Familial pituitary apoplexy as the only presentation of a novel *AIP* mutation

Dear Editor

Growth hormone (GH)-producing tumors in *AIP* mutation-positive patients are typically more aggressive than their sporadic counterparts. They are also frequently associated with onset in childhood and adolescence and appear to be less responsive to medical therapy (Beckers et al. 2013). A male predominance has been observed (Daly et al. 2010). We report on a unique clinical presentation of a kindred with a novel *AIP* mutation: only one of the three affected members had all the typical signs and symptoms of patients with an *AIP* mutation. On the contrary, the carrier father and brother had both partially empty sella turcica and, in fact, the latter ended being treated for anterior pituitary lobe hormonal deficiencies, including GH. This was presumably the result of pituitary apoplexy due to a rapidly growing *AIP*-induced adenoma.

Briefly, a 12 years 2 month-old boy was seen for tall stature and accelerated growth velocity that was first noticed at the age of 4 years. At initial presentation, his height was 186.6 cm (z-score +4.72), over the calculated mid-parental height (180.5 ± 4.5 cm), and his weight was 78.7 kg (z-score +2.59). He was also macrocephalic and he had several facial characteristics typical of gigantism. Hormonal investigation showed increased IGF1: 906 ng/ml (nv: 183–850) and GH: 18.3 ng/ml that did not suppress to oral glucose tolerance test (OGTT). The rest of pituitary hormones were in the lower normal range (Supplementary Table 1, see section on supplementary data given at the end of this article). Pituitary MRI showed the presence of a $1.3 \times 1.2 \times 1.1$ cm pituitary adenoma with suprasellar extension (Fig. 1A). He underwent partial resection of the pituitary adenoma. The surgical pathology evaluation confirmed the presence of a GH-positive, sparsely granulated tumor with globules of keratin (fibrous bodies) and lack of normal reticulin framework (Fig. 2A, B, C, and D). Areas of expanded acini clearly distinctive from the adenoma were detected suggestive of hyperplasia (Fig. 2E and F). Both parents had normal heights and no history of acromegaly.

A paternal uncle, however, had a history of acromegaly secondary to a GH-producing pituitary adenoma that had been operated in the distant past. Genetic analysis for mutations in *MEN1* and *CDKN1B* genes was negative, whereas a G deletion in exon 1 of *AIP* gene, not previously reported, which creates a premature stop codon 16 amino acids downstream (c.4delG/p.A2Rfs*16), was detected. The same mutation was detected in his clinically unaffected 41-year-old father, his younger brother, and seven other family relatives from the paternal side. The median age of the seven family members that were tested positive for the same mutation was 27 years (age range 6 months to 65 years).

None of them had a history of a GH-producing pituitary adenoma or any symptoms related to GH (or PRL) excess. Appropriate instructions were given for further biochemical and imaging investigation, which to this day has not been completed for all family members. The paternal uncle refused testing. Western blot of extracts from the patient's pituitary tumor cells showed almost no expression of AIP compared with another patient with acromegaly without an *AIP* mutation (Fig. 2G). The patient was placed on SST. At 2 years postoperatively, he had normal basic GH and IGF1 levels and adequate suppression of GH levels to OGTT. No deficiencies of the other pituitary hormonal levels were detected (Supplementary Table 1).

The 41-year-old father and the 8 years 6 month-old brother of the proband were evaluated for the presence of a pituitary adenoma since they were found to harbor the same mutation as the patient. The father's only symptom was decreased libido. Pituitary and target gland hormones were found to be in the lower quartile of the respective normal ranges. Pituitary MRI showed presence of a left-sided $4.3 \times 4 \times 3$ mm hypoenhancing area; the small pituitary tissue was peripherally located and the overall image was typical of a partially empty sella turcica (Fig. 1B).

Figure 1

(A) Pre-contrast coronal T1-weighted pituitary MRI showing a macro-adenoma with suprasellar extension (arrow). Post-contrast coronal T1-weighted pituitary MRI from proband's father (B) and younger brother (C), showing a subtle left hypoenhancing area (possibly a microadenoma) (small arrow) and partially empty sella (large arrow).

Review of the systems of patient's younger brother did not reveal any symptoms related to a hormone-secreting pituitary tumor but a reduced annual growth rate (2 cm/year for the last 2 years) was noted. His height was 136.8 cm (z-score: 1.6) and his weight was 35.8 kg (z-score: 1.8) and he, unlike his brother, was normocephalic. Hormonal investigation was consistent with partial hypopituitarism. Pituitary MRI findings were similar to those detected in his father (Fig. 1C). The patient was started on hydrocortisone, levothyroxine, and GH replacement.

Familial empty sella turcica in the context of an AIP mutation is a novel phenotype for patients with AIP mutations. There are two other reports (Villa *et al.* 2011, Dal *et al.* 2012) that demonstrate that rapid growth of an AIP loss-induced tumor may also lead to apoplexy before a hormonal syndrome becomes clinically detectable. In one of them, like in our case, pathological examination revealed multiple areas of pituitary hyperplasia along with the adenomatous tissue, which stained positively for GH, indicating somatotroph hyperplasia (Villa *et al.* 2011).

Subclinical pituitary apoplexy is not extraordinarily rare. This term has been used to describe cases of pituitary hemorrhages and infarctions detected incidentally on routine radiological studies, which are typically associated with mild symptoms or may even remain completely asymptomatic (Findling *et al.* 1981, Ostrov *et al.* 1989). In a retrospective review of 560 cases of pituitary adenoma, 93 tumors (16.6%) showed evidence of intratumoral hematoma, yet only 38 patients (6.8%) experienced an apoplectic event (Wakai *et al.* 1981). Mohr & Hardy (1982) reviewed 664 patients operated for pituitary adenomas over a period of 17 years. Classic apoplexy with the typical presentation was seen only in four patients (0.6%). However, 64 patients (9.6%) had evidence of hemorrhage or necrosis at surgery (Mohr & Hardy 1982). In addition, Yoshino *et al.* (2005) described two cases of nonfunctioning pituitary adenomas that underwent complete resolution through asymptomatic necrosis with the only finding being an empty sella on pituitary MRI.

Our unique case report provides new data for what appears to be a new phenotype for AIP mutation-positive patients: apoplexy and consequently pituitary deficiency (rather than hormone excess). If the index case had not manifested the full-blown acromegalic symptoms, the whole family would have probably remained undiagnosed. This suggests that the prevalence of the AIP mutations in FIPA kindreds may be higher than that reported in the literature (Beckers *et al.* 2013). It also indicates that the empty sella syndrome and/or apoplexy is one of the possible phenotypes of AIP defects.

Figure 2

Pituitary adenoma with proliferation of monotonous cells (A, H&E 20 $\times$) with breakdown of reticulin framework (B, reticulin stain 20 $\times$), diffuse staining for hGH (C, hGH stain 20 $\times$), and with characteristic juxtanuclear globular positivity corresponding to fibrous bodies (D, Cam 5.2, 40 $\times$).

The adjacent anterior pituitary shows expanded acini on HE (E, H&E 20 $\times$); reticulin stain highlight preserved reticulin fibers (F, 20 $\times$). (G) Western blot of AIP expression in a patient with acromegaly without AIP mutation (P1) and in our patient with the AIP mutation (P2).

Although no widely accepted guidelines for the clinical management of AIP mutation-positive families are available, baseline MRI and yearly screening for abnormal pituitary function have been proposed (Trivellin & Korbonits 2011, Beckers *et al.* 2013). This appears to be a reasonable approach, although one should add global pituitary function screening to include biochemical signs of subtle or partial hypopituitarism.

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Supplementary data

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Declaration of interest

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Author contribution statement

The contribution of each authors is as follows: P Xekouki performed most of the experiments described in the manuscript and prepared the manuscript. S A Mastroyiannis and D Avgeropoulos participated in the genetic testing and analysis of the described kindred. M de la Luz Sierra prepared the clinical specimens for genetic analysis. G Trivellin participated in manuscript preparation and editing. E A Gourgari was the physician who took care of the described kindred at the NIH. C Lyssikatos collected clinical specimen. M Quezado involved in pathology evaluation and immunohistochemistry studies. N Patronas involved in reading and interpretation of imaging studies. C Kanaka-Gantenbein was the primary care physician of the described kindred. G P Chrousos was the physician who originally identified and referred the family to the NIH. C A Stratakis was the senior investigator at NICHD, which provided most of the funding for this project under the NIH Intramural Research Program, and overall supervised the experiments, presentation of results, design of figures, and writing the manuscript.

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