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Review

Pituitary apoplexy associated with cabergoline therapy

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ABSTRACT

Pituitary apoplexy is a rare medical emergency which results from hemorrhage or infarction in the pituitary gland. One of the predisposing factors is treatment with dopamine agonists, especially bromocriptine. We report a 20-year-old Chinese man with prolactinoma who developed pituitary apoplexy 6 weeks after initiation of cabergoline. He was treated conservatively with supportive therapy, and recovered well with no loss of pituitary function. A literature search was conducted and a review of the reported patients with pituitary apoplexy during treatment with dopamine agonists is discussed.

1. Introduction

Pituitary apoplexy is an uncommon but life-threatening condition. It usually occurs in a pre-existing adenoma, although a normal pituitary gland can also develop apoplexy, especially during pregnancy. Patients usually present with severe headache, visual disturbances, cranial nerve palsies, nausea, vomiting, altered consciousness, and impaired pituitary function. The majority of patients do not have a particular cause but predisposing factors include radiotherapy, thrombocytopenia, pituitary dynamic testing, trauma, recent surgery, diabetes mellitus, hypertension, and medications such as anticoagulants and dopamine agonists. Most reports of pituitary apoplexy in patients with adenomas are related to treatment with bromocriptine. We report a patient with prolactinoma who developed apoplexy 6 weeks after cabergoline treatment.

2. Illustrative case report

A 20-year-old Chinese man presented to a neurologist with a 5 year history of chronic right sided headache requiring intermittent analgesia for pain relief. MRI of the brain revealed a intrasellar lesion extending to the suprasellar region resulting in compression of the optic chiasm. He was referred to our endocrinology service for assessment of tumor functionality.

He was an otherwise healthy individual and not taking any regular medications. He had no complaints of polyuria, polydipsia, nocturia, or visual disturbance. His secondary sexual development was normal. There was no family history of pituitary disease.

He weighed 58 kg and was 1.74 meters tall, with a body mass index of 19 kg/m^2. He was not Cushingoid, acromegalic, or eunuchoid. Secondary sexual characteristics were present and there was no gynecomastia or galactorrhoea. Formal visual field assessment with Goldman's perimetry was normal.

2.1. Laboratory investigations

Serum prolactin was markedly raised at 60394 milli-international units [IU]/L (reference interval [RI]: 77–274) while the rest of his hormonal profile was normal: testosterone 16 nmol/L (RI: 5–30), luteinizing hormone (LH) 3 IU/L (RI: 1–19), follicle stimulating hormone (FSH) 2 IU/L (RI: 1–19), free thyroxine (fT4) 11 pmol/L (RI: 8–21), thyroid stimulating hormone (TSH) 1.79 mIU/L (RI: 0.34–5.6), and insulin-like growth factor-1 145 ug/L (RI: 141–483). A short synacthen test was carried out using 250 mcg of intramuscular tetracosactrin. At 0 minutes his cortisol level was 298 nmol/L, at 30 minutes cortisol was 504 nmol/L, and at 60 minutes cortisol was 658 nmol/L. Adrenocorticotropic hormone was not tested.

2.2. Brain MRI

The MRI showed a large mass extending from the intrasellar to the suprasellar region, measuring 2.5 × 1.7 × 2.5 cm. It was heterogenous in nature and had both cystic and slightly enhancing solid components. The pituitary stalk was not visualized and the optic chiasm was compressed, more so on the left (Fig. 1).

2.3. Further management

The patient was offered medical management with dopamine agonists, and he was duly started on 0.25 mg cabergoline twice a

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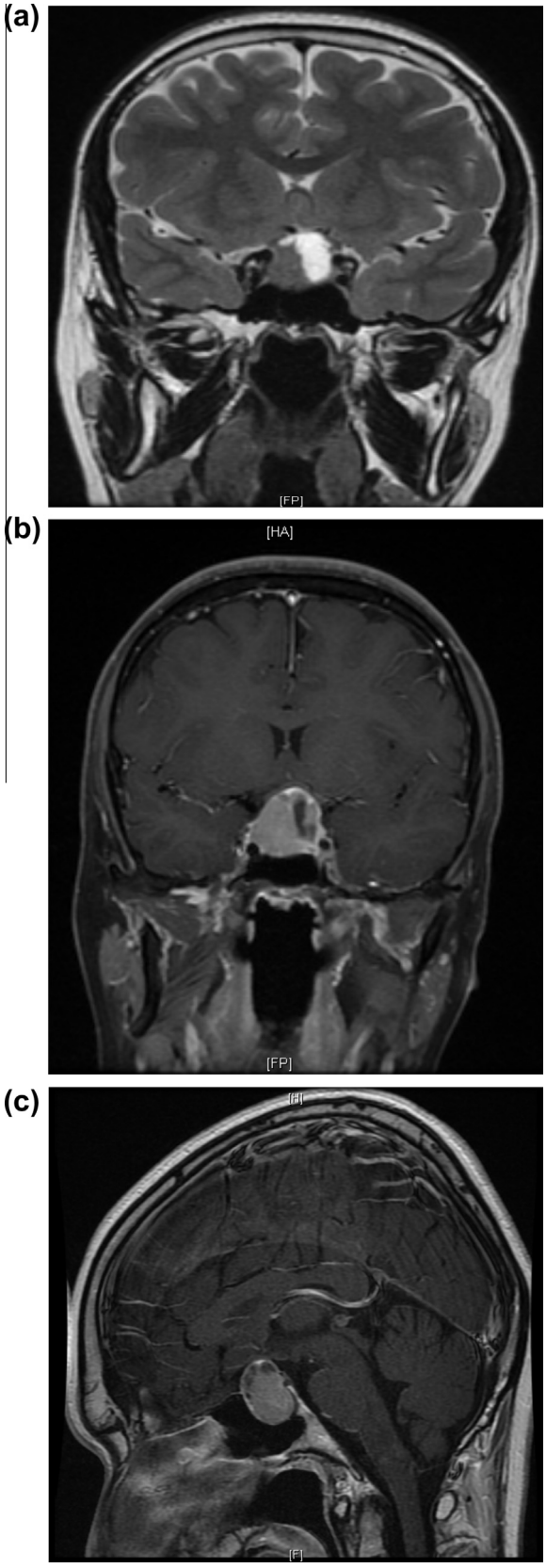

Fig. 1. (a) Coronal T2-weighted MRI showing a large sellar lesion with suprasellar extension, (b) coronal T1-weighted contrast enhanced MRI showing a large heterogenous sellar mass with cystic components with displacement of the pituitary stalk and optic chiasma, and (c) sagittal T1-weighted contrast enhanced MRI showing a large heterogenous sellar mass with displacement of the pituitary stalk.

week. A review 4 weeks later showed improvement in his headache and a drop in serum prolactin level to 584 mIU/L (RI: 77–274). He denied any side-effects and the dose of cabergoline was increased to 0.5 mg twice a week. He presented to the emergency department 6 weeks after the initial prescription with severe headache, nausea, and vomiting. An urgent MRI of the pituitary fossa showed a stable sized sellar/suprasellar mass which became more diffusely hypointense on T2-weighted images, with a larger non-enhancing component in the left side (Fig. 2). A short synacthen test was done (cortisol levels were 112 nmol/L at 0 minutes, 390 nmol/L at 30 minutes, and 512 nmol/L at 60 minutes) and 50 mg intravenous (IV) hydrocortisone was administered, followed by 100 mg three times a day as the patient's blood pressure was low in the ward. Fifty mcg of thyroxine was also started as his thyroid function test showed borderline central hypothyroidism with fT4 8 pmol/L and TSH 0.22 mIU/L. Serum prolactin remained suppressed at 103 mIU/L.

A CT scan of the head was done to further evaluate for hemorrhage; it showed a heterogeneously hyperdense 2.5 × 1.9 cm sellar and suprasellar mass with foci of eccentric calcification but with no evidence of intralesional hemorrhage seen. As the patient's symptoms improved, the consulting neurosurgeon recommended non-surgical supportive management with IV saline and IV hydrocortisone. His blood pressure gradually normalized and the hydrocortisone was slowly decreased and changed to 20 mg orally every morning and 10 mg at 5 pm daily upon discharge 5 days later. Cabergoline was continued albeit at a reduced dose of 0.25 mg twice a week.

The patient was well on review in the clinic 2 weeks post–discharge. A hormonal workup showed LH 2 IU/L, FSH 4 IU/L, fT 4 15 pmol/L, TSH 1.08 mIU/L, and prolactin 90 mIU/L. A short synacthen test showed cortisol levels of 271 nmol/L at 0 minutes, 486 nmol/L at 30 minutes, and 541 nmol/L at 60 minutes. He was continued on 0.25 mg of cabergoline twice a week, 50 mcg of thyroxine daily and hydrocortisone was reduced to 10 mg daily.

The patient remained well on review in the clinic 2 months later. He admitted to having stopped taking thyroxine and hydrocortisone, but remained compliant with cabergoline. His hormonal workup showed fT4 13 pmol/L, TSH 0.53 mIU/L, and prolactin 288 mIU/L. A short synatchen test showed cortisol levels of 325 nmol/L at 0 minutes, 652 nmol/L at 30 minutes, and 723 nmol/L at 60 minutes. MRI showed a significant size reduction of the sellar–suprasellar mass to 15.1 × 22.5 × 13.6 mm, with two well-defined rounded lesions on the left which showed high signal intensity on T1 and T2-weighted images, suggestive of subacute blood product (Fig. 3). In view of his rising serum prolactin level, cabergoline was increased to 0.5 mg twice a week.

His prolactin subsequently dropped to 52 mIU/L and 22 mIU/L when checked 2 and 5 months later, respectively. Cabergoline was then reduced to 0.25 mg twice a week (Table 1).

Currently, he remains well 10 months after admission for pituitary apoplexy and is still on cabergoline.

3. Discussion

The use of dopamine agonists has been listed as one of the risk factors for pituitary apoplexy. They cause apoptosis of lactotroph cells and this in turn decreases the metabolic demands. At the same time, the angiogenesis is inhibited but an imbalance between the two leads either to infarction with hemorrhage or hemorrhage only.

A literature search for patients reported between 1985 and 2011 revealed 10 patients[1–10] and two case series[11,12] of pituitary apoplexy with the use of dopamine agonists (Table 2). The earlier reported patients were treated with bromocriptine, while the more