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PITUITARY APOPLEXY ASSOCIATED WITH CABERGOLINE USE: A RARE COMPLICATION. CASE REPORT

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ABSTRACT

Introduction: Pituitary apoplexy (PA) is a neurosurgical emergency characterized by hemorrhage or infarction in the pituitary gland that usually occurs within a pituitary adenoma. Most PA cases in patients with adenoma are related to bromocriptine treatment, but it has also been reported that it may develop after treatment with cabergoline.
Case presentation: A 28-year-old woman, treated for three weeks with cabergoline 1 mg on an outpatient basis for the management of symptoms related to a prolactin-secreting pituitary macroadenoma, was admitted to the emergency department of a quaternary care institution in Bogotá (Colombia) due to right hemicranial throbbing headache of sudden onset, which did not improve with conventional treatment, as well as bitemporal hemianopsia and sudden deterioration of visual acuity, symptoms indicative of PA. The patient underwent endoscopic endonasal transsphenoidal surgery, achieving partial recovery of the field and visual acuity. However, a few weeks later, the symptoms reappeared with evidence of lesion rebleeding, leading to the scheduling of a second transcranial surgery. Finally, the patient was discharged in good general condition, although her vision did not recover completely. She was also prescribed treatment for hormone replacement.
Conclusion: PA is a medical emergency, so early treatment is essential, including hormone replacement and, in some cases, surgery for sella decompression and hematoma drainage. Cabergoline is a rare cause of PA.

RESUMEN

Introducción. La apoplejía hipofisaria (AP, por su sigla en inglés) es una emergencia médica rara causada por una hemorragia o infarto en la glándula pituitaria que, por lo general, se presenta dentro de un adenoma hipofisiario. La mayoría de casos de AP en pacientes con adenomas se asocian con el tratamiento con bromocriptina, pero también se ha reportado que puede desarrollarse luego del tratamiento con cabergolina.
Presentación del caso. Mujer de 28 años, quien, luego de tres semanas de tratamiento ambulatorio con cabergolina 1mg para el manejo de los síntomas de un macroadenoma hipofisario secretor tipo prolactinoma, ingresó al servicio de urgencias de una institución de cuarto nivel de atención de Bogotá (Colombia) por cefalea hemicraneal derecha de tipo punzante e inicio súbito, que no mejoraba con tratamiento convencional, así como hemianopsia bitemporal y deterioro súbito de la agudeza visual, síntomas indicativos de AP. La paciente fue sometida a cirugía endoscópica endonasal transesfenoidal, logrando una recuperación parcial del campo y la agudeza visual, pero semanas después los síntomas reaparecieron y se evidenció resangrado de la lesión, por lo que se programó una segunda intervención quirúrgica por vía transcraneal. Finalmente, la paciente egresó en buenas condiciones generales, aunque sin recuperación completa de la visión, y con

tratamiento para reposición hormonal.
Conclusión. La AP es una urgencia médica, por lo que es fundamental instaurar un tratamiento precoz que incluya reposición hormonal y, en algunos casos, intervención quirúrgica para la descompresión selar y el drenaje del hematoma. La cabergolina es una causa poco frecuente de AP.

INTRODUCTION

Pituitary apoplexy (PA) is a rare acute clinical syndrome that usually occurs within a pituitary adenoma (1) and is caused by bleeding or infarction of the pituitary gland (1-3). The estimated prevalence of PA is approximately 6.2 cases per 100 000 inhabitants, and its incidence is nearly 0.17 cases per 100 000 inhabitants per year (1,2).

PA can appear at any age, being more frequent in the fifth or sixth decade of life, with a higher incidence in men (approximate ratio of 2:1) (2). It sometimes develops during pregnancy or the immediate postpartum period, resulting in ischemic necrosis of the pituitary gland (Sheehan's syndrome) (2).

Its clinical presentation is highly variable and depends on the speed of infarction or hemorrhage onset, its extent, and whether there is necrosis and edema (1,2). Headache of sudden and severe onset is usually the initial symptom, occurring in more than 80% of cases; it is typically retro-orbital and accompanied by nausea or vomiting, mimicking meningitis or migraine. In addition, more than half of patients present with visual disturbances, most commonly bitemporal hemianopia. Other manifestations include meningeal irritation, altered level of consciousness, and, less frequently, focal neurological deficits or cardiovascular collapse (1). The most dreaded consequence of PA is sudden death, presumably caused by acute adrenal insufficiency. In 70–80% of cases, infarction or necrosis of the pituitary gland results in hypopituitarism, which is usually permanent (3).

PA occurs in both healthy pituitary glands and glands affected by inflammation, infection, or tumors (2). It is most common in nonfunctioning pituitary neuroendocrine tumors and prolactinomas, although it can occur in any histological type of pituitary tumor (2). PA has been classically associated with macroadenomas, but it has also been described in patients with pituitary microadenomas (2). In this regard, hemorrhage has been reported in 10% to 22% of pituitary adenomas; however, clinical PA is only associated with 0.6-9% of pituitary tumors (3).

The cause of PA in most patients is nonspecific although it has been established that some predisposing factors include trauma, hypertension, diabetes mellitus, radiotherapy, recent surgery, thrombocytopenia, and the use of anticoagulants and dopamine agonists (4). Most PA cases in patients with adenomas have been associated with the use of bromocriptine, but there are some reports of PA after treatment with cabergoline, albeit less frequently (4).

The following case describes a patient with a macroprolactinoma receiving cabergoline therapy who developed PA and required multiple surgical procedures.

CASE PRESENTATION

A 28-year-old woman presented to the outpatient clinic in March 2024 due to amenorrhea, galactorrhea, and headache lasting two years. An outpatient hormonal profile was requested, showing severe hyperprolactinemia, with prolactin levels of 600ng/mL (reference value: <25ng/mL in non-pregnant women), with no other endocrine alterations. An outpatient computed tomography (CT) scan of the skull showed a 2.7x2.8cm sellar and suprasellar lesion compatible with a prolactin-secreting pituitary macroadenoma.

Outpatient treatment with cabergoline 1 mg orally, twice a week for three months was prescribed, and subsequent follow-up was scheduled in order to evaluate clinical response. However, the patient had poor adherence to this pharmacological treatment (non-compliance with the prescribed dosage).

Three weeks after starting treatment, the patient visited the emergency department of a quaternary care institution in Bogotá (Colombia) due to sudden-onset right hemicranial stabbing headache that did not improve with conventional outpatient treatment (acetaminophen 1 000 mg orally every 8 hours for 5 days + ibuprofen 400 mg orally every 8 hours for 4 days). Physical examination showed no meningeal signs, alterations of vital signs, or clinical data suggestive of endocranial hypertension but bitemporal hemianopsia was detected via confrontation visual field testing.

On the same day of admission, a contrast-enhanced CT scan of the skull and magnetic resonance imaging (MRI) of the brain with contrast showed a cystic lesion of approximately 3.2 cm in the sellar and suprasellar region compressing the optic chiasm and the structures adjacent to the suprasellar cistern.
MRI showed hyperintensity in the T2 FLAIR sequence, as well as peripheral enhancement after intravenous contrast administration. The lower portion of the lesion, which was intrasellar, was isointense on the T1-weighted sequence with homogeneous enhancement after contrast administration (Figure 1).
The following results were reported in the admission hormonal profile: prolactin: 300ng/mL (reference value for non-pregnant women: <25ng/mL), adrenocorticotropic hormone (ACTH): 20pg/mL (reference range: 10-60pg/mL), cortisol: 10µg/dL (reference range: 5-25µg/dL), thyroid-stimulating hormone: 2.5mIU/L (reference range: 0.5-5.0mIU/L), and free T4: 1.5ng/dL (reference range: 0.8-1.9ng/dL).

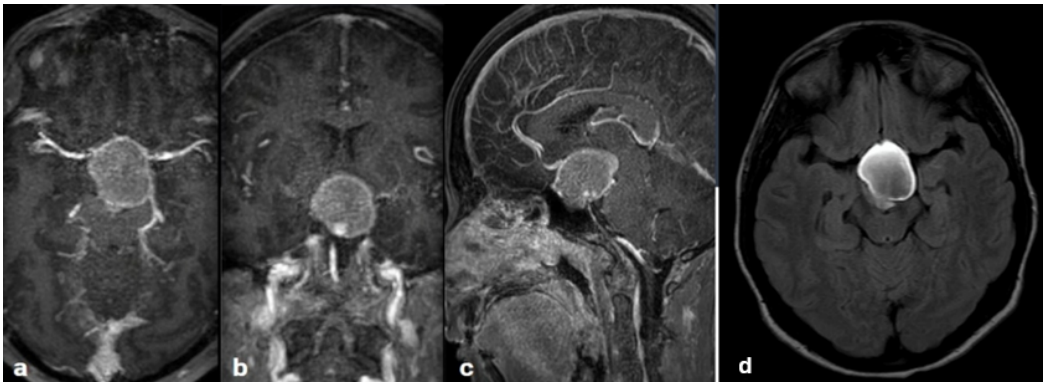

Figure 1. MRI of the brain with contrast in axial (a), coronal (b), and sagittal (c) views. A cystic lesion of approximately 3.2 cm is observed in the sellar and suprasellar region, compressing the optic chiasm and the structures adjacent to the suprasellar cistern. Axial T2 FLAIR sequence image (d) showing cystic lesion with hyperintense signal.

Source: Image obtained while conducting the study.

Considering the findings of the diagnostic studies, the patient was transferred to the ward 24 hours after her admission to the emergency department. Fifteen days after admission, while preparing for sellar lesion resection, she presented a new episode of intense headache together with anisocoria (left mydriasis) and decreased visual acuity in the left eye (vision of 20/30 in the Snellen test) associated with papilledema in the fundus, showing no changes compared to the findings previously described in confrontation visual field testing. In view of the above, the neurosurgery service decided to perform emergency endonasal endoscopic transsphenoidal surgery to decompress the optic chiasm and resect the lesion, and this surgery took place the following day.

During the surgery, a rubbery, reddish mass that was actively bleeding was partially resected. A cystic lesion with abundant hematic content was also observed in the sellar region and extending to the suprasellar region. The histopathological study confirmed a pituitary adenoma with fibrotic wall, corresponding to the tumor capsule. Immunohistochemistry was not available, so a definitive classification of the tumor subtype was not possible.

A follow-up CT scan was performed 8 hours after surgery, noting the presence of tumor residue and a partial reduction of the cystic component. Given the intraoperative evidence, the remnant was considered compatible with a hematoma secondary to PA, with probable spontaneous involution.

The patient was extubated 24 hours after the procedure, and the subsequent neurological evaluation showed isochoric and hyper-reactive pupils. In light of the above, 3 days after surgery, the ophthalmology service performed a confrontation visual field test, which showed a bitemporal defect in the visual field.

Two days after surgery, the patient presented alterations in consciousness, and laboratory tests showed low urine density and hypernatremia (sodium: 155 mEq/L). On suspicion of diabetes insipidus, a therapeutic test with desmopressin was

performed, resulting in subsequent improvement of urine output and serum sodium levels, which translated into a significant recovery of consciousness, thus confirming the diagnosis.

The follow-up hormonal profile performed three days after surgery showed suppressed ACTH (<0.5pg/mL) and cortisol (0.56µg/dL) levels, so treatment with hydrocortisone was started. During the postoperative period, 72 hours after surgery, the patient presented rhinolicuorrhea through the right nostril secondary to cerebrospinal fluid (CSF) leak, which was successfully treated with acetazolamide 250 mg orally every 8 hours and lumbar drainage for 72 hours.

On postoperative day 20, the patient presented fever (38.6°C), so a CSF analysis obtained by lumbar puncture was performed, showing hypoglycorrhachia (glucose: 2 mg/dL), pleocytosis (leukocytes: 108/mm^3), and elevated lactate (5mmol/L), findings compatible with meningitis. Although no microorganism was isolated in the CSF culture, blood cultures were positive for multidrug-resistant *Acinetobacter baumannii*. Therefore, under the guidance of the infectious disease team, empirical treatment with vancomycin 1 g intravenously every 12 hours and meropenem 2 g intravenously every 8 hours for 14 days was instituted 22 days after surgery. The patient completed antibiotic therapy with good outcomes (no new febrile peaks or signs of systemic inflammatory response) and was discharged 42 days after admission with indications for follow-up and new hormone profile 2 weeks after discharge.

Twenty days after discharge, the patient was readmitted to the emergency department of the same institution due to persistent frontal headache and blurred vision for two weeks. On the same day of readmission, a Snellen test was performed and visual acuity was found to be 20/30 in the right eye and 20/50 in the left eye. Confrontation visual field testing showed a temporal campimetry defect in the left eye, while CT scan of the brain showed a large pituitary tumor compressing the optic chiasm (Figure 2). The ophthalmology service evaluated the case 48 hours after readmission and made a diagnosis of optic neuropathy secondary to optic nerve atrophy in the fundus, probably related to damage to the visual pathway caused by the compressive effect of the tumor lesion.

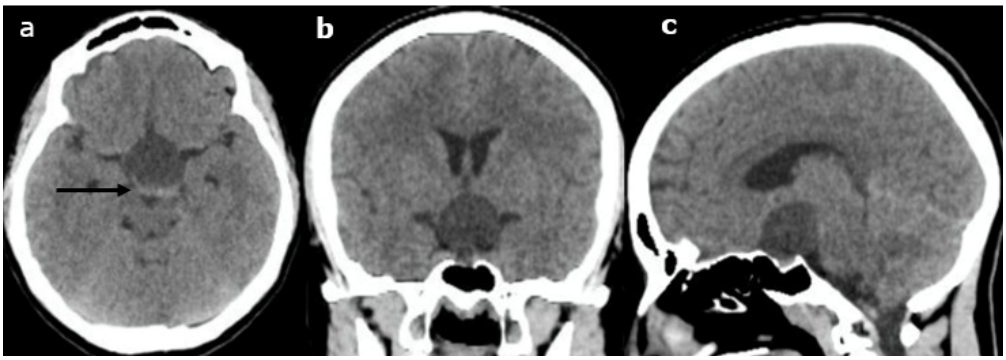

Figure 2. Computed tomography of the skull in axial (a), coronal (b) and sagittal (c) views. There is evidence of sellar mass reappearance and apparent hyperdensity that may indicate rebleeding of the lesion (arrow).

Source: Image obtained while conducting the study.

The patient was hospitalized under the care of the neurosurgery service and, taking into account the findings and the ophthalmology service analysis, it was decided to perform a second transcranial surgery 2 weeks after readmission. During the procedure, a dark encapsulated lesion was found in the interoptic cistern and in the left optico-carotid region, from which old blood material compatible with previous bleeding was drained.

Following surgery, the patient progressed satisfactorily and did not develop new visual deficits, so she was discharged 25 days after readmission with hormone supplementation with levothyroxine 50 mcg orally on an empty stomach, desmopressin 120 mcg orally every 12 hours, and fludrocortisone 0.1 mg orally every 24 hours indefinitely to treat postoperative panhypopituitarism and central diabetes insipidus.

The follow-up MRI performed 3 months after discharge showed adequate lesion shrinkage, with no tumor recurrence or associated collections (Figure 3). After 6 months of follow-up, the patient was still asymptomatic and with no further deterioration of visual acuity or visual fields. Her next follow-up is scheduled for 2026.

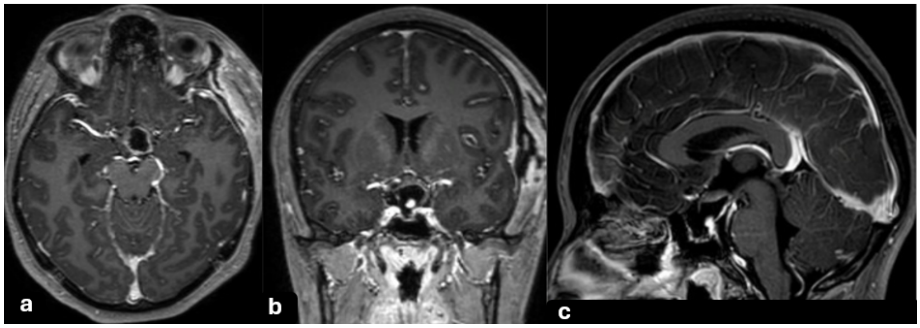

Figure 3. Postoperative magnetic resonance imaging of the brain with contrast in axial (a), coronal (b) and sagittal (c) views. There is evidence of adequate tumor resection with no apparent recurrence or associated collections.

Source: Image obtained while conducting the study.

DISCUSSION

PA is a rare syndrome occurring in 2-7% of patients with pituitary adenoma (5). Its pathophysiology has not been fully elucidated; however, it has been suggested that it involves tumor vascular occlusion secondary to tumor growth, decreased blood flow, and abnormal tumor vascularization (6).

Pituitary gland vascularization plays a crucial role in the development of PA because, compared to the surrounding glandular tissue, pituitary tumors often have reduced vascularization that increases vascular endothelial growth factor mRNA, which could be associated with abnormal vascularization (6).

It has been proposed that tumor growth and the resulting increased intrasellar pressure may cause compression of normal pituitary tissue, limiting adequate blood supply (1,2). Also, direct compression caused by the expanding tumor on the pituitary stalk may compromise blood flow within the hypophyseal portal system (1).

Dopaminergic agonists used to treat prolactinoma are a risk factor for PA; however, these drugs promote tumor regression due to lactotroph cell size reduction and degenerative and necrotic changes in tumor cells. Thus, cabergoline, just like bromocriptine, reduces the size of the prolactinoma after inducing apoptosis in the lactotroph cells. In this regard, it has been described that most patients treated with cabergoline present cystic degeneration in the prolactinoma on MRI, a finding considered a risk factor for the development of PA (4). In the present case, the MRI showed cystic degeneration of the prolactinoma associated with bleeding areas, which could be related to the effect of cabergoline on the tumor.

The literature on PA secondary to cabergoline use is scarce and restricted to case reports. For example, Chang and Dalan (4) published the case of a 20-year-old Chinese man with a prolactinoma, who developed PA six weeks after initiating treatment with cabergoline, with a satisfactory recovery and no loss of pituitary function after conservative treatment with supportive therapy. Similarly, Balarini *et al.* (7) reported the cases of three patients with cystic macroprolactinomas, who developed PA 7, 12 and 32 weeks after initiating cabergoline treatment and required lesion decompression by transsphenoidal surgery.

According to the literature, PA usually develops within pituitary adenomas (1), and there are some risk factors for its development such as high blood pressure, diabetes mellitus, major surgery, coagulation disorders, pregnancy, head trauma, radiotherapy, and use of drugs such as estrogens, somatostatin analogues, and dopamine agonists (2). In the present case, the patient had a prolactin-secreting pituitary macroadenoma that was treated with cabergoline, which may have caused the development of PA.

The clinical presentation of PA depends on the speed of infarction or bleeding onset and the volume of the hemorrhagic event (1,2). It may manifest acutely and

severely, with significant neurological deficits, coma, and even death. PA should be suspected when patients experience a sudden onset of severe retro-orbital, frontal, or suboccipital headache with a variable level of consciousness, nausea, vomiting, and cranial nerve symptoms such as diplopia, palpebral ptosis, and mydriasis (2). In our case, the predominant symptoms were headache and visual disturbances, which were the main reason of consultation.

The most common symptoms associated with PA are headache (86-89%), visual disturbances (52-78%), vomiting (40-69%), and extraocular palsy (25%) (2,8). Headache usually results from the rapid increase in intrasellar pressure caused by the hemorrhage and infarction in the pituitary gland and visual impairment; the latter, observed in 52-90% of patients, occurs due to compression of the optic chiasm exerted by the rapidly expanding mass, with manifestations ranging from visual field defects to complete blindness (8). In this case, the patient consulted due to persistent right hemicranial headache of sudden onset and during her hospital stay she developed visual disturbances.

Hypopituitarism is another frequent symptom of PA, with gonadotropin (75%), corticotropin (70%), and thyrotropin (50%) deficiencies being the most common alterations (2). Hyponatremia may occur in up to 40% of patients with PA secondary to adrenal insufficiency, central hypothyroidism, or syndrome of inappropriate secretion of antidiuretic hormone. To a lesser extent, epileptic seizures, hemiplegia, and diabetes insipidus (2) have also been reported, with the latter diagnosed in our patient.

Most patients with PA initially undergo CT scan of the skull to confirm the diagnosis; however, in recent years, MRI has become the preferred imaging modality because it identifies bleeding in up to 89% of patients, while CT detects hemorrhage in approximately 20–42% of cases (5,9). This is highly relevant as subclinical hemorrhagic episodes or episodes with minimal symptomatology have been shown to be far more frequent, occurring in up to 25% of pituitary adenomas (5). However, these tests must be time-sensitive because hemoglobin undergoes characteristic changes and blood degrades over time. Thus, blood products observed on CT are initially hyperdense (<6 hours from symptom onset), but their density progressively decreases until it approaches that of water (9).

On brain MRI, T1 hyperintensity signal usually increases between 24 and 48 hours due to the conversion of hemoglobin to intracellular methemoglobin, which lasts for 7 to 28 days, but decreases between days 14 and 28 as it becomes hemosiderin. In turn, T2 sequences demonstrate brightness in the hyperacute phase, while hypointensity persists in the acute and early subacute phases (1-7 days), becoming hyperintense with extracellular methemoglobin formation (7-28 days). During the chronic phase (>14-28 days), the T2 signal drops again as it becomes hemosiderin (9). In the present case, the patient underwent both CT and MRI on the day of admission and the results showed a cystic lesion, although

the MRI also showed hyperintensity in the T2 FLAIR sequence, as well as an isointense component in the T1 sequence with homogeneous enhancement after contrast administration, which guided the diagnosis.

ACTH deficiency is a life-threatening and frequent condition in patients with PA, in whom glucocorticoid replacement is recommended, requiring a supraphysiological dose to control edema on the parasellar structures: dexamethasone 8-16 mg per day or hydrocortisone 50 mg intravenous every 6 hours (6). In the reported case, the follow-up hormonal profile showed suppressed ACTH and cortisol levels, which led to the initiation of replacement therapy with hydrocortisone. It should be noted that thyroid hormone replacement, when necessary, should only be done after having provided glucocorticoids (8), as occurred in the present case, in which the patient, due to her hypocortisolism, initially required therapy with corticosteroids and, subsequently, levothyroxine supplementation.

PA treatment can be conservative or surgical, and its selection depends mainly on the clinical profile of the patient: patients with headache, mild or absent visual symptoms, without compromised consciousness, or with severe comorbidities that contraindicate surgical intervention, are usually considered for conservative management, while patients with significant visual symptoms, altered consciousness, or progressive neurological deterioration are candidates for surgery (10). Conservative management consists of the implementation of supportive measures such as hormone replacement therapy with glucocorticoids (11), electrolyte management, and close monitoring of visual symptoms. Surgical treatment consists of transsphenoidal resection of the lesion after stabilizing the patient's general condition (8). In the present case, the relevant visual alterations in the patient warranted surgical intervention.

According to the literature, patients presenting with visual compromise, extraocular paresis or altered consciousness should undergo early surgical decompression as soon as possible, since early surgical intervention has been shown to improve visual and, to a lesser extent, endocrine outcomes compared to conservative treatment (8,12). The patient in this case reported a sudden onset of visual symptoms, for which she underwent emergency surgery. She also experienced bleeding recurrence, requiring reintervention with favorable outcomes.

CONCLUSION

PA is a medical emergency because it can cause acute endocrine failure, severe visual impairment, and even death and it is therefore essential to establish early treatment including adequate hormone replacement and, in indicated cases, surgical intervention for sellar decompression and hematoma drainage.

Dopaminergic agonists, particularly bromocriptine, have been associated with the development of PA; however, drugs with the ability to induce cystic degeneration in prolactinoma patients, such as cabergoline, can also cause PA.

ETHICAL CONSIDERATIONS

The patient's informed consent was obtained for the preparation of this case report.

CONFLICTS OF INTEREST

None stated by the authors.

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