CHAPTER

Medical management of pituitary gigantism and acromegaly

12

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12.1 Introduction

Acromegaly is a rare disease caused by chronically raised growth hormone (GH) and insulin-like growth factor 1 (IGF-1) secretion; typically, this is due to a GH-secreting pituitary adenoma [1]. Acromegaly affects slightly more females than males and has a range of clinical signs/symptoms, the most classically recognized being enlargement of the extremities, soft tissue swelling, and mandibular enlargement affecting the face and skin and voice changes [2]. At a systemic level, acromegaly has pathological effects on the cardiovascular, metabolic and musculoskeletal systems that lead to a high burden of disease and increased mortality if GH and IGF-1 are not controlled [3]. While acromegaly usually presents in early middle age, there is significant phenotypic variation, and it can occur in children/adolescents and in the elderly. Pituitary gigantism represents one of the most severe clinical presentations of acromegaly, affecting as it does children and adolescents [4]. The young age at presentation reflects aggressive underlying molecular genetic processes leading to somatotrope tumor formation. Unlike in sporadic acromegaly where inheritable genetic causes are rare, nearly half of all cases of pediatric gigantism are caused by a pathological genetic or genomic change in a known gene [5]. These genetic abnormalities lead to dysregulation of somatotrope proliferation and secretion that result in tumorigenesis, by affecting molecular signals such as the aryl hydrocarbon receptor interacting protein (AIP), GPR101, $G_s$alpha, Protein kinase A, among others [6]. Individually, these dysregulated cellular processes can lead to the growth of large pituitary adenomas, hyperplasia, and high secreted levels of GH. The young age of patients with pituitary gigantism raises significant obstacles to optimal management as compared with sporadic acromegaly in adults. The presence of a macroadenoma in children of a very young age, such as those with X-linked acrogigantism (X-LAG), makes surgery more challenging. Similarly, the craniofacial fibrous dysplasia that can accompany McCune–Albright syndrome (MAS) can complicate the surgical approach.

An extensive series of consensus guidelines exist for the diagnosis and management of acromegaly, including the use of medical therapies [7–9]. Medical therapy in acromegaly consists of somatostatin analogs, the GH receptor antagonist pegvisomant, and dopamine agonists such as cabergoline. Among the somatostatin analogs, two general classes exist: long-acting depot versions of octreotide and lanreotide, which target somatostatin receptor subtype 2 and the more recently introduced multi-somatostatin receptor ligand, pasireotide, that preferentially binds receptor

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subtypes 5, 2, and 3. Pegvisomant acts by blocking the GH receptor and preventing the stimulation of IGF-1 release, while dopamine agonists have an adjunctive role in suppressing GH secretion from the pituitary. These medical therapies have been subject to large clinical trials, mainly placebo-controlled, and are integrated into consensus guidelines that recommend the order in which they should be used [7,8]. According to the 2014 Guidelines from the Endocrine Society, the main biochemical goals for treatment of acromegaly are an age-normalized serum IGF-1 value (disease control), a random GH < 1.0 μg/L (correlates with disease control), and to use the same hormonal assays throughout management [7]. For medical therapy, the guidelines note the following options:

- Medical therapy recommended in patients with persistent disease following surgery.
  - Somatostatin analogs or pegvisomant recommended as initial adjuvant medical therapy in patients with significant disease, namely moderate to severe signs and symptoms of acromegaly but without tumor mass effects.
  - Those with modestly elevated serum IGF-1 and mild clinical signs/symptoms of acromegaly, could receive a dopamine agonist, usually cabergoline, as initial adjuvant medical therapy.
  - Addition of pegvisomant or cabergoline is recommended in patients who respond inadequately to a somatostatin analog.
- Primary medical therapy with a somatostatin analog is recommended in those who cannot be cured by surgery, or have extensive cavernous sinus invasion, and do not have chiasmal compression, or are poor surgical candidates.

Medical therapy also requires vigilant follow-up for safety including, but not limited to assessments for cholelithiasis in symptomatic patients treated with somatostatin analogs, while hepatic function tests should be measured on a 6-monthly basis for patients receiving pegvisomant. Due to rare cases of tumor expansion during pegvisomant therapy, a plan should be in place for serial monitoring of tumor status using MRI [7]. While pasireotide has been licensed for use in acromegaly in many jurisdictions, it has not yet been integrated into all consensus guidelines. However, based on its specific labeling, pasireotide is generally used as second- or third-line therapy in acromegaly when surgery has failed or is not possible or where octreotide/lanreotide treatment has not led to control of acromegaly. In a recent update on treatment outcomes, an Expert Group provided some indications as to how pasireotide could be integrated into the treatment algorithm as shown in Fig. 12.1. Management of patients receiving pasireotide for the treatment of acromegaly requires specific assessment of glucose control as pasireotide is associated with impairment of glucose tolerance and diabetes mellitus [10].

While the goals for the treatment of acromegaly and pituitary gigantism are generally similar, some clinically relevant differences exist between pediatric and adult patients that can impact upon the expected efficacy of medical treatment and the timing of changes in treatment modalities. These factors include the importance of effective treatment to limit final adult height, the challenges of dose selection for medical treatment in the pediatric/adolescent population, the anatomical differences between the adult and pediatric patients, and the high incidence of molecular genetic diseases among the pituitary gigantism population.

Pituitary gigantism is a very rare condition and most data have come from case reports and small series. To address this relative lack of information, we implemented a large international collaborative study from 2011–15 that recruited 208 pituitary gigantism patients [5]. Focusing on the management of these patients, we noted that the therapeutic journey was often complex. Multimodal therapy is usual

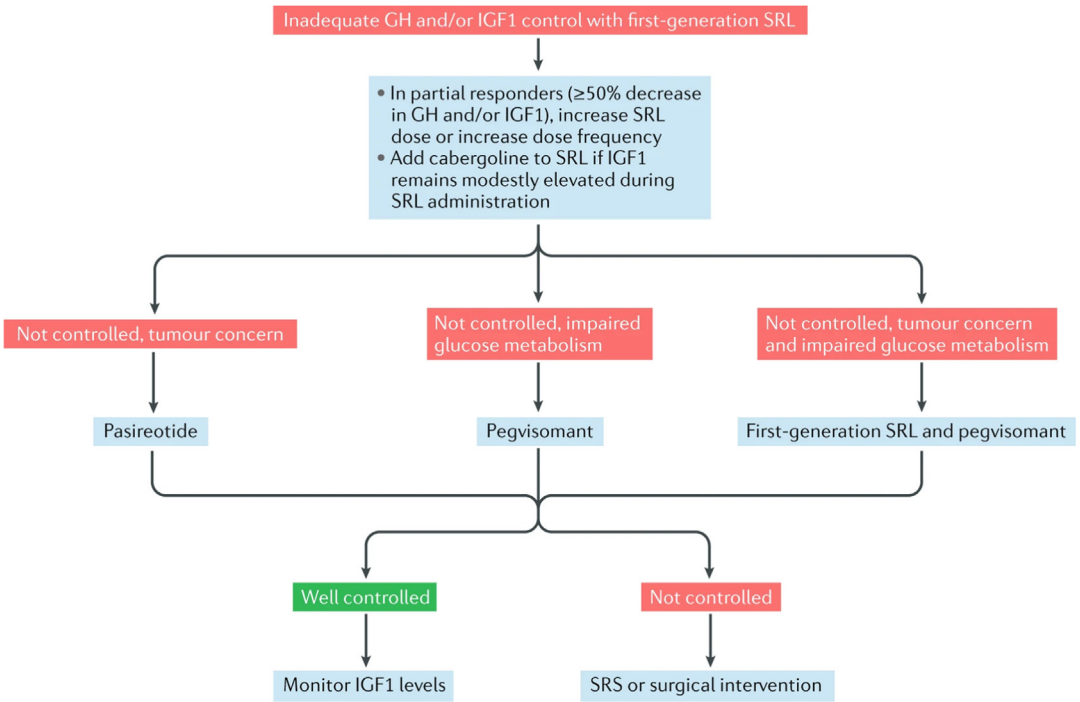

FIGURE 12.1

Suggested Expert Group algorithm for the medical management of acromegaly in patients with inadequate responses to octreotide and lanreotide. *IGF-I*, Insulin-like growth factor I; *SRL*, somatostatin receptor ligand/somatostatin analog; *SRS*, stereotactic radiosurgery.

Reproduced from Melmed S, Bronstein MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol 2018; 14(9):552–61. doi: 10.1038/s41574-018-0058-5 [9] under Creative Commons 4.0 Attribution International License.

in pituitary gigantism, and following primary medical or surgical therapy, patients often have recourse to reoperation or a wide variety of different combinations of medical therapy. As shown in Fig. 12.2, of 208 patients, only 7% and 15% of cases were controlled by primary medical therapy or surgery, respectively. Irrespective of whether surgery or medical therapy was the primary treatment option, pituitary gigantism patients frequently end up going through surgery on multiple occasions with adjuvant use of medical therapy. Multimodal therapy (≥3 separate surgeries or medical modalities) occurred in nearly a third of pituitary gigantism cases, and despite the high treatment burden only 39% of patients had long-term hormonal control [5].

12.1.1 *AIP* mutations

Germline mutations in the *AIP* gene are the main known cause of pituitary gigantism. In the first statistically controlled series of somatotropinomas, gigantism occurred in 32% of the *AIP*-mutated group as compared with 6.5% wild-type controls ($P < .000001$) [11]. Among pituitary gigantism

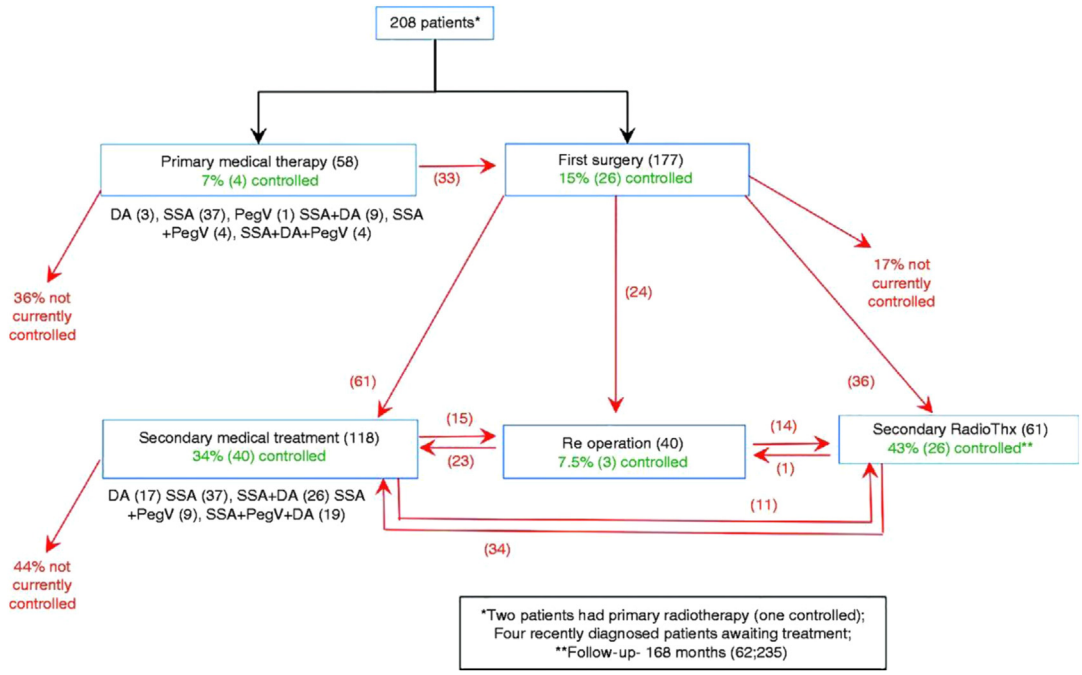

FIGURE 12.2

Schematic representation of treatments used in the management of patients with pituitary gigantism. Numbers in parentheses indicate the number of patients. *DA*, Dopamine agonists; *PegV*, pegvisomant; *RadioThx*, radiotherapy; *SSA*, somatostatin analog.

Reproduced by the authors from their work in Rostomyan L, Daly AF, Petrossians P, et al. Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. Endocr Relat Cancer 2015;22(5):745–57. doi: 10.1530/ERC-15-0320 [5] with permission.

patients themselves, 29% have an *AIP* mutation. The phenotype of *AIP*-mutated somatotropinomas is one that leads to large, extensive, and invasive tumors that predominantly secrete GH or cosecrete GH and prolactin. Patients with *AIP* mutations frequently present with familial isolated pituitary adenomas (FIPA), and family members with acromegaly or gigantism can be identified [11,12]. The median onset of disease is significantly younger among *AIP*-mutated somatotropinomas patients versus nonmutated acromegaly controls (17.5 vs 38.0 years; $P < .000001$). This 20-year difference is disease onset means that somatotropinomas due to *AIP* mutations typically overlap the years of maximum vertical growth, leading to a high risk of pituitary gigantism if hormonal control is not achieved.

The aggressive disease features of *AIP* mutation–related somatotropinomas also extend to significantly higher GH secretion at baseline than control acromegaly cases ($P = .00068$), while prolactin cosecretion is 1.9 times more frequent with *AIP* mutations than controls ($P = .00023$).

The young age at disease onset and the large, extensive tumor phenotype in *AIP*-related somatotropinomas imply that the tumor has either undergone years of occult growth or alternatively that

tumor grows and invades rapidly. Evidence to date suggests the latter possibility is the more likely. During the identical median latency period from first symptoms to diagnosis (5 years) in *AIP* mutation−related and acromegaly controls, tumors grow to a significantly larger size in the *AIP*-mutated group. This was illustrated recently in one *AIP* mutation−related somatotropinomas in a young female patient with pituitary gigantism, where dramatic progression of the tumor occurred over the 15 months preceding her diagnosis [13].

In *AIP*-mutated cases of pituitary gigantism, the large tumor size and the presence of invasion may reduce greatly the possibility of primary surgical control and reoperation in these patients is frequent [11]. As *AIP*-mutated tumors have high GH secretory potential, reoperation to debulk the tumor could be clinically helpful in an effort to facilitate hormonal decreases with subsequent somatostatin analog use, as has been shown in adult acromegaly [14]. A further problem associated with medical treatment of *AIP*-mutated cases of pituitary gigantism relates to their relative resistance to first-generation somatostatin analogs. As compared with nonmutated cases, significant impairment of GH ($P = .0004$) and IGF-1 inhibition ($P = .028$) is seen in *AIP* mutation−related somatotropinomas [11].

Resistance to first-generation somatostatin analogs like octreotide and lanreotide can be countered by use of the GH receptor antagonist, pegvisomant, in the setting of acromegaly and gigantism with or without *AIP* mutations [15−18]. Treatment with pegvisomant can take the form of monotherapy or it can be used in combination with somatostatin analogs. Either alone or in combination with somatostatin analogs, pegvisomant is an important and useful option for controlling IGF-1 excess and decreasing height gain in *AIP*-mutated pituitary gigantism cases that are resistant to somatostatin analogs alone [5,19]. The combination including a somatostatin analog could be useful to help control tumor growth, which can complicate pegvisomant therapy in a minority of cases [20]. As noted above, patients with *AIP* mutations frequently have tumoural cosecretion of prolactin and GH. Combination treatment with pegvisomant and the dopamine agonist cabergoline has also been shown to be successful in somatostatin analog resistant/intolerant pediatric cases of *AIP*-mutated pituitary gigantism [15].

Recently we reported two cases of *AIP* mutation−related somatotropinomas that were resistant to octreotide/lanreotide during extensive multiyear follow-up [13]. In one of the cases who had incipient pituitary gigantism, somatostatin receptor subtype 2 staining was very low/absent, but subtype 5 receptors were present. On switching to treatment with pasireotide, a multi-somatostatin receptor ligand, both patients experienced control of their GH and IGF-1 hypersecretion. With continued therapy over some years, significant tumor regression occurred (Fig. 12.3), and one patient stopped pasireotide without a return of elevated GH and IGF-1 and still remains controlled off treatment at this time. These data suggest that in some *AIP*-mutated patients with large and resistant tumors, pasireotide therapy might be a useful option, although the diabetes mellitus that can accompany pasireotide therapy adds to the therapeutic burden.

12.1.2 X-linked acrogigantism

Duplications on chromosome Xq26.3 involving the gene *GPR101* are responsible for X-LAG, the earliest onset form of pituitary gigantism described [21−23]. Transgenic pituitary over-expression of *Gpr101* in mice leads to chronic GH hypersecretion and overgrowth [24]. Patients with X-LAG typically develop signs of overgrowth in the first 12−36 months of life, with increased height and

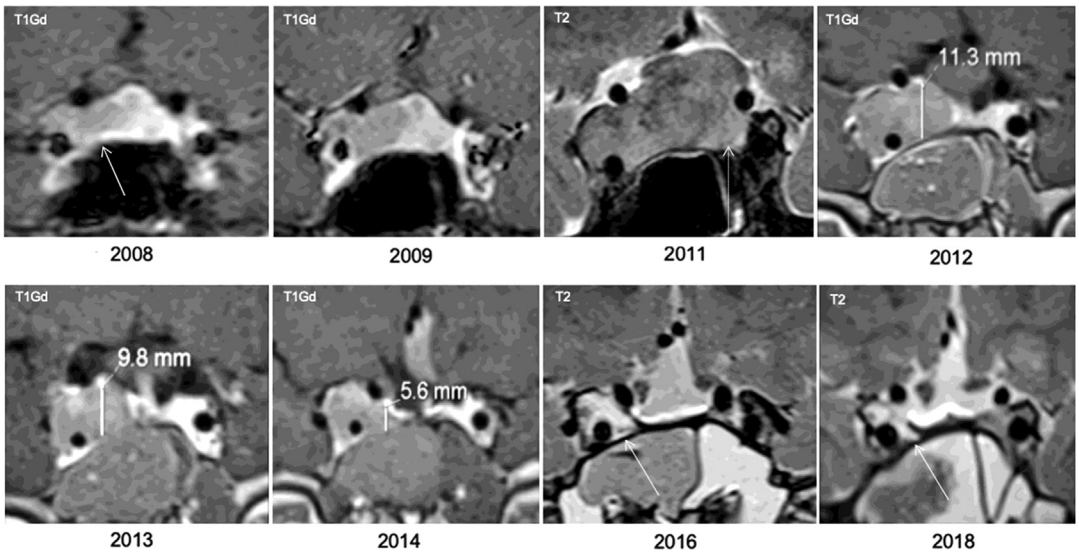

FIGURE 12.3

Evolution of pituitary adenoma size on MRI in a patient with incipient gigantism and a germline *AIP* mutation from diagnosis as a microadenoma to a large invasive pituitary macroadenoma. A sizable postoperative residue in 2012 shrank progressively on pasireotide LAR therapy and the follow-up image from 2018 shows only a small residue remained. *T1Gd*, T1-weighted gadolinium-enhanced image; *T2*, T2-weighted MRI image.

weight becoming increasingly prominent over time [21]. Along with increased stature, these young children also frequently have signs that are more typical of adult acromegaly, including enlarged hands and feet, increased interdental spacing, and coarsening of the facial features [21,22]. Children with X-LAG also may have increased appetite and signs of insulin resistance [22]. GH and IGF-1 levels (and almost always prolactin) are markedly elevated at diagnosis. In X-LAG pituitary macroadenoma occur either alone or in combination with hyperplasia; rare cases of hyperplasia alone can occur. In some patients in whom it was measured preoperatively, GH releasing hormone was increased in conjunction with GH, IGF-1, and prolactin, suggesting a hypothalamic element in the pathophysiology of X-LAG [25]. Without treatment ,patients with X-LAG suffer increasing tumor size and hormonal excess that can lead to severe gigantism [26,27].

Initial management of X-LAG usually involves the use of surgery or first-generation somatostatin analogs [5,21–23,28,29]. To control X-LAG surgically, a complete resection of the tumor and/or hyperplasia is required, as very small tumor remnants can maintain excess GH and IGF-1 secretion, in some cases for decades [21–23,30,31]. The benefits of extensive resection on GH secretion come at the cost of high rates of hypopituitarism, which is a problem in pituitary gigantism generally [5]. With extensive hyperplasia, discrete boundaries between pathological and

normal tissue are not evident, which further complicates primary surgical cure and can necessitate anterior hypophysectomy in some cases [21]. Despite expressing somatostatin subtype 2 receptors, X-LAG patients have a poor response to first-generation somatostatin analogs, even at the full adult dose [22]. Data on the efficacy of the multi-somatostatin receptor ligand pasireotide in X-LAG are not available. In cases where extensive surgical resection (debulking) has taken place, second line therapy with somatostatin analogs can reduce or control GH and IGF-1 in some cases [21,22]. In the growing patient, suboptimal control of excess GH/IGF-1 control should be avoided so as to prevent excessive final adult stature. Given the extended duration of disease in X-LAG due to its early onset and resistant phenotype, the risk of excessive height is very prominent. In those X-LAG patients, the addition of pegvisomant can provide rapid and prolonged IGF-1 control and blunting of height gain [21–23,25]. To optimize hormonal and growth parameters, when surgery and somatostatin analogs have proven inadequate, early introduction of pegvisomant can be considered. Pegvisomant is generally not indicated for treatment of pediatric patients, although case series and anecdotal reports have been widely published [15,17,18,32,33]. In X-LAG cases, addition of pegvisomant at a low dose has proven safe and effective in some individuals [21,22,25].

12.1.3 McCune–Albright syndrome

In MAS, mosaicism for a postzygotic activating mutation of *GNAS* leads to variable and diverse pathology affecting multiple tissues, classically, fibrous dysplasia of the bone, hormonal overactivity, and distinctive café au lait macules [34]. Acromegaly forms a part of the MAS spectrum and rarely can have an early onset in children/adolescents, leading to pituitary gigantism [35]. In the largest series of acromegaly characteristics in MAS, Salenave et al. reported on 112 cases published in the literature [36]. Among these, 40 were diagnosed between the ages of 3 and 16 years and in most cases, hormonal measures were confirmatory of somatotrope overactivity. Whereas excess GH/IGF-1 occurs in 20%–30% of patients with MAS, pituitary gigantism was less frequent than might be expected, possibly because of the counteracting influence of precocious puberty to reduce final height. The interpretation of height and hormonal abnormalities in young children with MAS is, therefore, complex [37]. In our series of 208 pituitary gigantism patients, 5% had MAS [5].

When somatotropinomas occur in the setting of MAS, craniofacial fibrous dysplasia is a significant factor to be considered, as it can complicate surgical access, and progression of cranial bone pathology in parallel with GH excess can worsen outcomes [36,38,39]. In MAS, the *GNAS*-activating mutation leads to diffuse disease affecting much of the anterior pituitary and can involve a mixture of hyperplasia and single or multiple adenomas [40]. The tumor/hyperplasia tissue type is usually mammosomatotrope or somatotrope in nature. Due to the difficult approach through skull base fibrous dysplasia (which can be highly vascular as well as thick) and the diffuse pituitary disease, surgical cures only occur exceptionally and medical therapy is necessary. The response to first-generation somatostatin analogs in terms of hormonal control in the Salenave et al. series was similar to that of unselected acromegaly patients (14%–46%) [36]. While hyperprolactinemia is usually present in MAS patient with pituitary disease, the use of dopamine agonists has relatively low efficacy in terms of hormonal control. Pegvisomant is, is contrast, an important treatment option for MAS patients with acromegaly or pituitary gigantism, as control of IGF-1 is usually achieved in compliant patients [36,41]. As with pituitary gigantism in general, early diagnosis and

hormonal control in MAS-related acromegaly leads to improved clinical outcomes, particularly in terms of optic nerve impingement in patients with craniofacial fibrous dysplasia [38].

12.1.4 Other genetic forms of pituitary gigantism

Rare conditions like Carney complex and multiple endocrine neoplasia type 1 (MEN1) account for a small minority of all pituitary gigantism cases (1% each) [5]. In Carney complex, *PRKAR1A* germline mutations lead to a syndrome of endocrine and nonendocrine pathologies that include pituitary adenomas/hyperplasia in about 10% of cases [42]. As with other genetic causes of pituitary adenomas, Carney complex is associated with an early onset phenotype that leads to somatotrope or somatomammotrope tumors/hyperplasia, resulting in pituitary gigantism in rare individuals [42–45]. In MEN1, pituitary adenomas form an integral part of the pathological entity, and have a tendency to occur at an earlier age than non-MEN1 cases [46]. Only exceptional cases of pituitary gigantism have been reported in MEN1 [47]. Management of pituitary gigantism in Carney complex and/or MEN1 is multimodal. Cases of overgrowth or gigantism linked to neurofibromatosis type 1 have been linked to optic tract gliomas, but the actual causative mechanism for overgrowth remains speculative [4].

12.2 Summary

Recent advances in pituitary adenoma research mean that nearly 50% of cases of pituitary gigantism now have an identified genetic cause. In general, pituitary gigantism represents the most severe form of acromegaly disease spectrum, as it occurs in the youngest patients and many of the genetic forms have an aggressive phenotype. In addition, certain genetic forms like *AIP* mutations and X-LAG syndrome lead to pharmacological resistance to the main medical form of therapy, somatostatin analogs. Indeed, the young age of patients at diagnosis and the aggressiveness of the pituitary disease mean that treatment is often multimodal in nature and that control of GH/IGF-1 and tumor require approaches that combine surgery with medical therapy. These factors provide a series of unique challenges and specific aims when managing the medical treatment of pituitary gigantism (Box 12.1). Unlike adult acromegaly, pituitary gigantism has a particularly important window of opportunity to modify final adult height. In addition to the consensus approaches to

Box 12.1 Aims and challenges in the management of pituitary gigantism.

Aims

- Control hormonal hypersecretion (GH, IGF-1, prolactin)
- Control tumor growth/expansion
- Decrease signs and symptoms of hormonal excess
- Avoid or minimize side effects of treatment (hypopituitarism)
- Minimize or prevent an abnormal final adult height
  - Early control of GH-IGF-1 decreases final height

(*Continued*)

Box 12.1 (Continued)

Challenges

- Early pediatric age at onset can complicate surgery
- Macroadenomas are frequent even in children/adolescents
- Genetic forms of pituitary gigantism often lead to extensive involvement of the anterior pituitary (hyperplasia plus adenoma)
- Need for extensive surgical resection can elevate the risk for hypopituitarism
- Onset in adolescence overlaps with pubertal growth spurt which can delay diagnosis
- Lack of dosing information or clinical trials of medical therapies in pediatric patients
- In McCune–Albright syndrome craniofacial fibrous dysplasia can complicate surgical access
- *AIP* mutation–related somatotropinomas are associated with decreased hormonal and tumor size control rates with first-generation somatostatin analogs
  - There may be a role for pasireotide in *AIP* mutation related acromegaly/acrogigantism
- In X-LAG, minimal tumor residue can lead to active disease and continued GH-IGF-1 driven overgrowth
  - Pegvisomant therapy is potentially useful to control IGF-1

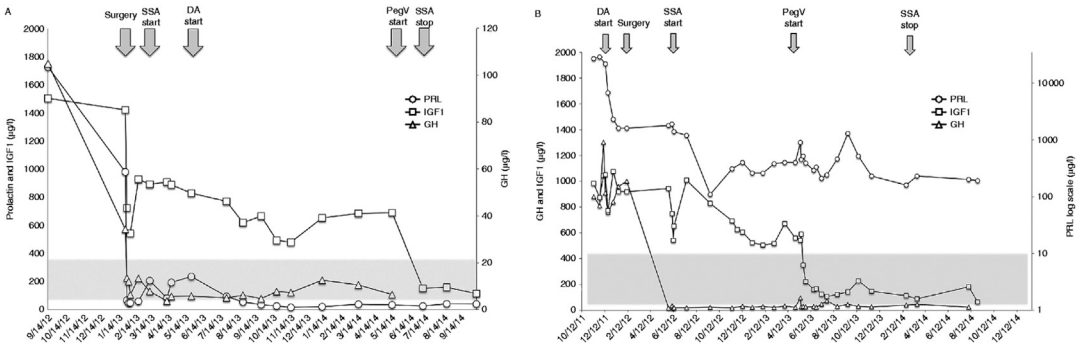

FIGURE 12.4

Treatment of two patients with X-LAG showing GH, IGF-1, and prolactin (PRL) levels over time. Figure A shows a male patient (56 months at diagnosis) who had elevated IGF-1 levels post operatively (IGF-1 normal range shown in gray) that did not normalize on a somatostatin analog and cabergoline. His growth was arrested by the addition of pegvisomant and octreotide was withdrawn. Figure B shows a similar profile in a female patient, who had a gross total resection but remained clinically and hormonally uncontrolled. Addition of octreotide LAR 30 mg/month and cabergoline did not control IGF-1. Pegvisomant rapidly brought IGF-1 levels and growth under control and octreotide was withdrawn.

Reproduced by the authors from their work in Beckers A, Lodish MB, Trivellin G, et al. X-linked acrogigantism syndrome: clinical profile and therapeutic responses. Endocr Relat Cancer 2015; 22(3):353–67. doi: 10.1530/ERC-15-0038 [22] with permission.

acromegaly in adults, management of pituitary gigantism requires early diagnosis and effective control to reduce final height. In pituitary gigantism cases where treatment with surgery and somatostatin analogs is not effective in the short to medium term (3–6 months), IGF-1 control with pegvisomant can often be achieved Fig. 12.4 and Table 12.1.

Table 12.1 Key differences in the characteristics of acromegaly and pituitary gigantism.

Features	Pituitary gigantism ($n = 208$)	Acromegaly ($n = 3173$)
Sex	78% male	54.5% female
Age at diagnosis (median; years)	21.0	45.2
Age at first symptoms (median; years)	14.0	33.5
Delay in diagnosis (median; years)	5.3	9.0
Maximum tumor diameter (median; mm)	22.0	15.0
Macroadenoma (%)	84.3	71.8
Invasion at diagnosis (%)	54.5	47.6
Prolactin cosecretion (%)	34	10

Adapted from Beckers A, Petrossians P, Hanson J, Daly AF. The causes and consequences of pituitary gigantism. Nat Rev Endocrinol 2018. doi: 10.1038/s41574-018-0114-1 [4] with permission.

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