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Case report

Brain and optic chiasmal herniation following cabergoline treatment for a giant prolactinoma: wait or intervene?

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ABSTRACT

OBJECTIVE: Dopamine agonists (DA) are the treatment of choice in patients with macroprolactinomas. Brain and optic chiasm herniation are unusual complications following treatment with DA. REPORT: We present a case of a giant prolactinoma complicated by visual deterioration following cabergoline treatment. A 42-year-old man was admitted with seizures, right visual loss and visual defect in the upper left temporal quadrant. Magnetic resonance imaging (MRI) identified a giant adenoma, which proved to be a prolactinoma, compressing the optic chiasm and extending into the suprasellar region. Treatment with cabergoline was initiated resulting in improvement in visual fields, tumor shrinkage and prolactin level decrease. Five months later and despite tumor reduction, a deterioration of his visual fields was observed. The second MRI revealed brain and optic chiasmal herniation into the pituitary sella. Cabergoline dose was reduced and surgical resection of the adenoma along with untethering of the optic nerve was performed leading to improvement of the visual defects. CONCLUSIONS: This report describes a rare case of brain and optic chiasmal herniation attributed to DA therapy for a macroprolactinoma. It is important for clinicians to examine visual fields and promptly identify any visual deterioration in patients with macroprolactinomas receiving DA treatment.

Key words: Brain herniation, Cabergoline, Giant prolactinoma, Optic chiasmal herniation, Visual deterioration

INTRODUCTION

Prolactinomas are the most common pituitary secreting tumors, accounting for 30-40% of all pituitary tumors,[1-4] while in autopsy series their incidence reaches 50%.[5] Macroprolactinomas occur less frequently than microadenomas and their incidence is higher in men compared to women. Giant prolactinomas, a rare subtype of macroadenomas, are characterized by large size (over 4 cm), very high prolactin levels (more than 1000 ng/ml) and invasive growth and are thus the most difficult to treat.[6,7] Clinical manifestations include mass effects leading to headache,

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visual field defects, opthalmoplegia and seizures. Pharmacologic treatment with dopamine agonists (DA) is currently the cornerstone of medical therapy for prolactinomas as it is well tolerated and effective in controlling clinical symptoms, reducing prolactin (PRL) levels and shrinking tumor size. Surgery is limited to cases of intolerance or resistance to DA or when acute complications, such as sudden visual impairment, occur.[2,3,8]

Common side effects of DA treatment include headache, nausea and vomiting, fatigue, orthostatic hypotension, peripheral vascular changes and depression. Pituitary apoplexy,[9] cerebrospinal fluid (CSF) rhinorrhea[10] and optic chiasm herniation are considered rare side effects of DA treatment. The latter can result from tumor involution causing optic chiasm prolapse into the partially empty sella and is manifested by visual deterioration.[11] Even rarer, brain herniation can occur simultaneously with optic chiasm herniation.[12,13]

In this article, we present an unusual case of secondary visual fields' deterioration during cabergoline treatment of a giant prolactinoma despite tumor shrinkage, this being the result of brain and optic chiasmal herniation. We briefly overview the existing literature, suggest potential underlying mechanisms for this complication and discuss the different therapeutic options.

CASE REPORT

A 42-year-old man (body mass index 26 Kg/m^2) presented at the emergency department with generalized epileptic tonic-clonic seizures and decreased level of consciousness. Cerebral computerized tomography (CT) imaging demonstrated a heterogeneous 5 cm pituitary mass eroding the sella turcica and extending into the suprasellar region. PRL levels were over 2000 ng/ml [normal range (NR) 3.46-19.4]. Tumor-induced seizures were treated with phenytoin and the patient was transferred to the endocrinology department. Medical history revealed right sight loss dating to several years previously, though without any clinical or radiologic evaluation at that time. The patient reported muscle weakness, episodes of headache, decreased libido and erectile dysfunction over the last 6 years, while the clinical examination confirmed the right visual loss and a hypogonadal habitus. Subsequent pituitary magnetic resonance imaging (MRI) identified a heterogeneous pituitary giant adenoma of 6x3.5 cm in diameter invading the sphenoid and cavernous sinuses and extending into the suprasellar region, thus compressing the optic chiasm as well as the third ventricle and the frontal horns of the lateral ventricles (Figure 1). Visual field perimetry revealed right vision loss and deficits in the upper temporal quadrant of the left eye, whereas visual acuity was normal in the left eye. The biochemical

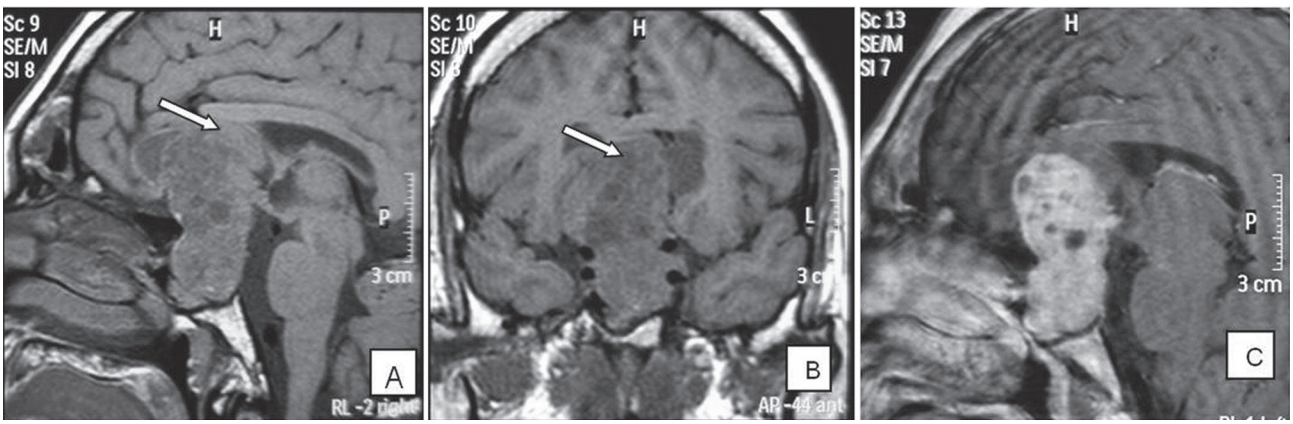

Figure 1. A-B. Pituitary sagittal and coronal T1-weighed MRI scan, respectively. **C.** Pituitary sagittal T1-weighed MRI scan after gadolinium enhancement. The pre-treatment MRI figures depicted a giant macroadenoma of 6 cm in craniocaudal diameter, with diffuse inhomogeneous enhancement after gadolinium administration, occupying the sella turcica and eroding the sella and the clivus. The tumor had suprasellar extension compressing the optic chiasm as well as the third ventricle and the frontal horns of the lateral ventricles (arrows) and infrasellar extension invading the sphenoid and cavernous sinuses. Encapsulated cerebrospinal fluid was also present around the upper edge of the lesion.

investigation was unremarkable except for anemia, while hormonal work-up confirmed markedly elevated PRL levels [4532 ng/ml (NR 3.46-19.4)] and multiple anterior pituitary hormones deficiencies: decreased free thyroxine [7.53 pmol/L (NR 9-21) (0.58 ng/dl)] and triiodothyronine [0.6 nmol/ml (NR 0.58-1.9) (38.9 ng/dl)] with inappropriately normal thyrotropin levels [TSH 1.85 μIU/ml, (NR 0.35-4.94)], low gonadotrophin (FSH 0.54 IU/L, LH 0.21 IU/L) and testosterone levels [0.277 nmol/L (NR 9.26-35.36) (0.08 ng/ml)], as well as cortisol [85.8 nmol/L (NR 138-690 08:00am (3.10μg/dl)], growth hormone [GH 0.2 μg/L (NR 0.6-6.6)] and insulin-like growth factor 1 levels [IGF-1 115 μg/L (NR 180-406]. There was no evidence of diabetes insipidus. Cabergoline was initially administered at a dose of 1.5 mg/week and weekly increased by 1 mg to a total dose of 3.5 mg/week in addition to replacement therapy with hydrocortisone (20 mg daily), thyroxine (100 μg daily) and intramuscular testosterone. The patient responded well to anti-epileptic treatment with no recurrence of seizure.

Two months after cabergoline therapy initiation, PRL levels were markedly reduced to 160 ng/ml, while follow-up MRI showed reduced tumor size (3.3×3 cm). Slight improvement of his visual fields was also observed. Three months later and while on cabergoline treatment, he complained of visual impairment in the left eye. The new MRI revealed prolapse of the right frontal lobe and the optic chiasm inferiorly into the empty pituitary sella, secondary to the tumor shrinkage (Figure 2).

PRL levels were relatively low (90.7 ng/ml) and visual field perimetry confirmed temporal hemianopsia in the left eye. Cabergoline dose was reduced to 1 mg/week and the patient underwent frontal craniotomy with resection of the macroadenoma, untethering of the optic nerve and reconstruction of the sella cavity. The surgical technique used in our patient is described in a correspondence letter by Gkekas N et al,[14] while the 6 months' post-surgical MRI is presented in Figure 3.

Histological investigation confirmed a lactotrope pituitary adenoma consisting of small cells with cytoplasmatic shrinkage within an extensive area of fibrotic tissue. These alterations were attributed to cabergoline treatment. Immunostaining was positive for PRL, while Ki-67 proliferation index was 1%. The possibility of adenoma infarction was ruled out since cell necrosis or hemorrhage were not observed.

The patient's course was complicated by a central nervous system infection which resolved after 6 days of antibiotic treatment. Follow-up exams revealed an improvement of the left eye's visual fields with only limited deficits in the upper temporal quadrant, while PRL levels further decreased to 42 ng/ml. Currently, the patient remains on cabergoline treatment at a dose of 2 mg weekly with simultaneous administration of hydrocortisone, thyroxine, and testosterone replacement therapy.

DISCUSSION

In this case report, we describe an unusual second-

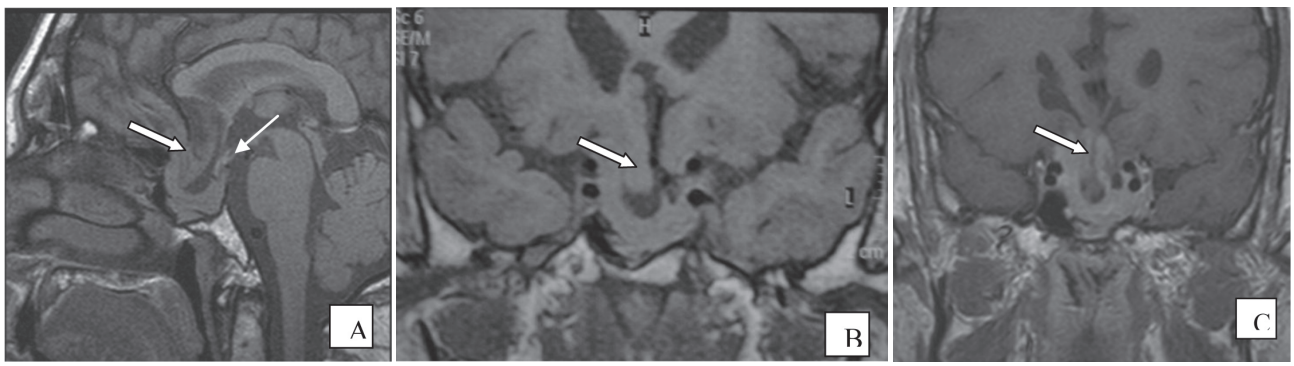

Figure 2. Pituitary T1-weighed images in sagittal (**A**) and coronal (**B**) and coronal after gadolinium enhancement (**C**) MRI scan, respectively, after 5 months under cabergoline treatment. Post-treatment figures depict a marked reduction of the tumor mass and a herniation of the inferior frontal lobe (thick arrow) and the optic chiasm (thin arrow) into the pituitary sella.

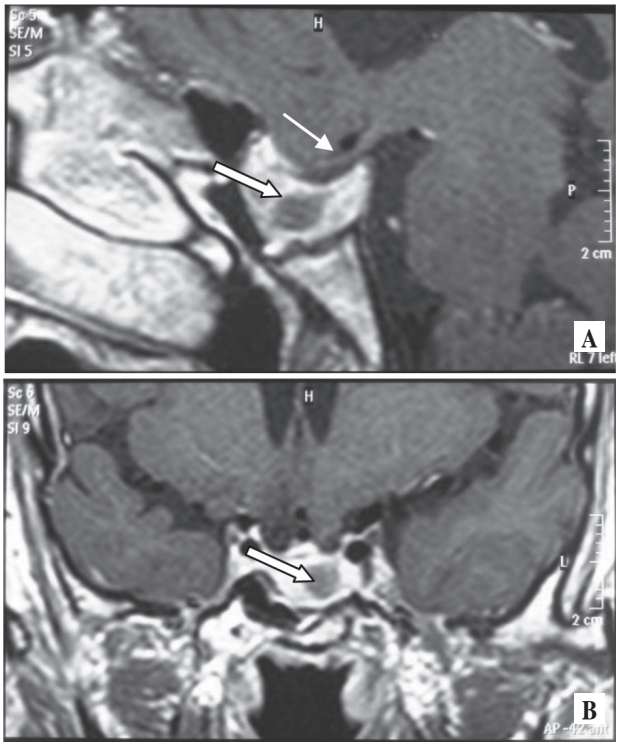

Figure 3. Pituitary T1-weighed sagital **(A)** and coronal **(B)** MRI scan respectively, after surgical resection of adenoma showing a residual tumour mass (8mm) in the sella (arrows). The reconstruction of the sella cavity is depicted. The left optic nerve is shown normal (thin arrow).

ary deterioration of visual fields during cabergoline treatment of an invasive giant pituitary prolactinoma that was attributed to optic chiasm and brain herniation into the sella. Given the tumor invasiveness, the right eye sight loss and the rapidly deteriorating visual fields, an increasing dose of cabergoline was initiated.

It is well known that the management of giant prolactinomas can be challenging. The aggressiveness of such tumors can cause compression of important anatomical structures, such as the optic chiasm, therefore requiring prompt intervention, either pharmacological or surgical.

Pharmacological management with DA is proposed as first-line treatment even in giant prolactinomas as it has been shown to be effective in reducing PRL levels and inducing significant tumor shrinkage.[6,7,15,16] In contrast to the time required to reduce PRL levels and tumor size, the effect of DA on visual acuity and visual fields is rapidly apparent after only a few days of treatment. A probable reason for the improvement of visual field defects could be the initial reduction of the craniocaudal tumor diameter followed by a decrement of the transverse diameter.[17]

On the other hand, surgical intervention is less effective compared to medical therapy and may be performed for rapid optic decompression and visual improvement or it may be selected for patients resistant to DA therapy.[8,18] Furthermore, total surgical removal of giant prolactinomas that expand into different directions in the supra-, para- and infrasellar areas is very difficult or even impossible.[19-21]

Secondary deterioration of visual fields after medical therapy for a macroprolactinoma may be due to pituitary hemorrhage, infraction, tumor recurrence or optic chiasm herniation. The latter, although unusual, has been described in patients with macroprolactinoma, treated with bromocriptine,[11,23,26] pergolide[24] or cabergoline.[27] In most cases, chiasm herniation did not correlate with the degree of visual deterioration,[25] while reduction of DA dose was usually accompanied by improvement of the visual defects despite the persistence of herniation.

Although chiasmal herniation is an unusual complication, simultaneous brain herniation has rarely been described. Inferior frontal lobe and chiasmal herniation into an enlarged sella has been observed following one year of successful bromocriptine therapy despite the almost complete disappearance of the macroadenoma and the normalization of PRL levels.[12] However, as there was no evidence of further visual deterioration, the patient continued treatment with bromocriptine. Secondary visual loss and seizures following 6 months of cabergoline treatment for a giant prolactinoma attributed to optic chiasmal and frontal lobe herniation into the sella has recently been described. In this case, the reduction of cabergoline dose resulted in marginal vision improvement.[13]

The case we present is the first that underwent surgical intervention which comprised frontal craniotomy, adenomectomy and left optic nerve untethering in order to preserve vision in the left eye, as the patient had already suffered from right eye sight loss. The alternative more conservative option of reducing the cabergoline dose and waiting with close follow-up was considered to harbor increased risk of vision damage in a patient who had already permanently

lost right eye vision. Certainly, the trans-sphenoidal approach is the intervention of choice in the surgical management of macroadenomas.[28,29] Nevertheless, tumor size, consistency and shape are important factors that should be taken into account and may lead to a decision for a transcranial approach. Despite a greater risk of postoperative pituitary dysfunction, there appears to be a trend towards a greater visual improvement.[30]

The pathogenesis of herniation into the partially empty sella remains unclear. Traction into the sella due to fibrosis or vascular compression of the suprasellar visual system by the abnormal tissue has been implicated. The adherence of the adenoma to the suprasellar visual system before DA treatment could compromise the vascular supply and predispose to the occurrence of herniation upon reduction of the adenoma size by treatment and subsequent development of empty sella.[11,22,23] Moreover, the dura consistency of the diaphragm varies between individuals.

In our case, the tumor was attached to the suprasellar visual system and the increase of cabergoline dose may have induced intratumoral intense fibrosis, tumor shrinkage, alteration of vascular supply and the development of empty sella, thus causing brain and optic chiasm herniation.

In general, the treatment of patients with chiasmal herniation consists of DA dosage reduction or surgical intervention. DA withdrawal and re-initiation at a lower dose is hypothesized to relieve the tension on the optic chiasm with only limited tumor regrowth.[11,27] Alternatively, surgical intervention can also show beneficial effects.[31,32] As in most pituitary operations, the experience of the neurosurgeon is an important factor and thus it is suggested that such operations should optimally be performed by high-volume neurosurgeons.

In conclusion, we describe a rare case of a giant prolactinoma complicated by brain and optic chiasmal herniation following therapy with cabergoline. Our report emphasizes the need for clinical awareness and frequent monitoring of visual fields in such patients. In the majority of cases, the risk of empty sella leading to brain and/or optic chiasm herniation does not counteract the well-established beneficial effects of DA therapy in reducing tumor size and PRL levels in macroprolactinomas. The prompt identification of visual defects should lead to optimization of medical treatment aiming at visual improvement and prevention of further deterioration.

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