CHAPTER

Gigantism: clinical diagnosis and description

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Iulia Potorac[1], Liliya Rostomyan[2], Adrian F. Daly[1], Patrick Petrossians[2] and Albert Beckers[2]

[1]*Department of Endocrinology, Centre Hospitalier Universitaire de Liège, Liège Universite, Liège, Belgium*

[2]*Service d'Endocrinologie, Domaine Universitaire du Sart Tilman, Universitè de Liège, Liège, Belgium*

Gigantism has always been a subject of interest among the general public due to connotations of otherworldly strength and abilities. Until quite recently, the study of gigantism as an illness has not attracted major scientific attention [1], probably due to its very rare nature. International collaborative research has now led to significant advances in our understanding of the molecular mechanisms responsible for some forms of pituitary gigantism.

The majority of cases of gigantism can be easily recognized even without medical training. In less clear-cut cases, the diagnosis can be more difficult to establish, due to intra- and interindividual variations of growth patterns. Scientifically, tall stature is defined as a height over 2 standard deviation (SD) above the mean for the same sex, age, and population of origin or over 2 SD above the midparental height, but it can also manifest as significantly increased growth velocity or an abnormal growth pattern [2].

Excessive growth can be secondary to endocrine or to nonendocrine disturbances, although, most frequently, it is a reflection of familial tall stature or constitutionally advanced growth. This chapter is dedicated to the type of tall stature that is due to excessive growth hormone (GH) secretion, pituitary gigantism. In very rare cases, GH can be secreted ectopically [3], or pituitary GH hypersecretion can be secondary to ectopic GH-releasing hormone (GHRH) secretion [4]. Very few cases of gigantism due to ectopic GH and/or GHRH secretion have been reported [5].

Excessive GH secretion can commence at any age. When it begins before the closure of growth plates, the clinical phenotype will be gigantism and when it occurs afterwards, it leads to acromegaly. Acromegaly and gigantism are, therefore, manifestations of the same hormonal anomaly occurring at different periods of growth. Certain underlying molecular genetic mechanisms that cause GH hypersecretion—usually due to a pituitary adenoma—can be more frequent in younger versus older patients.

3.1 Clinical diagnosis—general aspects

Patients with pituitary gigantism are mainly males. In the largest series of patients with pituitary gigantism studied so far, nearly 60%–80% of patients were males [6,7]. Rapid growth was found to begin generally in late childhood or early puberty; this occurred at a significantly earlier age in

Gigantism and Acromegaly. DOI: https://doi.org/10.1016/B978-0-12-814537-1.00015-4

females than males (11 vs 13 years, respectively) [6]. Only in X-linked acrogigantism (X-LAG) (see below) does rapid growth always begin much earlier, almost always during the first year of life.

Despite their young age, patients with pituitary gigantism can develop typical clinical features of acromegaly, with enlargement of the extremities and facial dysmorphism being the most common [6]. Other clinical consequences of GH hypersecretion are also found in this population, such as excessive sweating, cutaneous changes, arthropathies, and carpal tunnel syndrome. Metabolic consequences such as glucose intolerance and diabetes mellitus also occur, as does sleep apnea syndrome. The cardiovascular impact of GH hypersecretion translates into hypertension, present in over a third of patients above the age of 20, as well as other cardiac anomalies, among which left ventricular hypertrophy, diastolic and/or systolic dysfunction, valvulopathies, and dilated cardiomyopathy are the most frequent [6,8]. Development of cardiovascular complications seems to be related to a longer disease duration before diagnosis and longer delays in treatment and disease control. Whether increased GH/insulin-like growth factor 1 (IGF-1) have an enhanced pathological effect on the growing heart during childhood and adolescence remains to be explored.

Mass effect symptoms caused by the developing pituitary mass include headaches, which can rarely be due to apoplexy of the pituitary adenoma, and visual field defects due to optic chiasm compression, as these tumors often exhibit suprasellar extension in pituitary gigantism [6,7]. This is contrary to the situation in acromegaly, in which case somatotropinomas generally exhibit infrasellar extension [9]. Hypopituitarism is present in around 25% of patients at diagnosis, but it becomes more common during follow-up as a consequence of the various treatment methods and affects over half of pituitary gigantism patients [6,7]. Prolactin (PRL) cosecretion can lead to galactorrhea and irregular menses. If, before epiphyseal closure, the pituitary mass becomes large enough to suppress gonadotropin secretion or if concomitant hyperprolactinemia occurs, the resulting hypogonadism will further delay growth plate fusion, thereby worsening increased vertical growth.

Despite rapid growth starting around the age of 13, diagnosis of a pituitary adenoma is generally established much later, around the age of 21.5 years in males. Female patients, however, are usually diagnosed earlier, around the age of 16 [6]. Therefore several years pass between the appearance of the first signs and symptoms of the disease (rapid growth) and its diagnosis, which impacts management and disease control. In male patients, this delay was found to be around 6 years, whereas in female patients, it was found to be 2.5 years [6]. This late diagnosis of excessive growth may be due to the fact that it is comparatively rare, and the referral/investigation systems may not be as efficient as in short stature; in males, there may also be some inbuilt bias that deems tall stature as being less "urgent" to investigate than short stature.

The delay in diagnosis allows for abnormally excessive growth to continue for longer and represents another factor contributing to the increased final height. In the largest specific pituitary gigantism series, final height was found to be >3 SD above the median height for the population, with a median difference from the predicted midparental height of 20 cm [6]. Greater final stature was found to be related to a younger age of disease onset, larger tumors, and higher GH hypersecretion.

The diagnosis of pituitary gigantism relies on the presence of GH hypersecretion. IGF-1 production physiologically varies depending on whether puberty has started, with levels rising as puberty progresses. It also differs according to gender with female patients having lower levels than males as a consequence of estrogen-induced hepatic GH resistance. It is important, therefore, when evaluating a patient with tall stature, to use adequate normal ranges, according to gender and pubertal status. We found that IGF-1 levels were on average around 2.5 $\times$ the upper limit of normal (ULN),

while median GH levels at diagnosis were around 35 ng/mL [6,7]. PRL cosecretion was found in a third of patients with pituitary gigantism overall.

After biochemically confirming GH hypersecretion, its source should be located using pituitary magnetic resonance imaging (MRI). In pituitary gigantism, this is usually a pituitary macroadenoma. We found that the maximal pituitary adenoma diameter was around 22 mm [6], as later confirmed in other series [7], whereas nearly 15% of patients already had giant adenomas at diagnosis, measuring over 40 mm in maximal diameter [6]. Over half of the somatotropinomas responsible for pituitary gigantism were found to be invasive and over three-quarters exhibited extension outside the sella [6]. Rarely, an adenoma cannot be identified and diffuse hyperplasia of the pituitary is seen; this can sometimes precede adenoma formation, as detailed further below.

3.2 Clinical diagnosis—specific aspects

Pituitary gigantism can be an isolated occurrence, without other endocrine or nonendocrine manifestations related to a common pathophysiological mechanism, or it can develop in a syndromic context, present in the patient and/or their families. Depending on the underlying cause of GH hypersecretion, the clinical presentation varies as does the timing of the development of gigantism and its associated manifestations.

3.2.1 Nonsyndromic forms of GH hypersecretion

3.2.1.1 AIP *mutations*

About two decades ago, the disease entity familial isolated pituitary adenomas (FIPA) was originally reported in Liège, Belgium [10–13]. This familial condition consists of the occurrence of pituitary adenomas in two or more related members of the same family in the absence of other syndromic features or genetic anomalies corresponding to multiple endocrine neoplasia type 1 (MEN1) or Carney complex. International research revealed that unlike pituitary adenomas occurring sporadically, adenomas in FIPA patients were diagnosed at earlier ages and were larger at diagnosis [12]. Somatotropinomas are more frequent in the FIPA context than in sporadic cases, representing between 40% and 50% of FIPA cases [13,14]. In homogeneous somatotropinoma FIPA families, acromegaly can be diagnosed up to 10 years earlier than in heterogeneous FIPA families and in sporadic cases [13].

In 2006, Vierimaa et al. [15] discovered the role of the *aryl hydrocarbon receptor interacting protein* (*AIP*) gene in the predisposition towards the development of pituitary adenomas in FIPA kindreds. Further studies revealed that *AIP* germline mutations were responsible for 50% of the FIPA families with homogeneous acromegaly and 20% of FIPA kindreds in general [13,16]. Acromegaly patients bearing *AIP* mutations have a younger age of disease onset, with half manifesting symptoms during childhood and adolescence; most patients are males. Somatotropinomas in these patients are larger and associated with higher levels of GH hypersecretion at diagnosis than sporadic GH-secreting adenomas. Somatotropinomas of patients with *AIP* mutations generally require more surgical interventions and have a significantly worse response to somatostatin

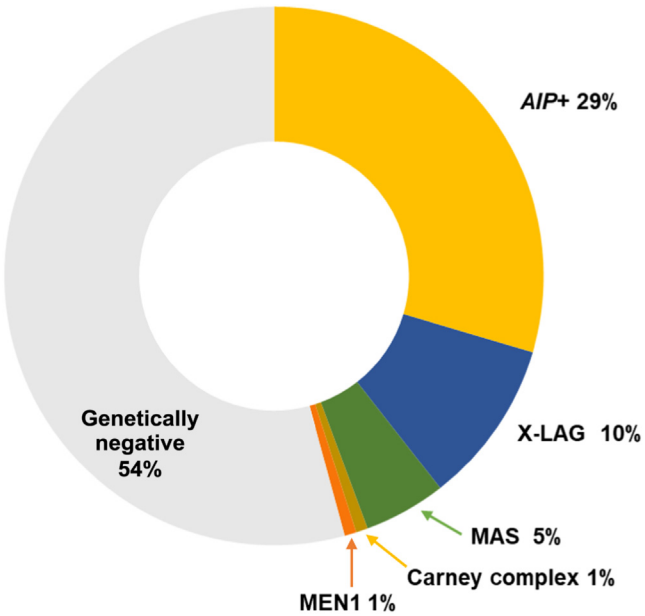

FIGURE 3.1

Prevalence of genetic forms of pituitary gigantism [6].

analog treatment (SSA) than sporadic acromegaly, both in terms of hormonal secretion and volume reduction [17].

Due to the younger age at disease manifestation, *AIP* mutation−positive somatotropinoma patients present with gigantism more frequently than *AIP*-negative somatotropinoma patients (32% vs 6.5%) [17]. Our study found that nearly a third of gigantism patients carried *AIP* mutations, thereby representing the most frequent genetic anomaly identified so far in this condition (Fig. 3.1) [6]. *AIP* mutation−positive patients with gigantism are predominantly males, with a disease onset around the age of 13. Most of the adenomas are large at diagnosis with a median maximal tumor diameter of 25 mm. Giant adenomas are found in 10% of the patients presenting with macroadenomas (Fig. 3.2). IGF-1 levels at diagnosis are around 2× ULN and nearly a third of cases exhibit PRL cosecretion.

3.2.1.2 X-linked acrogigantism

X-LAG is the most recently identified condition associated with pituitary gigantism. It manifests at a very early age, generally around the age of 1−2 years and leads to severe gigantism during adolescence if untreated. Children with this syndrome are usually born at full term, with normal height and normal weight (Fig. 3.3) [19,20]. Some X-LAG patients can show clinical features of acromegaly at diagnosis: acral enlargement, coarse facial features, prominent mandible with increased interdental spaces, and soft tissue swelling. Over a third of patients can

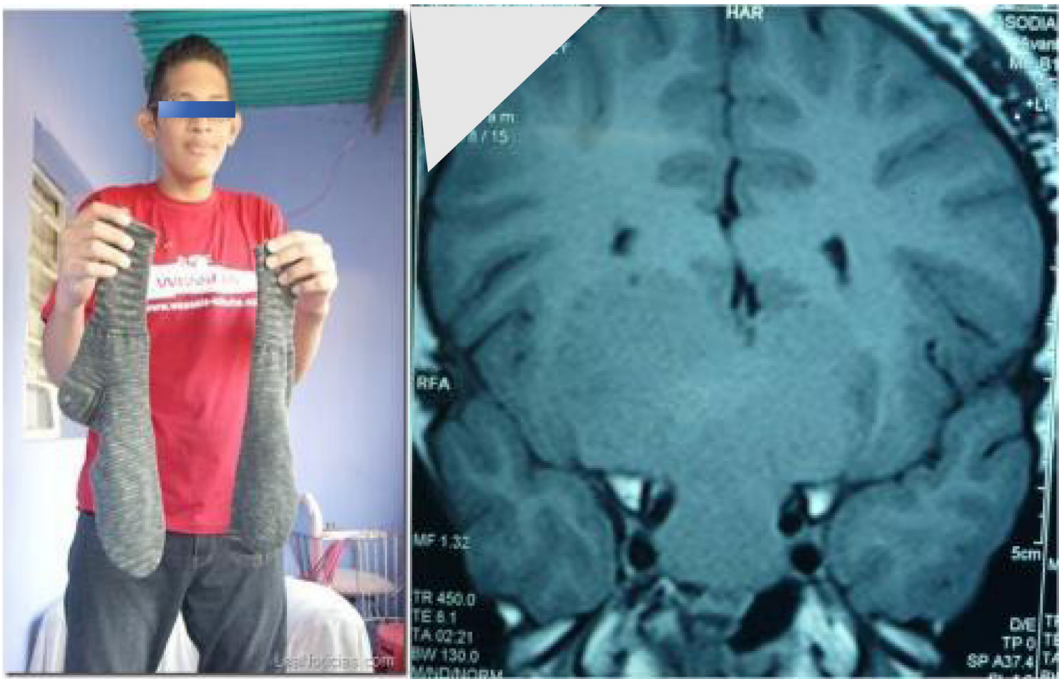

FIGURE 3.2

A case of *AIP*-related gigantism secondary to a giant pituitary somatotropinoma [18].

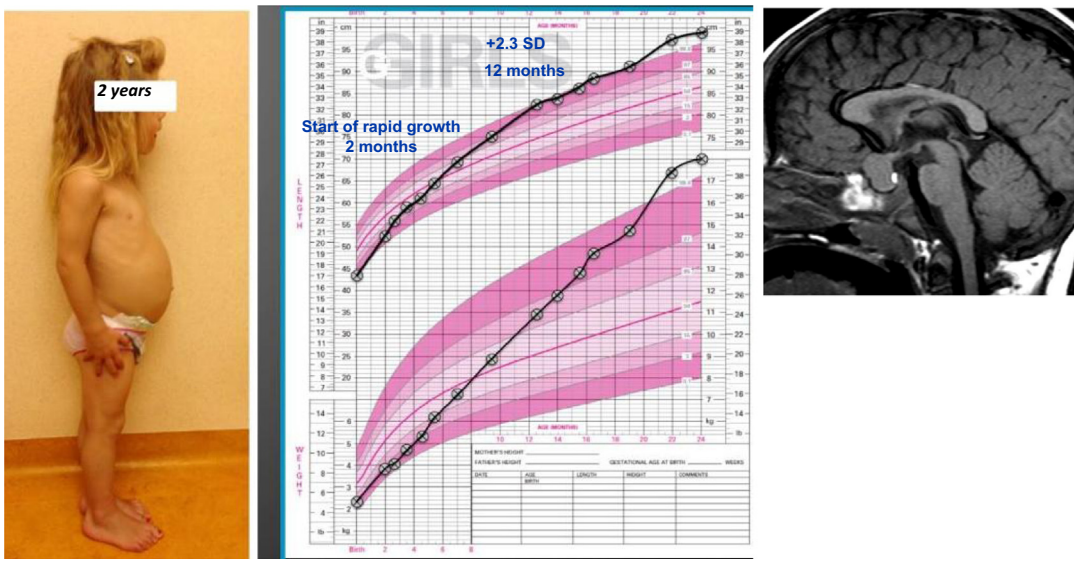

FIGURE 3.3

Overgrowth in X-LAG syndrome. Diffuse pituitary hyperplasia on MRI [19].

have an increased appetite, which seems to be uncommon among other causes of pituitary gigantism and some X-LAG patients present with acanthosis nigricans as a sign of insulin resistance [20]. X-LAG was found to be the cause of pituitary gigantism in 10% of the population studied by our group. Among X-LAG patients, unlike other forms of pituitary gigantism, the majority of patients ($>70\%$) are females [6,19].

On MRI, X-LAG patients exhibit either pituitary macroadenomas (with a median tumor diameter of 18 mm) or diffuse pituitary enlargement corresponding to hyperplasia. However, dramatic cases with giant adenomas have been described (Fig. 3.4) [21]. Adenoma extension is mostly found to be suprasellar, with rare cases of cavernous sinus invasion [20].

Biologically, GH levels are generally greatly above the ULN, without suppression during the oral glucose tolerance tests, while IGF-1 is $>3\times$ ULN. Most cases have associated hyperprolactinemia, with PRL levels as high as $90\times$ ULN [20].

X-LAG is due to microduplications in Xq26.3 including the *GPR101* gene, which encodes for an orphan G-protein-coupled receptor [19]. *GPR101* appears to be responsible for the phenotype [22]. X-LAG can occur sporadically or as FIPA in kindreds with acrogigantism [20]. The microduplication can be constitutional or occur as somatic mosaicism, which is the case in male sporadic patients [23].

3.2.1.3 Genetically negative cases

We found that about 50% of cases of pituitary gigantism have no detectable genetic anomaly explaining the phenotype (genetically negative patients) [6,7]. These patients are mostly male and older at diagnosis compared to *AIP*-positive and X-LAG patients (Fig. 3.5). They have levels of IGF-1 that are intermediate between the very high secretion in X-LAG patients and the values in *AIP*-positive cases. PRL cosecretion is also present in over a third of these patients at diagnosis [6,7]. They have large pituitary adenomas, just as in *AIP*-positive and X-LAG patients [6,7], but with disease control that is more difficult to achieve.

3.2.2 Syndromic forms of GH hypersecretion

Syndromic GH hypersecretion can appear in the context of MEN1 or MEN4; Carney complex; McCune–Albright syndrome (MAS); and 3PAs—pheochromocytoma, paraganglioma, and pituitary adenoma association.

3.2.2.1 Multiple endocrine neoplasia type 1

MEN1 is a tumor predisposition syndrome that mainly involves the parathyroids, the endocrine pancreas and digestive tract, and the pituitary. Primary hyperparathyroidism is present in over 90% of cases due to parathyroid hyperplasia [24]. Enteropancreatic tumors are found in 30%–70% of MEN1 patients [24]. Less frequently, adrenal cortical tumors, thymic and bronchial neuroendocrine tumors, cutaneous tumors (angiofibromas, collagenomas, lipomas), meningiomas and rarely, pheochromocytomas are also encountered.

In terms of pituitary involvement, the pituitary adenomas associated with MEN1 are more frequently prolactinomas, followed by somatotropinomas. Nonfunctioning and adrenocorticotrophic

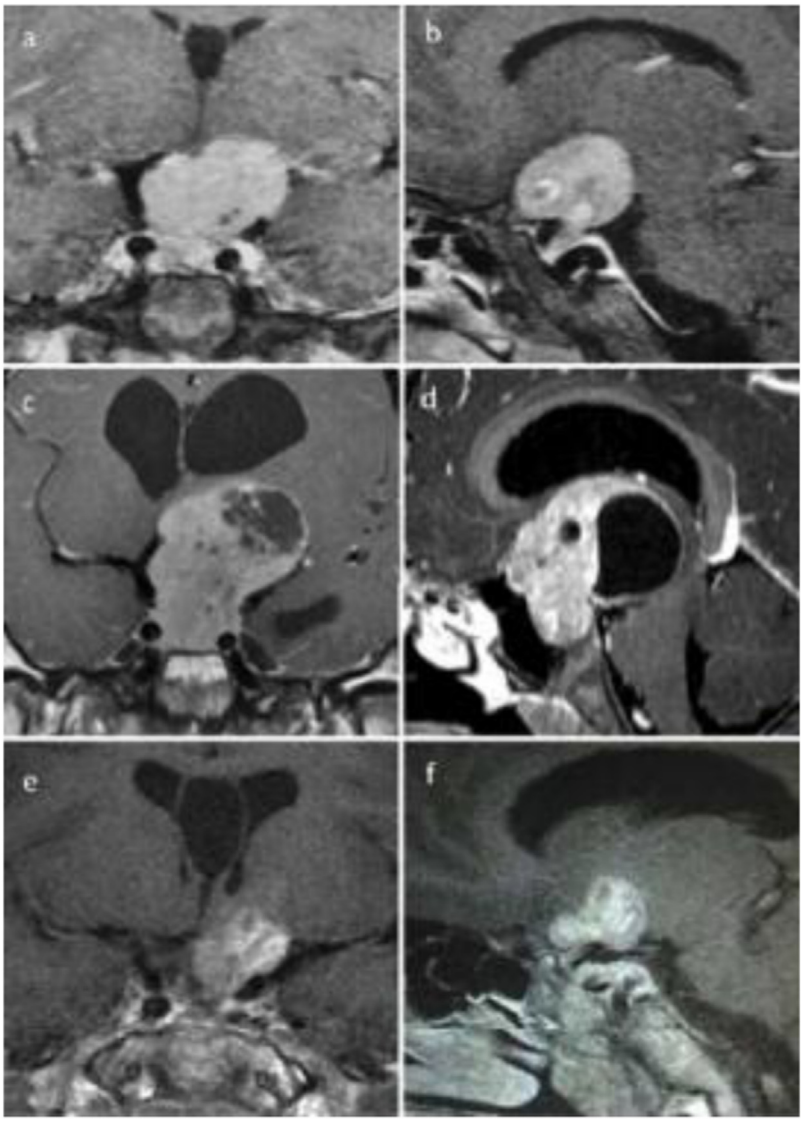

FIGURE 3.4

Natural history of somatotropinoma in X-LAG. (a, b) *First presentation* (5 years 8 months): history of excessive growth for >2 years; height 163 cm (+10 SD); noninvasive sellar mass (33 × 24 × 29 mm). *Second visit* (c, d) at the age of 10 years (no treatment): headaches, seizures, visual disturbance; height 197 cm (+7.33 SD); invasive mass (56 × 58 × 45 mm), compression of optic chiasma. Panels e, and f, show the MRI image three months after surgical debulking—no control with maximum doses of SSA + high-dose cabergoline [21].

FIGURE 3.5

A case of "genetically negative" gigantism—a 24-year-old man measuring *192 cm* next to his mother [18].

hormone-secreting adenomas are rare. Cases of pituitary carcinomas have also been reported in MEN1 patients [25–27]. GH-secreting pituitary adenomas are found in approximately 10% of MEN1 patients with pituitary lesions, are diagnosed at a mean age of 43, and are generally macroadenomas at diagnosis [28]. However, as reported by Stratakis et al. [29], tall stature with growth acceleration can appear as early as 5 years in relation to a *MEN1* mutation. In that reported case, the adenoma had mixed GH/PRL secretion. Only 1% of patients in the largest series of patients with pituitary gigantism studied so far had *MEN1* gene anomalies [6].

MEN1 should be suspected in patients with gigantism in case of family or personal history of primary hyperparathyroidism, which can manifest as early as 8 years, while digestive tumors can be diagnosed as early as 5 years. In nearly 20%–30% of MEN1 cases, pituitary adenomas are the first manifestation of the syndrome [28,30,31]. According to current guidelines, in MEN1 families, screening for pituitary tumors should comprise PRL and IGF-1 measurement on an yearly basis and pituitary MRI every 3 years starting from the age of 5 [24].

3.2.2.2 Multiple endocrine neoplasia type 4

A MEN1-like phenotype was described in 2006 and found to be due to mutations in the *CDKN1B (cyclin-dependent kinase inhibitor 1B)* gene. It was named MEN4 when occurring in humans and MENX in rats [32]. Primary hyperparathyroidism and different types of secretory pituitary adenomas characterize MEN4 [33]. Gastrointestinal neuroendocrine, thyroid, uterine, and adrenocortical tumors have also been reported [34]. Cases of GH-secreting adenomas have been described, and cases of gigantism might, exceptionally, occur in this context [35].

Several studies have been dedicated to the identification of mutations in the *CDKN1B* gene in at-risk populations. In 124 *AIP* mutation−negative patients from FIPA families, two possibly pathogenic *CDKN1B* mutations were found. One of them occurred in a patient with a GH-secreting adenoma. However, there was no proof of segregation of the mutations with the presence of pituitary adenomas in the two FIPA families [36]. In a series of over 400 patients with acromegaly, none was found to carry *CDKN1B* or *MEN1* gene mutations, illustrating the limited role of these genetic anomalies in the pathogenesis of GH-secreting pituitary adenomas [37].

3.2.2.3 Carney complex

Carney complex is a rare tumor predisposition syndrome with both endocrine and nonendocrine manifestations, due in most cases to mutations of the *PRKAR1A* gene coding for the 1A regulatory subunit of the protein kinase A. It was first described in 1985 by J.A. Carney as the association of myxomas, spotty skin pigmentation, and endocrine overactivity [38]. The endocrine anomalies are, by order of frequency, primary pigmented nodular adrenal disease causing hypercortisolism, testicular and ovarian tumors, pituitary GH/PRL hypersecretion, and thyroid tumors [39]. Nonendocrine manifestations can be cutaneous (lentigines, blue nevi, myxomas, café-au-lait skin spots), cardiac and breast myxomas, psammommatous melanotic schwannomas, or osteochondromyxomas [40].

In terms of pituitary involvement, somatomammotroph hyperplasia appears to be the first pituitary anomaly that precedes adenoma formation [41]. Nearly 75% of patients exhibit increased IGF-1 and PRL levels and abnormal GH responses to glucose or thyrotropin-releasing hormone, but GH-secreting pituitary adenomas are only present in around 10% of cases [40]. Acromegaly appearing in a Carney complex setting can be diagnosed at a younger age compared to sporadic cases (before age 30) [42]. Microadenomas are responsible for nearly half of the cases [42], meaning that somatotropinomas in this context are generally smaller than in sporadic cases [9]. The evolution of acromegaly is slow, but the risk of recurrence after adenoma surgical removal is high due to the multifocal hyperplasia [41].

In a recent review of the literature, six cases of gigantism diagnosed in Carney complex patients have been reported. Information on these cases is incomplete, but all of the pituitary adenomas with reported dimensions at diagnosis were macroadenomas. IGF-1 levels at diagnosis were not very elevated, being between 1.4 and 1.8 of the ULN for age and sex [42].

3.2.2.4 McCune–Albright syndrome

McCune-Albright syndrome (MAS) consists of the triad *café-au-lait* skin spots, fibrous dysplasia, and hyperfunctioning endocrinopathies. The *café-au-lait* skin macules are already present at birth or appear shortly afterwards. They usually respect the body's midline and have irregular borders (similar to the coast of Maine appearance), unlike the spots in neurofibromatosis type 1 with smoother edges (coast of California aspect). Fibrous dysplasia is generally polyostotic and is the most common feature of MAS [43]. In terms of endocrinopathies, these are most often gonadal

leading to precocious puberty, but thyroid (hyperthyroidism), pituitary (GH and PRL hypersecretion), adrenal (Cushing syndrome), and renal (renal phosphate wasting) lesions are well described.

Activating postzygotic mutations of the *GNAS1* gene that encodes the stimulatory α-subunit of the G protein (Gs) are the genetic basis underlying the development of MAS. These mutations lead to constitutive activation of the cAMP (cyclic adenosine monophosphate) pathway.

Around 20%−30% of MAS patients develop GH excess, with a mean age at diagnosis of acromegaly of 24 years according to a study by Salenave et al. [44]. Pituitary adenomas in patients with acromegaly and MAS were mostly macroadenomas (over two-thirds of cases). Similar to Carney complex, adenomas seem to develop from diffuse somatotroph hyperplasia [45]. As nearly all patients with acromegaly and MAS also have craniofacial fibrous dysplasia, surgery is rendered more difficult due to restricted access to the pituitary when the sphenoid bone is affected and also due to the risks of hemorrhage secondary to the hypervascular nature of fibrous dysplasia [44]. Radiotherapy is to be avoided as it is thought to increase the risk of malignant transformation [46].

Gigantism due to MAS was found in 5% of patients in our series of pituitary gigantism cases [6]. In a series of MAS acromegaly patients, Salenave et al. [44] defined gigantism as a final height over 2 m, which represented 7% of the series. Although acromegaly was diagnosed before the age of 16 in over a third of the 112 patients included in that study, 57% of these also had precocious puberty, which probably limited their final height. Gigantism in MAS can be associated with extensive craniofacial fibrous dysplasia, most likely worsened by the lack of control of GH excess, as illustrated by our case in Fig. 3.6 [47]. The thorough histological and genetic analysis of this case underlines that the *GNAS1*

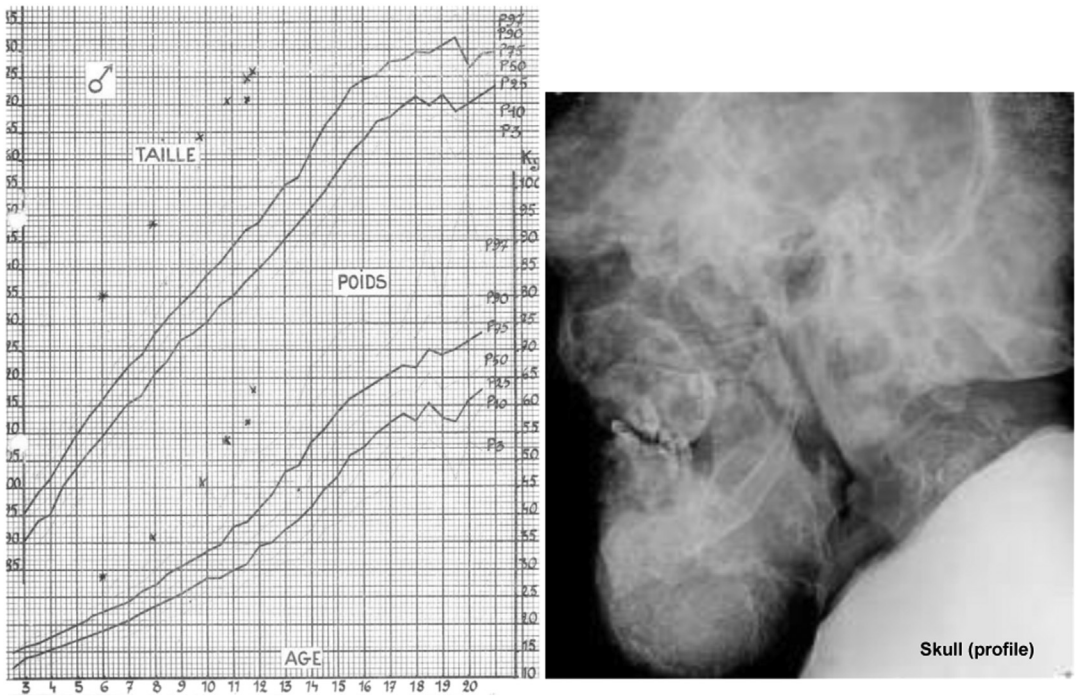

FIGURE 3.6

A case of MAS-related gigantism and severe craniofacial fibrous dysplasia [47].

mutation and tumor formation can affect both classical and less well known tissue targets in endocrine (parathyroids and pancreas), and nonendocrine nature (thymus, fat and normal skin).

3.2.2.5 Pheochromocytoma, paraganglioma, and pituitary adenoma association (3PAs)

This recently characterized multiple endocrine neoplasia association consists of pheochromocytomas and paragangliomas associated with pituitary adenomas. It is mainly due to mutations in genes encoding subunits of succinate dehydrogenase (*SDHx*), which induce a state of pseudohypoxia [48]. *MEN1* and *RET* mutations in a 3PAs context have also been described [48,49], as well as, recently, *MAX* gene defects [50]. Acromegaly in a patient with a paraganglioma was reported in 2012 due to a *SDHD* mutation [51]. SDHx-related pituitary adenomas appearing in a 3PAs context seem to more frequently be macroadenomas with an aggressive behavior as they require several forms of treatment [48].

When 3PAs occurs in a familial pheochromocytoma/paraganglioma context, *SDHx* mutations are found in 62.5%−75% of cases. For patients with *SDHx* mutations, screening for pituitary adenomas should be performed [48].

So far, cases of gigantism appearing in a 3PAs context have not been reported.

3.3 Conclusion

Pituitary gigantism is a rare cause of tall stature, developing as a consequence of early-onset GH hypersecretion. The same biological anomaly causes the development of acromegaly, but the latter occurs after the closure of growth plates, whereas gigantism occurs before epiphyseal fusion. Typical acromegaly clinical features and complications sometimes accompany the excessive growth, whereas in syndromic cases, other manifestations characteristic of an underlying genetic disorder can also be found. The condition is often diagnosed late, which complicates management and control of the excessive growth. Unlike in acromegaly, hereditary genetic anomalies frequently underlie the GH hypersecretion in pituitary gigantism, with more severe and aggressive manifestations. Better awareness of pituitary gigantism might favor an early diagnosis and rapid, effective management, which is essential for these patients.

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