Clinical Features and Treatment of Pediatric Somatotropinoma: Case Study of an Aggressive Tumor due to a New *AIP* Mutation and Extensive Literature Review

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Key Words

AIP · Mutation · Pediatric somatotropinoma · Pegvisomant

Abstract

Context: Pediatric somatotropinoma is uncommon but usually more aggressive than in adults, creating therapeutic challenges. No treatment guidelines are available. **Objectives:** To describe the features of pediatric somatotropinomas and to assess therapeutic strategies based on an extensive literature review. **Design:** We describe a pediatric case of aggressive somatotropinoma with an *AIP* mutation. We identified 137 pediatric somatotropinoma cases published between 1981 and 2010, and found 41 cases with *AIP* mutations in the main review. **Results:** We found a slight male preponderance (59%). Median age was 9 years at symptom onset and 14 years at diagnosis. Macroadenomas accounted for 90% of the tumors; 2/3 of the children had hyperprolactinemia at diagnosis. The first-line treatment was pharmacotherapy in one third and surgery in 2/3 of the patients. Pegvisomant was used in 7 patients and produced significant improvement in 4. The male preponderance was higher in the

subgroup with *AIP* mutations. Mutations leading to severe protein abnormalities were more common than reported in adults. **Conclusion:** Higher invasiveness and tumor volume in pediatric somatotropinomas require complex treatment combinations, which produce variable results. Pegvisomant is an effective drug whose usefulness in children remains to be determined. Genetic screening, particularly for *AIP* mutations, should be performed routinely.

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Introduction

Pituitary adenomas are uncommon in children, in whom they make up less than 3% of all supratentorial tumors [1]. Somatotropinomas account for 5–15% of pituitary adenomas, being less common than prolactinomas and corticotropinomas [1, 2]. The clinical presentation of growth hormone (GH) oversecretion by a somatotropinoma depends on the epiphyseal plate status. In patients with open epiphyseal plates, the excess GH accelerates growth, leading to gigantism. As the time of epiphyseal

Fig. 1. **a** Growth curves of the patient. **b** Plasma IGF-1 concentrations according to the treatments used. TS = Transphenoidal surgery; TC = transcranial surgery; P = proton therapy; Pegvis = pegvisomant. **c** Pre-operative MRI (T₁-weighted images).

fusion approaches, the clinical features become more similar to those seen in adults [1, 2]. Somatotropinomas in children are often larger than in adults [6], and their behavior is invasive in 30–60% of cases [7, 8]. These characteristics raise treatment challenges, particularly as no therapeutic guidelines are available for children. Highly variable results have been reported with conventional treatments (surgical excision, pharmacotherapy, and radiotherapy). The newly introduced GH receptor antagonist pegvisomant decreases IGF-1 production and controls the symptoms in adults [9–11], but has not been adequately evaluated in children.

The objectives of this paper were to describe the epidemiology, features, and treatment of pediatric somatotropinoma based on an extensive literature review and on a case report. We compared the pediatric management with recommendations issued for adults. This work has also given us the opportunity to review the published pediatric cases with mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene known to predispose carriers to somatotropinoma, particularly in younger patients.

Material and Methods

Case Report

An 8-year-old boy presented at the Necker-Enfants Malades Hospital with a 2-year history of growth acceleration (fig. 1). He was born at full term with a weight of 3,710 g, a length of 52.5 cm, and a head circumference of 35 cm. His growth was normal until 5 years of age when he started gaining both weight and height at an accelerated rate. Parental heights were 187 cm (father) and 168 cm (mother). On physical examination, he was prepubertal. His height was 151.7 cm (over +4 SDs) and his weight was 40 kg (+3 SDs). He displayed mild prognathism, macroglossia, and right ocular ptosis. He also complained of knee pain, profuse sweating, and snoring. He reported no headaches, visual disturbances, polyuria, or polydipsia.

Hormone assays showed increased levels of IGF-1 (968 ng/ml; normal = 72–336 ng/ml) and basal GH (34–45 ng/ml). A glucose tolerance test revealed normal carbohydrate tolerance, but no suppression of GH concentrations. The IGFBP-3 level was very high [9.03 µg/ml; normal = 0.3–4.7]. Levels were normal for prolactin, thyroid hormones, and adrenal hormones. His bone age matched his chronological age. Cerebral MRI showed a large homolateral macroadenoma (30 mm in diameter) extending to the suprasellar area. The visual field was normal.

Treatment with lanreotide (60 mg monthly) had no effect on the IGF-1 levels (850–1,000 ng/ml), GH levels (>50 ng/ml), or tu-

mor size (no change). Cabergoline (0.5 mg weekly) was added 3 months later but was not effective [IGF-1 850–1,300 ng/ml, GH >50 ng/ml]. After 5 months of pharmacological treatment, partial tumor excision was performed via the transsphenoidal approach. Immunohistochemical staining confirmed the diagnosis of GH-secreting adenoma and showed a high proliferative index (12% of MIB-1-positive cells). Two months after surgery, lanreotide and cabergoline were discontinued. Pegvisomant (10 mg daily) was given for 4 months but then stopped because of continued tumor growth with the development of visual disturbances. These visual symptoms prompted emergency transcranial surgery, which allowed only partial tumor excision. Another transcranial surgical procedure 4 months later also failed to ensure complete tumor excision. Lanreotide (90 mg monthly) was given for 7 months, then discontinued because of gastrointestinal side effects. Transsphenoidal surgery allowed nearly complete tumor resection, with only small intrasellar and suprasellar remnants. Thyrotropin insufficiency developed after the last surgery, requiring hormone replacement therapy. Proton therapy was given at a total dose of 52.2 Gy. At his last visit 15 months after proton therapy, he was 11 years old, his IGF-1 level was 452 ng/ml (normal = 72–336 ng/ml), his GH level was 0.7 ng/ml, and his growth velocity had decreased. MRI showed a decrease in remnant size (13×12 mm).

Genetic analysis of blood and tumor tissue identified a novel heterozygous c.2T>C mutation in exon 1 of the *AIP* gene in peripheral blood cells from the patient and his mother and brother, as well as loss of the wild-type *AIP* allele in the patient's tumor tissue. This is the first reported mutation of the initiation codon ATG, which is responsible for mRNA translation in the *AIP* gene.

Informed consent was obtained from the parents for publication.

Literature Review

We searched the Medline database using the key words 'gigantism', 'acromegaly', 'children', 'adolescent', 'somatotropinoma', 'somatotroph adenoma', and 'GH-secreting adenoma'. We identified 137 cases of pediatric somatotropinoma diagnosed between 0 and 18 years of age for which the available data (demographic and clinical features, laboratory data, imaging study findings, immunohistochemistry findings, and treatment) were sufficient for analysis. These 137 cases were reported in 45 articles published between 1981 and 2010 (see 'Appendix'). Follow-up ranged from several months to 30 years.

Furthermore, it was from this review that we found the 41 pediatric cases of *AIP* mutations reported between 2006 and 2010.

Statistical Analysis

The data were analyzed using the χ^2 and Wilcoxon tests. *p* values <0.05 were considered significant.

Results

Table 1 shows the main features of the 137 previous cases and our case. Symptoms of GH oversecretion predominated, followed by symptoms of compression. Two asymptomatic children were diagnosed by family screen-

ing. Macroadenomas accounted for almost 90% of the tumors, and immunohistochemistry showed equal proportions of GH-secreting and GH/PRL-secreting adenomas.

Table 2 shows the treatments and outcomes in 68 patients for whom relevant data were available (67 previously published cases and our case). The first-line treatment was surgical in two thirds of patients and pharmacological in the remaining third. Repeated surgical procedures were required in one fifth of patients. Among children given first-line pharmacotherapy, 80% received somatostatin receptor ligands. Radiotherapy was used in one third of patients. The GH receptor antagonist pegvisomant was used in 7 children, as the third- or fourth-line treatment. At last follow-up, disease control was achieved in almost 70% of children. Among them, 32% were still being treated and 37% had stopped treatment. GH oversecretion persisted in 26% of patients, and the tumor recurred in 4% of patients.

Figure 2 reports the 41 published pediatric cases with *AIP* mutations. The analysis of the cohort found a male preponderance (70%) and a high proportion of macroadenomas (85%).

Discussion

We analyzed 138 cases of pediatric somatotropinoma from an extensive literature review and 1 personal case. Despite the limitations of our work related to the variations in available data, management, and follow-up duration, our results provide a useful overall picture of pediatric somatotropinoma.

Males predominated slightly (59%). Median age was 9 years (0.2–17) at symptom onset and 14 years (0.8–18) at diagnosis, indicating considerable diagnostic delay, in keeping with earlier data [12]. Accelerated growth, which was a feature in 66% of patients, should alert professionals to the possibility of somatotropinoma. However, the long time to diagnosis indicates inadequate awareness of this condition among physicians and families. Acromegalic features were present in as many as 37% of patients, despite the young age. Variable pubertal disorders occurred in 24% of patients. The available data did not allow us to determine whether amenorrhea and hypogonadism were related to gonadotropic insufficiency or to hyperprolactinemia. Previous publications did not provide explanations to the occurrence of precocious puberty or adrenarche.

Pediatric somatotropinomas are usually large [6], a feature that explains the 23% rate of compression symp-

Table 1. Main features in 138 pediatric patients with somatotropinoma

	Total		Males		Females	
	n	range or %	n	range or %	n	range or %
<i>General characteristics</i>						
Number	138		82	59.4	56	40.6
Median age at symptom onset, years	9	0.2–17	9	0.5–17	7.2	0.2–17
Median age at diagnosis, years	14	0.8–18	15	2.2–18	14	0.8–18
<i>Clinical features</i>						
Number with data	117		69		48	
Gigantism	77	65.8	44	63.8	33	68.8
Acromegalic features	43	36.8	23	33.3	20	41.7
Amenorrhea						
Primary	8	6.8	n.a.	n.a.	8	16.7
Secondary	5	4.3	n.a.	n.a.	5	10.4
Not known	4	3.4	n.a.	n.a.	4	8.3
Precocious puberty or adrenarche	8	6.8	5	7.2	3	6.3
Hypogonadism	3	2.6	3	4.3	n.a.	n.a.
Compression symptoms						
Number	27	23.1	20	29.0	7	14.6
Headache	18	15.4	14	20.3	4	8.3
Visual disturbances	18	15.4	12	17.4	6	12.5
Asymptomatic	2	1.7	1	1.4	1	2.1
<i>Hormone profile</i>						
IGF-1						
Number with data	29		15		14	
Median level, ng/ml	855	460–1,963	778	460–1,963	937	495–1,540
GH						
Number with data	69		37		32	
Median level, ng/ml	51	4.6–730	47	4.6–730	74	9.7–475
Prolactin						
Number with data	58		29		29	
High prolactin level, ng/ml	38	65.5	17	58.6	21	72.4
<i>Associated pituitary deficiency</i>						
Number with data	65		n.a.	n.a.	n.a.	n.a.
Deficiency	23	35.4	n.a.	n.a.	n.a.	n.a.
No deficiency	42	64.6	n.a.	n.a.	n.a.	n.a.
<i>Tumor size</i>						
Number with data	111		66		45	
Macroadenoma	98	88.3	57	86.4	41	91.1
Microadenoma	13	11.7	9	13.6	4	8.9
<i>Immunostaining</i>						
Number with data	106		62		44	
GH alone	55	51.9	35	56.5	20	45.5
GH + prolactin	51	48.1	27	43.5	24	54.5
n.a. = Not applicable.						

Table 2. Therapeutic strategy and outcomes in 68 patients

	Total	%	Males	%	Females	%
n	68		40	58.8	28	41.2
<i>Primary pharmacotherapy</i>						
n	23	33.8	14	35.0	9	32.1
SRL	12	52.2	7	50.0	5	55.6
DA	5	21.7	3	21.4	2	22.2
SRL + DA	6	26.1	4	28.6	2	22.2
<i>Primary surgery</i>						
n	45	66.2	26	65.0	19	67.9
Approach						
TS	38	84.4	25	96.2	13	68.4
TC	5	11.1	1	3.8	4	21.1
Not specified	2	4.4	0	0.0	2	10.5
Removal						
Complete or macro. complete	17	37.8	9	34.6	8	42.1
Incomplete	25	55.6	16	61.5	9	47.4
Not specified	3	6.7	1	3.8	2	10.5
<i>Secondary surgery</i>						
Number	22	32.4	13	32.5	9	32.1
Approach						
Transsphenoidal	19	86.4	11	84.6	8	88.9
Transcranial	3	13.6	2	15.4	1	11.1
Removal						
Complete or macro. complete	11	50.0	5	38.5	6	66.7
Incomplete	11	50.0	8	61.5	3	33.3
<i>Subsequent treatments</i>						
Radiotherapy						
Conventional	23	33.8	13	32.5	10	35.7
Proton therapy	2	2.9	1	2.5	1	3.6
Pegvisomant	7	10.3	4	10.0	3	10.7
Other surgery(ies)	14	20.6	8	20.0	6	21.4
<i>Therapeutic outcomes</i>						
Disease controlled after treatment	25	36.8	12	30.0	13	46.4
Primary surgery	14	56.0	8	66.7	6	46.2
Primary pharmacotherapy	11	44.0	4	33.3	7	53.8
Disease controlled under treatment	22	32.4	12	30.0	10	35.7
Primary surgery	14	63.6	6	50.0	8	80.0
Primary pharmacotherapy	8	36.4	6	50.0	2	20.0
Persistent disease	18	26.5	14	35.0	4	14.3
Primary surgery	14	77.8	10	71.4	4	100.0
Primary pharmacotherapy	4	22.2	4	28.6	0	0.0
Recurrence	3	4.4	2	5.0	1	3.6
Primary surgery	3	100.0	2	100.0	1	100.0
Primary pharmacotherapy	0	0.0	0	0.0	0	0.0
Secondary pituitary deficiency	21	30.9	12	30.0	9	32.1

Results are from the last follow-up. SRL = Somatostatin receptor ligand; DA = dopamine agonist; macro. = macroscopically.

Fig. 2. Reported *AIP* mutations in pediatric patients with acromegaly. **a** *AIP* gene: the arrows indicate the positions of the mutations within the *AIP* gene. FKBP = FK506-binding protein; TPR = tetratricopeptide repeats; AHR = aryl hydrocarbon receptor; DCR = distal C-terminal region. **b** Description of *AIP* mutations reported in pediatric studies.

toms. Among patients for whom relevant data were available, most had macroadenoma and frequently para- or suprasellar extension. Microadenomas were found in only 12% of patients, compared to 20–30% in adults [13].

Hyperprolactinemia is common at presentation and correlates with GH-PRL co-staining within the tumor. At diagnosis, 65% of patients in our cohort had increased prolactin levels. More than 90% of patients with high prolactin levels (nearly 50% of the entire cohort) had adenomas with double GH/PRL staining.

In our patient, peripheral blood cells were heterozygous for an *AIP* gene mutation (c.2T>C in exon 1) and the tumor tissue did not contain the normal *AIP* allele. These genetic abnormalities were recently implicated in the pathogenesis of familial pituitary adenomas and, more rarely, of sporadic cases [14–21]. *AIP* mutations account for about 15% of cases of familial isolated pituitary adenomas and 50% of cases of isolated familial somatotropinomas [15, 16, 22]. These mutations are associated chiefly with GH-secreting tumors but also with prolactinomas, non-secreting adenomas, and rare cases of ACTH-secreting adenomas [15, 16, 22]. As a result of their low penetrance, germline *AIP* mutations are also observed in sporadic pituitary adenomas, especially in young males with invasive macroadenomas [23] (35/37 children with *AIP* mutations in fig. 2 had macroadenomas). Few data are available for determining the prevalence of *AIP* mutations in pediatric patients. However, 10–15% of acromegalic patients younger than 20 or 25 years of age may have *AIP* mutations [23], and the onset of somatotropinoma symptoms occurs in childhood or adolescence in about 50% of patients with *AIP* mutations [24]. We also noted genetic data of adults with acromegaly and *AIP* mutation published in the same period, to compare adult and pediatric cases. Of interest, children have significantly higher rates of mutations leading to a truncated, or probably absent, *AIP* protein that might explain severe phenotypes with early onset and familial involvement [90.2% (37/41) vs. 47.0% (32/69), $p < 0.001$]. Moreover, somatotropinomas with *AIP* mutations are associated with higher GH levels at diagnosis and a higher prevalence of prolactin oversecretion [24]. All these characteristics complicate the treatment and reduce the probability of achieving disease control [24].

The absence of pediatric guidelines creates challenges in the treatment of children with gigantism. To date, no studies evaluating treatment strategies have been published. According to recommendations for adults [25], transsphenoidal surgery is the cornerstone of the treatment of intrasellar microadenomas and noninva-

sive macroadenomas, with normal GH secretion being achieved in approximately 70 and 50% of cases, respectively [26]. In children, the small nostril diameter and incomplete sphenoid sinus pneumatization create technical challenges when performing transsphenoidal surgery, and the neurosurgeon's experience is a major predictor of success [8, 25]. Invasive adenomas are unlikely to be controlled with surgery alone and often require multiple treatment modalities (primary pharmacotherapy or surgical debulking, postoperative medical therapy and/or radiotherapy) [25].

The best initial treatment in children is unclear. Similarly, in adults, the benefits of presurgical pharmacotherapy remain debated. Preoperative treatment with somatostatin receptor ligands improved surgical outcomes and disease control in some studies [28–30] but not in others [31, 32]. Of the 68 children in this review for whom therapeutic data were available, 34% received primary pharmacological treatment and 66% immediate surgery. In patients with macroadenomas, surgical excision was complete or macroscopically complete in 55% of patients given preoperative pharmacotherapy compared to 32% of the other patients ($p = 0.12$). At the last follow-up, the disease appeared controlled in 85% of patients given first-line pharmacotherapy and in 53% of the other patients ($p = 0.028$). However, follow-up duration varied across patients, and these results are insufficient to conclude that first-line pharmacotherapy is beneficial in children with macroadenomas. We are fully aware of the limitations of an analysis based on a literature review.

Three types of drugs are available for treating somatotropinoma. For adults [25], somatostatin receptor ligands are recommended as the first-line treatment when a surgical cure is unlikely to be achieved or as second-line treatment when surgery fails to achieve biochemical control. Dopamine agonists are often used as add-on therapy when a somatostatin receptor ligand in the maximal dosage fails to normalize the hormone levels. Dopamine agonists are also indicated in patients with hyperprolactinemia and/or moderately increased IGF-1 and GH levels [25]. Contrary to adult recommendations, only 14 (56%) of the 25 patients treated with primary incomplete surgery in this review received postoperative pharmacotherapy as second-line treatment, whereas the remaining patients were treated with radiotherapy.

The third type of drug is the GH-receptor antagonist pegvisomant, which was introduced recently for the treatment of somatotropinoma in adults. Pegvisomant is used off-label in pediatric somatotropinoma. It has no effect on tumor size but normalizes IGF-1 levels in 70–97%

of adults after 12–14 months [9–11]. Pegvisomant is particularly valuable in patients who are unresponsive to somatostatin receptor ligands. Patients notice improvements after only a few weeks of treatment. In our review, 7 children received pegvisomant, usually as rescue therapy. Among them, 4 experienced significant clinical and biological improvements, without adverse effects [33, 34]. One child responded inadequately to the drug [35]. The remaining 2 patients were taken off pegvisomant when they experienced tumor growth despite an initial good response (our case, [33]). This complication is infrequent (<2%) and incompletely understood [10, 11, 36]. It may reflect not only abolition of the negative IGF-1 feedback on GH secretion but also the natural course of highly aggressive tumors [36]. Previous publications [37, 38] suggest that combining pegvisomant with a somatostatin receptor ligand may help to prevent this complication and to improve hormonal control. This combined treatment may also be helpful before surgery, with pegvisomant decreasing the IGF-1 levels and the somatostatin receptor ligand diminishing tumor volume – 2 effects associated with successful surgery [8, 27]. In a recent pediatric case report, Bergamaschi et al. [34] suggested pegvisomant as a first-line treatment option, given the high failure rate of primary surgery. Other pediatric studies are needed to define the optimal use of this new drug. Tumor status should be carefully monitored during pegvisomant therapy.

Current recommendations indicate that radiotherapy should be used only as the last resort, usually as a third-line treatment [25]. In our review, 25 children received radiotherapy, usually as second-line treatment (15/25). None received primary radiotherapy. In contrast to surgery and pharmacotherapy, radiotherapy has delayed effects, with several years being needed to achieve disease control [25, 39]. Conventional fractionated radiotherapy achieves a biochemical remission in 35–75% of patients, usually after 10 years [39]. Techniques characterized by greater accuracy with less damage to healthy tissue include stereotactic radiosurgery (gamma-knife or proton therapy), which is associated with decreased radiation exposure, faster effects, and lower rates of hypopituitarism [39]. In our patient, proton therapy improved hormonal control and decreased tumor size within only 15 months. Panhypopituitarism, the main complication of radiotherapy, occurs in over 50% of patients treated with conventional fractionated radiotherapy [10, 39] and in 30% of those treated with radiosurgery. In our review, follow-ups were usually too short for an accurate evaluation of radiotherapy effects, but panhypopituitarism developed in at least 28% of children given radiotherapy.

In conclusion, this large review provides a detailed picture of pediatric somatotropinoma. The vast majority of somatotropinomas in children are extensive macroadenomas. The treatment generally requires multiple modalities. Thus, surgery is combined with pharmacotherapy in many patients and with radiotherapy in some. Somatostatin receptor ligands and, less often, dopamine agonists are used for hormonal control and may shrink the tumor. GH-receptor antagonist therapy is still very rarely used but usually provides biochemical control and should be considered a first-line treatment option. Pediatric patients with pituitary adenomas should be routinely investigated for *AIP* mutations, which are often associated with familial forms and with large aggressive tumors.

Appendix

List of 45 Publications Used for Literature Review

- 1 Espiner EA, Carter TA, Abbott GD, et al: Pituitary gigantism in a 31 month old girl: endocrine studies and successful response to hypophysectomy. *J Endocrinol Invest* 1981;4:445–450.
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