TREATMENT OF RESISTANT PAEDIATRIC SOMATOTROPINOMAS DUE TO AIP MUTATION WITH PEGVISOMANT

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Background:

- Somatotropinomas are rare in childhood and are frequently associated with genetic mutations.
- Prior to epiphyseal fusion, `gigantism' occurs; after epiphyseal fusion acromegaly signs/symptoms predominate.
- *AIP* mutations are the most common genetic cause of pituitary gigantism (29%) and occur in 20% cases of sporadic pediatric adenomas; they usually cause somatotropinomas that are large, aggressive and treatment resistant

Objective:
To assess response to pegvisomant, a GH receptor antagonist in two children with sporadic somatotropinomas due to *AIP* mutation, where resistance to somatostatin is a recognized phenomenon.

Patients and Methods:

We report two children, a 13 year old boy and a 10 year old girl who presented with rapid growth and visual compromise and were found to have evidence of GH hypersecretion. MRI confirmed presence of a pituitary macroadenoma with parasellar extension in both cases. Multiple surgical attempts were needed to debulk tumour mass. Residual tumour in cavernous sinus was not amenable to further surgery. Genetic analysis showed mutations in the AIP gene is both cases, patient 1:c.562delC (p.Arg188Glyfs*8) and patient 2: c.140_163del24 (p.Gly47_Arg54del8). They were initially treated with long acting somatostatin analogues (Sandostatin LAR 60 mg/week). Pegvisomant was subsequently started, at 10mg per day subcutaneously, increased to 20mg/day. Sandostatin was ceased due to patient intolerance and lack of biochemical control of GH excess. Radiotherapy was administered to both, as definitive treatment, for long term disease management.

Results:

Patient 1 had normalisation of IGF1 to 64.8 nmol/L (20-71) after 5 months of combined therapy with pegvisomant and cabergoline. Patient 2 was controlled after 2 months of cabergoline and pegvisomant, with normalisation of IGF1 to 34.4nmol/L (12-59); see Table 1. Her clinical course was complicated by cholelithiasis and abnormal liver function, induced by somatostatin and which resolved after cholecystectomy.

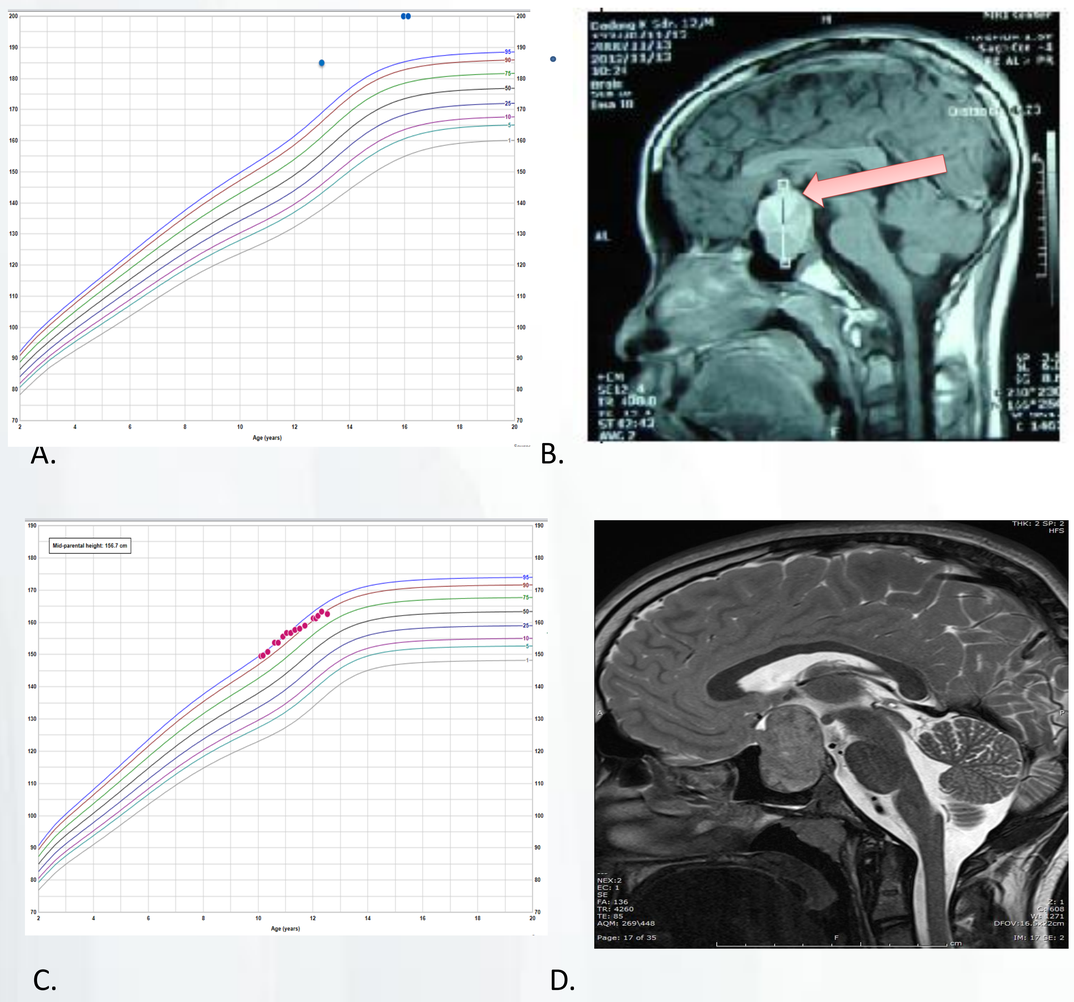

Fig 1. A . Growth chart of patient 1. B. Pre op MRI image of patient 1 showing large pituitary adenoma with suprasellar extension. C Growth chart of patient 2. D. MRI of patient 2 showing multilobulated pituitary adenoma with suprasellar extension

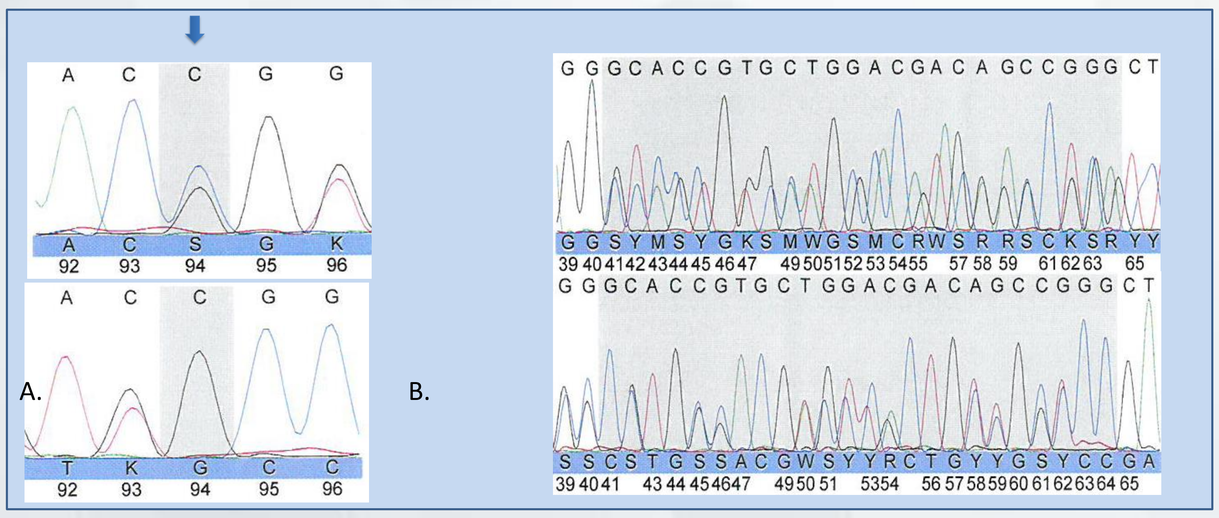

Fig 2. Sequencing data for the AIP gene showing the mutation in the heterozygous state in A. Pt1: c.562delC (p.Arg188Glyfs*8) and B. Pt 2: c.140_163del24 (p.Gly47_Arg54del8) with the wild type sequence below.

Table 1: Hormonal profile of patient 2 showing response to medical therapy

Date	GH (mIU/L)	IGF1 (nmol/l) (12-59)	Management
30/9/13	812	92	LAR 20 mg monthly
17/12/13	17.25	95.3	LAR 30 mg monthly
6/2/14	45.7	98	LAR 60 mg monthly
8/4/14		123.5	Cabergoline added
3/6/14		111.8	LAR 90 mg monthly
25/9/14		108.5	Same continued
11/2/15		96.7	Started on Pegvisomant, Sandostatin gradually tapered
24/3/15	78.6	51.5	
23/4/15	98.7	34.4	Sandostatin stopped
25/5/16	40.1	18	Pegvisomant 20 mg/day

Conclusion: *AIP* mutation associated tumors are resistant to medical management with somatostatin receptor ligands. Pegvisomant can safely be used in this situation to normalise IGF1 levels and help in disease control.

References: 1. Daly, A. F., et al. (2010). "Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study." J Clin Endocrinol Metab **95**(11): E373-383. 2. Rostomyan L et al. Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. Endocr Relat Cancer. 2015 Oct;22(5):745-57

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Growth

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