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CEREBROSPINAL FLUID LEAK SECONDARY TO CABERGOLINE THERAPY IN AN INVASIVE MACROPROLACTINOMA: CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Prolactinomas account for approximately 45% of pituitary tumors, and dopamine agonists are the first-line treatment. A rare but potentially serious complication of this therapy is cerebrospinal fluid (CSF) leak, resulting from rapid tumor shrinkage that exposes pre-existing bony and dural defects. We report a case of cabergoline-induced CSF leak in an invasive macroprolactinoma and review key pathophysiological and therapeutic aspects. Case report: A 39-year-old man presented with longstanding migraine-like headaches, decreased libido, and erectile dysfunction. Magnetic resonance imaging revealed an invasive macroprolactinoma (32×25×22.5 mm) involving the right cavernous sinus (Knosp 4) with pituitary stalk deviation; initial prolactin was 1325 ng/mL. Cabergoline 1 mg/week was initiated, leading to rapid clinical improvement and a marked prolactin decline. One month later, he developed continuous unilateral watery rhinorrhea, worsened by leaning forward. MRI showed tumor shrinkage with sphenoid sinus involvement. CSF leak was confirmed, and the patient underwent successful endoscopic endonasal repair. He recovered without recurrence, with sustained biochemical control and a stable residual lesion on follow-up imaging. Conclusions: dopamine agonists-induced CSF leak occurs in 5-13% of invasive macroprolactinomas, particularly in large tumors with supra- and infrasellar extension and prolactin levels >1000 ng/mL. Given the significant risk of meningitis, early clinical suspicion and prompt endoscopic surgical repair are essential. Conservative management is rarely effective.

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CEREBROSPINAL FLUID RHINORRHEA SECONDARY TO CABERGOLINE THERAPY IN AN INVASIVE MACROPROLACTINOMA: CASE REPORT AND REVIEW OF THE LITERATURE

INFO ARTÍCULO

Palabras clave:
fugas de líquido cefalorraquídeo, cabergolina, prolactinoma.

RESUMEN

Los prolactinomas representan cerca del 45% de los tumores hipofisarios y los agonistas dopaminérgicos constituyen su tratamiento de primera línea. Una complicación poco frecuente, pero potencialmente grave, es la fístula de líquido cefalorraquídeo (LCR) secundaria al rápido colapso tumoral, que expone defectos óseos y durales preexistentes. Caso clínico: Varón de 39 años con cefalea crónica, disminución de la libido y disfunción eréctil. La resonancia magnética evidenció un macroprolactinoma invasivo (32×25×22,5 mm) con compromiso del seno cavernoso derecho (Knosp 4) y desviación del tallo hipófiso; la prolactina inicial fue de 1325 ng/mL. Se inició cabergolina 1 mg/semana, con rápida mejoría clínica y caída marcada de prolactina. Un mes después presentó rinorrea acuosa unilateral, exacerbada al inclinarse. La resonancia magnética mostró reducción tumoral con ocupación del seno esfenoidal. Se confirmó fístula de LCR y se realizó reparación endoscópica endonasal con cierre exitoso. El paciente evolucionó sin complicaciones, con normalización sostenida de prolactina y lesión residual estable en controles posteriores. Conclusiones: La fístula de LCR inducida por agonistas dopaminérgicos ocurre entre el 5 y el 13% de los macroprolactinomas invasivos, especialmente en tumores grandes, con extensión supraselar e infraselar y prolactinemia >1000 ng/mL. Dado el riesgo de meningitis, la sospecha clínica y la reparación endoscópica tempranas son esenciales. El tratamiento conservador raramente resulta eficaz.

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INTRODUCTION

Prolactinomas account for approximately 45% of all pituitary tumors –and up to 60% of functioning adenomas– with an estimated prevalence of 60 to 100 cases per million population [1,2]. They are classified as microprolactinomas (<10 mm) and macroprolactinomas (>10 mm). Most lesions exhibit slow growth and are confined within the sella. While microadenomas are more common in women, macroadenomas are diagnosed more frequently in men (≈80%), in whom they typically present with mass effects such as headache and visual field defects [3]. Some degree of hypopituitarism may be observed in up to 90% macroprolactinomas, with gonadotroph deficiency being the most common, followed –in decreasing order– by thyrotroph, corticotroph, and somatotroph impairment [3,4]. In addition, these tumors may invade the cavernous sinus, sphenoid sinus, and nasopharynx, as well as erode skull base structures [4].

Dopamine agonists are the first-line treatment for most prolactinomas [5]. These include bromocriptine (introduced in 1971) and cabergoline (introduced in 1986), both widely used even in large and invasive tumors [4]. Cabergoline, a selective dopamine D2-receptor agonist, is currently the preferred agent due to its superior efficacy, lower resistance rates, better tolerability, and more convenient dosing

schedule compared with bromocriptine [6,7]. dopamine agonists therapy provides multiple benefits: normalization of prolactin levels, tumor volume reduction through shrinkage of lactotroph cells, and recovery of gonadal function, along with resolution of galactorrhea and improvement of visual impairment in most patients [8].

Cerebrospinal fluid (CSF) leak induced by dopamine agonists therapy is an uncommon but potentially serious complication, reported with both bromocriptine and cabergoline [9,10].

The aim of this report is to present a case of cabergoline-induced CSF leak during treatment of a macroprolactinoma and to provide a literature review addressing its pathogenesis and current therapeutic strategies.

CASE REPORT

A 39-year-old man with no relevant comorbidities had a history of chronic migraine-like headache –pulsatile, localized to the right hemicranium, with more than 10 years of evolution– refractory to multiple treatments and associated with significant functional impairment. He also reported decreased libido and erectile dysfunction, both progressively worsening over recent months.

Due to persistent symptoms, he was referred to neuroimaging evaluation. Sellar magnetic resonance imaging (MRI) at the time of diagnosis revealed a 32×25×22.5 mm pituitary expansile lesion with homogeneous contrast enhancement, marked suprasellar extension with compression and displacement of the optic chiasm, and invasion of the right cavernous sinus, where the mass completely encased the internal carotid artery (ICA), consistent with right-sided Knosp grade 4 and left-sided Knosp grade 1 involvement (Figure 1a). The pituitary stalk was markedly displaced toward the left.

Hormonal testing confirmed severe hyperprolactinemia (PRL 1325 ng/mL) with secondary hypogonadism (total testosterone 1.56 ng/mL, low–normal gonadotropins), with preserved thyroid and adrenal function (Table 1). With a diagnosis of invasive macroprolactinoma, cabergoline was initiated orally at 1 mg/week in a specialized Endocrinology outpatient clinic.

Table 1. Evolution of hormonal parameters over the follow-up period

Hormona	Valores de referencia	Basal (a)	Guardia (b)	Alta (c)	Seguimiento 4 meses	Seguimiento 16 meses
GH	≤2.5 ng/mL	0,07	—	—	—	—
IGF-1	109-240 ng/mL	SR	—	—	—	—
PRL	4.04-15.2 ng/mL	1325	4.26	1.63	5.31	1.75
FSH	1.5-12.4 mUI/mL	2.67	—	4.25	2.64	4.76
LH	1.7-8.6 mUI/mL	3.64	—	4.37	3.51	—
Testosterona total	2.49-10.7 ng/mL	1.56	—	3.01	—	3.02
Cortisol	6.24-18 µg/dL	15.2	—	—	—	14.1
TSH	0.27-4.2 µUI/mL	1.27	—	1.14	—	1.11
T4 libre	0.93-1.7 ng/dL	1.19	—	1.41	1.49	1.21

(a) Baseline evaluation. (b) Emergency department visit. (c) Hospital discharge. Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor 1; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; Free T4, free thyroxine.

One month later, the patient reported a marked improvement in headache. However, he presented to the emergency department with continuous watery rhinorrhea, positional in nature (worsening when bending forward). Follow-up sellar MRI showed a reduction in tumor volume (25×18×22 mm), persistent involvement of the right cavernous sinus, occupation of the right recess of the sphenoid sinus, and contact with the right optic nerve and medial temporal lobe (Figure 1b). These findings, together with the clinical presentation, were consistent with a CSF leak secondary to rapid tumor collapse induced by cabergoline.

The patient was evaluated by the Neurosurgery Department, and an endoscopic endonasal repair was performed without intraoperative complications. Subsequently, in the context of probable transient corticotroph axis impairment, oral hydrocortisone was initiated with a tapering schedule, and cabergoline was continued at a reduced dose of 0.5 mg/week.

At 6-month follow-up, MRI demonstrated a residual lesion measuring 25×15×12 mm, still invading the right cavernous sinus (Knosp grade 4), but no longer in contact with the optic nerve and with improved delineation of the remaining pituitary tissue (Figure 1c). Finally, the 2-year follow-up showed a stable, partially cystic residual lesion encasing the ICA without compromising its flow, mild sphenoidal sinusopathy, and adequate decompression of the optic chiasm (Figure 1d).

The patient remains under outpatient follow-up, asymptomatic, with no recurrence of the CSF leak, normalized PRL levels (1.75-5.31 ng/mL), recovery of the gonadal axis (testosterone 3.01-3.02 ng/mL), and preserved functional stability of the remaining pituitary axes (Table 1).

This work was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patient for publication of the case. The study was reviewed and approved by the institution's Research Ethics Committee.

DISCUSSION

The incidence of dopamine agonists–induced CSF leak in macroprolactinomas is not fully established. Although most reports consist of isolated cases or small series, some cohorts suggest a frequency between 5% and 8.7-13.3% in patients treated with dopamine agonists [3,9]. This variability reflects both the rarity of the event and differences in tumor characteristics across published cohorts.

The most widely accepted pathophysiological mechanism is the so-called *"uncorking effect"* [4,11]. dopamine agonists -particularly cabergoline- can induce rapid and substantial tumor shrinkage, thereby exposing areas of the skull base previously eroded by the tumor's expansile growth. Invasive prolactinomas often extend preferentially into the infrasellar region, eroding the sphenoid bone and creating bony and dural defects that, once unprotected following tumor collapse, allow communication between the subarachnoid space and the nasosinusal cavities.

The chronology of the CSF leak is variable: it may occur early (within weeks, with an average of 45 days) or late, presenting even months or years after treatment, underscoring the need for long-term follow-up.

Several factors have been associated with an increased risk of developing this complication [12]:

- **Tumor size:** complicated adenomas tend to be significantly larger (43±12 mm vs. 25±12 mm).
- **Tumor extension:** the combination of suprasellar and infrasellar extension increases risk.
- **Severe hyperprolactinemia:** baseline levels >1000 ng/mL have been consistently associated with complicated cases.
- **Radiological invasion:** involvement of the cavernous sinus and sphenoid sinus, as well as bony erosion detected on computed tomography (CT), constitute important predictors.

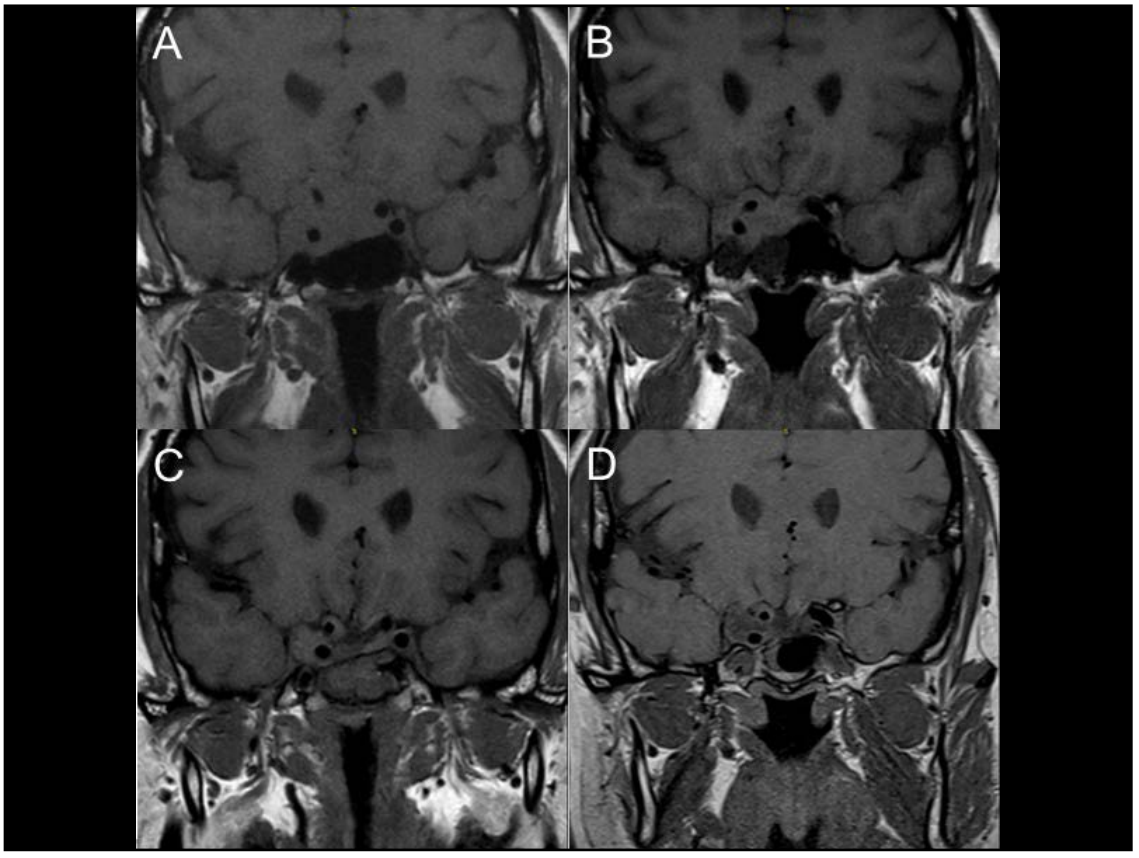

Figure 1. Radiological evolution on sellar MRI (T1 with gadolinium) of an invasive macroprolactinoma under cabergoline treatment.

A) Baseline. Large expansile lesion of the adenohypophysis (32×25×22.5 mm; transverse, craniocaudal, and anteroposterior axes) with homogeneous post-contrast enhancement. It extends into the suprasellar cistern, causing displacement and compression of the optic chiasm. On the right, it completely encases the internal carotid artery and occupies the cavernous sinus, with minimal extension into the temporal fossa. On the left, it does not cross the intercarotid line (right Knosp grade 4, left Knosp grade 1). The pituitary stalk is markedly deviated to the left. **B)** Emergency department visit (≈1 month of treatment). Irregular lesion measuring 25 × 18 × 22 mm with post-contrast enhancement, located in the right portion of the adenohypophysis. Persistent invasion of the right cavernous sinus with encasement of the internal carotid artery and contact with the right optic nerve and medial temporal lobe. Residual left-sided pituitary tissue is visible, along with persistent stalk deviation. Occupation of the right recess of the sphenoid sinus is noted. **C)** Hospital discharge (≈3 months of follow-up). Residual lesion measuring 25×15×12 mm with post-contrast enhancement, still invading the right cavernous sinus and encasing the internal carotid artery (Knosp grade 4), now without contact with the optic nerve. The pituitary stalk remains deviated to the left. Mild sphenoidal sinusopathy is observed. **D)** Sixteen-month follow-up. Residual lesion involving the right cavernous sinus, hypointense on T1 and hyperintense on T2, compatible with a cystic component, encasing the internal carotid artery without altering flow signal. The pituitary stalk remains deviated to the left. Mild sphenoidal sinusopathy persists, with patent suprasellar cisterns and cavernous sinuses of normal appearance. The hypothalamic–chiasmatic region appears mildly retracted caudally, without significant chiasmal compression.

Other proposed factors include male sex –potentially associated with later diagnosis and more aggressive tumors– primary or secondary resistance to dopamine agonists, markers of increased tumor proliferation, and a rapid decline in prolactin levels after treatment initiation [3,4].

A CSF leak carries a high risk of ascending meningitis (~20%), particularly due to *Streptococcus pneumoniae* and *Haemophilus*

influenzae [13,14]. A significant clinical challenge is underdiagnosis, as a watery nasal discharge may be mistaken for allergic or vasomotor rhinitis. The presence of unilateral clear nasal drainage that worsens when bending forward, or a salty taste in the oropharynx, in a patient receiving dopamine agonists therapy should alert the clinician. Confirmation requires analysis of the nasal fluid: β2-transferrin or a CSF glucose level >30 mg/dL are reliable markers.

Optimal management remains a matter of debate. Conservative treatment, including temporary discontinuation of dopamine agonists therapy, may be considered in selected cases but is rarely successful [15]. Because of the significant risk of meningitis, most authors recommend early surgical repair of the dural defect. Endoscopic transnasal–transsphenoidal surgery is the preferred approach, offering high success rates and low recurrence. One review reported that 49 of 60 patients with dopamine agonists-induced CSF leak required surgery, whereas conservative management was successful in only 4 of 52 cases [16]. Reconstruction typically involves autologous grafts, fascia lata, fibrin glue, or nasoseptal flaps, and lumbar drainage is frequently used to prevent recurrence [17].

There is ongoing debate regarding partial tumor resection performed simultaneously with CSF leak repair. Some authors suggest avoiding it, as continued medical therapy may achieve greater tumor shrinkage than surgery at this stage [18].

Taken together, invasive macroprolactinomas treated with dopamine agonists require close monitoring, particularly during the first months, when tumor shrinkage is most pronounced. Early recognition of a CSF leak is crucial to reduce the risk of meningitis and improve outcomes. The present case highlights the importance of patient education, rigorous clinical follow-up, and early surgical intervention –cornerstones of the safe management of this uncommon but potentially serious complication.

CONCLUSION

Dopamine agonists therapy is highly effective for invasive macroprolactinomas; however, it may be associated with CSF leak induced by rapid tumor collapse – an uncommon but potentially serious complication. This event reflects the typical pattern of invasion and bony erosion observed in some prolactinomas. Patients with large tumors, combined suprasellar and infrasellar extension, and baseline prolactin levels >1000 ng/mL should be considered high risk and require close clinical monitoring. Although management may range from observation to surgery, once a CSF leak is confirmed, early transnasal–transsphenoidal endoscopic repair is the recommended strategy to reduce the substantial risk of meningitis and optimize clinical outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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Author contributions

Melina Masiero, Mariela Savina, and Carlos Javier Herrera performed the literature search and drafted the initial manuscript. Pablo Ferrada critically reviewed the initial manuscript and developed the final version of the manuscript.

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