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Sustained Clinical Inactivity and Stabilization of GH/IGF-1 Levels in an Acromegalic Patient after Discontinuation of Somatostatin Analogue Treatment

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Abstract. Background: A 38-year-old woman first presented complaining of foot enlargement, finger numbness, arthralgia, fatigue, galactorrhoea and oligomenorrhea. Her symptoms in conjunction with her coarsened facial features and prognathism led to the suspicion of acromegaly. Basic procedures: Oral glucose tolerance tests (OGTT) were performed at initial presentation and almost yearly thereafter for a period of 14 years. Pituitary computerized tomographies (CT) were performed annually for the first six years and magnetic resonance imaging every two years thereafter. Main findings: The diagnosis of acromegaly was confirmed by OGTT at presentation. A pituitary CT revealed a large invasive pituitary macroadenoma. She remained acromegalic after adenomectomy (evidently partial tumor resection), but was controlled with subsequent long-term somatostatin analogue (SRL) administration. After eight years of SRL administration, she had acceptable stabilization of acromegaly and at that point SRL administration was discontinued. The patient maintained the same control for the following six years up to the present time without further SRL administration. Principal conclusion: This is the first case with stabilization of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) to nearly normal levels and clinical inactivity of acromegaly after withdrawal of long-term treatment with SRLs.

Key words: Acromegaly, Pituitary adenoma, Somatostatin analogues, Insulin-like growth factor-1 (IGF-1), Growth hormone (GH)

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ACROMEGALY is caused by growth hormone (GH) hypersecretion typically by a somatotroph cell pituitary adenoma. It is a debilitating disorder that usually develops over many years. It has an annual incidence of approximately 3–4 cases/million. Its prevalence is estimated at 40 cases/million, but may be as high as 90 cases/million [1]. Inadequate disease control reduces life quality and expectancy. Acromegaly may be treated by several modalities. Despite the impressive advances in neurosurgery, radiotherapy and medical treatment achieved in the last decades, the majority of patients require a combination of therapeutic approaches for the disease to be controlled [2].

The criteria of biochemical remission of acromegaly have changed over the years, in particular with the availability of more sensitive GH assays (immunoradiometric or chemiluminescent assays rather than radioimmunoassay). However, variability in assay performance, coupled with use of inappropriate conversion factors and reference ranges, undermines the applicability of international consensus criteria to local practice [3]. In the past, remission of acromegaly was defined by finding random GH levels less than 5 μg/L (subsequently, was reduced to less than 2.5 μg/L) and/or a suppression of GH to less than 5 μg/L (subsequently then to 2 μg/L) after oral glucose tolerance test (OGTT) [2]. Recently, the biochemical criteria for diagnosis and cure of acromegaly have become stricter. Adequate control is defined as nadir GH level after 2-hour OGTT<1 μg/L and insulin-like growth factor-1

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(IGF-1) level within normal range for age and gender [4].

The mean integrated 24-h GH levels of less than 2.5 μg/L also exclude acromegaly. However, these values correlate tightly with the results of the OGTT, which is most cost-effective [5].

Even though surgery is the treatment of choice in patients with resectable tumors, in cases of large or invasive tumors the possibility of surgical cure is low, and somatostatin analogues (or somatostatin receptor ligands, SRLs) may be a reasonable primary therapeutic modality, provided that the tumor does not threaten vision or neurological function [6–8]. Moreover, the SRLs have been shown to be effective as secondary or adjunctive therapy for acromegaly in patients that have already been treated with surgery and/or radiation [9, 10]. Two long-acting forms of SRLs, octreotide LAR (long-acting release) and lanreotide PR (prolonged release) are at present available [11]. SRLs induce GH and IGF-I suppression, relief of soft tissue symptoms and control of tumor growth [4].

In this report, we describe an acromegalic woman who was subjected to adenomectomy 14 years ago. Due to residual tumor, she remained acromegalic and her disease was controlled with long-term SRL administration. After eight years of SRL administration, acromegaly was acceptably stabilized and, at that point, SRL administration was discontinued. The patient retained the same control for the following six years (until now) without further SRL administration.

Methods

OGTTs were performed at initial presentation and almost yearly thereafter as depicted in Table 1. The measurements of serum GH, IGF-1 and prolactin (PRL) concentrations were performed by automated radioimmunoassay (RIA) (Cobra Auto-Gamma, Packard, Boston, MA, USA) before 2000 and by automated immunochemiluminescent assay (ICMA) (Immulite 2000, DPC, Los Angeles, CA, USA) since 2000. The intra-assay and inter-assay coefficients of variation for RIA were 12.3% and 12.1%, respectively, for GH (basal reference range 0–30 ng/mL), and 7.7% and 9.1%, respectively, for PRL (reference range 0–20 ng/mL). The intra-assay and inter-assay coefficients of variation for ICMA were 4.6% and 6.6%, respectively, for GH (basal reference range 0–5 ng/mL), 3.9% and 8.1%, respectively, for IGF-1 (gender- and age-adjusted reference range 94–252 ng/mL) and 3.6% and 8.2%, respectively, for PRL (reference range 4.5–40.0 ng/mL).

Case description

A 38-year-old woman was first examined at the Department of Endocrinology, Hippokratio General Hospital, complaining of foot enlargement, finger numbness, arthralgia, fatigue, galactorrhoea and oligomenorrhea. Her symptoms had started gradually about 3 years before presentation. She had previously visited a rheumatologist and received anti-inflammatory drugs without improvement. She had no headaches or visual defects, but her coarsened facial features and prognathism led to the suspicion of acromegaly. The diagnosis was confirmed by an OGTT with 75 g glucose (her GH values were: 41.5 μg/L, 45.5 μg/L, 51.0 μg/L, 51.0 μg/L and 51.0 μg/L at time 0 h, 30 h, 60 h, 90 h and 120 h, respectively). The serum PRL level was 70.1 ng/mL. A pituitary computerized tomography scan (CT) revealed a large invasive pituitary macroadenoma with destruction of posterior clinoids and protrusion into the suprasellar sterna and the left cavernous sinus. Two months later, the patient underwent transsphenoidal adenomectomy. Postoperatively the patient received prednizolone (5 mg daily), which was discontinued after ten months. One month after surgery, a post-surgical CT revealed a residual mass (1.5 × 1.2 cm) protruding into the left cavernous sinus and an OGTT confirmed active acromegaly (Table 1). Subsequently, the patient received therapy with short-acting somatostatin analogue (octreotide, 0.1 mg twice a day) and bromocriptine (5 mg three times a day).

The patient experienced clinical improvement (decrease of foot enlargement, finger numbness, arthralgia, fatigue, galactorrhoea, oligomenorrhea) as well as biochemical improvement (lower GH values in OGTT, normal PRL) after six months of therapy (Table 1). Her compliance to the treatment was not ideal and the disease was not completely controlled for seven years after surgery, as it was proved by serial OGTTs (Table 1). PRL levels were elevated during a period of patient non-compliance to treatment, but were easily normalized when the patient restarted her treatment regularly (Table 1). Seven years after surgery bromocriptine was discontinued. At that point, GH was still elevated and

Table 1. A synopsis of clinical and biochemical course of the patient

Date	Notes	OGTT					IGF-1	PRL
		GH (0 min)	GH (30 min)	GH (60 min)	GH (90 min)	GH (120 min)		
Feb-93	Presentation at our department	41.5	45.5	51	51	51		70.1
May-93	Transsphenoidal surgery, prednizolone (5 mg daily)							
Jun-93	Residual pituitary mass, start of octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3) + prednizolone (5 mg daily)	13.6	15.7	21.5	19.9	23.6		30
Jan-94	Octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3), clinical improvement	3.3	1.5	1.1	0.8	0.9		16.6
Mar-95	Octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3)	4.4	3.8	11.4	13.3	12.2		
Apr-95	No treatment compliance, octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3)	19	17.4	35.5	32.1	33.8		
Apr-96	Octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3)	3.1	1.6	9.5	6.8	5		
Jul-96	Octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3)	4.7	1.3	1	1.4	2.2		
Oct-97	No treatment compliance, octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3)	14.4	10.2	15.1	12.6	16.8		50
Nov-98	Octreotide (0.1 mg × 2) + bromocriptine (5 mg × 3)	4.7	4.1	12.8	10.1	11.6		20.3
Oct-99	Change in octreotide LAR (20 mg, once monthly), discontinuation of bromocriptine							
Apr-00	Octreotide LAR (20 mg, once monthly)	2	2	4.2	4.8	4.7		6
May-01	Octreotide LAR (20 mg, once monthly)	1.1	1.1	1.8	2.8	3.2		7
Jul-01	Discontinuation of octreotide LAR							
Oct-01	No treatment, no clinical symptoms	2	2.3	3.5	3.2	3.1		
Jun-02	No treatment, no clinical symptoms	2	1.6	3.2	3.1	3.3		13.5
Nov-03	No treatment, mild headache	2.4	2	3.1	2.7	2.5	322	12.3
Dec-04	No treatment, no clinical symptoms	1.9	1.8	3.1	3.1	3	294	6.9
Jan-06	No treatment, no clinical symptoms	1.5	1.3	2.1	2.1	2.1	245	6.2
Jan-07	No treatment, no clinical symptoms	1.5	1.3	2.1	1.9	2.2		7.1

Reference ranges before 2000 (RIA): basal GH = 0–30 ng/mL, PRL = 0–20 ng/mL and since 2000 (ICMA): GH = 0–5 ng/mL, IGF-1 = 94–252 ng/mL, PRL = 4.5–40 ng/mL

the short-acting SRL was switched to a long-acting SRL [octreotide LAR (Sandostatin LAR), 20 mg monthly]. Compliance to the new treatment was good and the clinical and biochemical control of the disease was acceptable (the nadir GH level in OGTT 17 months after initiation of octreotide LAR was 1.1 μg/L). The PRL levels remained within the reference range, and normal function of the pituitary-thyroid, pituitary-adrenal and pituitary-gonadal axis was documented.

The residual mass of adenoma remained unchanged after surgery, as it was monitored in serial CTs performed annually for six years after surgery and in serial magnetic resonance imaging (MRI) performed every two years thereafter.

The clinical and biochemical inactivity of the disease and the unchanged size of the adenoma, led us to discontinue the octreotide LAR after completion of approximately two years of treatment with this medication (6.5 years of the short-acting octreotide preceded the octreotide LAR). To this day the patient has not received any other medical treatment or irradiation. The disease has remained clinically inactive and annually repeated OGTTs during the last six years showed a stabilization of GH nadir and IGF-1 to levels approximating the new targets for GH control (Table 1) [4].

Discussion

This report concerns a case of acromegaly with incomplete adenomectomy and subsequent administration of SRL and bromoctriptine for several years, after which sustained remission of disease activity for 6 years after discontinuation of treatment was

observed.

The therapeutic goals in acromegaly consist of the elimination of morbidities associated with the disease and its increased mortality, as well as the control of tumor growth [4].

Pituitary surgery ameliorates mass effects but rarely restores GH and IGF-1 secretion to normal, without causing hypopituitarism [4, 12]. The cure rate in the best surgical series ranges between 80 and 90% in microadenomas, near 50% in non-invasive macroadenomas, and far less in invasive macroadenomas [13]. Preoperative use of SRLs may be beneficial in some cases [14].

The use of SRLs as adjunctive therapy to surgery or radiotherapy and recently as first-line treatment has been very promising [6, 9, 10]. SRLs normalize elevated GH and IGF-1 in about 80% of acromegalic patients [15] and induce significant tumor shrinkage in 55–80% of patients [16, 17]. Long-acting depot SRLs are more effective and have replaced the short-acting agents [18]. In our case, better patient compliance and disease control was achieved after switching from short-acting to long-acting SRLs.

SRL action is mediated by five somatostatin receptor subtypes (SST_1 through SST_5) that are differentially expressed in a tissue-specific pattern, conferring both functional and therapeutic specificity. Each of the subtypes activates distinct intracellular signalling pathways. So, the antiproliferative effects of somatostatin and SRLs are mediated via the tyrosine phosphatase pathway, which induces cell cycle arrest (through SST_1, SST_2, SST_4, SST_5) and apoptosis (through SST_2) [16]. On the other hand, the inhibition of the voltage-dependent calcium channels and adenylyl cyclase activities may control GH secretion [19]. Although the mechanisms that underlie the inhibition of hormone secretion and tumor growth are only partially understood, the antisecretory and antiproliferative effects may occur independently [20–22].

Somatotroph cells express predominantly SST_2 and SST_5. The same receptors are also expressed in the majority (90%) of GH-secreting adenomas, which are consequently potential targets to pharmacotherapy with SRLs [15, 23].

Oral dopamine agonists, which are very effective in treating prolactinomas, have also been used in acromegaly [24]. Before the introduction of octreotide, bromocriptine was routinely used, albeit with limited results, as pharmacotherapy for acromegaly in larger doses than that required for prolactinomas. Combined treatment with octreotide and bromocriptine has an additive suppressive effect on GH and IGF-1, and bromocriptine bioactivity has been shown to increase when the drug is administered together with octreotide [24, 25]. The newer dopamine agonists, such as cabergoline, appear to be even more promising in GH-secreting adenomas, especially in patients who have resistance to maximal doses of SRLs [26]. It has been suggested that the presence of elevated pre-treatment PRL levels increase the chance of GH response [4, 27].

To our knowledge, our case is the first where a six-year stabilization of GH and IGF-1 was achieved after withdrawal of long-term treatment with SRLs. This outcome has not been reported before and usually GH and IGF-1 increase to their pre-treatment levels, shortly after octreotide withdrawal, even after continuous therapy for over three years [28]. The possibility that the patient had pituitary apoplexy was excluded since she did not exhibit acute severe headache during or after cessation of medication, suggestive of such an occurrence. Furthermore, there was no change in MRI findings indicative of pituitary apoplexy and the pituitary reserve after repeated testing remained stable. The duration of GH suppression after treatment withdrawal may vary but has never exceeded a period of 6 months [29]. The same effect is noticed after lanreotide withdrawal [30]. Tumor size also returns to pre-treatment level when the SRLs are discontinued [15, 31–33].

On the contrary, prolonged suppression of a PRL secreting adenoma leads to permanent cure in many cases and PRL is shown to remain low after discontinuation of long-term bromocriptine administration [34, 35].

In our case, the size of the residual mass of adenoma remained unchanged, *i.e.* did not increase, after discontinuation of octreotide, contrary to the commonly reported observations [15, 31, 32]. On the other hand, its size did not further decrease despite the clinical and biochemical stabilization of acromegaly. This observation might represent a dissociation of antisecretory and antiproliferative effects in a reverse way than that recently published [20]. In addition, bromocriptine treatment that has been associated with increased fibrosis of prolactin-secreting tumors [36, 37], might have contributed to tumor size stabilization.

The decrease of GH and IGF-1 in our patient is similar to that observed in acromegalic patients after pituitary irradiation, but our patient had never received

radiation therapy. It is well-established that pituitary irradiation is effective in lowering the GH and IGF-1, but this result is slow and might take between two and twenty years after irradiation [38, 39].

At this point, there cannot be a specific explanation to our finding. Presuming that PRL was co-secreted by the adenoma, a plausible explanation to this outcome might be a beneficial effect of bromocriptine on GH secretion in parallel with the positive effect that was actually shown on PRL. However, the response to pharmacotherapy was not simultaneous and the patient continued to have active acromegaly even after discontinuation of bromocriptine. Alternatively, common transcriptional and/or post-transcriptional regulatory mechanisms for SSTs (*i.e.* Gsp oncogene) within GH-secreting adenomas may modify the response to SRLs and could have contributed to the long-term disease remission [23].

A limitation to this report is the lack of IGF-1 measurements before 2003, which would have made clearer the effect of treatment and its discontinuation. We acknowledge that this is a single case observation that needs verification from other cohorts of acromegalic patients, but it implies that there is still a lot to be learned about the molecular physiology of adenomas and the effects of pharmacotherapy.

In conclusion, this is the first case with stabilization of GH and IGF-1 to nearly normal levels and clinical inactivity of acromegaly after withdrawal of long-term treatment with SRLs. Although we offer no explanation for our case, we feel that it would be interesting to see whether our colleagues in other institutions have had similar cases and to study the complex mechanisms that may result to this uncommon phenomenon.

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