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CASE REPORT

Remission of acromegaly following long-term therapy with cabergoline: report of two cases

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Abstract Dopamine agonists are effective in some patients with acromegaly and in this condition treatment is considered to be chronic. We describe two acromegalic patients who responded adequately to the long-acting dopamine agonist cabergoline, but surprisingly maintained normal GH and IGF-I levels once therapy was discontinued after 42 and 76 months because of possibly related side effects. A 32-year-old woman with mild acromegaly (IGF-I: 423 μg/l, GH after OGTT: 2.5 μg/l, adenoma 4 mm) was treated with cabergoline as primary therapy and reached safe GH levels (2 μg/l or less) and normal IGF-I levels with 3.5 mg cabergoline weekly. After 42 months of therapy the patient experienced a progressive decrease of libido, which she attributed to the intake of cabergoline. After stopping medication, serum levels of GH and IGF-I remained normal during the following 2.5 years. A 53-year-old man with moderate acromegaly (serum IGF-I: 547 μg/l, GH after OGTT: 5.9 μg/l, adenoma 7 mm) preferred cabergoline as primary therapy. Serum GH levels below 2 μg/l and normal levels of IGF-I were obtained with 3.5 mg cabergoline weekly. When the patient experienced severe stomach pains after 76 months of treatment, cabergoline was held responsible and discontinued. Serum GH and IGF-I did not increase again and stayed at the same level during a follow-up of 5.5 years. These two cases demonstrate that acromegalic patients with a good response to cabergoline may occasionally remain in remission after stopping therapy. This phenomenon has previously only been described in patients with a prolactinoma.

Keywords Acromegaly · Therapy · Dopamine agonist · Cabergoline · IGF-I

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Introduction

Current therapies for acromegaly are neurosurgery, external radiotherapy and pharmacotherapy with dopamine agonists, somatostatin analogues or GH receptor antagonists. The main goal of therapy for acromegaly is to control excessive GH and normalize IGF-I levels, thereby reducing the associated morbidity and the 2- to 3-fold increased mortality [1, 2]. Neurosurgery is usually the initial choice of therapy, but the outcome is highly dependent on the tumour size and degree of tumour invasion [3]. External radiotherapy controls tumour volume and reduces GH/IGF-I levels, but the slow onset of action, the high incidence of hypopituitarism and the cerebro-vascular complications have minimized its role [4]. Therefore, pharmacotherapy is often required following surgery or chosen as first-line therapy for non-resectable tumours. Dopamine agonists are the least effective form of pharmacotherapy, but in case of limited disease activity or prolactin co-secretion the long acting dopamine agonist cabergoline attained safe GH levels and normal IGF-I in almost 50% [5]. Somatostatin analogues, usually given by monthly injections, are the most commonly used drugs as they normalize GH and IGF-I in about 40–60% of patients and induce tumour shrinkage in 30% [6–8]. Diarrhoea, cramping and gallstones are the most important side effects. Pegvisomant, the newest therapeutic option, blocks GH action at peripheral receptors and is usually given by daily injections. It normalizes IGF-I levels

in more than 80% of patients, but does not induce tumour shrinkage [9]. Hepatotoxicity is a possible side effect, and continuing growth of the pituitary adenoma has been described in a small number of patients not irradiated to the pituitary. Pegvisomant is the preferred drug in patients resistant to or intolerant of somatostatin analogues.

We report the first observation of two patients with a mildly active and dopamine-responsive acromegaly in which dopamine agonist treatment could be stopped without recurrence of disease activity. This phenomenon has previously only been described in prolactinomas.

Case reports

Case 1

A 32-year-old woman was referred to investigate a pituitary lesion found on CT-scan performed because of hearing problems. She also complained of headaches, tiredness, sleep disturbances, painful teeth and abnormal sweating. Limited clinical signs of acromegaly were noted such as enlarged and sweaty hands. Both baseline levels of serum GH was 4 μg/l and IGF-I 423 μg/l (Standard Deviation Score or SDS 3.94, normal ≤ 2) were elevated. GH failed to suppress during an oral glucose tolerance test (OGTT) with a nadir GH of 2.5 μg/l (normal 1 μg/l or less). Remaining pituitary function, including prolactin level of 6.3 μg/l (normal less than 20 μg/l) and menstrual cycle, were normal. Magnetic resonance imaging (MRI) demonstrated the presence of a 4 mm large right-sided pituitary adenoma.

Mild acromegaly was diagnosed and the therapeutic options were discussed with the patient. With cabergoline in a dose of 1 mg/week levels of GH and IGF-1 dropped immediately. The evolution of random GH and IGF-I SDS levels during cabergoline therapy are depicted in Fig. 1a. The dose of cabergoline was progressively increased until ''safe'' random GH levels (2 μg/l or less) and normal IGF-I levels were finally reached after 12 months with a dose of 3.5 mg/week.

After 42 months of therapy, the patient complained of loss of libido and decided to discontinue her medication. Unexpectedly, random GH and IGF-I levels did not go up again after stopping treatment with cabergoline, making it unnecessary to start another treatment.

Two and a half years off therapy, a new check-up was performed showing normal serum IGF-I (190 μg/l, SDS -0.71) and safe random GH (1 μg/l). An OGTT was repeated showing now a normal glucose suppressed GH level of 0.4 μg/l. Repeat MRI confirmed the presence of the adenoma with unchanged characteristics.

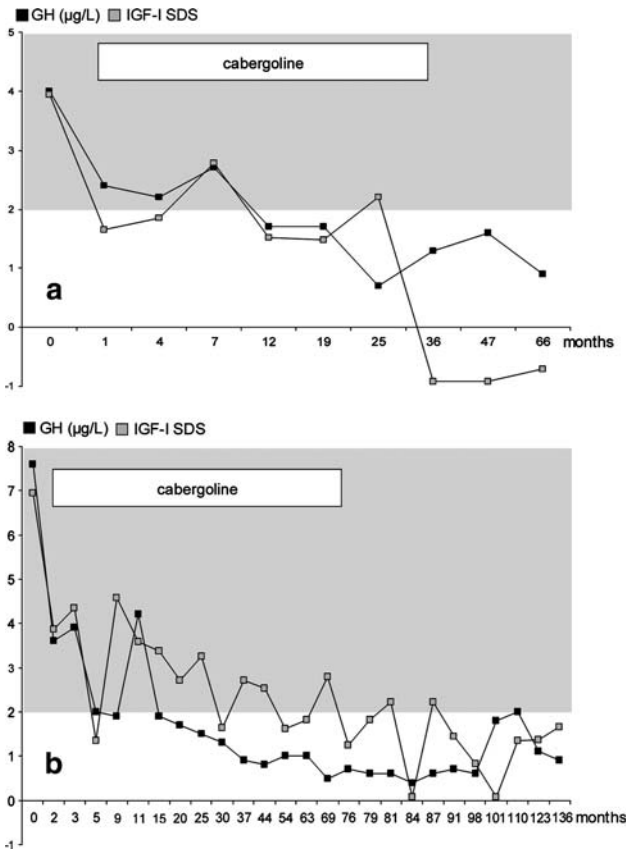

Fig. 1 Evolution of serum IGF-I levels (SDS) and random serum GH (μg/l) before, during and after cabergoline therapy in patient 1 (1a-upper panel) and patient 2 (1b-lower panel). Shaded area indicates abnormal high levels (>2 both for GH and IGF-I)

The patient was considered in continuous remission off therapy.

Case 2

A 53-year-old man with tinnitus was referred by an ENT doctor who noticed acromegalic features. The patient complained over the last 4 years of increased sweating, enlargement of his feet, tiredness and more pronounced facial coarsening. Medical history revealed resection of a left-sided hypernephroma 14 years earlier, mild hypertension, and lumbar arthrosis. Moderate acromegalic facial features and macroglossia were present, while hands and feet were enlarged and swollen.

Hormonal evaluation showed elevated baseline serum GH (14.6 μg/l) and IGF-I (547 μg/l, SDS 6.94) concentrations. GH was insufficiently suppressed during an OGTT with a nadir GH of 5.9 μg/l (normal 1 μg/l or less). Serum prolactin (5.2 μg/l) and the remaining pituitary function were normal. MRI demonstrated a right-sided intrasellar pituitary adenoma with a maximal diameter of 7 mm.

Moderate acromegaly was diagnosed and cabergoline was started at a dose of 1 mg/week. Serum levels of IGF-1 and GH decreased, but cabergoline had to be increased stepwise to 3.5 mg/week because GH and IGF-I remained too high. The changes in random GH and IGF-I SDS levels during cabergoline therapy are shown in Fig. 1b.

After 5 months of treatment IGF-I levels were normal for age and sex and random GH levels safe (≤ 2 μg/l). Thereafter IGF-I started to rise again, although GH levels remained below 2 μg/l. Since the patient felt well, he did not want to change to another therapy. Over the following period a progressive new decline in IGF-I levels was observed.

After more than 6 years (76 months) of treatment the patient experienced stomach discomfort and cabergoline was stopped, with the intention to start somatostatin analogue therapy as soon as GH and IGF-I concentrations would rise. Unexpectedly, levels of GH and IGF-1 remained at the same level without therapy for the next years.

At the last check-up, 5.5 years off therapy, IGF-I levels were still normal (185 μg/l, SDS 1.67) and random GH levels safe (0.9 μg/l). An OGTT was repeated showing a nadir GH of 1.0 μg/l. On a control MRI a 7 mm intrasellar microadenoma could still be identified with similar radiological characteristics. The patient was considered in continuous remission off therapy.

Methods

In patient 1, serum IGF-I was measured by a radioimmunoassay (Biosource, Fleurus, Belgium) with a gender and age specific reference range both at diagnosis and at the most recent control. Serum GH was measured using a two-site immunoradiometric assay (Pharmacia Diagnostics hGH RIA, Pharmacia, Uppsala, Sweden) at diagnosis and by IRMA (Biosource, Fleurus, Belgium) at the latest control.

In patient 2, serum IGF-I was initially measured by a two-site immunoradiometric assay (LEGENDO, Leuven, Belgium) with a gender and age specific reference range and by IRMA (DPC Immunolite 2000, Los Angeles, USA) at the most recent control. Serum GH was measured using a two-site immunoradiometric assay (Pharmacia Diagnostics hGH RIA, Pharmacia, Uppsala, Sweden) at diagnosis and by IRMA (DPC Immunolite 2000, Los Angeles, USA) at the latest control.

Discussion

In this paper we showed for the first time that the suppression of GH and IGF-I levels by cabergoline in acromegalic patients responsive to dopamine agonist therapy, can exceptionally be maintained after stopping the medication. It is of interest that in both patients GH/IGF-I levels dropped immediately after starting cabergoline but were completely controlled only after a prolonged period of therapy.

Dopamine agonists stimulate GH secretion in normal individuals, but paradoxically can suppress GH hypersecretion in a subgroup of patients with acromegaly. With the first generation dopamine agonists such as bromocriptine overall efficacy in acromegaly was limited despite the use of high doses. As an example, serum GH/IGF-I was normalized in only 10% of 549 acromegalic patients collected from 31 studies, although the majority experienced some clinical and biochemical improvement [10]. Better results have been obtained with the newer dopamine agonists. The long-acting non-ergot dopamine agonist quinagolide was able to normalize GH/IGF-I in about one third of acromegalic patients, using 2–4 times higher doses than in prolactinoma patients [11]. The ergot derivative cabergoline has a more specific D2-receptor binding capacity and possesses a much longer half-life than bromocriptine. These characteristics avoid large fluctuations in dopamine agonist activity and enhance clinical efficacy and reduce side-effects [12]. In terms of efficacy and tolerability cabergoline was clearly superior to bromocriptine in the treatment of hyperprolactinemia [13–15].

The therapeutic effect of cabergoline in acromegaly has been reported in three smaller and one larger study. In the first study, normal serum IGF-I levels were reached in 3 out of 6 patients with a weekly dose of 0.3–0.6 mg [16]. An increase in the dose to 1.2 mg in the three other patients was insufficient to obtain normalization of IGF-I. In the second study, 11 patients were treated with a weekly dose of cabergoline of 1.0–2.0 mg [11] resulting in a significant decrease in serum IGF-I levels, but without normalization in any of the patients. In the third study, 10 patients received each a weekly dose of 3.5 mg cabergoline [17]. Significant decreases in serum IGF-I and GH were observed in seven patients and biochemical remission was achieved in 2 of them. In the large multi-centre trial of 64 patients, a decrease in IGF-I below 300 μg/l could be obtained in 39% of patients, and a decrease in GH below 2 μg/l in 46% of patients [5]. Co-secretion with prolactin and less active acromegalic disease (baseline IGF-I < 750 μg/l) predicted a better than average response rate. Cabergoline has also be found to be very useful in acromegalic patients partially resistant to somatostatin analogues, irrespective of co-secretion of prolactin, with response rates over 40% when given together with somatostatin analogues [18–20].

The possibility to discontinue cabergoline has also been observed in patients with a prolactinoma. Colao and co-

workers were able to stop cabergoline in a high number of well-controlled hyperprolactinemic patients without relapse [21]. Remission rates depended on the initial tumour size and the degree of tumour shrinkage during therapy: in microprolactinoma 75% in case of complete tumour regression and 60% in case of partial regression; in macroadenomas 68% in case of complete tumour regression and 22% in case of partial regression. Other authors also described long-term remissions in patients with microprolactinomas previously treated with cabergoline, although to a lesser degree: 19 and 36%, respectively [22, 23]. Compared to prolactinoma, acromegaly is known to be much less responsive to dopamine agonist therapy, making the possibility to stop cabergoline therapy probably also much smaller. It is currently unknown in what percentage of acromegalic patients therapy can be stopped but the number is assumed to be low. Indeed, to our knowledge, these two patients are the only ones in which the phenomenon has been observed.

The reason why the patients in the current study remained in remission long after cabergoline was discontinued is not obvious. Cabergoline has a very long half-life and a therapeutic effect can be expected several months after stopping therapy. In our patients, however, cabergoline had been stopped 2.5–5.5 years making this possibility unlikely. Adenoma infarction or apoplexy either spontaneous or induced by dopamine agonist therapy has been described [24–26], but the patients had no history of headaches and no change in tumour size or characteristics was visible on MRI. Apoptosis of tumoral cells induced by the medication is probably one likely mechanism, as evidenced in prolactinomas [27]. Secondly, dopamine agonists are capable to suppress cell proliferation during prolonged therapy, an effect also demonstrated in prolactinomas [28]. An argument for the second mechanism is the long period, which was needed in both patients before IGF-I to become completely normal. An effect of dopamine agonists on microvessels density is a third possibility, but no data are available yet [28]. Nonetheless, it remains intriguing why inhibition of pathological cell growth and proliferation by long-term dopamine agonist therapy is permanent in some patients, allowing therapy discontinuation, and temporary in others, necessitating therapy resumption.

In conclusion, these two cases demonstrate that some acromegalic patients with an initial good response to cabergoline may remain in remission after stopping therapy, a phenomenon previously only described in hyperprolactinemic patients. A trial to stop cabergoline after several years of therapy in dopamine-sensitive acromegalic patients in order to see whether medication is still necessary may therefore be considered.

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