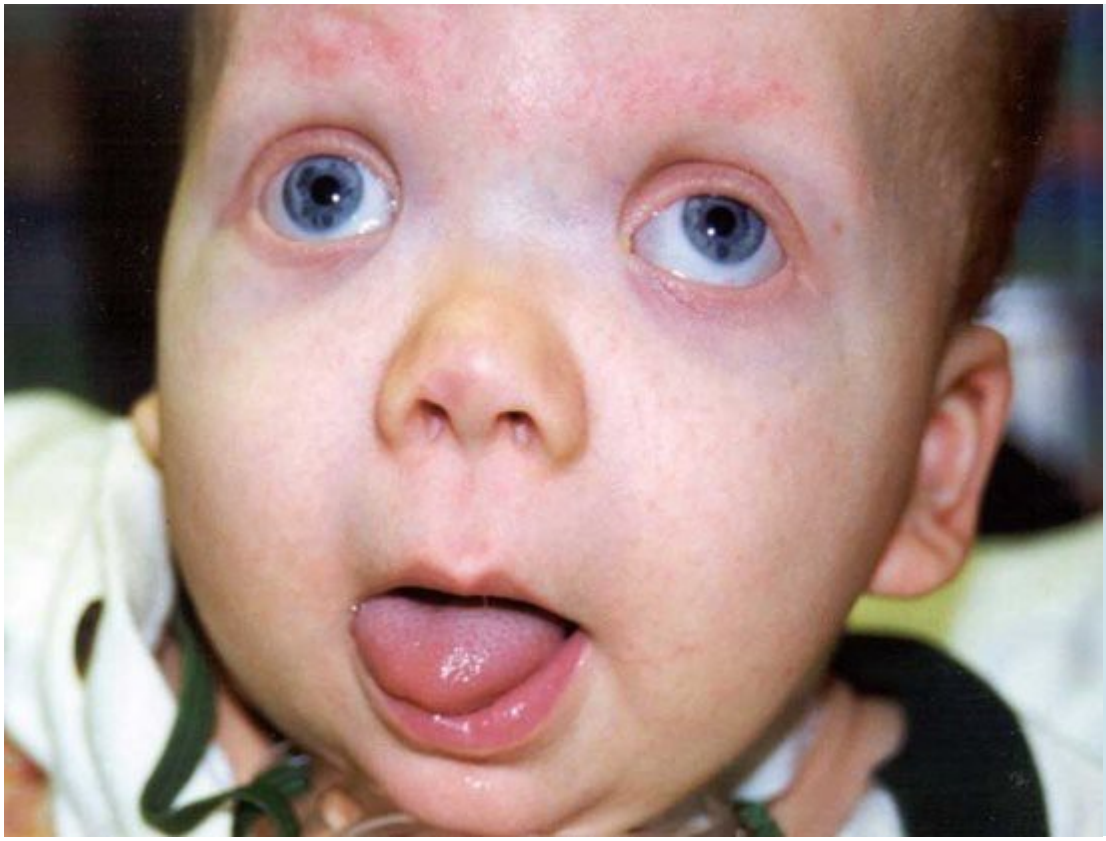
syndrome is usually within the normal range for the general population (161), which has been attributed to the combination of an advanced bone age and a relatively early onset of puberty. Classic facial features include macrocephaly with dolichocephaly, hypertelorism, high-arched palate, prominent forehead and a pointed chin (162). Additional oral findings may include premature tooth eruption and supernumerary teeth(163). Developmental delay is ubiquitous, particularly in the area of speech and language acquisition (163-165) .Children with Sotos syndrome are often described as being clumsy, with a tendency toward aggressive behavior (163;166). A minority have seizures, as well as structural abnormalities of the brain such as enlarged ventricles and absence of the corpus callosum.

Sotos syndrome is typically sporadic, although autosomal dominant transmission has been reported(163;167). Isolated cases of identical twin pairs who are concordant as well as discordant for the condition have also been described (163;168). Historically, the diagnosis was based entirely on clinical criteria. However, it is now known that Sotos syndrome is caused by a variety of molecular genetic alterations resulting in haploinsufficiency of the nuclear receptor-binding SET domain-containing protein 1 (NSD1) gene at 5q35 (163;169-171) in ~90% of cases. The NSD1 gene encodes for a nuclear protein believed to function as a basic transcription factor and transcriptional regulator. Heterozygous mutations in the NFIX gene (Nuclear Factor I, X) have also been identified in some children with Sotos syndrome (172). While genotype-phenotype correlations have been suggested (173;174), this needs to be confirmed by additional studies of affected patients.

Beckwith-Wiedemann Syndrome (BWS)

Two physicians independently reported the first recognized cases of BWS in the 1960's (175;176). Since that time, tremendous progress has been made in unraveling several aspects of this complex disorder. BWS is typified by the combination of prenatal and postnatal overgrowth, congenital malformations and a predisposition to embryonal tumors. Characteristic features noted in the neonatal period include macroglossia, abdominal wall defects such as umbilical hernia, ear creases, visceromegaly and hyperinsulinemic hypoglycemia (177). A variety of additional abnormalities are found in a subset of patients, including hemihypertrophy or isolated facial asymmetry(178). While intelligence may be normal, mild to moderate developmental delay may also be present. Although usually sporadic, several families manifesting heterogeneous inheritance patterns have been reported in whom there are several generations of affected individuals (1 7 9) . The reported incidence of malignancy in children with BWS varies between 4-21% (180), with the majority consisting of Wilms tumor. Therefore, frequent screening via abdominal ultrasonography during infancy and early childhood is essential (181), especially in patients with hemihypertrophy, which is known to be associated with an increased risk of cancer (182). Insights into the pathophysiology of the abnormal growth in this condition emerged with the discovery of abnormalities in imprinting of a number of growth regulatory genes within three regions of chromosome 11p15, including IGF-2, H19 and CDKN1C (181;183). The molecular genetic defects resulting in BWS are extremely heterogeneous, and include maternal hypomethylation of 11p15, paternal uniparental disomy of this region, and unbalanced translocations leading to trisomy of the 11p15 locus (184;185). Enhanced understanding of the relationship between tumor risk and the molecular subtype in BWS will result in improvements in targeted screening (186;187). Interestingly, an association has been noted between assisted reproduction and risk of imprinting disorders such as BWS (188), although the risk appears to be small (189). Figure 6 demonstrates several classic clinical features in a child with BWS.

Figure 6: Young child with Beckwith-Wiedemann syndrome. Note the macroglossia, prominent eyes, eyelid nevus flammeus and barely visible linear ear creases.



Simpson-Golabi-Behmel syndrome (SGBS)

SGBS is a complex X-linked overgrowth disorder sharing many features with BWS. It is characterized by prenatal and postnatal overgrowth, coarse facial features and congenital anomalies. Some of the most commonly reported abnormalities include skeletal/hand defects, supernumerary nipples, macroglossia and visceromegaly However, a wide spectrum in severity has been noted, ranging from mild features in carrier females to a lethal form of the disorder in affected males (190). Similarly, cognitive abilities vary from within the normal range to severe developmental delays. Approximately 36% of patients have a cardiac abnormality, the most common of which is a cardiovascular malformation (191). As is the case in BWS, an increased incidence of embryonal tumors during early life is present. Delineation of the molecular genetic cause of SGBS has provided significant insight as to the reason for the striking similarities between this disorder and BWS. Inactivating mutations of the glypican-3 (GPC3) gene at Xq26 have been demonstrated in 28-70% of individuals with SGBS (192;193). GPC3 is a member of a multigene family known to have critical roles in growth and development through the modulation of cellular responses to growth factors, including IGF-2 (194). Exactly how abnormal levels of GPC3 promote tumorigenesis is poorly understood, but it may be through a disruption of the normal GPC3/IGF-2 complex, which is believed to be involved in IGF-2 modulation (195). An alternative proposal is that the physical manifestations of SGBS are due to abnormal interaction between GPC3 and CD26, a protein with important roles in the regulation of cell growth and immunologic response (196). Application of GPC3 mutational analysis in patients with unspecified overgrowth conditions has resulted in an extension of the SGBS phenotype (197) and the establishment of an international registry will be invaluable in providing information regarding the natural history and pathophysiology of this interesting condition. The oldest case of SGBS on record was discovered in an anatomical museum in the form of a macrosomic newborn who had

died neonatally from unknown causes and was traced through following the family tree of a newly identified GPC3 mutation in an affected patient (198).

Weaver Syndrome

Weaver syndrome is a rare condition that was first reported in 1974 (199). Major features include prenatal or postnatal overgrowth, characteristic facies and advanced skeletal maturation. The typical appearance includes tall stature, macrocephaly, hypertelorism, large ears and micrognathia. A subset of patients have been reported to have cervical spine abnormalities (200), and the occasional development of neoplasia has also been noted in this population. The majority of individuals with Weaver syndrome have developmental delay, which is typically mild. Initially believed to be sporadic, multiple instances of familial occurrence have pointed strongly toward an autosomal dominant form of transmission (201). In 2011, mutations in the histone methytransferase, EZH2, were shown to cause Weaver syndrome (174). Heterozygous mutations in embryonic ectoderm development (EED) have also been identified in patients with Weaver syndrome (202;203). Significant phenotypic overlap between Weaver syndrome and Sotos syndrome often makes it difficult to differentiate between these overgrowth conditions (158;202). Thus, the availability of molecular genetic testing will aid in the diagnostic process.

CONCLUSION

In summary, the differential diagnosis of gigantism includes a significant number of heterogeneous disorders exhibiting a vast array of clinical and genetic features (204). In most cases, the history, physical examination and adjunctive biochemical and/or molecular genetic testing will ultimately reveal the likely diagnosis. Albeit rare, diseases resulting in gigantism afford the unique opportunity for a glimpse into the complex mechanisms of growth regulation. Thus, continued clinical and scientific investigation will enhance not only individual patient care, but also collective insight into the intricacies of the fundamental processes of human growth.

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