Medical Science

When does prolactinoma require neurosurgical intervention?

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ABSTRACT

Patients with macroprolactinoma (MPRL) resistant to dopamine agonists and its rare complications, such as CSF rhinorrhea is rarely seen by physicians. This report presents a clinical case of a 51-year-old female with MPRL complicated by CSF leakage. She had been experiencing visual impairment and headaches for six months. The diagnosis of MPRL was made based on serum prolactin level and MRI images. After three months of cabergoline treatment, a follow-up MRI scan revealed tumor shrinkage. However, the patient developed CSF rhinorrhea, a severe complication requiring urgent surgical intervention. The main objective of the article is to discuss risk factors, diagnostic approaches, and therapeutic management of CSF rhinorrhea.

Keywords: CSF Rhinorrhea, Dopamine Agonist, Macroprolactinoma, Sellar Floor Erosion

1. INTRODUCTION

Macroprolactinoma (MPRL) is a rare tumor of the anterior lobe of the pituitary gland with a size over 10 mm, that secretes prolactin. The most common symptoms of hyperprolactinemia include amenorrhea, irregular menstruation, galactorrhea, gynecomastia, male infertility, erectile dysfunction and low libido. Moreover, patients with pituitary tumor-associated hyperprolactinemia may experience mass-effect symptoms such as vision disturbances, behavioral changes, and headaches (Auriemma et al., 2023). MPRL can also cause erosion of the sella turcica and invasion into the sphenoid sinus (Česák et al., 2018).

A serum prolactin level exceeding 500 ng/ml strongly suggests the presence of MPRL (Majumdar and Mangal, 2013). Cabergoline is the first-line treatment for MPRL, effectively reducing prolactin levels in up to 95% of patients (Paepegaey et al., 2017).

Studies indicate that dopamine agonist (DA) resistance occurs in 25.8% to 29% of MPRL cases (Kim et al., 2021). DA resistance is generally defined as the failure to achieve normalized prolactin levels or a reduction of at least 50% in tumor size (Gillam et al., 2006).

Risk factors include male gender, young age, invasion of the cavernous or sphenoid sinus (visible on CT/MRI), pituitary insufficiency, hemorrhagic, cystic, and necrotic tumor components, as well as genetic predispositions (Kim et al., 2021). DA resistance is significantly more frequent in patients with MPRL and CSF rhinorrhea than those without (30% vs. 5%) (Suliman et al., 2007). The mortality rate associated with DA resistance is up to 4.3%, primarily due to pituitary carcinomas and neurological complications from rapid tumor growth (Vroonen et al., 2012).

2. CASE PRESENTATION

A 51-year-old female veterinarian with a diagnosed pituitary tumor measuring 36×34×24 mm visited an endocrinology clinic. She had been experiencing visual disturbances and headaches for six months. Her blood prolactin level was 4,211 ng/ml (Table 1, Graph 1). She was diagnosed with MPRL and started on cabergoline with a gradually increasing dosage. The final dose was 1.5 mg per week. The patient reported improved vision, and her prolactin levels decreased to 138 ng/ml (Table 1, Graph 1).

After three months of treatment, a follow-up MRI revealed tumor size reduction. However, two weeks later, the patient developed CSF rhinorrhea. She had no history of head trauma and exhibited no symptoms of active infection. Upon hospital admission, CT and MRI scans were performed. The CT scan detected metallic material in the maxillary sinus, while MRI revealed erosion of the sellar floor and tumor invasion into the sphenoid sinus. At this stage, her prolactin level had further decreased to 22.8 ng/ml (Table 1, Graph 1).

The patient underwent partial endoscopic transsphenoidal tumor resection with skull base reconstruction. The multilayer reconstruction involved Duragen, a mucosal flap harvested from the nasal septum, and an additional Duragen layer. The cavernous sinus was packed with Spongostan. The surgeon also removed masses covering dental material in the maxillary sinus.

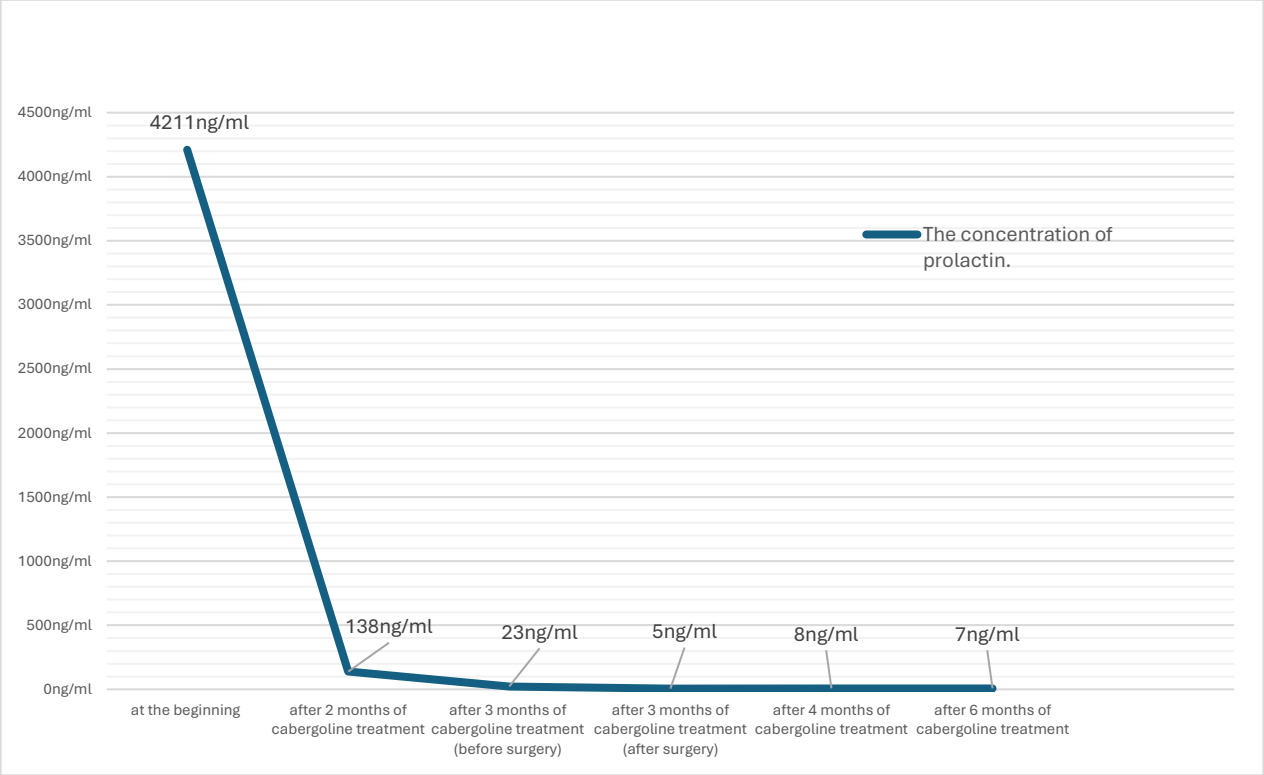
Pathological examination confirmed pituitary adenoma and revealed numerous colonies of fungi with morphology consistent with Aspergillus. Immunohistochemical staining for ACTH, FSH, LH, GH, PRL, and TSH confirmed prolactin-secreting adenoma with low proliferative activity (Ki-67 <1%).

The patient was discharged five days post-surgery and referred for endocrinological follow-up. However, one week later, she was readmitted due to adrenal insufficiency, experiencing severe headaches, poor appetite, and nausea. Lab tests revealed hyponatremia (128 mmol/L) and hyperkalemia (7.96 mmol/L). Blood cortisol levels had dropped from 17 μg/dL to 9.79 μg/dL. Hydrocortisone supplementation resolved her symptoms and normalized her lab parameters.

At three-month follow-up, prolactin levels normalized, and MRI showed a tumor size of 25×33×24 mm (Figure 1). A subsequent MRI four months later revealed no significant further tumor size reduction (Figure 2).

Table 1 Changes in prolactin level due to cabergoline treatment.

Time since the initiation of cabergoline treatment.	The concentration of prolactin. norm: (4,79-23,3 ng/ml)
at the beginning	4211 ng/ml
after 2 months	138 ng/ml
after 3 months (before surgery)	22,8 ng/ml
after 3 months (after surgery)	5,48 ng/ml
after 4 months	7.55 ng/ml
after 6 months	7.4 ng/ml



Graph 1 Changes in prolactin level due to cabergoline treatment.

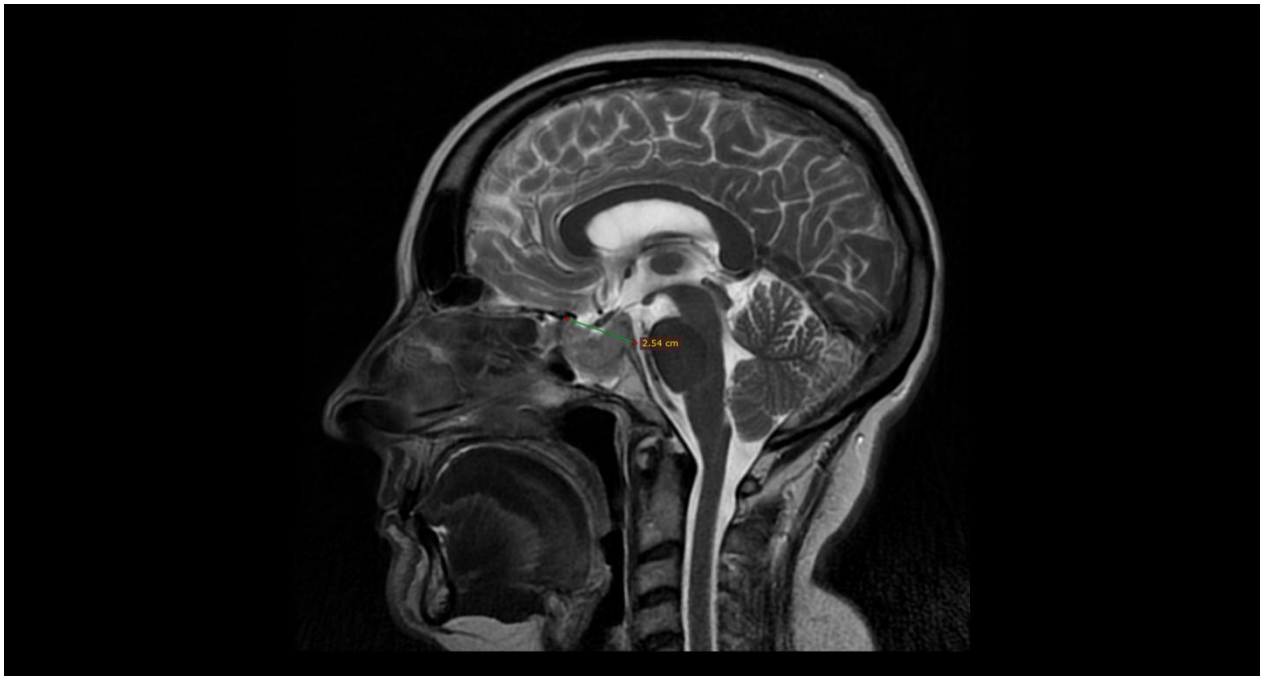


Figure 1 MRI showed a tumor size of 25×33×24 mm

Figure 2 MRI four months after with no significant further tumor size reduction

3. DISCUSSION

Our patient developed CSF rhinorrhea after cabergoline treatment for MPRL. What made her case atypical was her age, gender, and absence of pituitary insufficiency. Cabergoline effectively normalized prolactin levels and improved visual disturbances, meaning she does not meet the criteria for DA resistance. CSF rhinorrhea is a severe complication of pharmacological MPRL treatment, requiring urgent surgical intervention. If untreated, the mortality rate can reach 50% (Suliman et al., 2007). Research suggests that CSF rhinorrhea typically occurs within one and a half to four months after DA initiation (Arimappamagan et al., 2019). Reducing or discontinuing DA is not recommended because most patients still require surgical intervention, and due to DA's long half-life, stopping the medication does not provide immediate benefits (Lam et al., 2012).

Some authors suggest that skull base erosion in MPRL, followed by tumor size reduction due to DA treatment, creates a pathway for CSF to leak (Singh et al., 2011). This explanation aligns with our case, where MRI demonstrated significant tumor shrinkage after three months of therapy. Additionally, a CISS sequence MRI performed three days after the onset of CSF rhinorrhea showed a CSF signal along the medial wall of the ethmoid sinus, below the olfactory bulb.

4. CONCLUSIONS

Patients suffering from MPRL with CT/MRI-confirmed skull base invasion should be closely monitored and receive appropriate guidance. Clear nasal fluid discharge is a critical warning sign, as it may be challenging to differentiate between CSF leakage and a common cold, leading to delayed diagnosis. The clinical approach to distinguish CSF rhinorrhea from nasal discharge is to check glucose levels in the fluids. However, during clinical assessment, it is crucial to consider conditions that may lower CSF glucose levels, such as purulent or tuberculous meningitis.

Authors' Contributions

Conceptualization, M.B and P.K.; Methodology, J.B.K., M.L.; Software, P.K.; Validation, M.L., A.Z. and M.B.; Formal Analysis, A.B, J.B.K, A.M., K.H.; Investigation, P.K., M.B.; Resources, K.H., M.B.; Data Curation, P.K., K.S., K.H.; Writing – Original Draft Preparation, A.B., M.L., A.M., K.S. and A.Z.; Writing – Review & Editing, M.K., M.W., P.K., K.H. and J.B.K.; Supervision, A.B., A.M.; Project Administration, A.B., J.B.K., A.Z., M.L., A.Z., K.S., M.K., A.M., K.H, M.B.

Informed consent

Written & Oral informed consent was obtained from individual participant included in the study.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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