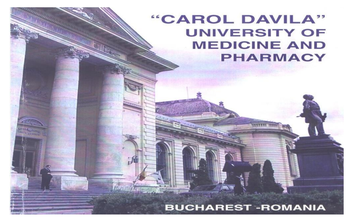
EVOLUTION IN ACROMEGALIC PATIENTS WITH DISCORDANT GH-IGF1 LEVELS DURING MEDICAL TREATMENT



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INTRODUCTION. In acromegalic treated patients, GH and IGF1 discrepancies are not rare and pose a challenge for the management of this disease. The reported therapeutical efficacy of somatostatin analogs (SSA), *i.e.* normalization of GH and IGF-1, is 50 – 70%. In Romania this specific treatment is financially supported by the Romanian National House of Health Insurance for patients with acromegaly.

AIM OF STUDY: To evaluate the characteristics and evolution in patients with discordant GH-IGF-1 levels during medical treatment.

METHOD: A retrospective review of 22 patients (18 F, 4 M) with acromegaly admitted at the "C.I. Parhon" Institute, Bucharest and treated with SSA and/or cabergoline (CAB) (2011-2015) according to the Protocol of the Romanian National House of Health Insurance for patients with acromegaly, which states that in patients with suboptimal control of the disease at 3 – 6 months, the dose of SSA should be increased +/- CAB or +/ only pegvisomant.

Criteria for disease control: Optimal response to SSA was considered when random GH ≤ 1 ng/mL and normal age-adjusted IGF-1 level were attained. Radiological evaluation included pituitary CT/MRI.

RESULTS

Six patients out of 22 were controlled on SSA+/- CAB treatment (27%), 9 were not controlled (41%). In 7 of 22 patients (31.8%), all women, we found discordant GH –IGF1 values during follow-up. The patients had a mean number of 6.7 evaluations of IGF-1 and GH (3 – 8) during a mean follow-up of 34.5 months (25 – 42).

Mean elevated IGF-1 was 1.43 x upper limit of normal (1.08 – 1.85).

All 7 patients were treated with SSA (4 also + CAB), 4 had previous pituitary surgery, 1 had also previous radiotherapy.

Table 1. Baseline characteristics of patients with discordances

Initials	Age (yrs) at diag	BMI (kg/m²)	T* before SSA (mm)	Previous Surgery/ Radiotherapy**
D. A.	61	25.5	m/7.2	SS
I.M.	49	25	M/12	SS
J.D.	27	21	M/10	SS; GK
K.I.	46	30.4	M/20	-
T.M.	35	28	m/7.5	-
T.G.	36	34.5	m/3.5	SS
T.J.	63	53.6	M/23	-

*T= tumor maximal diameter, M=macroadenoma, m=microadenoma,
**SS/FS=transsfenoidal/transfrontal surgery,
GK=Gamma-Knife; HVR=High Voltage radiotherapy

Table 2. Follow-up of GH, IGF-1, treatment and outcome in patients with GH-IGF-1 discordances

Medical treatment	GHr before SSA (ng/ml)	IGF1 before SSA (xULN*)	No. of evalu-ations	No. of discor-dances	GHr after SSA (ng/ml)	IGF1 after SSA (xULN)	Treatment option	Outcome GH-IGF1 / T
LAN PR 30 mg/2 wks	3.7	2.15	5	4	0.9 0.73 0.49 0.86	**1.35** **1.38** **1.25** **1.42**	Stable SSA dose	Discordant/ Stable T
OCT LAR 20-30 mg/4 wks	10.6	2.66	6	2	**1.55** **1.04**	0.97 0.87	Increased dose at 30 mg/4 wk, added CAB	Normalized / T↑25%
OCT LAR 20-30 mg/4 wks	13.5	1.32	3	3	0.43 **5.9** **1.2**	**1.08** 0.77 0.65	Increased dose at 30 mg/4 wks	Normalized/ T↓20%
OCT LAR 20 mg/4 wk	6	3.96	7	1	1	**1.19**	Increased dose, added CAB	Discordant/ T↓5%
OCT LAR 20 mg/4 wks	7.1	1.27	6	1	**5.6**	0.98	Increased dose then HVR+ Pegvisomant	Both increased / T↑16%
OCT LAR 20-30 mg/4 wks	1.7	1.7	8	3	0.92 0.43 0.79	**1.17** **1.17** **1.14**	Increased dose at 30 mg/4 wks	Normalized/ Stable T
OCT LAR 20-30 mg/4 wks Autogel 120 mg/4 wks	4.35	7.4	6	5	0.3 0.39 0.5 0.15 0.24	**1.83** **1.85** **1.5** **1.83** **1.73**	Increased dose, added CAB	Discordant/ T↓>50%

*ULN=upper limit of normal

Table 3. Evolution of complications in patients with GH-IGF-1 discordances

Name	BMI	Hypertension	Glycemic status		
			DM/IFG/IGT	HbA1c pre-SSA	HbA1c post-SSA
D.A.	↓ 3%	Stable, controlled	DM II, controlled	6.4	7.4
I.M.	↓ 11%	No	No	4.9	5
J.D.	Stable	No	No	4.8	4.9
K.I.	↑ 6%	Stable, controlled	Stable IFG	5	5.5
T.M.	Stable	No	No	4.9	4.9
T.G.	↑ 10%	Stable, controlled	Stable IFG	5.8	6
T.J.	↑ 10%	Stable, controlled	IFG, aggravated to DM II	6.2	6.2

Table 4. PreSSA characteristics in patients with discordances compared with with controlled & uncontrolled patients

Pre SSA treatment	Nadir GH in OGTT	IGF1 (x ULN)	Tumor size (mm)
Controlled on SSA	9.90	3.08	16.33
Uncontrolled on SSA	15.21	2.80	21.99
Discordant GH-IGF-1	6.15	2.18	11.89

DISCUSSIONS

• **Elevated IGF-1 despite normal GH levels have been described in adolescence, pregnancy, hyperthyroidism, hepatic or renal insufficiency (excluded in our patients), early postoperative period or mild active acromegaly. There are controversies regarding obesity as a contributing factor (42% of patients were obese, 42% were overweight). The long-term evolution in acromegalic patients with GH-IGF-1 discordance and the indication for treatment are not well established. [1]**

CONCLUSION

•**Greater uniformity of the assays is needed in order to reduce these discrepancies and enable a correct therapeutic management.**

•**Management of acromegalic patients with discordant GH – IGF-1 values needs to be individualized and long-term studies on morbidity and mortality are needed**.

[1] ***Freda PU,*** *Clin Endocrinol (Oxf). 2009 Aug;71(2):166-70*