THUNDERCLAP HEADACHE CAUSED BY A PITUITARY NON-FUNCTIONING TUMOUR PRESENTING AS SPONTANEOUS PITUITARY APOPLEXY

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ABSTRACT

Hemorrhagic or ischemic pituitary apoplexy is a rare neuro-endocrine emergency, potentially leading to coma. Neuro-ophthalmic symptoms or complications are amongst the most prevalent clinical features at onset, especially in previously asymptomatic patients. Usually, permanent pituitary insufficiency of various degrees follows, implying long-term hormone substitutive therapy. Rarely, the association of pituitary apoplexy with diabetes insipidus has been noticed. We report the case of a young, apparently healthy 32-year-old man presenting with thunderclap headache, fever, optic chiasm compression, central diabetes insipidus and central thyro-gonadic insufficiency. Magnetic resonance imaging and neurosurgery revealed a clinically non-functioning macro-adenoma developing pituitary hemorrhage. One year after the apoplectic episode, complete recovery of diabetes insipidus and pituitary function was confirmed.

Key words: thunderclap headache, pituitary apoplexy, pituitary tumour, transsphenoidal surgery, magnetic resonance imaging

INTRODUCTION

Hemorrhagic or ischemic pituitary apoplexy is a rare neuro-endocrine emergency potentially leading to coma. The main clinical symptoms are thunderclap headache, nausea and vomiting, fever, loss of consciousness, ophtalmoplegia, visual field impairment, monocular blindness and neck stiffness (meningeal irritation). The diagnosis is most challenging in apparently healthy subjects, in whom neurological complications such as stroke (Das, 2008; Dogan, 2008), meningitis (Villegas, 2008), diffuse subarachnoid haemorrhage or optic tract haemorrhage (Nakahara, 2006; Kim, 2007) may develop. Occasionally, pituitary apoplexy may present as isolated unilateral or bilateral third (Lau, 2007) or sixth nerve palsy.

In most cases, pituitary apoplexy complicates the evolution of previously diagnosed adenomas. In a retrospective review of 28 cases with pituitary adenoma, 14% of patients were incidentally diagnosed after pituitary apoplexy (Dekkers, 2007) and

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in a follow-up of 42 patients with incidentally found non-functioning pituitary adenoma, apoplexy complicated the natural course of the disease in 9.5% of cases (Arita, 2006). On the other hand, in a large series of 45 cases of subjects with pituitary apoplexy, only 18% were known to have pituitary adenoma at presentation (Sibal, 2004). Likewise, in a larger series of 62 patients with this clinical condition, 81% of subjects had no previous medical history suggesting pituitary tumour (Semple, 2005).

Pituitary insufficiency of various degrees follows the onset of pituitary apoplexy. Moreover, pituitary function does not commonly recover after resolution of the acute haemorrhage, implying lifelong substitutive adrenal, thyroid or sex hormone therapy. Rarely, the association of pituitary apoplexy with permanent or transient diabetes insipidus has been reported in isolated cases; in two larger studies, of 62 and 40 patients, respectively, only 8% of subjects developed antidiuretic hormone (ADH) deficiency (Semple, 2005; Lubina, 2005).

We here report the case of a young, apparently healthy men presenting with thunderclap headache, fever, diabetes insipidus and thyro-gonadic pituitary failure. Magnetic resonance imaging (MRI) and neurosurgery revealed a non-functioning macro-adenoma developing pituitary haemorrhage. One year after the event, complete recovery of diabetes insipidus and pituitary function was demonstrated.

CASE REPORT

A 33-year-old man was admitted to the Neurology Clinic Cluj-Napoca with thunderclap headache, followed by a one-week history of heavy left frontal-parietal headache. Symptoms, including general weakness, fever and severe diffuse headache worsened despite ongoing antibiotic therapy for suspected left frontal sinusitis. Subsequently, a polyuria-polydypsia syndrome developed. The patient and his wife were, unsuccessfully, trying to conceive for about one year. Laboratory evaluation revealed an inflammatory syndrome with erythrocyte sedimentation rate 40-75 mm/1-2 h, C-reactive protein 48 mg/dl and serum fibrinogen 496 mg/dl; serum creatinine was 1.1 mg/dl with a daily urinary volume of 6590 ml with decreased spontaneous and after the water deprivation test urine specific gravities of 1001-1007. Water balance normalized during the vasopressin test, suggesting central diabetes insipidus. Magnetic resonance imaging detected a 2.0/2.5/1.2 cm sella turcica mass with a central component suggesting haemorrhage. The mass compressed both the pituitary stalk and the optic chiasm. Correspondently, a bitemporal superior quadrantic defect was noticed at computerized visual field analysis. Basal pituitary function evaluation suggested multiple hormonal pituitary failure: gonadotropin insufficiency with low-normal serum follicle stimulating hormone (FSH) of 2.06 UI/l (normal values 1.5-12.4 UI/l), low serum luteinizing hormone (LH) of 1.07 UI/l (normal values 1.7-8.6 UI/l) and low serum total testosterone (Te) of 0.598 nmol/l (normal values 9.9-27.8 nmol/l) and central thyroid hormone insufficiency with low serum thyrotropin (TSH) of 0.102 mUI/l (normal values 0.27-4.2 mUI/l and low serum free thyroxin (FT4) of 10.99 pmol/l (normal 12-22 pmol/l). In addition, a low serum prolactin (PRL) level of 90.58 mUI/l (normal 98-456 mUI/l) was detected. Therapy with dexamethasone (8 mg daily i.m.), desmopressin acetate 300 µg daily, L-thyroxin 50 µg daily and testosterone undecanoate 120 mg daily was followed by clinical improvement. Two-weeks later, magnetic resonance imaging revealed a persistent pituitary mass of 1.4/2.5/1.4 cm (Fig 1A, 1B) without compression of the optic chiasm. Due to the large pituitary mass and important thyrotropin and gonadotropin hormone insufficiency, the patient underwent pituitary decompression by transsphenoidal approach. Histologically, the resected tumour was composed of adenohypophyseal cells with normal appearance, confirming the presence of a pituitary adenoma. Unfortunately, immunohistochemistry of the tumour was not available at that time. Post-surgery, laboratory re-evaluation showed persistence of diabetes insipidus with basal pituitary function improvement and disappearance of the inflammatory syndrome. Three-months after surgery, our patient had a normal spermiogram and subsequently an ongoing pregnancy was achieved by the patients' wife. The symptom-free patient was reexamined in the outpatient service of the Endocrinology Clinic Cluj-Napoca one year after surgery. Magnetic resonance imaging showed a normal, inhomogeneous, slightly asymmetric pituitary. Functionally, pituitary hormones were within normal limits (FSH 4.77 mU/ml, LH 2.29 mU/ml, Te 12.99 pmol/l, TSH 1.33 µUI/ml, FT4 14.03 pmol/l, PRL 109.5 µUI/ml) and complete resolution of diabetes insipidus was demonstrated by normal basal water balance and adequate response to water deprivation.

DISCUSSION

Pituitary apoplexy is known as a rare complication of pituitary tumours. Epidemiologic data from

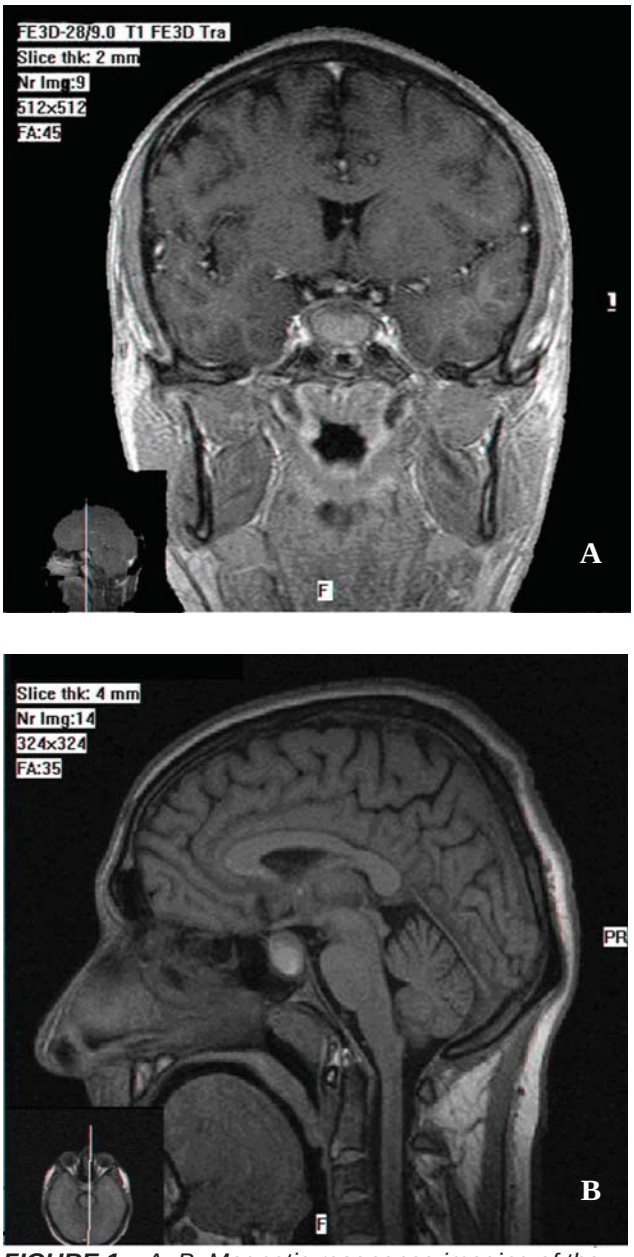

FIGURE 1 *– A, B. Magnetic resonance imaging of the pituitary gland showing the presence of an enlarged intrasellar mass with a central heterogeneous, slightly hyper-intense signal suggesting haemorrhage, which compresses the pituitary stalk and is tangent to the optic chiasm. 1A. shows coronal T1-weighted image and 1B shows mid-sagittal T1-weighted image of the pituitary gland.*

literature are variable, apoplexy being observed in 1.6% (Dubuisson, 2007) to 21% (Nielssen, 2006) of either non-functioning or GH-, PRL- and ACTH-secreting pituitary adenomas. Evidence of pituitary haemorrhage after therapy with LHRH analogues (Hernandez, 2003, Davis, 2006) suggests that apoplexy also complicates gonadotropin-secreting tumours, known to appear often as clinically non-functioning. Rarely, pituitary haemorrhage may develop after partial tumour resection (Goel, 1995) or in a previously healthy pituitary gland, after head trauma or in patients with diabetes mellitus or sickle cell anemia or in association with acute hypovolemic shock (Melmed, 2003). Apoplexy may lead to complete remission of a secreting pituitary adenoma, as a "spontaneous" cure, reported in GH- or PRL-secreting macro-adenomas with or without surgery (Nishioka, 2005). Exceptionally, spontaneous resolution of a non-functioning adenoma was reported in a patient in whom neither diabetes insipidus nor pituitary dysfunction was documented before surgery (Kachhara, 2000).

We here report the case of a previously undiagnosed pituitary non-functioning adenoma in a young man, presenting as spontaneous pituitary apoplexy diagnosed as a neurologic emergency. The leading symptom in our patient was thunderclap headache, a nonspecific clinical feature associated frequently to severe underlying diseases such as aneurismal subarachnoid haemorrhage, basilar artery dissection, stroke, cerebral venous thrombosis or cerebral vasospasm. Pituitary apoplexy is easily suspected in patients with previously diagnosed pituitary pathology, but subtle endocrine changes in subjects with unknown clinically non-functioning tumours, as our case, may be overlooked; moreover, association of fever and inflammation explains pituitary apoplexy mimicking meningitis (Chibarro, 2007; Smidt, 2007) meningoencephalitis (Jassal, 2004) or sinusitis (Arita, 2001) or even subarachnoid haemorrhage. In this regard, magnetic resonance imaging or computed tomography may suggest the correct diagnosis. Neuroradiological differential diagnosis is made with craniopharyngioma and pituitary abscess (Pepene, 2008).

While multi-hormonal pituitary deficiency is frequently associated with pituitary apoplexy, the development of diabetes insipidus is more rarely seen, between 0% (Dubuisson, 2007) and 8% of subjects (Semple, 2005; Lubina, 2005), with only a few cases developing transient forms of ADH insufficiency. Almost all apoplectic patients will continue to manifest long-term hypopituitarism of variable severity, needing permanent substitutive hormonal therapy (Dubuisson, 2007, Nielssen, 2006), although in some studies normal pituitary hormonal function after pituitary surgery was mentioned in up to 24% of cases, with except of growth hormone secretion remaining subnormal (Nielssen, 2006). In our case, both central diabetes insipidus and pituitary insufficiency were transient, with full recovery of pituitary function and ADH secretion one year after the apoplectic episode. Unfortunately, postoperative GH secretion was not tested in our

patient, mainly because substitutive GH therapy in adults is not available in our country. Pituitary dysfunction secondary to pituitary stalk compression by the pituitary mass cannot be completely excluded in our patient, explaining rapid resolution of hormonal insufficiency. On the other hand, the low PRL level documented preoperatively is suggestive of functional destruction of pituitary tissue.

Therapy guidelines in patients with pituitary apoplexy indicate either conservative therapy with glucocorticoids or the neurosurgical approach. Most authors indicate surgery, claiming that this improves outcome regarding both visual and pituitary function. Transsphenoidal surgery is the first line approach in subjects with blindness or severe visual field impairment (Muthukumar, 2008). However, there is no clear data on indications of surgery in the rest of cases and in a recent retrospective analysis on 33 patients developing pituitary apoplexy, Ayulk et al. suggested that patients in whom visual deficits are stable or improving after glucocorticoid therapy may be managed expectantly (Ayulk, 2005). Despite decompression of optic chiasm after dexamethasone, we decided for the neurosurgical approach in our patient, mainly based on tumour size, significant hormonal dysfunction in a relatively young patient and risk of late tumour regrowth. Although in the study of Ayulk there was no difference between patients managed conservatively or by surgery with respect to persistence of central adrenal or thyroid insufficiency, it cannot be excluded that the excellent endocrine outcome in our subject is related to early surgical haemorrhage drainage. On the other hand, Sibal et al., 2004 showed that conservative therapy is at higher risk for a recurrent apoplectic episode.

To conclude, pituitary apoplexy may represent a severe complication of pituitary tumours irrespective of the patients' age and health status. By association of visual field defects, cranial nerve palsy, meningeal irritation, neurological complications and multi-hormonal dysfunction, pituitary apoplexy is a serious disease with a multidisciplinary management. In rare cases, appropriate diagnosis and treatment may lead to complete restitution of pituitary function and preservation of visual field. Clinical studies are needed to establish predictive factors of a favourable outcome in patients with pituitary adenoma complicated with apoplexy.

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