Combined treatment with Octreotide LAR and Pegvisomant in patients with Acrogigantism: Clinical Evaluation and Genetic Screening

Liliya Rostomyan[1], Ruth Mangupli[3], Emilie Castermans[2], Jean-Hubert Caberg[2], Paul Camperos[3], Jaime Krivoy [3], Elvia Cuauro[3], Vincent Bours[2], Adrian F Daly[1], Albert Beckers[1]

(1) Department of Endocrinology and (2) Department of Clinical Genetics, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium (3) Section of Neuroendocrinology, Department of Neurosurgery, Hospital Universitario de Caracas, Caracas, Venezuela

Pituitary gigantism is a rare condition caused by growth hormone hypersecretion, usually by a pituitary tumor. Acromegaly and gigantism cases that have a genetic cause are challenging to treat, due to large tumor size and poor responses to some medical therapies (e.g. *AIP* mutation affected cases and those with X-linked acrogigantism (X-LAG) syndrome.

Objectives

We studied a gigantism cohort from Venezuela for genetic defects and their response to treatment.

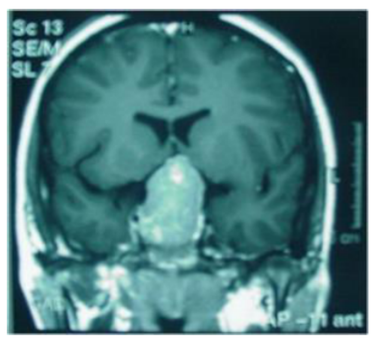
Methods

We performed a retrospective study to identify gigantism cases among 160 somatotropinoma patients treated between 1985 and 2015 at the University Hospital of Caracas, Venezuela. We studied clinical details at diagnosis, hormonal responses to therapy and undertook targeted genetic testing that included *AIP* and *MEN1* sequencing and MLPA, and aCGH for Xq26.3 duplications.

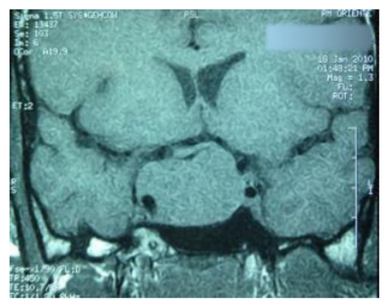
Results

Among the 160 cases, 8 patients (6 males; 75%) were diagnosed with acrogigantism, all developed their 1st clinical symptoms before 21 years. The most frequent clinical signs at presentation (apart from tall stature) were acral enlargement (7/8) and headache (5/8). All patients had GH secreting pituitary macroadenomas (Median max diameter 31mm, IQR: 25.5-41.5) with cavernous sinus invasion in 75% and prolactin hypersecretion in 50%. Six cases received primary treatment with the long-acting SSA octreotide LAR 20 mg/28 days for 6-12 months, in 2 cases SSA was administrated after unsuccessful surgery (radiotherapy was also used in 1 case). Cabergoline was added in those with elevated prolactin. None of the patients had hormonal control. Additional administration of Pegvisomant 20 mg daily resulted in a decrease of IGF-1 to normal ranges while tumor volume was stable in all patients. Regression of clinical symptoms was seen after 1-4 months of treatment including a decrease in growth velocity. None of the patients had evidence of MEN1, Carney complex, FIPA or McCune Albright syndromes. Novel *AIP* mutations were the found in three patients. None of the patients had *MEN1* mutations/deletions or Xq26.3 microduplications.

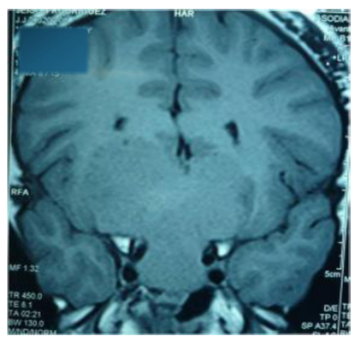
T1-weighted coronal MR imaging



Patient #1



Patient #5



Patient #7

Patient #	Sex	Age (years)	Height (cm)	Height SDS	Tumor size (cm)	*AIP* mutation	*AIP* variants	GH (µg/L) 0 5 10 15 20 25 30 35 40	IGF-1 (%ULN) 0 50 100 150 200 250 300 350 400
1	M	21	218*	7.62	2.6 x 2.2	No	p.D172D; p.Q228K§; p.Q307R§		
2	M	28	192*	3.44	3.4 x 2.2	No	p.Q228K§; p.Q307R§		
3 TSS	F	13	178	4.08	1.7 x 1.6 x 1	Not studied	Not studied		
4	F	23	186*	5.05	2.5 x 1.8 x 1.4	No	p.Q228K§; p.Q307R§		
5	M	24	192*	3.44	3 x 4 x 2.5	No	p.D172D; p.Q228K§; p.Q307R§		
6	M	15	195	3.96	6 x 6 x 3.5	c.715_721delins TCAACTAC	p.G12G; p.Q228K§; p.Q307R§		
7	M	13	185	4.08	2.8 x 1.9 x 1.2	c.455T>G (p.M152R)	p.Q228K§; p.Q307R§		
8 TCS, RTh	M	14	174	1.82	4.3 x 4.3	c.707_716delins GGC	p.Q228K§; p.Q307R§		

Basal
GH and IGF-1 on SSA
IGF-1 on SSA & PegV

RTh- radiotherapy; TSS-transsphenoidal surgery; TCS – transcranial surgery; * – stopped growing; § – normal

Conclusions

Patients with gigantism have large and aggressive GH secreting pituitary lesions that are difficult to control with conventional treatment options. Prolactin co-secretion is frequent. Treatment of acrogigantism is frequently challenging; delayed control increases the harmful effects of GH excess, such as, excessive stature and symptom burden. Combined therapy (long-acting SSA and pegvisomant) as primary treatment or after pituitary surgery and radiotherapy can permit the normalization of IGF-1 levels and achieve clinical improvement in these difficult to manage patients.

ECE 2016
889--EP
Pituitary - Clinical
Liliya Rostomyan
Poster presented at: ECE2016 28 – 31 May 2016 MUNICH, GERMANY 18th EUROPEAN CONGRESS OF ENDOCRINOLOGY