A RARE CAUSE OF PITUITARY APOPLEXY: CABERGOLINE THERAPY

B. Aydin¹, O. Aksu², H. Asci³, M. Kayan⁴, H. Korkmaz^{5,*}

¹Adiyaman State Hospital, Endocrinology and Metabolic Disease, Adiyaman, ²Aydin State Hospital, Endocrinology and Metabolic Disease, Aydin, "Suleyman Demirel" University, Faculty of Medicine, ³Department of Pharmacology, ⁴Department of Internal Medicine, ⁵Department of Radiology, Isparta, Turkey

Abstract

Pituitary apoplexy (PA) is a life-threatening clinical syndrome. Dopamine receptor agonists are the drugs of choice in the treatment of prolactinomas. The use of cabergoline is reported to cause an increased risk of PA, particularly in macroprolactinomas of cystic nature. In this report, we present a patient with a cystic macroprolactinoma who developed PA on the 16th week of cabergoline treatment.

Key words: Pituitary apoplexy, cystic macroprolactinoma, cabergoline.

INTRODUCTION

Pituitary apoplexy (PA) is a life-threatening clinical syndrome and arises due to hemorrhage and/or infarction in the pituitary gland or adenoma. PA was first described by Bailey in 1898. It is characterized by several symptoms such as headache, nausea, vomiting, blurred vision, third nerve palsy, confusion, and coma (1). Sudden onset severe headache is the first manifestation in more than 80% of the patients. Bromocriptine is a commonly used dopamine agonist in the primary treatment of prolactinoma. Major effect of bromocriptine is to reduce the prolactin secretion and the tumour size. However, its use has been limited due to intolerance or resistance. Cabergoline is a novel dopamine agonist, and it has been known to have higher efficacy and fewer side effects comparing to bromocriptine (2). However, cabergoline has been associated with an increased frequency of the development of PA, especially in the patients with macroprolactinoma of cystic nature (3). The contribution of dopamine agonists to the occurrence of PA could not be explained explicitly. However, these agents may lead to necrosis and replacement fibrosis, hence culminate in irreversible tumour shrinkage and

intratumoral hemorrhage (4). We aimed to present a case of PA developed during treatment with cabergoline in a patient with cystic macroprolactinoma.

CASE REPORT

A 49-year-old male patient was presented to our clinics with the complaints of headache for one month and blurred vision for three days. Systemic examination revealed the other symptoms such as erectile dysfunction and reduced sexual desire for one year. He had diabetes mellitus and hypertension for 2.5 years. The patient had been taking metformin 2000 mg/day and ramipril 2.5 mg/day. On physical examination; blood pressure was 110/70 mm/Hg, heart rate 82/min, respiration rate 18/min, and temperature 36.8°C. Confrontation test revealed bilateral hemianopia. Complete blood count, liver tests, renal function tests, and electrolytes were in normal limits. Hormonal parameters were as followings: HbA1c 6% (<5.7%)(0.65 nmol/L), prolactin 436 ng/mL (2.6-13), cortisol 9.7 mcg/dL (2.3-19.4), ACTH 9.3 pg/mL (0-46), TSH 0.21 mIU/L (0.43-4.2), fT4 0.92 ng/dL (0.61-1.12), FSH 2.58 mIU/mL (2.3-7.8), LH 3.2 mIU/mL (1.2-8.6), total testosterone 155 ng/dL (175-781), growth hormone (GH) 0.034 ng/mL (0-5), IGF-1 116 ng/mL (94-252). With a prediagnosis of prolactinoma, pituitary magnetic resonance imaging (MRI) was performed. The MRI detected a pituitary macroadenoma 21x20x21 mm in diameter (height x transverse x anteroposterior) with cystic components (Fig. 1). The patient was diagnosed as prolactinoma. He did not use any drugs causing TSH suppression. Antithyroid peroxidase and anti-thyroglobulin antibodies were in normal limits. Thyroid ultrasonography showed thyroid parenchymal heterogeneity and did not reveal any nodule. Considering the hypophyseal macroadenoma,

*Correspondence to: Hakan Korkmaz MD, Edirne State Hospital, Endocrinology and Metabolic Disease, 22030 Edirne, Turkey, E-mail: drhkorkmaz@yahoo.com.tr

Figure 1. Coronal T2 weighted (a) and unenhanced sagittal T1 weighted images (b) show a macroadenoma with cystic component.

we thought secondary hypothyroidism. Visual field analysis showed significant tunnel vision in both eyes. Cabergoline was given and its dose was gradually increased to 1mg/week. Corticosteroid treatment was not started because the patient had no signs or symptoms of adrenal insufficiency likewise fatigue, nausea, vomiting or hypotension. The patient was informed concerning the necessity of the usage of corticosteroid in stress conditions (e.g., infection). He was discharged and had been called 3 months after discharge.

After 3 months, his headache was improved and the visual acuity was significantly restored. Hormonal results were as followings: prolactin 14.6 ng/mL (2.6-13), cortisol 7.0 mcg/dL (2.3-19.4), ACTH 9.5 pg/mL (0-46), TSH 0.05 mIU/L (0.43-4.2), fT4 0.8 ng/dL (0.61-1.12), FSH 3.1 mIU/mL (2.3-7.8), LH 4.2 mIU/mL (1.2-8.6), GH 0.021 ng/mL (0-5), total testosterone 215 ng/dL (175-781). The pituitary MRI showed the adenoma 12x15x13 mm in size (height x transverse x anteroposterior). It had shrunken significantly, and MRI demonstrated markedly visible cystic components (Fig. 2).

The visual field analysis revealed that the tunnel vision was still persistent in the right visual field but it was significantly improved in the left visual field, particularly in the superior field. Cortisol levels decreased from 9.0 mcg/dL to 7.0 mcg/dL; therefore, hydrocortisone 20 mg/day was added. Cabergoline (1 mg/week) was continued and control examination was recommended. Cabergoline (1 mg/week) and

hydrocortisone (20 mg/day) were prescribed and the patient had been advised to refer to our clinics for the next visit three months later. However, one month after the initial follow-up visit, the patient was presented to the neurosurgery department in another health care center with the complaints of sudden onset headache and visual loss. Preoperative MRI showed the increase in the size of macroadenoma measured as 21x27x24 mm (height x transverse x anteroposterior). Transsphenoidal surgery was performed (Fig. 3). Reoperation was needed due to sudden loss of consciousness and intracranial hemorrhage 8 hours after the operation, then the patient died.

DISCUSSION

Recent studies have shown that the use of cabergoline in the patients with cystic macroprolactinoma was associated with the increased risk of PA (2, 5, 6). Similarly, our patient was presented with a cystic macroprolactinoma and developed PA in the 16th week of cabergoline therapy. A number of risk factors had been reported for PA, such as dopamine agonist, thrombocytopenia, cranial trauma, and radiotherapy (7) (Table 1). Although tumour size has been known to be positively correlated with a higher risk for apoplexy, the exact mechanism of this association remains unknown. Some authors suggest the idea that the tumour growth leads to increased intrasellar pressure, thus leading to the compression of the normal pituitary gland and decreased blood flow.

Figure 2. After medical treatment, coronal T2 weighted (a) and enhanced sagittal T1 weighted images (b) show the regression of both cystic and solid components of the macroadenoma.

Figure 3. MRI performed in a patient with sudden-onset headache and loss of vision reveals subacute phase haemorrhagic infarction within a pituitary macroadenoma. The intrasellar cystic component of adenoma appears slightly hyperintense on coronal T2 weighted (a) and unenhanced sagittal T1 weighted images (b). Coronal T2 weighted images show impression of optic chiasm.

Table 1. Recognized precipitating factors for pituitary apoplexy

- Major surgery, in particular cardiac surgery
- Dynamic pituitary function tests with gonadotropin-releasing hormone, TSH-releasing hormone or corticotrophin-releasing hormone
- Treatment with gonadotropin-releasing hormone agonist
- Treatment with anticoagulants (e.g. warfarin, heparin) and thrombolytic agents (e.g. streptokinase)
- Coagulopathies (e.g. thrombocytopenia)
- Initiation or withdrawal of dopamine receptor agonists (e.g. bromocriptine, cabergoline) or somatostatin analogs (e.g. octreotide)
- Head injury
- Acute systemic illness (e.g. acute myocardial infarction, severe sepsis)

In addition, the direct compression of the pituitary stalk due to tumour growth leads to the obstruction of the blood flow in the hypophyseal portal system, hence to the formation of PA. Moreover, the fragile structure of tumour vessels leads to increased risk of hemorrhage (6). Cabergoline is a selective D2 receptor agonist and has been known as a potential predisposing factor for PA. However, this association is known to be more obvious for bromocriptine, another dopamine agonist. Bromocriptine is a semi-synthetic ergot derivative and it affects the prolactinoma in various ways. Dopamine agonists reduce the size of prolactinoma by decreasing intracellular cAMP production through the inhibition of adenylate cyclase. Dopamine agonist therapy inhibits the prolactin gene transcription, thereby leading to a further decrease in prolactin synthesis. In addition, dopamine agonists lead to tumoral regression and degenerative necrotic tumour cells by reducing the tumour volume. Moreover, degenerative necrotic tumour cells are likely to increase the risk of intratumoral hemorrhage and thus the risk of PA (2).

There is no study reporting an association between cabergoline dosage and the risk of PA; however, in most case reports, the dose of cabergoline ranges between 0.5-3 mg/week (2, 5, 6). PA has occurred in our patient under cabergoline of 1 mg/week.

The primary treatment of PA often includes supportive therapy as well as fluid-electrolyte management and the replacement of deficient pituitary hormones, particularly cortisol. Since corticotropin deficiency is encountered in the most of the patients with PA, corticosteroid therapy should be promptly initiated both for the patients treated conservatively and surgically. Moreover, corticotropin deficiency may be life-threatening unless treated. There is a consensus on performing surgical decompression in the PA patients presenting with serious neuro-ophthalmic signs including sudden loss of vision, and clouding of consciousness (8).

Nevertheless, there is no consensus on an optimal treatment for the PA patients presenting with mild or stable neuro-ophthalmic signs. In such patients, conservative approach seems to be a reliable treatment choice (9).

In conclusion, it should be noted that the risk of PA is increased in the patients with a cystic macroprolactinoma under cabergoline therapy. Therefore, these patients should be closely monitored.

Conflict of interest

The authors declare that they have no conflict of interest.

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