

Recurrence of GH-secreting pituitary adenomas during puberty in children with germline *AIP* mutations: a clinical challenge

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Introduction

Germline *AIP* mutations (*AIP*^{mut}) predispose to young onset somatotroph pituitary adenomas (GHPA) and gigantism. *AIP*^{mut} GHPA are often aggressive and resistant to pharmacological treatment, which may be especially challenging in a pediatric setting. We report our experience with two young Italian male patients, who developed incipient gigantism (Fig.1) due to *AIP*^{mut} pituitary macroadenomas. After successful surgery, both experienced recurrent GH/IGF1 hypersecretion followed by tumour regrowth during puberty. Diagnostic and therapeutic challenges are reported.

Case 1. Patient A developed incipient gigantism in a familial *AIP*-related setting (*AIP*^{R304X}) at the age of 8 yrs-old. Two years after successful transphenoidal surgery for an intrasellar macroadenoma (12 mm) (Fig.2) spontaneous puberty occurred and IGF1 increased progressively. Final diagnosis of disease recurrence was made at the age of 14.5 yrs and pharmacological treatment with cabergoline (CAB) and somatostatin analogues (SSA) was started with a partial and transient response, and a recent shift to pegvisomant. A small intrasellar recurrence recently appeared and second surgery is being considered. Height has stabilized at 191 cm.

Case 2. Patient B complained of visual defects at the age of 11.5 yrs in a context of accelerated growth. MRI showed a pituitary macroadenoma with suprasellar extension (27 mm) (Fig.3), which was successfully operated on. Plasma GH/IGF1/PRL and growth velocity normalized. A germline *AIP*^{A277P} mutation was found (Fig.4). Spontaneous puberty occurred and IGF1 increased progressively. Two years after surgery, he was started on CAB due to modest biochemical/clinical worsening and initial tumour regrowth. The recurrence become increasingly aggressive, requiring multiple treatment modalities with SSA, CAB and/or pegvisomant. He was re-operated at 14 and 18 yr-old s and irradiated at 19 (2013). Medical therapy was progressively withdrawn, and GH/IGF1 hypersecretion is currently controlled with a still preserved pituitary function. Final height is 190 cm.

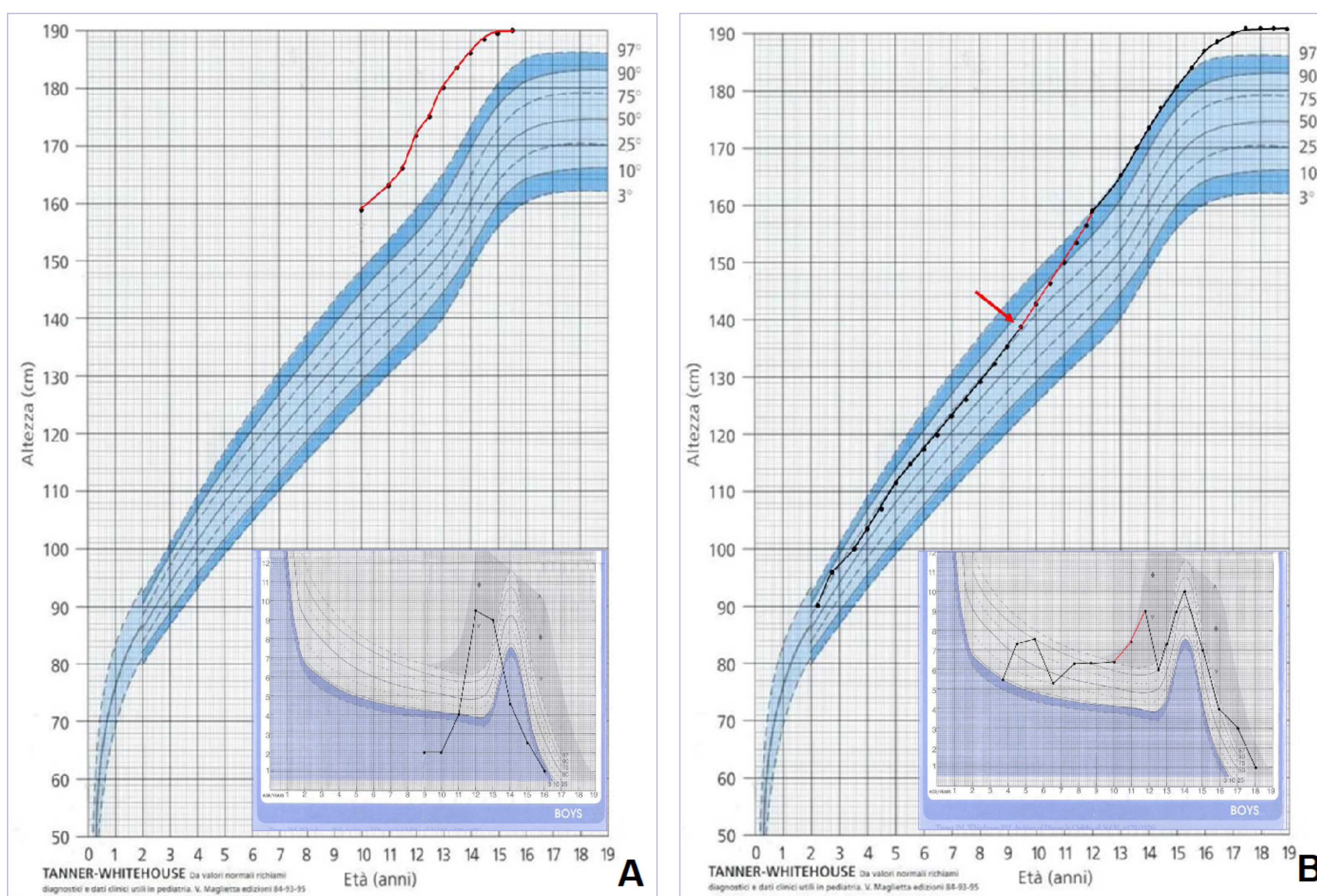


Fig. 1: Tanner growth chart and height velocity in two *AIP*^{mut} pediatric patients (A: Case 1; B: Case 2)

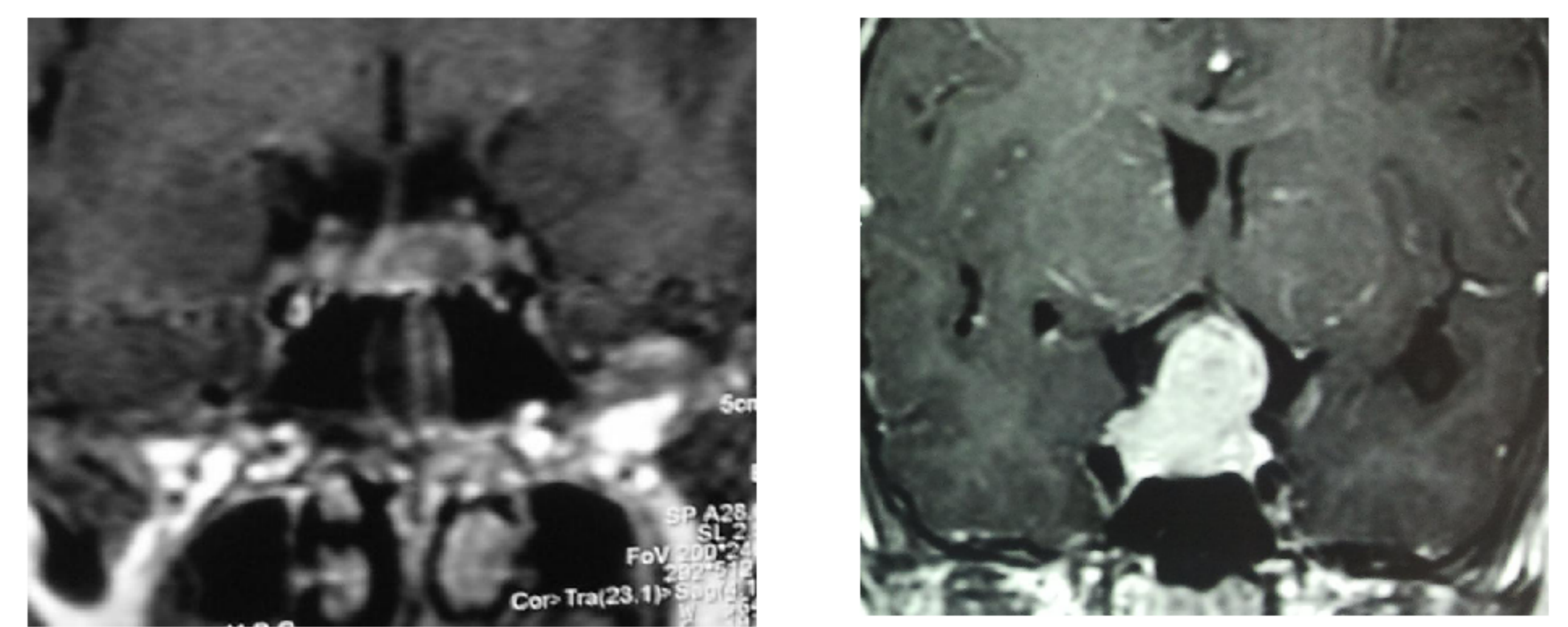


Fig. 2: An intrasellar pituitary macroadenoma (Case 1).

Fig. 3: An invasive pituitary macroadenoma (Case 2).

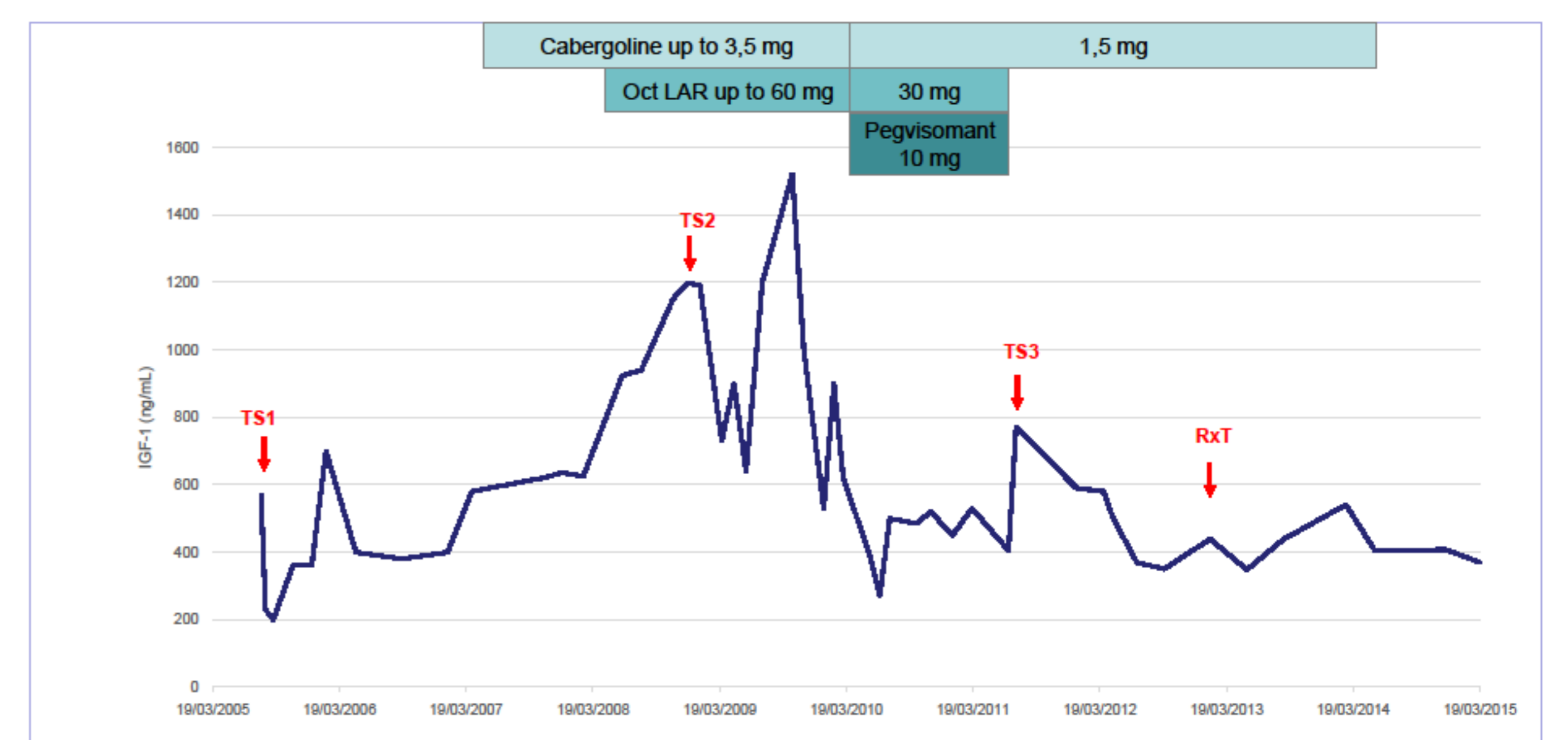


Fig. 4: IGF-1 values variations in patient 2

Conclusion. While confirming that *AIP*^{mut} patients may develop pituitary adenomas very early, thereby supporting pre-pubertal screening in *AIP*^{mut} kindreds, these observations illustrate the peculiarities of peri-pubertal disease management in this setting. Most of the IGF1 levels were beyond the upper normal IGF1 limits for age during puberty, despite active disease, and MRI was of limited help in the early phase of recurrence. In both cases increasing resistance to SSA and CAB occurred, but the IGF1 target on Pegvisomant treatment is ill-defined. Thus, although the early diagnosis and treatment of disease recurrence is of special importance in patients with incipient gigantism, this may be very challenging during puberty. Indications for repeated surgery and/or radiotherapy at a young age should also be balanced with the risk of long-term complications.

References: Jaffrain-Rea ML & al Genetic susceptibility in pituitary adenomas: from pathogenesis to clinical implications *Exp Rev Endocr Metab* 2011;6:195-214. Beckers A & al. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the *AIP* gene. *Endocr Rev*. 2013;34:239-277.

