Case Report

Complicated Clinical Course in Incipient Gigantism Due to Treatment-resistant Aryl Hydrocarbon Receptor–Interacting Protein—mutated Pediatric Somatotropinoma

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Abstract

Background: Our objective was to describe the clinical course and treatment challenges in a very young patient with a pituitary adenoma due to a novel aryl hydrocarbon receptor–interacting protein (AIP) gene mutation, highlighting the limitations of somatostatin receptor immunohistochemistry to predict clinical responses to somatostatin analogs in acromegaly.

Case Report: We report the case of a 7-year-old boy presenting with headache, visual field defects, and accelerated growth following failure to thrive. The laboratory results showed high insulin-like growth factor I (IGF-I) (standardised deviation scores (þ3.49) and prolactin levels (0.5 nmol/L), and magnetic resonance imaging identified a pituitary macroadenoma. Tumoral/hormonal control could not be achieved despite 3 neurosurgical procedures, each time with apparent total resection or with lanreotide or pasireotide. IGF-I levels decreased with the GH receptor antagonist pegvisomant. The loss of somatostatin receptor 5 was observed between the second and third tumor resection. In vitro, no effect on tumoral GH release by pasireotide (with/without cabergoline) was observed. Genetic analysis revealed a novel germline AIP mutation: p.Tyr202* (pathogenic; class 4).

Discussion: In vitro response of tumor tissue to somatostatin may better predict tumoral in vivo responses of somatostatin analogs than somatostatin receptor immunohistochemistry.

Conclusion: We identified a novel pathologic AIP mutation that was associated with incipient acrogiantism in an extremely young patient who had a complicated course of disease. Growth acceleration can be masked due to failure to thrive. Tumoral growth hormone release in vivo may be predicted with in vitro exposure to somatostatin receptor analogs, as it cannot be assumed that all AIP-mutated somatotropinomas respond well to pasireotide.

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Introduction

Pituitary adenomas have a prevalence of 1 clinically-relevant case per 1000 adults.1 Most pituitary adenomas are sporadic, but 5% have a familial background, the most common being familial isolated pituitary adenomas.1,2 In familial isolated pituitary...
Adenomas, 15% to 30% of cases are associated with pathologic germline variants in the aryl hydrocarbon receptor–interacting protein (AIP) gene, a tumor suppressor gene located on chromosome 11q13.2-6 Germline AIP mutations are particularly associated with growth hormone- (GH) or mixed GH–prolactin–secreting pituitary adenomas.3-6 Patients with AIP mutations are often men and have an aggressive clinical phenotype due to large invasive tumors. AIP mutations are the most frequent genetic cause of pituitary gigantism (29%).2,5,7,8 In large case series, AIP-mutated pituitary adenomas usually present in adolescence or early adulthood.3 Early pediatric presentations of patients with AIP mutations and GH-secreting pituitary adenomas are rarely described, and responses to medical and surgical management in this challenging population are not well-understood. Here, we report the challenges faced in the presentation, diagnosis, and management of a young boy with a novel AIP mutation that led to a recurrent and resistant GH-secreting macroadenoma.

Case Description

A 7-year-old boy was hospitalized for the evaluation of multiple progressive complaints over the previous 2 years, including frontal headache, fatigue, tics, leg pain, nocturnal sweating, constipation, and poor food intake. He had a normal birthweight/height following an unremarkable pregnancy, and his family history was normal. His growth curve showed normal growth until the age of 3 years, followed by a marked decrease to about −2 standardised deviation scores (SDS) at the age of 6 years (Fig. 1). Thereafter, his growth increased rapidly compared with the Dutch national standards. His parents were of modest stature (father, 170 cm and mother, 164 cm) by the current Dutch median height standards (men, 182.9 cm and women, 169.3 cm). A sellar tumor with an enlarged sella turcica was discovered (Fig. 2). Laboratory analysis showed an insulin-like growth factor I (IGF-I) level of 56.5 nmol/L (normal range [NR], 8.3-38.2; SDS, +3.49), prolactin level of 0.5 nmol/L, and an elevated IGFbinding protein 3 (IGFBP3) level of 0.5 nmol/L (NR, ≤0.5). The patient was diagnosed at the age of 7 years. The blue arrow corresponds with LAN treatment, the purple arrow corresponds with PAS treatment, and the red arrow corresponds with PEGV surgery. One month after switching to pasireotide, the first transsphenoidal resection was performed. Two months thereafter, pegvisomant was started. After 1 month of pegvisomant, the tumor volume increased; pegvisomant was stopped, and a second resection followed. Six months thereafter, the third surgery was performed. LAN = lanreotide; PAS = pasireotide; PEGV surgery = pegvisomant and surgery.

Fig. 1. Growth chart of the patient with incipient gigantism. The initial normal growth of the patient declined from 3 to 6 years of age, but then deflected markedly upward. The patient was diagnosed at the age of 7 years. The blue arrow corresponds with LAN treatment, the purple arrow corresponds with PAS treatment, and the red arrow corresponds with PEGV surgery. One month after switching to pasireotide, the first transsphenoidal resection was performed. Two months thereafter, pegvisomant was started. After 1 month of pegvisomant, the tumor volume increased; pegvisomant was stopped, and a second resection followed. Six months thereafter, the third surgery was performed. LAN = lanreotide; PAS = pasireotide; PEGV surgery = pegvisomant and surgery.
nmol/L (NR, <0.36 nmol/L), TSH level of 1.07 mU/L (NR, 0.6-5.6 mU/L), free thyroxine level of 20.2 pmol/L (NR, 13-26 pmol/L), afternoon cortisol level of 270 nmol/L (NR, <700 nmol/L), and undetectable luteinizing hormone and follicle-stimulating hormone (normal for prepubertal state). Over time, the growth rate accelerated further (Fig. 1), in parallel with rising IGF-I (71.2 nmol/L; +4.53 SDS), a random GH of 30.8 μg/L (NR, <4.0 μg/L), and prolactin increase to 0.75 nmol/L. The nadir GH value during an oral glucose tolerance test was 26.7 μg/L. He complained of vomiting and loss of appetite.

Treatment of the GH-secreting macroadenoma was initiated with lanreotide 120 mg once in 4 weeks, which resulted in no biochemical response (IGF-I level, 76.6 nmol/L and GH level, 28.0 μg/L) or inhibition of tumor growth after 4 doses. Lanreotide was switched to pasireotide 60-mg long-acting release (LAR) once in 4 weeks. One month after switching, he developed a new onset of bitemporal field defects and headaches that indicated symptomatic optic chiasmal compression, and he underwent transsphenoidal surgery for the first time. Two months postoperatively (3 months after the initiation of pasireotide LAR), IGF-I (70.3 nmol/L) and GH (23.4 μg/L) levels remained elevated. Pasireotide LAR showed no hormonal or tumoral effects, and the GH receptor antagonist pegvisomant was started with a weekly dose of 40 mg. Although IGF-I levels dropped to 34.1 nmol/L (NR, 10.9-47.3 nmol/L; 0.87 SDS), the local GH assay, which does not detect pegvisomant, continued to show an elevated random GH level (48.6 μg/L). After 1 month of pegvisomant, severe headaches returned, and bitemporal hemianopsia reoccurred due to an increase in tumor volume (Fig. 2). Pegvisomant was stopped, and a second transsphenoidal resection followed (Fig. 2). The histopathologic report revealed a pituitary adenoma staining positive for GH and negative for prolactin (Fig. 3). One month after the second transsphenoidal surgery, his IGF-I level declined to 29.3 nmol/L (0.4 SDS). GH level was 2.7 μg/L, and prolactin level declined from 0.60 to 0.38 nmol/L (NR, 0.1-0.5 nmol/L). Five months after surgery, the headaches returned, and magnetic resonance imaging 1 month later showed a small remnant lateral to the right internal carotid artery (Fig. 2). IGF-I increased again to +2.9 SDS. A third transsphenoidal surgery was performed, leading to the normalization of GH and IGF-I levels. Thirteen months after his last surgery, he received stereotactic radiotherapy (34 Gy), and 4 months after radiotherapy, his last IGF-I was ~0.8 SDS.

Due to the presentation with a macroadenoma at a young age, germline genetic testing for sequence variants and deletions in AIP and MEN1 genes was performed. A novel heterozygotic truncating variant in the AIP gene was discovered (c.606C>G; p.Tyr202*; GnomAD database mean allele frequency (0), which was accompanied by a second missense variant (c.695C>T; p.Pro232Leu; mean allele frequency, 0.00002502), both of which were paternally inherited. Screening by magnetic resonance imaging and hormone evaluation of his 37-year-old father was negative.

Histopathologic analysis revealed a loss of SSTR5 expression between the second and third operations (Fig. 3). In vitro characterization of the second surgical sample showed no statistically significant inhibition of GH secretion to incubation with pasireotide (10 nM) or coinubation with pasireotide and cabergoline (both 10 nM; Fig. 4). Other compounds could not be tested due to the limited amount of available tissue. These interesting findings should be confirmed in a wider series of tumors from patients with AIP mutations and in appropriate wild-type acromegaly controls.

Given the lack of tumor size control with first- and second-generation somatostatin analogs (SSAs) and the unresectable remnant that required radiotherapy at the age of 10 years, the patient will require intensive (endocrinological) follow-up, although no pituitary deficiencies have occurred to date. If needed, excessive GH can be controlled by pegvisomant, albeit with high vigilance for tumor regrowth.

**Discussion**

This case report describes a complicated somatotropinoma leading to accelerated longitudinal growth that was masked by an unexpected initial period of failure to thrive, which likely occurred due to poor feeding because of nausea. The disease was diagnosed at the very young age of 7 years and was found to be due to a previously undescribed AIP mutation that was inherited from his unaffected father. Decreased clinical SSA sensitivity may be related to the evolving tumor biology between surgeries, particularly the loss of tumoral somatostatin receptor (SSTR) 5 expression, whereas in vitro, there was no tumoral response of GH to pasireotide and cabergoline.

Somatotropinomas are primarily treated with (transsphenoidal) neurosurgery, SSAs, dopamine agonists, or GH receptor antagonists. Overall, in acromegaly, long-acting SSAs can achieve biochemical normalization of GH and IGF-I in 50% to 60% and often lead to modest tumor shrinkage. Patients with AIP mutations...
have, however, significantly less tumor shrinkage and lower hormonal responses to first-generation SSAs.

SSAs act via SSTRs 1 to 5. The first-generation SSAs octreotide and lanreotide have the highest affinity for SSTR2 and have a low affinity to SSTR3 and SSTR5, whereas the second-generation SSA pasireotide has the highest affinity for SSTR5, followed by SSTR2, SSTR3, and SSTR1. As reported previously, pasireotide resistance is possibly more related to SSTR2 expression than to SSTR5 in the general acromegaly population. SSA resistance may occur if the tumor is lacking SSTR2. Daly et al recently reported 2 AIP-mutated acromegaly patients with resistance to first-generation SSA, in whom pasireotide treatment led to marked tumor shrinkage and persistent hormonal control. In 1 case, very low-to-absent SSTR2 levels were seen, and the efficacy of pasireotide must have been through other SSTRs like SSTR5. Due to this, we initially expected that our patient would respond better to pasireotide despite resistance to first-generation SSAs, but this was not the case. The resistance to pasireotide probably relates in part to the low SSTR5 expression, since SSTR2 expression remained present. Nevertheless, signaling via SSTR2 may be affected while leaving the receptor expression unaffected. Possible factors in this phenomenon include ZAC1 and miR-34a, both of which influence SSTR2 signaling. In these cases, it may be preferable to test the in vitro response of the tumor tissue assessed by decreases in GH secretion. In the study by Coopmans et al that included 45 acromegaly patients who were previously treated with first-generation SSAs combined with pegvisomant, SSTR2 immunoreactivity scores were found to be related to significant tumor shrinkage in patients treated with pasireotide, which was not the case for SSTR5. Muhammad et al found in the same cohort that IGF-1 lowering effects of pasireotide correlated with SSTR2 instead of SSTR5. However, the timing of the change in responsiveness and change in SSTR5 expression occurred simultaneously in the current case. In the study by Iacovazzo et al that included 39 patients with somatotropinomas, SSTR5 expression predicted responsiveness to pasireotide.

Our case exemplifies the many challenges that can be faced in the recognition of acromegaly, especially when occurring at an extremely young age. Acrogigantism can occur with increased growth velocity in young patients, even without extremely elevated height compared to age-/sex-matched references. An appreciation of the totality of the abnormal growth characteristics is important when assessing children with aberrant growth. In this case, a novel AIP mutation, p.Tyr202*, was found. The unresponsiveness of the tumor to pasireotide may be better assessed by in vitro responsiveness as opposed to somatostatin receptor evaluation. Future
studies are necessary to test this hypothesis in cohorts with more patients and with a control group.

Conclusion

This informative case of incipient gigantism in a 7-year-old child with a novel AIP mutation, p.Tyr202*, was associated with a highly treatment-resistant somatotropinoma. Although previous literature suggests a favorable response to pasireotide in some patients with AIP mutations and acromegaly, pasireotide had only limited effect in our patient, possibly related to decreasing SSTR5 expression of the tumor. In vitro GH suppression in the cultured tumor tissue may predict in vivo treatment response better than SSTR assessment. Genetic testing of the AIP gene should be advocated in all patients with GH-secreting pituitary adenomas occurring in childhood and/or (incipient) pituitary gigantism.

Disclosure

The authors have no multiplicity of interest to disclose.

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