PITUITARY GIGANTISM

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ABSTRACT

Pituitary gigantism in a child is an extraordinarily rare condition that results from excessive production of growth hormone. It can present as early as infancy or not until adolescence. It may be congenital or acquired, occurring as a sporadic condition or in the context of a known syndrome in which hypersecretion of GH is a 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 (adult-onset GH excess) and include surgery, medication, and radiation. Great strides have been made in identification of the molecular genetic basis for pituitary gigantism, affording novel insights into the mechanisms underlying normal and abnormal growth. Etiologies, phenotypic features, and diagnostic and treatment considerations are reviewed in this chapter.

ILLUSTRATIVE CASE

A 13 year 6-month-old boy presents for evaluation of rapid growth. Parents report that he was always tall as a child, but they have noticed that he is now taller than most classmates. He developed signs of puberty (body odor, pubic hair) a year ago coincident with the onset of rapid growth. His parents are concerned and want to make sure "everything is normal". He is asymptomatic other than periodic headaches that developed during the last year.

He was born appropriate for gestational age (AGA) at term following an uncomplicated pregnancy. By 1 year of age he was noted to be tall for his age, but this was attributed to the tall stature of his parents. Father

stands 6’2” and Mother is 5’8”. They are both healthy. He is an only child.

Upon review of his medical record he has a growth velocity of 19 cm/year (7.5 in/year) over the last calendar year; last year at the PCP the height was 160 cm, which is at 82.7% (0.9SDS)

He is currently at the 99.0 % for height at 179 cm/70.5 inches (+2.36 SDS) thus confirming the rapid gain in height. (See attached growth curves. Figure 1) On physical examination he is tall, but proportionate. Visual field testing shows normal vision in all fields. Thyroid examination is normal. There are no areas of skin hyperpigmentation and no obvious skeletal abnormalities other than acral enlargement. Pubic hair is Tanner stage 3 and testicular volumes are 10 and 12 cc.

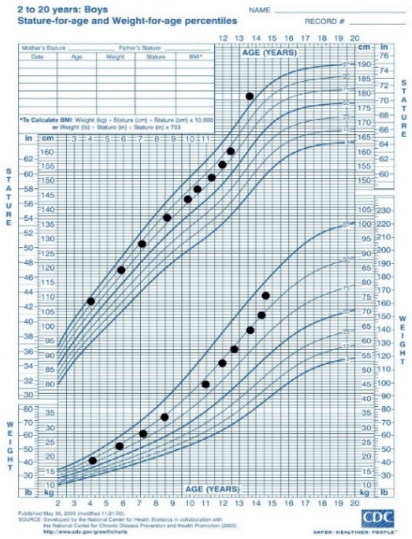

Figure 1. Growth curves

Bone Age is 14 years yielding a predicted adult height of 193.1 cm (76 inches) which, at +2.35 SDS, is above his family genetic height potential. A random serum GH concentration in the morning is 15 ng/ml with a corresponding IGF1 level of 720 ng/ml. (normal range for age and pubertal status in a male: 123-701 ng/ml). Because of the excessive growth and elevated IGF1, a GH suppression test was conducted. GH concentration 120 min after 75g of glucose administered orally was 4 ng/ml. An MRI of the brain was ordered.

Approach

Statural growth is a dynamic process that varies in children during development. Unlike adults who reach a final height greater than 2 SDS for their genetic, sex, and ethnic population of origin, the definition of gigantism in children must include a growth pattern that diverges from normal. This would include the child who exceeds expected growth curve (moving up from established percentiles) or has a growth velocity exceeding the normal range for sex, pubertal stage, and age. Once the growth rate is determined to be significantly greater than normal, establishing biochemical evidence of growth hormone hypersecretion is critical to the evaluation. Measuring IGF1 levels and assessing the suppressibility of GH following a glucose load are the most useful

biochemical tests. Prompt MRI imaging evaluating size, invasiveness, and extrasellar extension of a pituitary adenoma is key. Since close to 50% of patients with pituitary gigantism have a discernable genetic cause, genetic counseling and testing are helpful in management. The case is continued at the end of the chapter.

INTRODUCTION

The association between gigantism and acromegaly was recognized as early as the late 1880's (1), when it was noted that pituitary giants invariably developed acromegalic features such as progressive enlargement of the head, face, hands, and feet (2). (See Appendix) The major difference between these two conditions is that pituitary gigantism results from excessive GH production during the period of active skeletal growth whereas acromegaly results from GH excess ensuing after epiphyseal fusion. 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), pituitary gigantism 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, a degree of clinical overlap is evident by the observation that 10% of patients with acromegaly have tall stature (4), indicating that the onset of GH excess pre-dated epiphyseal fusion in many.

GH hypersecretion may occur sporadically or within a constellation of abnormalities in the setting of several well- recognized syndromes. Conversely, a genetic predilection to the development of GH-secreting pituitary adenomas only 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 chronic GH hypersecretion in childhood are indistinguishable, and the initial diagnostic evaluation standardized. The various categories and sources of GH excess along with their associated genetic abnormalities are discussed individually.

IDIOPATHIC SPORADIC FORMS OF PITUITARY GIGANTISM

Unlike in acromegalic adults, in whom discreet pituitary adenomas are present in the overwhelming majority (6), several different pathologic mechanisms underly childhood GH hypersecretion. These relate to the concept that pituitary gigantism represents a distinct entity, with different characteristics in terms of pituitary morphology and function. Supporting this view are 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 separate pathologic processes. This dual hormonal secretion has been attributed to the presence of mammo-somatotrophs (9;10), which are rare in adults 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 bi-hormonal mammo-somatotrophs when exposed to 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).

GH-secreting tumors are all derived from PIT1-lineage cells. Those composed of somatotrophs may be densely granulated, resembling normal somatotrophs, or sparsely granulated with unusual fibrous bodies. As mentioned above, those composed of mammo-somatotrophs also produce prolactin whereas rare pluri-hormonal tumors composed of cells that resemble mammo-somatotrophs also produce TSH. Some pituitary neuroectodermal tumors (PitNETs) composed of immature PIT1-lineage cells that do not resemble differentiated somatotrophs, mammo-somatotrophs, lactotroph, or thyrotrophs may also cause GH excess. An unusual oncocytic PIT1-lineage tumor known as the acidophil stem cell tumor is predominantly a lactotroph tumor but may express GH. Immature PIT1-lineage cells that express variable amounts of hormones alone or in combination can also sometimes cause GH excess (14)

Table 1. Clinical Characteristics in Syndromic and Familial Pituitary Gigantism						
Disorder	**Mode of Inheritance**	**Clinical Features**	**Frequency of Gigantism**	**Typical Age of Presentation**	**Pituitary Morphology**	**Screening**
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 sheath tumors	10%	Usually 3rd & 4th decade	Pituitary adenoma or pituitary hyperplasia	Annually beginning post-pubertally
3PA Association	Autosomal Dominant or Sporadic	Pheochromocytoma, paraganglioma, pituitary adenoma	Unknown	Usually 3rd & 4th decade	Pituitary adenoma with intracytoplasmic vacuoles	As clinically indicated in unaffected family
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
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

An additional cause of sporadic pituitary gigantism 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, produce GHRH (15;16) and are 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 further supports a central role for abnormal GHRH secretion in the development of gigantism or acromegaly in these cases (18).

SYNDROMIC AND FAMILIAL FORMS OF PITUITARY GIGANTISM

A second major category of childhood GH hypersecretion is that which occurs in the setting of a recognized syndrome. In these cases, gigantism may be the sole presenting feature or it may be detected during clinical follow-up for endocrine or nonendocrine 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 (19). Syndromes that are associated with the development of childhood GH excess are reviewed below. Table 1 outlines the characteristics of the GH excess and other clinical features in these disorders.

Neurofibromatosis-1 (NF-1)

Beginning in the 1970's, reports of gigantism occurring in young children with NF-1 have appeared in the medical literature (20). In these cases, excessive growth has been noted as early as 6 months of life (21). Neuroimaging in these patients typically reveals an optic glioma (22), 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 (23,24). Several investigations aimed at identifying the precise etiology of the gigantism in these children have been conducted, but in all cases in which tumor tissue has been available, immunostaining for GH, GHRH, and somatostatin has been uniformly negative (25;26). 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 showed an increase in GH secretion, contrary to the expected lack of response to arginine, which acts through somatostatin inhibition (27). 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 (28). Interestingly, all affected patients had a tumor involving the optic chiasm, without pituitary involvement. Optic pathway tumors are usually identified on magnetic resonance image scans as a contrast enhancing mass. (28). Interestingly, growth

hormone excess has also been reported in children with sporadic optic pathway tumors without associated NF-1 (29). Figure 2 demonstrates the linear growth acceleration and figure 3 the café-au-lait pigmentation observed in a young boy with NF-1 and gigantism.

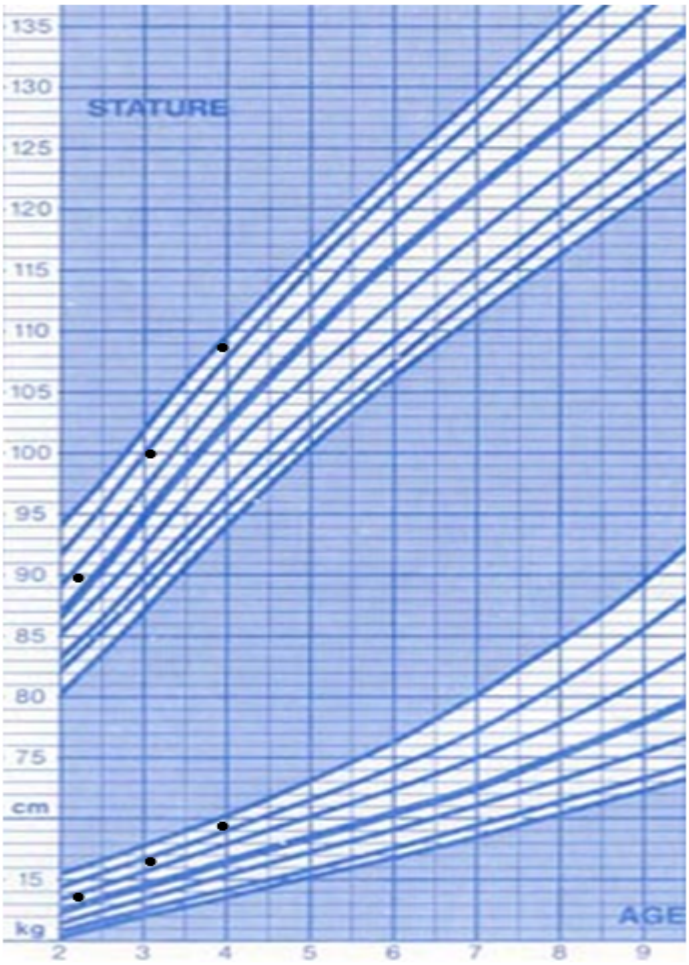

Figure 2. Growth acceleration seen in neurofibromatosis and gigantism.

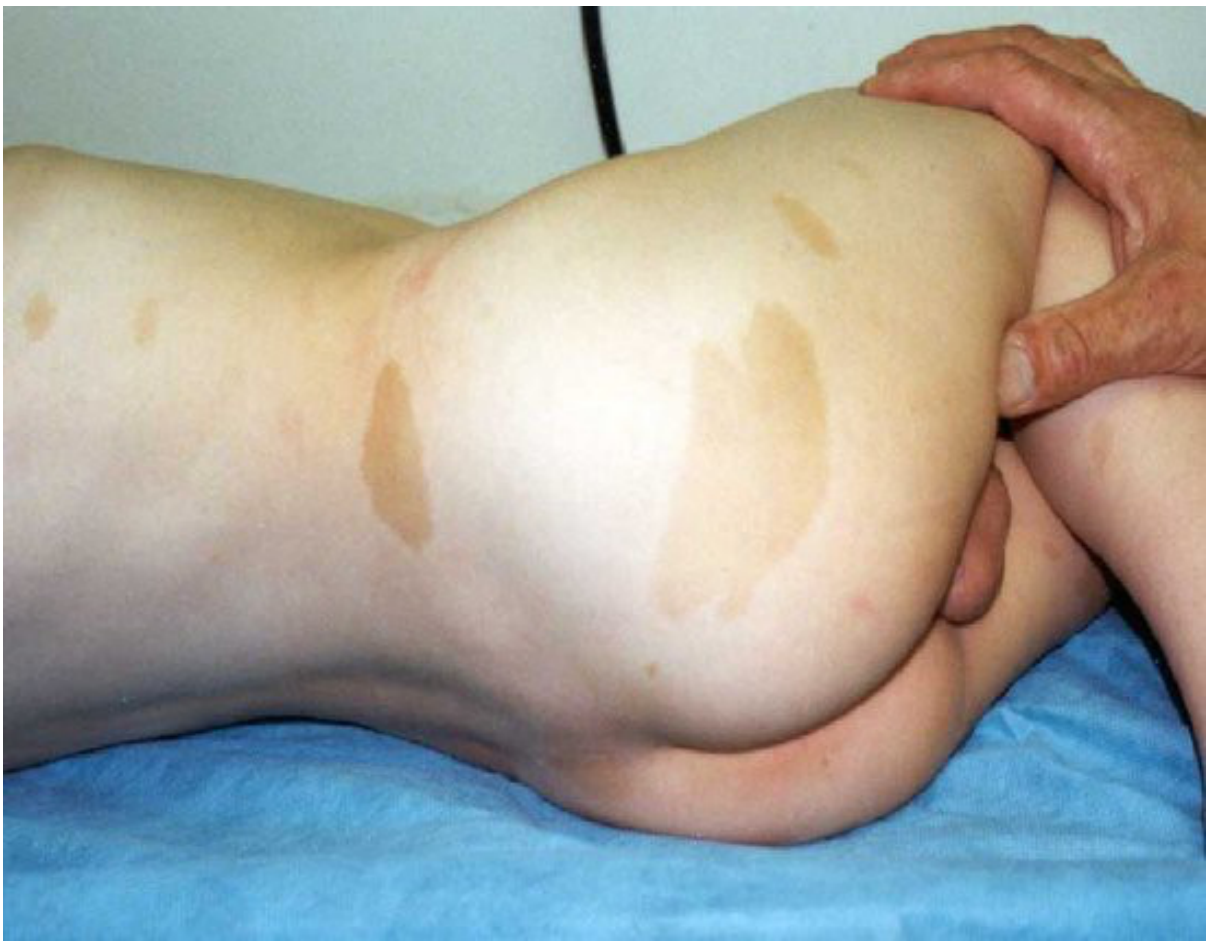

Figure 3. Characteristic “coast of California” café au lait macules in a child with neurofibromatosis and gigantism.

McCune-Albright Syndrome (MAS)

MAS is a complex and heterogenous disorder in which GH excess typically arises in conjunction with additional endocrinopathies and other abnormalities. In the classic form, MAS displays 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 several additional endocrine disorders including gigantism or acromegaly (30).

Elucidation of the molecular genetic defect in MAS in the early 1990’s (31) illuminated the mechanism underlying the abnormal hormone secretion. Activating mutations of Gsα, the stimulatory subunit of the heterotrimeric G-protein complex involved in intracellular signaling, are the basis for nearly all of the clinical manifestations of MAS (32). 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. All affected individuals are mosaic for the mutation, which may make confirmation with a molecular diagnosis challenging. 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 been reported to be 15-21% (33.34) and may be more common in males (34). However, enhanced recognition of the frequency of atypical or *forme fruste* variants of MAS have the potential to increase the estimated frequency. Indeed, several 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 (35.36). Subclinical growth hormone excess has also been reported in MAS, in which the only clinical manifestation may be the presence of normal stature as an adult (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, a rise in serum GH following a TRH test, and hyperprolactinemia (37). Growth hormone excess in MAS is typically accompanied by skull base fibrous dysplasia and is notorious for increasing craniofacial morbidity and macrocephaly (38). Early diagnosis and treatment have been found to decrease the risk of optic neuropathy in these patients (39).

A variety of pituitary morphologic abnormalities are found on histology and imaging in MAS patients with GH hypersecretion (40), ranging from discrete pituitary adenomas (41,42) to diffuse pituitary hyperplasia (7), to no discernible radiographic abnormality (43). Of note is the fact that the Gsα mutation found in MAS is identical to that implicated in the pathogenesis of sporadic GH-secreting pituitary adenomas, where it results in the formation of the *GSP* oncogene. Up to 40% of somatotroph adenomas in adults contain either an Arg201 activating mutation, or a related point substitution of glutamine at position 227 (44). 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 (45). Figure 4 demonstrates an area of classic café au lait skin pigmentation that crosses midline and has serrated edges in a patient with MAS.

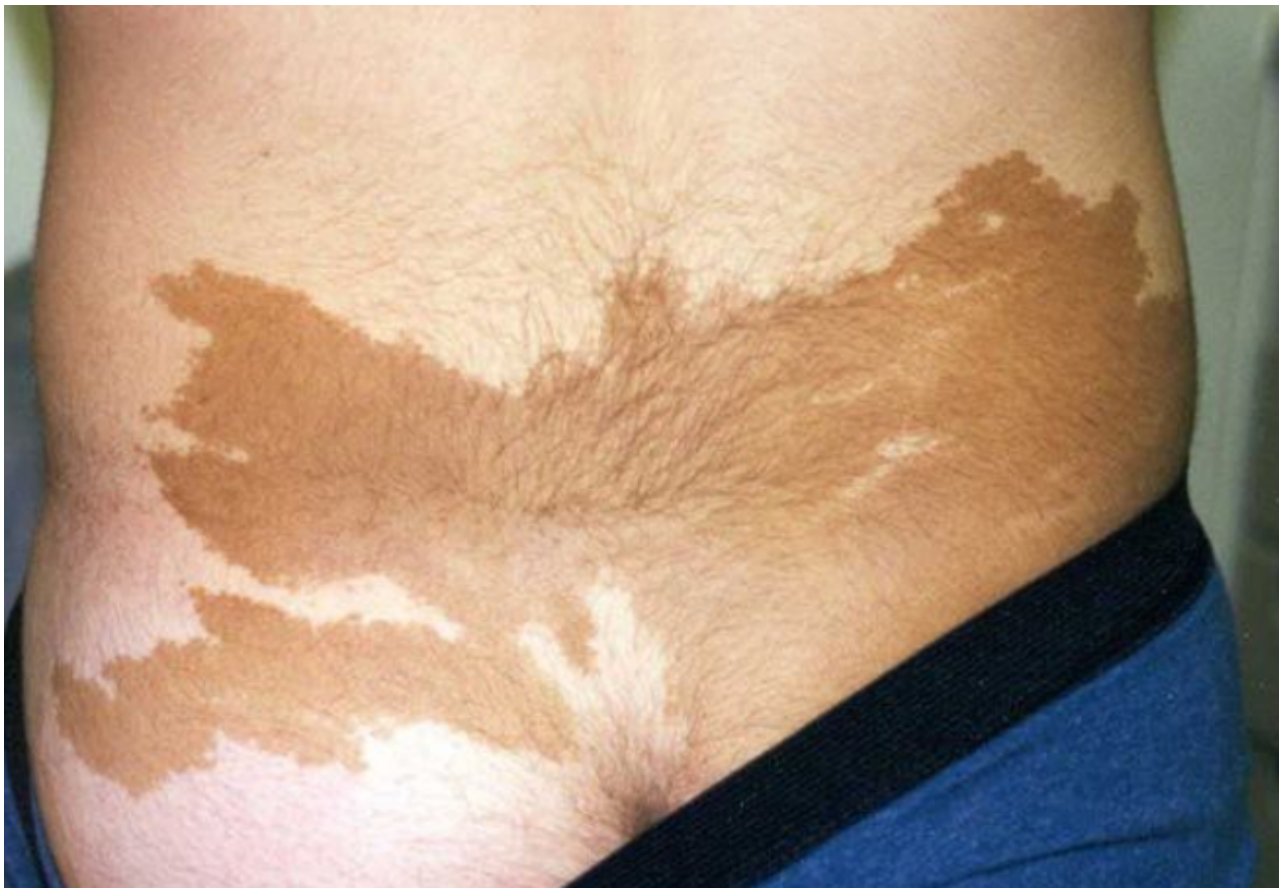

Figure 4. Café au lait pigmentation in the typical "coast of Maine" configuration in an individual with McCune-Albright syndrome.

Multiple Endocrine Neoplasia-Type I (MEN1)

MEN1 is a familial cancer syndrome 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 MEN1 are parathyroid, pancreatic, and pituitary adenomas (46). The gene for MEN1, which had previously been mapped to chromosomal locus 11q13, encodes the 610 amino acid nuclear protein, menin (47). Many different molecular genetic abnormalities within the menin gene have been identified in kindreds with MEN1, including nonsense, missense, deletion, insertion, and donor-splice mutations (48); genotype/phenotype correlations have not been observed. In all cases of MEN1, 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 *MEN1* mutation, leading to a heterozygous loss of the *MEN1* gene in every cell (49). As menin is believed to function as a tumor suppressor protein, the second hit involves a somatic *MEN1* mutation in one cell, with subsequent abnormal cellular transformation and clonal expansion. Indeed, somatic biallelic *MEN1* mutations have been demonstrated to be present in at least 15% of sporadic pituitary adenomas, including somatotroph tumors (50). Anterior pituitary adenomas

in individuals with known MEN1 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 (51). Of these, the majority are prolactinomas, with GH-secreting adenomas developing in approximately 10% of individuals with MEN1 by age 40. The youngest reported case of gigantism in MEN1 occurred in a 5-year-old boy, who presented with growth acceleration and a GH-secreting mammo-somatotroph adenoma in the context of a family history of MEN1 (52). Molecular genetic analysis confirmed the germline and tumor tissue *MEN1* 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 MEN1, as well as ascertaining MEN1 carrier status by germline mutation testing in several clinical situations (53). Interestingly, GH excess due to ectopic elaboration of GHRH from a pancreatic neuroendocrine tumor has also been reported in several individuals with MEN1 (54).

Multiple Endocrine Neoplasia-Type 4 (MEN4)

MEN4 is caused by germline mutations in the CDKN1B gene which encodes the putative tumor suppressor p27Kip1 (55). Affected patients are typically heterozygous for mutations in CDKN1B and exhibit a phenotype similar to that seen in MEN1. Because of the low number of individuals diagnosed with MEN4, screening protocols for patients and their family members have not yet been established (56).

Carney Complex (CNC)

Initially described in 1985 (57), 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 MEN1 (multiple endocrine tumors), MAS (endocrine hyperfunction and skin pigmentation) and Peutz-Jeghers syndrome (mucosal lentiginoses and gonadal tumors), but has a unique clinical and molecular genetic identity. Two distinct genetic abnormalities have been implicated in the pathogenesis of CNC. The first is found on 2p16 (58), although a specific candidate gene within this region has not been identified. The second involves mutations in the gene encoding the protein kinase A regulatory subunit (1α) (PRKAR1A) and explains 35-44% of both familial and sporadic cases of CNC (59). This protein, which is intricately involved in endocrine cell signaling pathways, is thought to function as a tumor suppressor. 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 (60).The identical mutation has also been found in some sporadic endocrine tumors. As with MEN1, 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 (61). 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 (62) and concomitant hyperprolactinemia (63) 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 subunits of succinate dehydrogenase (56;64). Growth hormone excess typically occurs in the 3rd and 4th decades of life (65). To date, no pediatric patients with pituitary 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 condition, "Familial Isolated Pituitary Adenomas" (FIPA), is defined as "the development of pituitary adenomas of any type in two or more members of a family in the absence of clinical and genetic evidence of other known syndromic diseases". At least 46 different affected kindreds have been reported (66). Unlike in MEN1 and CNC, GH excess tends to arise 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 (67) and a more virulent course than is seen in sporadic somatotropinomas has been suggested by a case series (68). Once assumed to represent a variant of MEN1, mutations within the menin gene as the etiology for FIPA were conclusively excluded (69;70). 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 MEN1. 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 (71-73) 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! Interestingly, a second potential locus for FIPA has been mapped to 2p12-16, very close to the region implicated in several kindreds with CNC (66). 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 MEN1, 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 occur in different members of the same kindred (76;77) . Macroadenomas with invasion into the cavernous sinus are common in the setting of FIPA, and treatment is notoriously difficult (77).

X-Linked Acrogigantism

An additional cause of familial gigantism and acromegaly is due 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 (78; 79). 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. The condition can result from either germline or somatic duplications in *GPR101* and has a female predominance (80, 81). That more girls than boys have X-LAG might be related to their greater number of X chromosomes. However, a potentially lethal effect of an Xq26.3 microduplication on hemizygous male embryos is also a proposed explanation (82). Mosaicism for *GPR101* duplication resulting in X-LAG has also been reported in sporadic cases involving boys (83). 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 (84). 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.

A summary of the genetic abnormalities causing gigantism and their putative abnormalities is shown in figure 5.

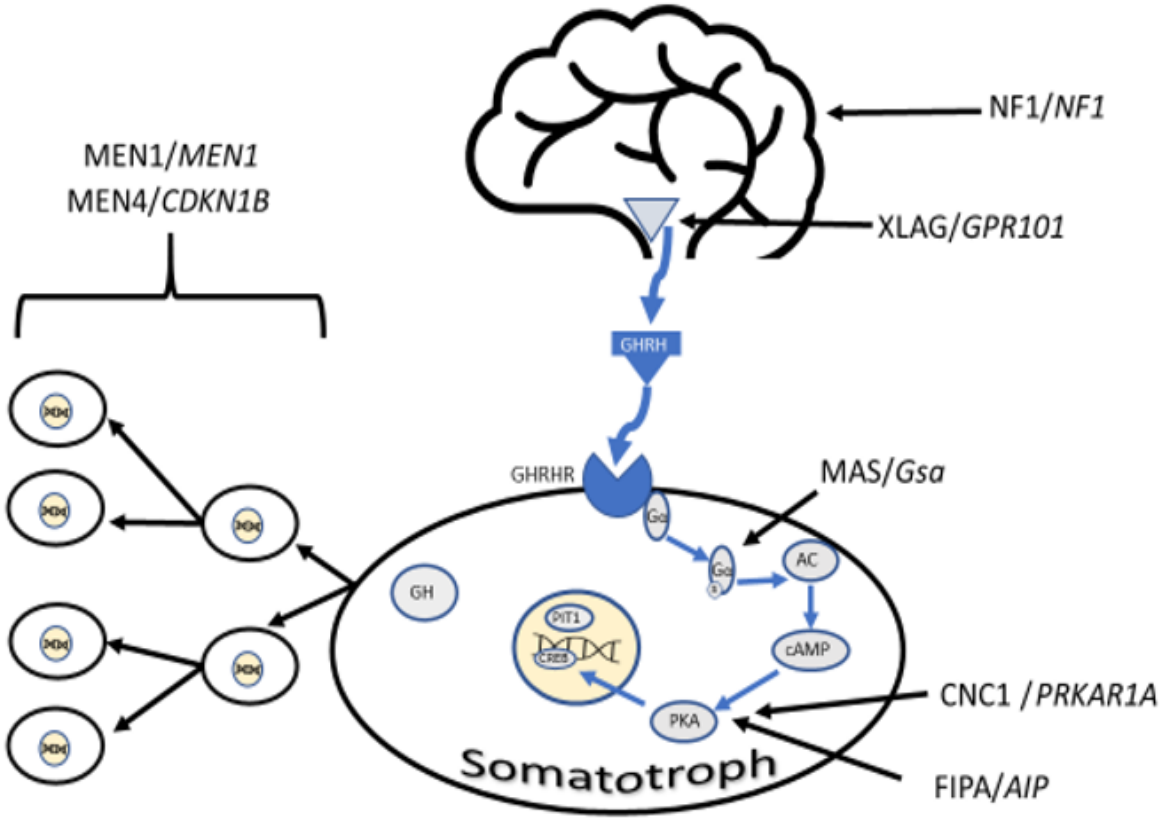

Figure 5. Schematic of disorders leading to pituitary gigantism, genetic loci, and their putative targets. NF1: Neurofibromatosis type 1; XLAG: X-linked acrogigantism; MAS: McCune-Albright syndrome; CNC1: Carney complex type 1; FIPA: Familial isolated pituitary adenomatosis; MEN1: Multiple endocrine neoplasia syndrome type 1; MEN4: Multiple endocrine neoplasia syndrome type 4. The MEN syndromes

display unrestrained cell replication due to lack of a tumor suppressor whereas the others affect the GH secretory pathway at the points shown. See text above for details.

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. However, the excessive linear growth observed in young children with gigantism may be accompanied or even preceded by macrocephaly and or increased weight for height. (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 (85). 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 been reported to be normal or advanced, even in the complete absence of sex steroid production. Figure 6 demonstrates the prognathism, coarse facial features and typical tall stature seen in a 12-year-old boy with gigantism, and Figure 7 illustrates enlargement of the hands in this same patient.

Figure 6. Twelve-year-old boy with pituitary gigantism measuring 6’5” with his mother. Note the coarse facial features and prominent jaw.

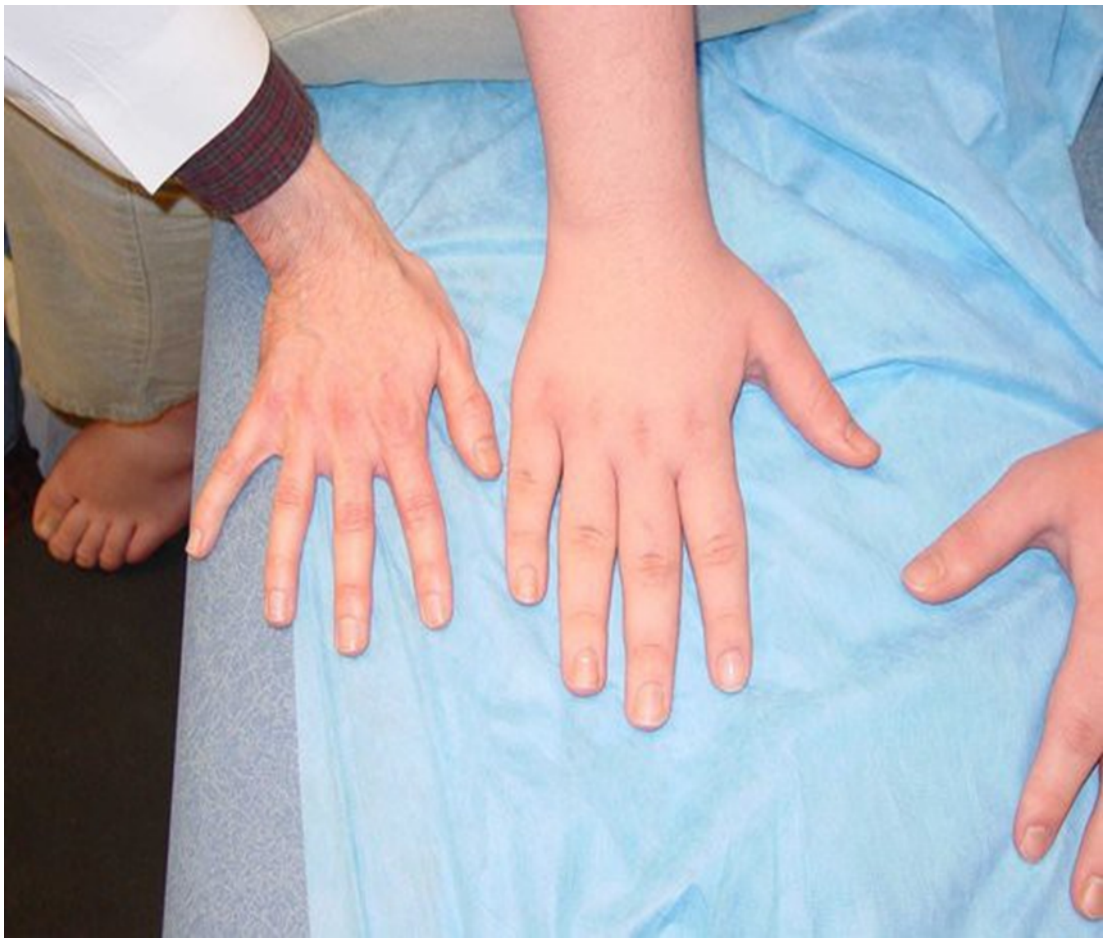

Figure 7. Enlarged hand of the same patient in comparison with the hand of an adult male with a height of 6'1". The patient's middle digit has a circumference of 9 centimeters.

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 (86). 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 MEN1. Rarely, alterations in glucose tolerance brought about by GH excess may result in the development of overt diabetes, leading to transient diabetic ketoacidosis (87-89) which may even be the presenting feature in rare instances (90). 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 (91). 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 (92)

DIAGNOSTIC EVALUATION OF GH EXCESS

The gold standard for making the diagnosis of GH excess relies on the inability to suppress serum GH concentration 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 (93). A normal response to a standardized glucose bolus (1.75 gm/kg up to 75 grams) utilizing the newer IRMA/ICMA assays is a GH level below 1 ng/ml (94). However, given the observation that recurrence of GH excess may be detected in patients with a GH nadir less than 1 ng/ml, and that healthy subjects nearly always suppress to below 0.14 ng/ml, some investigators have suggested that the 1 ng/ml cut-off is too liberal (95). The nadir in serum GH is typically occurs within the first 2 hours of the test. Occasionally, 24-hour integrated GH assessment may be helpful in cases in which an equivocal response to OGTT is seen (96). 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 (97). 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 8 illustrates the typical appearance of a GH-secreting pituitary macroadenoma in an adolescent with gigantism.

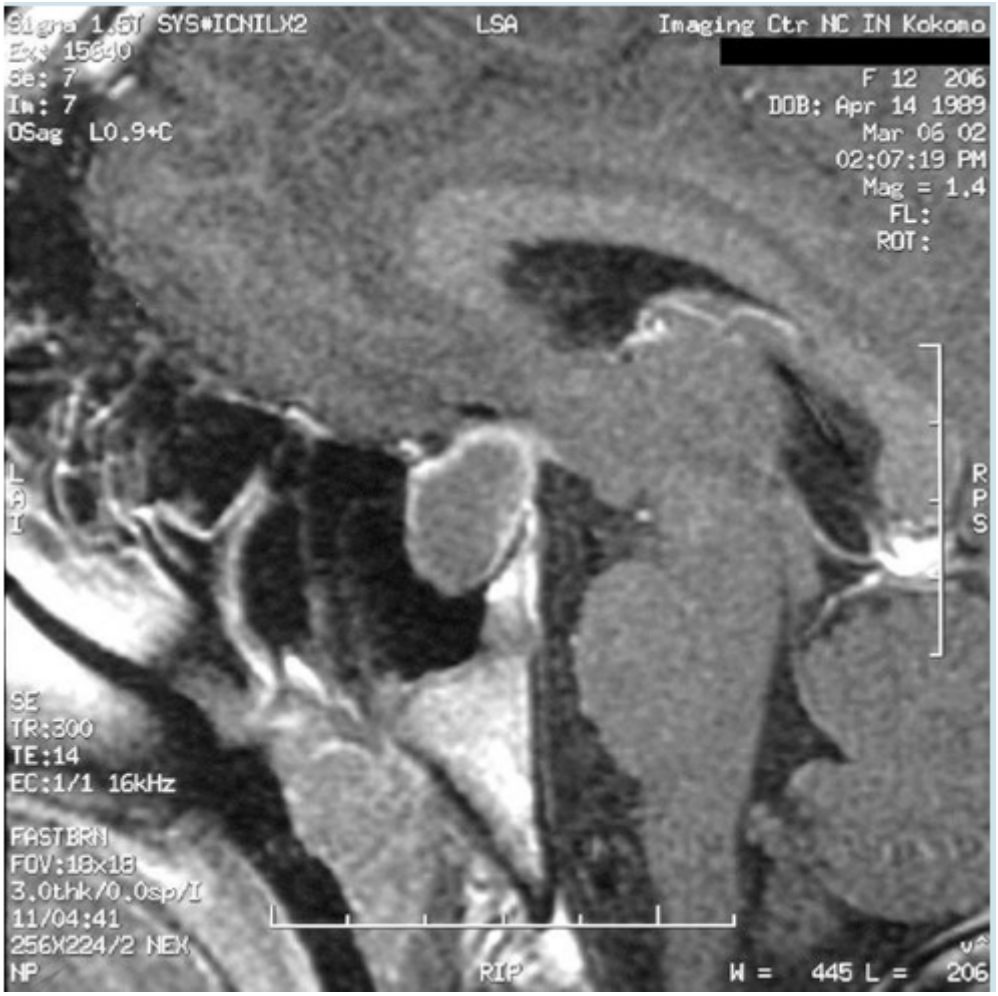

Figure 8. Pituitary somatotroph macroadenoma in an adolescent with gigantism.

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 (98). 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 (99). The effect of sex steroids on IGF-1 and GH suppression must also be considered 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 (100). Therefore, both screening and definitive testing for GH excess should be performed in the context of high clinical suspicion, and IGF-1 levels interpreted according to age and pubertal stage-adjusted normal ranges (see figure 9).

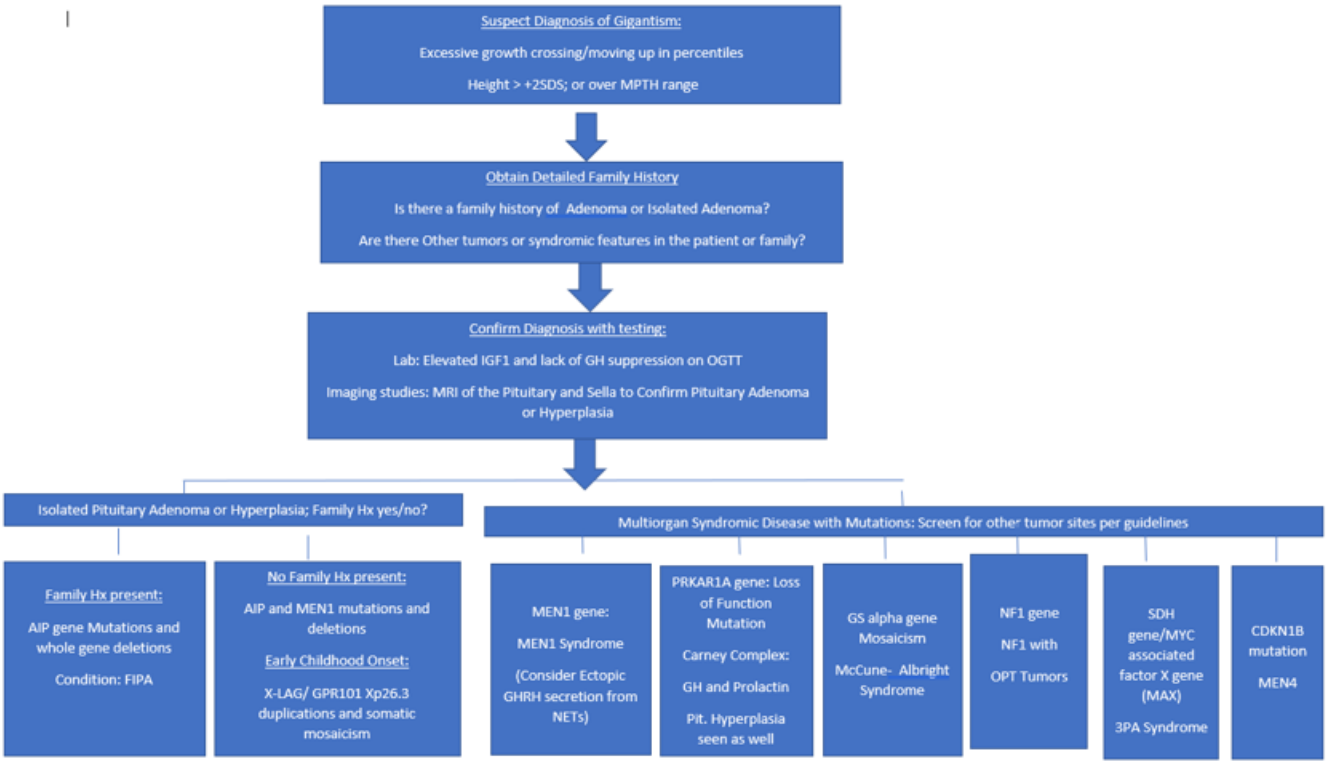

Figure 9. Schematic evaluation of patients with suspected pituitary gigantism

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 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 (101). Of all parameters investigated, GH levels themselves appear to correlate best with overall morbidity and mortality in acromegaly (102). Table 2 summarizes the current therapeutic options as they pertain to pediatric patients, each of which is discussed below.

Table 2. Therapeutic Modalities in GH Excess in Pediatric Patients			
Modality	**Specific Options**	**Current Indications**	**Pediatric Experience**
Surgery	Transphenoidal resection	Pituitary microadenoma or macroadenoma	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 Ectopic GH excess	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 equivalent 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 (103), with the objective being preservation of pituitary function in association with the elimination of the GH excess, as evidenced by a rapid normalization of serum GH levels (often within one hour) and response to OGTT. Not surprisingly, the expertise of the individual surgeon impacts the likelihood of success (104). However, while surgery cures the majority of patients with microadenomas, less than 50% of patients with macroadenomas are cured of their disease (105, 106). 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 (107;108). In one large retrospective study of 208 patients with pituitary gigantism, long-term control of GH/IGF1 was achieved in only 39% (108). Experience with surgical treatment of gigantism in children and adolescents has been comparable to that observed in adults (109;110), 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 (111).

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 (112). Additional concerns particularly relevant to children include potential adverse neurocognitive effects and the possible development of hypothalamic obesity, both of which have been linked to cranial irradiation in pediatric patients (112;113). Therefore, radiation therapy would be considered a last resort. Improved precision and safety are 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 (112;114-116).

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 (117), 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 act by binding to somatostatin receptors within somatotroph adenomas (118). By far the greatest experience in the United States has been with octreotide, which is typically administered subcutaneously in three divided doses daily. Short-term administration of octreotide decreases GH levels within one hour in > 90% of patients with acromegaly (119), while sustained use normalizes GH and IGF-1 levels in up to 65% of patients (120). 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 (121;122). Continuous subcutaneous infusion of octreotide has also resulted in superior efficacy in controlling GH hypersecretion in a pubertal patient (123). 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 (124). This allows for monthly IM administration, resulting in a safety and

efficacy profile that is comparable to or improved in contrast to traditional dosing (125). Both slow-release preparations have also been used in the treatment forms of GH excess due to ectopic GHRH secretion (126) and in MAS associated gigantism (127-129), and have been noted to have equivalent safety and efficacy (130). The development of novel somatostatin analogues has the potential to improve efficacy over existing agents (131). The major side effect of all the somatostatin analogues is an increased risk of biliary sludge and gallstones after sustained use, necessitating periodic ultrasound examinations in patients treated long-term (132).

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 also 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 (128).

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 (133). This is achieved through alterations in GH structure altering receptor binding compared to the native GH molecule (121), 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 (134). 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 (135;136), long-term follow has demonstrated that these complications are rare and that efficacy is very good (137;138). Combination therapy using pegvisomant along with a dopamine agonist or somatostatin analogue also appears promising (137). 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 (139). This approach resulted in successful normalization of IGFI levels in a 4 year old with NF-1 (140), a 12 year old with MAS (141), and a couple of children with persistent GH hypersecretion following surgical removal of a pituitary adenoma who had failed a somatostatin analogue (142;143). 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 (144).

Treatment of Tall Stature

Medical treatment of children and adolescents with tall stature was more common in the past (145), particularly for girls, but is now strongly discouraged except in exceptional cases. This is because of increased cultural acceptance of tall stature and recognition of side effects of treatment, which include reduced fertility (146) and increased prevalence of depression (147) not related to adult height. 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 in these exceptional cases. When

this is the case, acceleration of epiphyseal fusion can be achieved with exogenous sex steroids (145). 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 (148;149). 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 (150;151).

CONCLUSION

The differential diagnosis of pituitary gigantism includes a significant number of heterogeneous disorders exhibiting a vast array of clinical and genetic features (66). In most cases, the history, physical examination and adjunctive biochemical, imaging, and/or molecular genetic testing will ultimately reveal the diagnosis. Albeit rare, pituitary gigantism affords 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.

CASE OUTCOME

The MRI revealed a pituitary macroadenoma after which he underwent transsphenoidal surgery. Histopathological diagnosis was mammosomatotropic adenoma. Three months after surgery, IGF-1 normalized, nadir GH during OGTT suppressed to less than 1 ng/mL and no residual tumor was found on the MRI. Genetic testing identified a mutation in the *AIP* gene. This case points out the importance of early diagnosis of gigantism, as treatment delay increases long-term morbidity.

KEY LEARNING POINTS

- Pituitary gigantism is rare but important condition resulting from excessive secretion of GH (and therefore IGF1) before fusion of epiphyseal growth plates leading to tall stature, acral enlargement, facial changes, headaches, and excessive sweating.
- Excessive linear growth is the cardinal feature of excessive GH production in children and adolescents who have open epiphyseal growth plates.
- There is a male preponderance (78%) in pituitary gigantism in contrast to the slight female predominance (54.5%) observed in acromegaly.
- Once growth hormone (GH) hypersecretion has been established, prompt studies to examine pituitary anatomy and define the etiology via family history and genetic testing should be performed.
- Normalization of GH and IGF-1 levels is the goal of therapy
- Because nearly 50% of patients with pituitary gigantism have a known underlying genetic cause, these patients should receive genetic counseling and testing for mutations.
- Somatotropinomas in pituitary gigantism are usually large (macroadenomas) and difficult to cure with surgery or medical therapy alone.
- Patients with large tumors and multiple surgeries and radiotherapy are often left with multiple pituitary hormone deficiencies.

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APPENDIX

Research into the function of the pituitary, and GH in particular, started with clinical observations and anatomical descriptions of people with gigantism and adults with acromegalic features (1). In 1884, the Swiss general physician Fritsche reported in great detail the history of a 44-year-old man developing the characteristic features of acromegaly — a term later coined by Pierre Marie in 1886 (2) — and an enlarged pituitary, which was observed post-mortem (3). Minkowski proposed the connection between the pituitary and acromegaly before eosinophilic tumors of the anterior pituitary emerged as the anatomical basis of gigantism and acromegaly (4).

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