Pegvisomant in childhood acromegaly: report of two cases.

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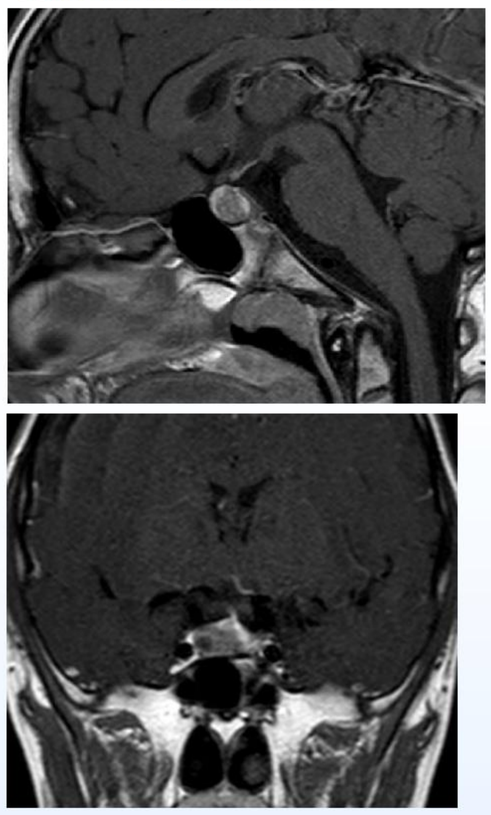
Background :

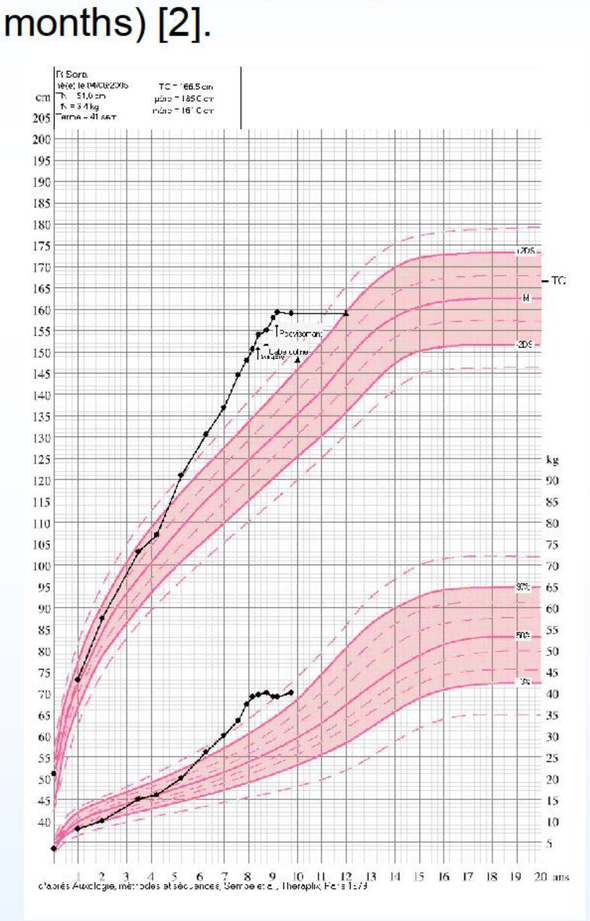
Treatment with growth hormone (GH) receptor antagonist, pegvisomant, results in improvement in clinical and biochemical symptoms of acromegaly but experience with this drug in pituitary gigantism is limited.
We present results of pegvisomant therapy in two girls with invasive GH pituitary macroadenomas.

Case 1 :

A somatotroph pituitary macroadenoma was diagnosed in a 8-year-old girl with progressive tall stature (height: 148 cm, >+3 SD ; growth velocity (GV):11 cm/year), GH hypersecretion without suppression during oral glucose loading (serum GH nadir : 34 mU/l), high serum IGF-I (691 ng/ml) and high serum prolactin (270 mUI/l) levels. Bone age was 10 years without onset of puberty (Tanner stage P2S1). Pituitary MRI showed an invasive pituitary macroadenoma [1]. Transphenoidal surgical tumour removal was incomplete. Histological examination showed a mixed GH and prolactin-secreting adenoma. Serum IGF1 and GH levels remained high after surgery (GH serum nadir during oral glucose loading : 5mUI/l, IGF1 : 908ng/ml) and after cabergoline treatment (10.6mUI/l, 590ng/ml). Pegvisomant 10mg/d in combination with cabergoline quickly led to IGF1 normalization (180, 115, 123 and 208ng/ml after respectively 1, 4, 7 and 10-months treatment) and growth arrest (GV: 0 cm/7 months, 2 cm/12 months) [2].

[1] MRI at diagnosis, case 1.





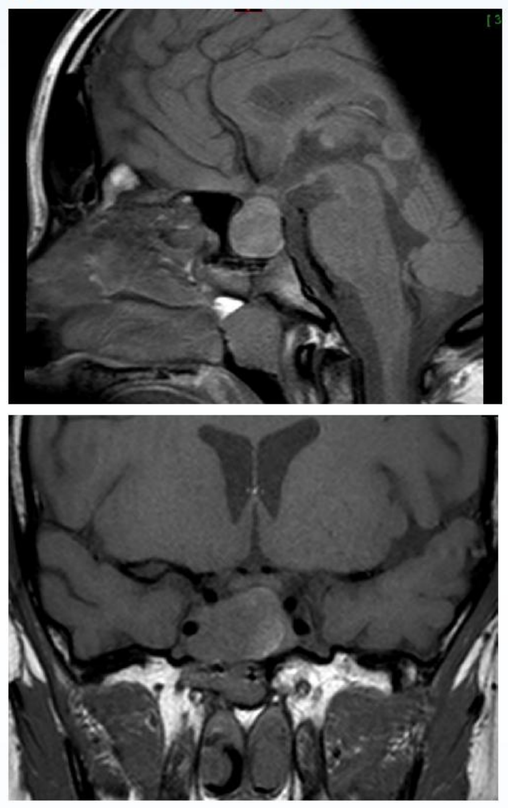
[2] Clinical and hormonal parameters evolution, case 1.

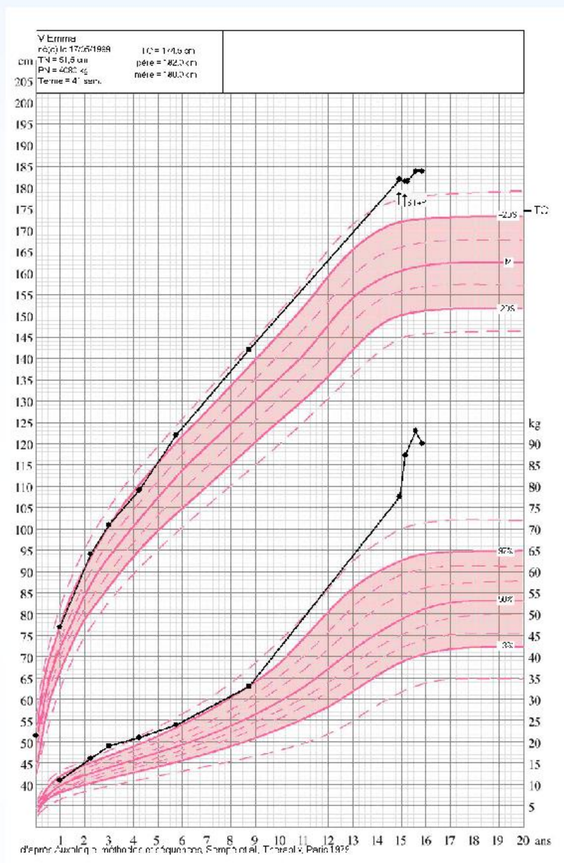
DATE	26/8/2013	7/11	6/3/2014	25/6/2014	25/8	24/9	17/12	25/3/2015	25/6
HEIGHT (cm)	150,6	154	154,5	158	159,3	158,7	159,3	159	160.3
GV	11 cm/y	3,6 cm/2,5 m	0,5 cm/4m	4 cm/3,5m	1,3 cm/2m	0	0	0	1.3 cm/3m & 2 cm/y
TANNER	P2S1	P2S2	P2S2	P3S2	P3S2	P3S2	P3S2	P3S2	P3S3(R) S2(L)
BA (years)	10			11					
TREATMENT	0	***debulking***	0	Cabergoline 0,5 mg x 2/w	Cabergoline 0,5 mg x 2/w + Pegvisomant 10mg/d			Cabergoline 0,5 mg x 2/w + Pegvisomant 10mg/48h	
IGF1 (ng/ml)	768	770	908	590	558	180	115	123	208
GH (mUI/l)	33,9	26,3	20,3	23,5	15				28,1
GH nadir OGT (mUI/l)	25,7		15,1	10,6					
PROLACTIN (ng/ml)	137	48,7	64,2	6,2	4,7	3	3,3		1,3

Case 2 :

A 15-year-old girl presented with clinical and biochemical evidences of acromegaly : tall stature (182 cm, >3 SD, no GV available), pubertal stage IV, bone age 13 years, high IGF1 and GH serum levels (776 ng/ml,109 mUI/l). Pituitary MRI revealed a large and invasive mass [3]. An AIP mutation was found. She was treated with a combination of oestrogen -to accelerate epiphyseal fusion-, somatostatin analogs and pegvisomant titrated up to 40 mg/day. Medical treatment failed to normalize IGF1 and stop growth (GV:2 cm/6 months) but major weight gain was noticed (+14 kg/6 months). Therefore tumour was partially resected by a trans-sphenoidal surgical approach. Histological characterization confirmed the diagnosis of GH-secreting adenoma. Pegvisomant adjuvant therapy 40mg/d was resumed to improve IGF-I serum level control (IGF1 571ng/ml after surgery, 447 after 3-months post-surgery treatment, 221 and 204ng/ml respectively by month 5 and 8) and stop physical growth (0cm/ 7 months) [4].

[3] Pituitary MRI at diagnosis case 2.





[4] Clinical and hormonal parameters evolution, case 2.

DATE	6/5/14	31/7	1/9	31/10	19/12	28/1/15	27/2	30/3	4/5
HEIGHT (cm)	182	182	182	184		184		184	184
GV	?			2cm/6m					0cm/6m
WEIGHT (kg)	77,5	83		93		94		90	94
TANNER	IV								
BA (years)	13y, Risser 3			Risser 4					
TREATMENT	EE 150µg/d	+ Somatuline LP 90mg/m	+ Pegvisomant 20 mg/d	Sandostatin LP 30 mg/m, Pegvisomant 40 mg/d, EE 150µg/d	***Debulking*** Just after surgery: EE 150µg/d	Sandostatin LP 30 mg/m, Pegvisomant 40 mg/d, EE 150µg/d			Idem EE 100µg/d
IGF1 (ng/ml)	776	924	889	1104	392	571	747	447	221
GH (mUI/l)	109	99	99	103	11	16		25	
GH nadir OGT (mUI/l)	99								
PROLACTIN (ng/ml)	21				11	6		5	

Conclusion :

In childhood acromegaly, pegvisomant appears to be effective in stunting growth and normalizing IGF-I but only after pituitary tumor debulking.

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