

## Giant Prolactinoma Complicated by Cerebrospinal Fluid Rhinorrhea, Behavioral and Neurological Changes Following Dopamine Agonist Therapy: A Case Report

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### Abstract

**Introduction:** Giant prolactinomas, defined as pituitary PRL-secreting adenomas whose size exceeds 40 mm and with a PRL level of >1000 ng/ml, are very rare. Their treatment and outcome can be unpredictable and challenging for clinicians.

**Case Report:** A 47-year-old male was referred to the Neuroendocrine Department due to a large pituitary tumor invading the suprasellar region, both cavernous and sphenoidal sinuses, and pharyngeal space. He had been suffering from intensive headaches and visual deterioration for two years; he had also experienced sexual dysfunction.

**Discussion:** We detected extremely high serum PRL levels (>700000 mU/l) and hypopituitarism. Bromocriptine therapy (BRC) was started with a gradual dose increase. Ten days after the commencement of medical treatment, cerebrospinal fluid (CSF) rhinorrhea appeared. He underwent neurosurgery two months later; the bone erosion was localized and repaired. Tumor biopsy revealed a PRL-secreting tumor with a low proliferative index (Ki67<0.5). After surgery, he continued with BRC and shortly after experienced behavior changes, such as mood oscillations, anxiety, impulsivity, irritability, impaired concentration, and tremor. To control his tumor, pramipexol and levodopa treatment were introduced but with a moderate effect. However, only after the reduction of the BRC dose, his mental and neurological complaints abated significantly. A close follow-up for the next three years detected a low prolactin level and significant tumor shrinkage (MRI), with visual field improvement and reversion of pituitary function.

**Conclusion:** Giant prolactinomas are invasive but respond well to dopamine agonists. However, CSF rhinorrhea, behavioral and neurological changes can occur during medical treatment, suggesting a need for vigilance throughout the dopamine agonist therapy.

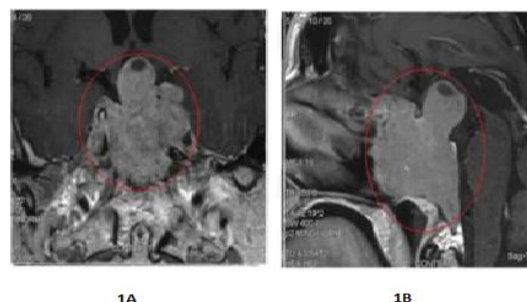
**Keywords:** Giant prolactinoma; Dopamine agonist; CSF rhinorrhea; Behavioral and neurological changes

### Introduction

A 47-year-old male was referred to the Neuroendocrine Department for hormonal evaluation because of a large pituitary tumor with propagation in the suprasellar region, both cavernous and sphenoidal sinuses, and infiltration of pharyngeal space (Figures 1A and 1B). He had been suffering from intensive headaches, visual deterioration, sexual dysfunction, and ataxia for two years prior to treatment. Bitemporal hemianopsia was diagnosed, suggestive of optic chiasm compression. Hormonal evaluation showed extremely high serum PRL levels of 706210 mU/l, with low testosterone, cortisol, and thyroxine levels; his IGF1 was slightly increased (Table 1). Treatment was commenced with bromocriptine, 1.25 mg once daily with a gradual dose increase and extremely good drug tolerance. However, ten days later, at a bromocriptine dose of 7.5 mg, the patient suffered from a leaking clear fluid from his nose. He approached his neurosurgeon, who diagnosed CSF rhinorrhea and advised him to wait for a possibly spontaneous cessation of leaks. Since that did not happen, the patient underwent neurosurgery two months after starting his medical therapy, when the bromocriptine dose was 15mg. The preoperative prolactin level was 129 mU/l.

### Case Report

The endoscopic trans nasal exploration of the anterior skull base and sphenoid sinus was performed; bone defect was detected and sealed



**Figures 1:** Coronal (A) and sagittal (B) MRI T1-weighted sequence at presentation, before Bromocriptine therapy. A giant intrasellar pituitary tumor (labeled in the figure by a red circle) with propagation in the suprasellar region, invasion of both cavernous and sphenoidal sinuses, and infiltration of pharyngeal space.

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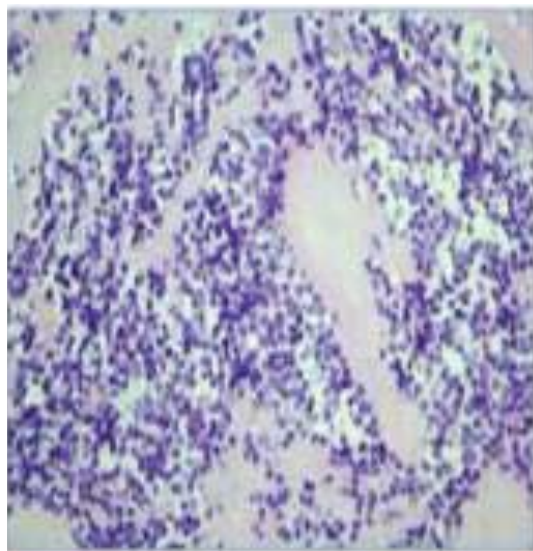
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with a fat graft, fascia lata and Beriplast. The tumor was biopsied, and histopathology revealed a PRL-secreting tumor (Figure 2A) with a low proliferative index (Ki67 <0.5). A few days after surgery, our patient continued with the bromocriptine therapy. Shortly after, he started with psychiatric symptoms, such as mood oscillations, anxiety, impulsivity, apathy and irritability, verbal aggressiveness against his wife, impaired concentration, forgetfulness, and lack of energy (Figure 2B). Furthermore, he manifested a hand tremor; items were falling out of his hands. Initially, his behavioral changes were ascribed to the patient's knowledge about the presence of a tumor and the need for long-term treatment. There were no mental disturbances in his previous medical history. His psychiatrist tried treatment with antidepressants, which resulted in discrete clinical improvement. Then, dopamine agonists, levodopa and pramipexol, were added to control the hand tremor.

The diagnosis of idiopathic parkinsonism was excluded. Nevertheless, the patient's complaints persisted, but were less expressed. However, when the bromocriptine dose was decreased from 15.0 to 7.5 mg, his mental and neurological complaints abated significantly. Significant restoration of his psychiatric status was achieved, and the hand trembling almost completely disappeared. Close follow-up every 3-6 months for the next 3 years, with a maintenance dose of 7.5 mg of bromocriptine, demonstrated a low prolactin level. Remarkable tumor shrinkage was detected in the first year of medical therapy, with a reduction in tumor size of 70 to 35 mm in diameter (Figures 3A and 3B), but with no further noticeable changes on the MRI. Following the bromocriptine treatment, his visual field was normalized, the pituitary function was completely reverted, and his body weight decreased by 12 kg.

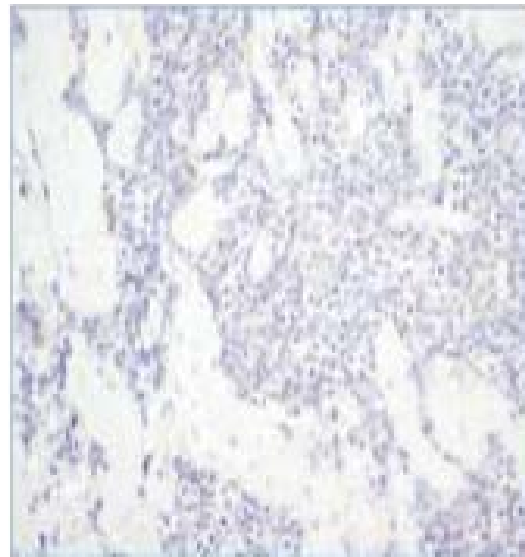
Hormone	Before DA	10 days DA (Brc7.5 mg)	2 months DA (Brc 15 mg)	3 months DA (Brc 15 mg)	3 yrs DA (Brc 7.5 mg)
		CSF leaking started	Presented hormonal analyses taken at Neurosurgery day	Psychiatric and neurological changes started Presented hormonal analyses taken after one year of DA (Brc 15 mg)	Improvement of mental and neurological status
PRL (100-414 mU/l)	706 210	--	129	88	52
Testosterone (2.8-8.0 ng/ml)	9,4	--	17.8	18.1	20
Cortisol (131-642 nmol/l)	203	--	368	392	475
FT4 (7-18 ng/ml)	5.9	--	8.6	9.8	12.8
TSH (0.3-5.5 mU/l)	0.6	--	1.9	2.0	1.4
IGF 1 (94-252 ng/ml)	312	--	250	--	192
MRI	Giant pituitary tumor	--	Moderate tumor shrinkage	--	Significant tumor shrinkage

**Table 1:** Hormonal evaluation and cranial MRI (Magnetic Resonance Imaging) following treatment with dopamine agonist (DA) – Bromocriptine.



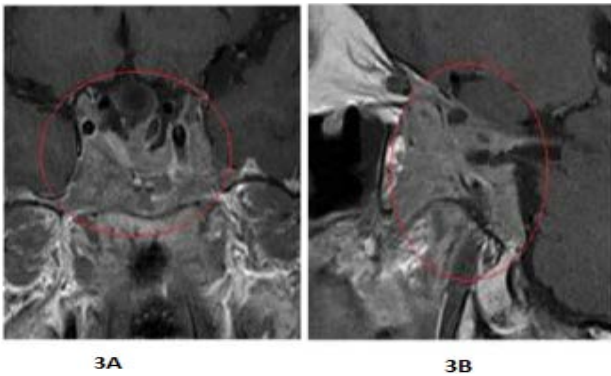
**2A**

**Figure 2A:** Hematoxylin and eosin staining. Tumor consisted of small cells, focally clear lined with scant pale pink cytoplasm and round dark nuclei, sometimes with obvious nucleolus. Tumor tissue is permeated by a wide stripe of interstitial fibrosis. Blood vessels showed thickened, hyalinized walls. Slightly smaller calcification is observed in tumor tissue. Mitosis are rare, necrosis is not perceived (HE, 40x).



**2B**

**Figure 2B:** Immunohistochemical staining. Tumor cells are positive for CK8 (diffuse, intense in perinuclear zone) and PRL (focal, intense in the Golgi zone (PRL, 40x)). Ki-67 proliferative index is less than 0.5%. Tumour cell nuclei are p53-negative. Based on the morphological and immunohistochemical findings, the tumour represents prolactinoma which has been treated with the dopamine agonist.



**Figures 3:** Coronal (A) and sagittal (B) MRI T1-weighted sequence detected significant tumour shrinkage (labelled in the figure by a red circle) following Bromocriptine therapy.

## Discussion

Giant prolactinomas (gPRLoma) are rare pituitary tumors; they account for less than 0.5% of pituitary tumors [1,2]. Unlike non-giant prolactinomas, these kinds of PRL-secreting tumors are more common in males with a male-to-female ratio of 9:1. The mean age at their diagnosis is around 40 years. This type of tumor is characterized by a size of >40 mm and a PRL level of >1000 ng/ml. Shimon et al. reported a series of 18 very rare subclasses of giant macroprolactinoma, which are larger than 60 mm in maximal diameter and are characterized by aggressive behavior and invasiveness with severe extrasellar extension [3]. The presented patient belongs to this group of patients because he had a prolactinoma 70 mm in diameter, which was invading the surrounding structures and secreting a significant amount of PRL (over 700000 mU/l). Besides the usual signs and symptoms characteristic for this type of tumor (visual field defect, headache, and hypogonadisms), atypical manifestations, such as nasopharyngeal obstruction, unilateral exophthalmus, psychosis, seizures, ataxia, and nerve palsies have been reported. The presence of hypopituitarism is observed in about one third of patients with gPRLoma [4]. Initially, our patient manifested a deficiency in testosterone, cortisol, and thyroxine, while IGF1 was slightly increased. Treatment with dopamine agonists (DAs) resulted in complete recovery of his pituitary function. Scarce data about the degree of recovery of the pituitary axes in patients with macroprolactinoma have shown that the pituitary dysfunction is mostly irreversible in response to DAs, except for hypogonadism that showed restoration [5]. Due to the rarity of gPRLoma, information regarding their management is very limited in literature. Despite their enormous size and the immense production of PRL, these tumors are highly responsive to DA treatment [6]. Maiter and Delgrange summarized the efficacy of primary treatment with DAs in 13 different cohorts of patients with gPRLoma, including 140 subjects; they detected PRL normalization in 60% of the treated patients and tumor shrinkage in 74% of the subjects [4].

A recent study evaluated 47 patients with gPRLoma and demonstrated the normalization of PRL levels in 68% and the reduction of >50% in tumor volume in 87% of them, following cabergoline treatment [7]. Neurosurgery should be reserved for acute complications, such as apoplexy or leakage of cerebrospinal fluid, or for patients with DA resistance or intolerance. Patients with aggressive and invasive gPRLoma, which are not controlled despite combined medical and surgical treatments, can be candidates for irradiation and temozolomide therapies. The treatment of patients suffering

from gPRLoma requires a multidisciplinary approach and should be individualized [8,9]. Currently, bromocriptine is not used as frequently as cabergoline, mainly due to a higher incidence of drug intolerance. We treated the presented patient with bromocriptine because of good response, good tolerance, and because our healthcare does not cover the expenses of cabergoline treatment.

In some cases, the beneficial effect of DAs on tumor shrinkage can be complicated by the CSF rhinorrhea, which is a life-threatening circumstance that can lead to meningitis and pneumocephalus [10]. Prolactinomas of a large diameter are especially prone to this rare complication due to rapid shrinkage of the tumor. It is emphasized that dopamine agonist-induced CSF rhinorrhea is a consequence of fistula that arise because of bone erosion of the sellar floor and anterior skull base. Our patient developed a CSF leak ten day after commencing with the bromocriptine therapy. His giant prolactinoma showed high sensitivity to DAs regarding the rapid decline of PRL level. This is in accordance with literature data stating that this rare complication occurs usually within 4 months after introducing dopamine agonist. Leakage can occur, even because of minimal tumor shrinkage, within days of the commencement of treatment [11]. However, in some reports CSF rhinorrhea occurred even 13 months after the initiation of cabergoline [12]. The longest reported period of onset CSF leaks after starting medical therapy is 17 months [13]. It is hypothesized that a rapid decrease in serum PRL may predict CSF rhinorrhea [14]. The risk of developing a CSF leak might be even greater with cabergoline than with other DAs, because of the high sensitivity of prolactinomas to cabergoline [11]. However, some authors have reported that CSF rhinorrhea is more common in patients with invasive macroprolactinoma resistant to DAs [15]. The incidence of CSF rhinorrhea in prolactinoma is not well documented; most information about this rare phenomenon is based on single case reports and small series. Suliman et al. analyzed 114 patients with macroprolactinoma and detected dopamine agonist-induced CSF rhinorrhea in 6.1% of them [14]. Wu et al. investigated a ten-year clinical outcome of invasive giant prolactinoma in 25 patients, of whom 16 primarily received bromocriptine. Over the course of this medical administration, cerebrospinal fluid leakage occurred in one patient, who subsequently underwent transsphenoidal surgery to have it repaired [10]. Most of studies suggest surgery as soon as is feasible to be the treatment of choice for repairing a CSF leak following DA treatment. Some authors advise the withdrawal of DAs to allow tumor re-growth to stop the leak [16]. Rare cases have been reported describing a spontaneous cessation of the leakage on continued bromocriptine therapy [17].

Patients with hyperprolactinemia frequently experience various mood and quality of life changes and mental symptoms [18]. Acting on the nervous system, hyperprolactinemia induces changes in behavior, emotions, and feelings. These symptoms often remit after the normalization of the prolactin level [19]. A study that compared 32 patients with hyperprolactinemia and 15 individuals with normal prolactin levels found higher rates of anxiety of 24% and depression of 20% in the hyperprolactinemic patients [20]. In addition to hyperprolactinemia, an enormous gPRLoma can be presented with psychiatric disturbances because of the compressive effects. Bukowcan et al. have reported impairment of cognitive function in giant prolactinoma and successful restoration after tumor involution with medical therapy [21]. However, some mental disorders have been considered as side effects of DA therapy, though few have been discussed in literature. In addition to the well-known side effects of bromocriptine and those less likely of cabergoline, such as nausea, vomiting, dizziness, headache, and postural hypotension, the adverse



effects of DAs include increased anxious and depressive feelings and psychiatric symptoms like nightmares, hallucinations, psychosis, and insomnia. Multiple aspects of quality of life are impaired in female patients with macroprolactinoma after several years of successful treatment with DAs, when compared with control subjects [22]. These patients noticed more anxiety and depression, reduced motivation, fatigue, and decreased emotional reaction. The study demonstrated that neither dopamine agonist therapy, nor the duration of dopamine agonist use, nor the present prolactin levels have any influence on patient's well-being. Serious mental disturbances, such as impulse control disorders (ICD), which involve pathological gambling, compulsive shopping or eating, and hypersexuality have been reported with DA treatment [23]. Some reports suggest a prevalence of 10% of ICD among patients with prolactinoma treated with DAs [24]. The mechanism of developing ICD seems to be an interaction between the dopamine agonists and the D3 receptors in the mesolimbic system, which is responsible for the stimulation of the dopaminergic reward systems, leading to pleasurable activities and compulsive behavior [25]. In serious cases, cabergoline can induce a mania with potential psychotic features [26].

Literature data about the neurological side effects of DAs following treatment of prolactinoma are also sparse. Dyskinesia is occasionally reported; it is assumed to be mediated via D2 receptors with effects on the extrapyramidal motor system [27]. Typically, these adverse effects are dose dependent and will usually abate by switching to a different DA. The described problems have been reported mainly in neurological patients suffering from Parkinson's disease. The reason for this is the treatment with high doses of DAs, particularly with a highly specific D3 agonist - pramipexol. However, cabergoline and bromocriptine, which are typically used in the management of prolactinomas, are less selective for dopamine receptors but may also be responsible for problems regarding behavior changes [28]. Our patient developed behavioral changes and neurological symptoms approximately three months after the introduction of bromocriptine therapy, when low PRL levels were achieved and the tumor shrank. Thereby, we excluded high PRL levels and compressive tumor effect as possible reasons for mental changes in the presented case. The introduction of antidepressants, levodopa and pramipexol, moderately alleviated the tremor and psychiatric complaints. However, only the reduction of the bromocriptine dose resulted in a significant improvement of the patient's mental status and almost the complete disappearance of hand tremors. So, we consider the bromocriptine treatment to have been related to his mental and neurological complaints.

## Conclusion

We presented a patient with a rare tumor subpopulation of giant prolactinoma with a maximal diameter larger than 60 mm. While excellent responsiveness to bromocriptine therapy has been achieved regarding dramatic reduction of prolactin levels and tumor size, our patient experienced rare adverse effects of dopamine agonist therapy - CSF rhinorrhea, behavioral changes, and neurological disturbances. The described case suggests a need for vigilance throughout therapy with dopamine agonists in the treatment of prolactinoma.

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