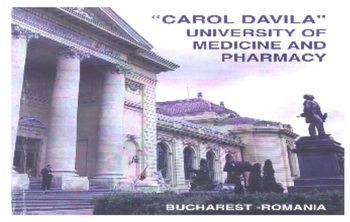
LONG-TERM REMISSION (CURE?) OF ACROMEGALY AFTER DISCONTINUATION OF SOMATOSTATIN ANALOGS



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INTRODUCTION. The prevalence of acromegaly is estimated to range from 38 to 80 cases per million, and the annual incidence of new patients is 3 to 4 cases per million, with a higher prevalence in Europe. Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) act both independently and dependently to induce hypersomatotropism. In a metaanalysis of 4464 patients treated with a somatostatin analog (SAA), average GH control rates and IGF-1 normalization rates were 56% and 55%, respectively (1). Usually, the disease relapses biochemically within few months after treatment withdrawal. We describe 2 rare cases with apparent cure of the disease after treatment with somatostatin analogs.

CASE 1

A 50 years woman came with typical acromegalic features, headache and carpal tunnel syndrome.

Acromegaly confirmed by:
GH in oral glucose tolerance test (OGTT): 4.9 ng/ml;
IGF-1 for age and sex = 3.8 x upper limit of normal (931 ng/ml, N<244);
She had normal visual field examination and no other hormonal dysfunction.
Pituitary MRI showed a sellar mass of 14/13/15 mm.

Treatment 1: transsphenoidal pituitary surgery.

2 months after surgery: GH nadir in OGTT was elevated (8.3 ng/ml), with an IGF-1 of 2.6 x ULN (651.5 ng/ml).
Pituitary MRI: sellar mass of 9/8/12 mm.

Treatment 2: Octreotide LAR 30 mg/28 days for 3 years, achieving control after association with cabergoline 2 mg/wk: random GH 0.85 ng/ml, with normal IGF-1 (212,4 ng/ml, N < 244).
Pituitary MRI: minimum tumor shrinkage (11/8/7 mm).

After treatment withdrawal: At 6 months and 2 evaluations after medication withdrawal, the patient has no agravations of acromegalic signs.
Normal GH nadir in OGTT: 0.51 – 0.94 ng/ml.
Slightly elevated IGF-1 (1.2 x ULN).
Pituitary MRI: stable 11/8/7 mm pituitary nodule.

CASE 2

A 53 years old obese female patient came for acral enlargement, acromegalic features and paroxistical hypertension (up to 220/160 mmHg).

Acromegaly confirmed by:
GH in OGTT: 6.6 ng/ml;
IGF-1 for age and sex: 2.9 x ULN (1130 ng/ml, N < 380);
She had left ventricular hypertrophy on ecocardiography. No visual field impairment; no pituitary insufficiency.
Pituitary MRI: sellar mass of 18/16/19 mm.

Treatment 1: transsphenoidal pituitary surgery.

2 months after surgery: GH nadir in OGTT was mildly elevated (1.2 ng/ml), with IGF-1 of 1.36 x ULN (326 ng/ml, N < 238);
Pituitary MRI: sellar mass of 11.5/7/13.5 mm.

Treatment 2: Octreotide LAR 20 mg/28 zile for 3 years, during which the clinical features improved and she achieved disease control: normal GH nadir in OGTT 0.33 ng/ml, with normal IGF-1 (192 ng/ml N < 229);
Pituitary CT: significant tumor shrinkage (sellar mass of 4/6 mm).

After treatment withdrawal: At 1.5 yrs and 3 yrs evaluations after SSA withdrawal, she has stable obesity (BMI 34.5 kg/sqm) and improved clinic features.
Normal GH nadir in OGTT (0.7 – 0.3 ng/mL);
Slightly elevated IGF-1 (1.1 x ULN);
Pituitary CT: stable 4/6 mm pituitary nodule.

Treatment 3: she received Cabergoline 1 mg/wk for 5 months, which did not improve the IGF-1 level (1.2 x ULN).

OGTT Case 1	At diagnosis				2 months after surgery			
	0	30	60	120	0	30	60	120
Glycemia (mg/dl)	98.1	170.4	120.8	59.9	80.7	149.8	92.7	70.8
GH (ng/ml)	**4.9**	7.8	6.4	6.1	10.6	**8.3**	10.9	9.8
IGF-1 (ng/ml)	931.8 N < 244				651.5 N < 238			

OGTT Case 2	At diagnosis				2 months after surgery			
	0	30	60	120	0	30	60	120
Glycemia (mg/dl)	97.4	195.6	171.3	99.4	82.1	88.4	73	79.1
GH (ng/ml)	7.6	**6.6**	13.3	8.9	1.7	1.4	**1.2**	1.8
IGF-1 (ng/ml)	1130 N < 380				326 N < 238			

DISCUSSION

A substantial number of patients (48.0–72.4%) have persistent acromegaly despite treatment with surgery, medical therapy, and/or radiotherapy and ~2–8% of patients who achieve remission with surgery experience disease recurrence within 5 years (2).
There are potential areas of improvement in the monitoring of patients with acromegaly, such as integrating other clinical and molecular biomarkers to complement GH/IGF1 in assessing treatment response, such as sKlotho (3), Ki-67 levels, positive *AIP* mutation, large tumor size, or sparse granular pattern (4, 5).
Cure after SSA has rarely been reported. It is possible that the apparent cure described in our patients is a long-term remission of the disease, and they should be followed-up.

CONCLUSION

With an improved array of therapeutic options available, it is possible to provide long-term disease control to a majority of patients with acromegaly. However, it has rarely been reported cure of acromegaly after somatostatin analogs. If this apparent cure is a long-term persistent suppression of GH secretion as a result of SSA therapy or a true cure of the disease, only long-term follow-up will tell.

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