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Macrocorticotropinoma shrinkage and control of hypercortisolism under long-term cabergoline therapy: case report

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Abstract Cushing's disease is the result of chronic overproduction of ACTH by a pituitary tumor. Although the optimal treatment is surgical removal of the adenoma, medical treatment might be an option in selected cases. A 40-year old woman with Cushing's disease was treated with cabergoline, a neuromodulatory drug, for a corticotrophic macroadenoma. Treatment was initiated at a weekly dose of 0.5 mg and then, on the basis of the evolution of UFC values, adjusted until it reached 6 mg/week. With cabergoline treatment the patient was asymptomatic, the pituitary adenoma showed a significant shrinkage on MRI and urinary cortisol excretion remained within the normal range during 7 years. We show the effectiveness of cabergoline in maintaining long-term biochemical control of hypercortisolism with significant reduction and stabilization of macroadenoma volume in a patient with Cushing's disease.

Keywords Cabergoline · Cushing disease · Corticotrophic macroadenoma

Introduction

Cushing's disease (CD) is caused by excessive cortisol secretion induced by an ACTH-secreting pituitary adenoma. Its primary treatment is pituitary surgery, followed by radiotherapy, drug therapy or adrenalectomy in cases of persistent or relapsed disease. Cabergoline (CAB) is a D_2 receptor agonist with higher affinity and longer half-life than bromocriptine. Its effectiveness and tolerance has been demonstrated in the treatment of different pituitary tumors [1, 2]. We describe here the biochemical and tumor response to long-term CAB administration in a patient with CD due to a corticotrophic macroadenoma. To our knowledge, this is the first report showing both tumor shrinkage and biochemical control of hypercortisolism under treatment with cabergoline during 7 years.

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Case report

A 40-year old woman was referred to our hospital because of headache and loss of visual acuity. Her past medical history was negative except for previous trans-sphenoidal pituitary surgery 3 years before with the diagnosis of non-functioning pituitary adenoma. She had never had any signs or symptoms of Cushing's disease. The immunohistochemical study revealed positive staining for ACTH in 20% of the cells and it was negative for the rest of the hormones. Postoperative follow-up with yearly magnetic resonance imaging (MRI) showed stable residual tumor.

At the time of consultation, she had a 6-month history of acne, galactorrhea, oligomenorrhea and weight gain. Clinical examination revealed high blood pressure (140/100 mmHg) and a body mass index of 29.5 kg/m2. Typical cushingoid features such as buffalo hump, facial plethora, red striae, muscle weakness and truncal obesity were not observed, but she presented acne, fatigue, skin atrophy, acanthosis nigricans and galactorrhea.

Twenty-four-hour urinary free cortisol (UFC) was elevated at 426 μg (nv: 20–90) and plasma ACTH was 127 pg/ml (nv: <46). After overnight low-dose dexamethasone suppression

test (1 mg) serum cortisol was 28.1 μg/dl nv: <1.8). Prolactin was 27.8 ng/ml (nv: 3–26). Glicemic profile was always normal. As plasma triglycerides, LDL and total cholesterol were increased before and under treatment with cabergoline, she required hypolipidemic treatment. Six years after diagnosis, bone mineral density test showed osteopenia.

Ophthalmological examination showed a right temporal quadrantopsia. MRI revealed pituitary tumor regrowth with suprasellar extension and chiasma compression. The patient was reluctant to undergo a second surgical procedure so a trial with cabergoline was initiated at a weekly dose of 0.5 mg with a good tolerance and then, on the basis of the evolution of UFC values, adjusted to 1.5 mg/week. Urinary cortisol dropped from 426 to 54 μg/24 h and ACTH fell from 127 to 63 pg/ml at 60 days, accompanied by a complete regression of acne, fatigue and galactorrhea along with normalization of arterial blood pressure without using antihypertensive drugs. Six months later, control MRI showed a significant (more than 50%) shrinkage of the macroadenoma (Fig. 1).

During the following 5 years, the patient remained asymptomatic, the pituitary adenoma size stabilized on MRI, and urinary cortisol excretion remained within the normal range (36–60 μg/24 h) under cabergoline. After that period, the patient again noticed signs of Cushing's disease (weight gain–with central obesity– and acne) accompanied by a huge increase in UFC to 2,280 μg/24 h and in ACTH to 250 pg/ml. At this time, MRI showed regrowth of the tumor with suprasellar extension. This was interpreted as an escape phenomenon and cabergoline dosage was progressively increased 1 mg at a time to 6 mg/week according to UFC values (in 3 weekly doses) which was followed by a drop in UFC to 30 μg/day and of ACTH to 70 pg/ml, with improvement of the clinical manifestations. Evolution of UFC is shown in Fig. 3. The pituitary mass shrank again on MRI after 6 months under this dose of cabergoline (Fig. 2) and remained clinically and biochemically (UFC 30 μg/24 h) stable for as long as 18 months, without signs of tumoral regrowth. Cardiac

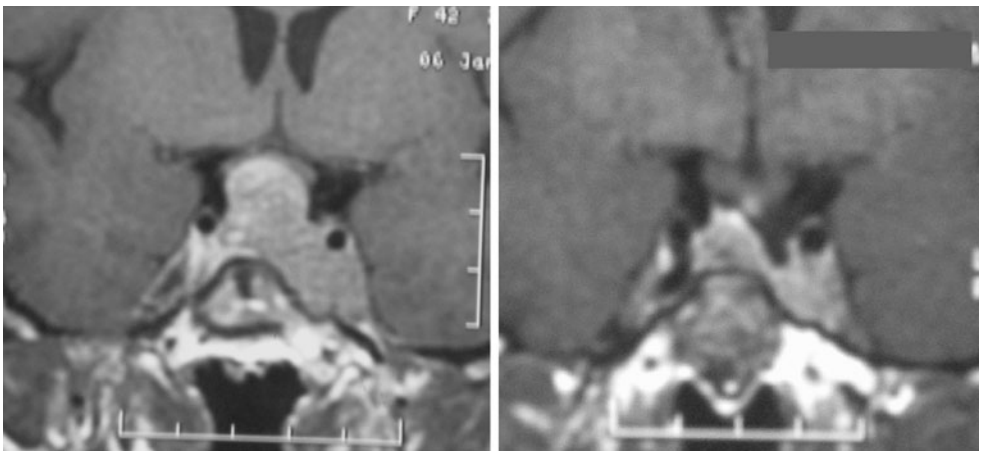

Fig. 1 Pituitary MRI before and after a 6-month treatment with cabergoline 1.5 mg/week

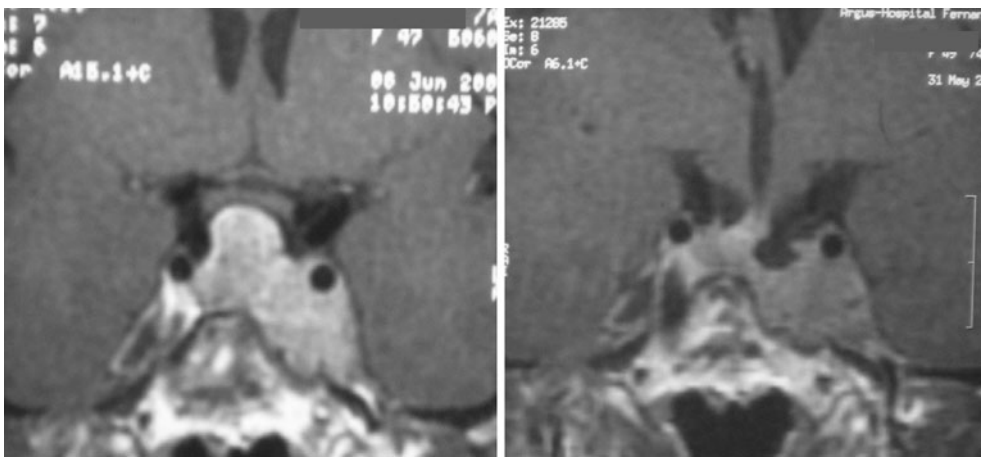

Fig. 2 Pituitary MRI after increasing cabergoline to 6.0 mg/week because of tumor regrowth

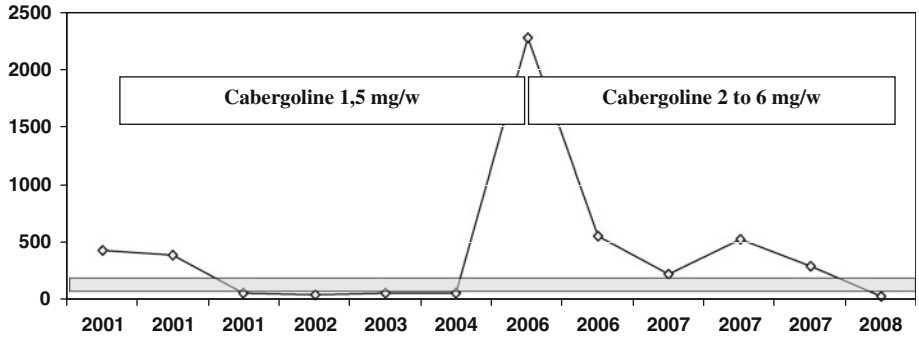

Fig. 3 Evolution of urinary free cortisol (μg/24 h) during 7 years of treatment with cabergoline (see text for details of treatment)

ultrasounds showed normal valvular morphology without regurgitation during these years of treatment.

Discussion

We report here a case of an ACTH secreting macroadenoma showing a significant shrinkage and optimal biochemical control under long time cabergoline treatment.

Cushing's disease is caused by chronic overproduction of ACTH from pituitary corticotropes. The majority of ACTH-secreting pituitary tumors are microadenomas. Macroadenomas are much less frequent. The optimal treatment for Cushing′s disease is surgical removal of the pituitary tumor. However, whereas the cure rate with this procedure is about 80–90% for microadenomas it amounts only to up to 50% for macroadenomas [5]. Patients whose condition is not controlled by surgery are referred for pituitary irradiation -which may achieve control of hypercortisolemia in approximately 50–60% of patients within 3–5 years—or for bilateral adrenalectomy [3]. Prolonged drug treatment of Cushing′s disease might also be an option in selected cases, usually performed with adrenal-blocking drugs which act directly at the adrenal level [4].

Recently, there has been renewed interest in the use of neuromodulatory drugs. Data on the effect of chronic bromocriptine therapy on ACTH and glucocorticoid levels and on the size of ACTH-secreting adenomas are limited and largely confined to isolated case-reports or very small series of patients [5]. Cabergoline is a dopamine D_2 receptor agonist with a higher affinity and longer half-life than bromocriptine. In a previous work, Pivonello et al. [6] demonstrated D_2 receptor expression in approximately 80% of corticotroph pituitary tumors along with the effectiveness of CAB administration in short-term control of cortisol hypersecretion. Cabergoline was then reported to be effective in as much as 27.5% [7] and 40% [8] of patients with Cushing's disease; reduction in tumor volume was described in 4 out of 20 patients so treated, although no individual data were given [8]. Recently, Godbout et al. [9] reported 30 patients with Cushing's disease treated with cabergoline for a mean of 37 months (12–60 months) with a mean dose of 2.1 mg/week; in 9 out of 30 patients (30%) UFC levels remained normal in the long term. Vilar et al. [10] showed that after 6 months of cabergoline monotherapy, 3/12 (25%) patients with CD -unsuccessfully treated with surgery- normalized UFC levels.

On the other hand, CAB has been reported to induce a complete remission of Nelson's syndrome [11] and a significant shrinkage of a silent ACTH-secreting pituitary tumor [12]. Bruno et al. [13] showed an adrenalectomized patient with ectopic ACTH secretion treated with cabergoline, who after an 8-year-follow-up significantly reduced ACTH secretion and improved the clinical syndrome of hyperpigmentation.

In our patient, ACTH and cortisol secretion rapidly decreased and remained in the normal range for 5 years under cabergoline 1.5 mg/week; a dramatic tumor shrinkage with stable tumor volume was also observed. After 5 years of good control, the patient had a treatment escape with an important regrowth of the tumor. The cabergoline dose was significantly increasead, cortisol hypersecretion was controlled and the tumor volume decreased again.

To the best of our knowledge, this is the first report showing the effectiveness of cabergoline in maintaining long-term (more than 7 years) biochemical control of hypercortisolism with significant reduction and stabilization of macroadenoma volume in Cushing's disease.

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Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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