Giant Prolactinoma presenting with facial nerve palsy and hemiparesis

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Reprint request to be sent to corresponding author.

No grants associated with the work.

No disclosures.

Declarations

No acknowledgements.

No funding to declare.

No conflict of interest.

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

AS wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript and any revised version.

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.
Abstract

**Background:** Giant prolactinomas are an exceedingly uncommon type of pituitary adenomas that usually occur in men, cause extremely high prolactin levels and mass related symptoms. Rarely, patients may experience neurological deficits resembling ischemic events.

**Methods:** We describe an unusual case of a young man who presented with stroke-like symptoms and was found to have a giant prolactinoma.

**Clinical Case:** 25-year-old man presented with the left facial droop and gradually progressing upper and lower extremity weakness for evaluation of stroke. He reported recent weight gain and erectile dysfunction. Physical exam revealed left homonymous hemianopsia, left VII nerve palsy, and left hemiparesis. MRI of the brain showed an enormous mass in the sella turcica, which invaded the sphenoid sinus and right side of the skull base. Prolactin level was elevated at 13580 ng/mL, and the testosterone level was low. The patient was started on cabergoline and had marked improvement in his symptoms in a few months. Fifteen months after starting treatment, he has had more than 90% reduction in tumor volume and a 93% reduction in prolactin level.

**Conclusion:** Giant prolactinomas are uncommon and present with compressive symptoms that can be mistaken for a stroke. Our case is a unique report of a facial nerve palsy and hemiparesis secondary to giant prolactinoma in the absence of stroke or pituitary apoplexy.

**Keywords:** Giant Prolactinoma, facial palsy, hyperprolactinemia, hemiparesis
Introduction

Lactotroph adenomas are the most common pituitary adenomas and can cause infertility and menstrual irregularities in women; hypogonadism and gynecomastia in men [1-3]. Most prolactinomas are described as microadenomas with a diameter of less than 10 mm and are more prevalent in women [1]. Giant prolactinomas (GPs) are a subset of pituitary macroadenomas with limited literature on their management. Giant prolactinoma (GP) occur more commonly in men, and, by definition, grow to more than 4 cm in diameter and produce prolactin levels above 1000 ng/ml [4].

Symptoms from GP are usually due to mass effect on surrounding tissue and significant elevation in prolactin, causing hypogonadotropic hypogonadism. Dopamine agonists (bromocriptine and cabergoline) are considered first-line therapy in GP treatment; however, a surgical approach may be necessary if the tumor continues to cause mass effect and impending visual threat [5-6]. Although palsies of cranial nerves III-VI have been reported, facial nerve palsy and hemiparesis are relatively unique presentations [4].

We describe an unusual case of a young man who presented with symptoms of motor weakness in the upper and lower extremities with concern for stroke, who on evaluation was noted to have a large multi-lobular mass in the region of the right cavernous sinus. He was subsequently diagnosed with a giant prolactinoma based on an elevated prolactin level. He was started on medical therapy with cabergoline with complete resolution of the motor deficits over the next few months.
Case description

A 25-year-old previously healthy, dominant left-hand man presented to the walk-in clinic for an evaluation of stroke with longstanding left-sided facial asymmetry, and new weakness of the left arm and leg.

His symptoms started several months prior to the presentation when he returned from a summer camp and noticed a left-sided facial droop. He presented to his primary care office, where he tested negative for Lyme disease and was thought to have Bell’s palsy. Six months later, he noted a new weakness in the left upper and lower extremity, which affected his gait. Due to worsening symptoms and concern about a possible stroke, a magnetic resonance imaging (MRI) of the brain was ordered, and once the mass was identified, he was advised to report to the emergency department for admission.

At the time of admission, his symptoms included facial asymmetry and left-sided weakness. He reported occasional nausea and vomiting but denied having headaches, visual changes, loss of sensation, rhinorrhea, or ear discharge. He did report unknowingly bumping into things in the last few weeks. He noted a weight gain of 50 pounds in the last six months due to increased appetite. History was also positive for decreased libido and loss of morning erections. Family history was negative for brain tumors.
On physical exam, the patient was alert and oriented. He demonstrated right eye proptosis and loss of nasolabial fold on the left. He was able to close his left eye, forehead, and eyebrow movements were preserved consistent with central facial nerve palsy. Pupils were round, equal, reactive, and extraocular movements were intact. The ophthalmic exam showed normal fundus, unremarkable visual acuity with left-sided temporal visual field deficit. Left upper and lower extremity weakness was noted. Sensory testing was normal. There was no ataxia or dysmetria, and the gait was normal. Galactorrhea or gynecomastia was not appreciated, and testicular size was normal.

MRI of the brain was performed, and results were consistent with an enormous extra-axial multilobulated mass arising in the region of the right cavernous sinus invaginating deep into the base of the right cerebral hemisphere and producing a mass effect on the pons, right-sided midbrain, right temporal lobe, and right basal nuclei. In overall dimensions, the mass measured 60mm x 55mm x 75mm (anteroposterior, transverse, and craniocaudal, respectively) without ischemic findings (Fig. 1). The tumor was enhanced homogenously except for cystic and hemorrhagic areas. The patient underwent computed tomography angiogram, which demonstrated displacement of the right internal carotid artery and anterior displacement of the right middle and anterior cerebral artery. There was no significant vascular stenosis, and the mass demonstrated moderate vascularity. Magnetic resonance venography confirmed the invasion of cavernous sinuses and the right petrosal sinus without thrombosis.

Initial laboratory testing revealed a serum prolactin level of 13580 ng/ml (ref: 2.64-13.13 ng/ml). Further work-up demonstrated a thyroid stimulating hormone of 1.71 uU/ml (ref: 0.35-4.94 uU/ml) with a free T4 of 0.6 ng/dl (ref: 0.61-1.82 ng/dl), a morning cortisol of 4.8 ug/dl (ref: 7-23 ug/dl), an adrenocorticotropic hormone of 18 pg/ml (ref: 7-69 pg/ml), an insulin-like growth factor 1 of 112 ng/ml
(ref: 99-283 ng/ml), and a growth hormone level of <0.05 ng/ml (ref: 0.05-3.00 ng/ml). A co-syntropin stimulation test demonstrated a normal cortisol levels at 30 and 60 minutes. Gonadal panel showed a luteinizing hormone of 0.31 mIU/ml (ref: 1.24-8.62 mIU/ml), a follicle stimulating hormone of 0.9 mIU/ml (ref: 1.27-19.26 mIU/ml), a sex hormone binding globulin of 15 nmol/L (ref: 11-80 nmol/L), and a testosterone level of 42 ng/dl (ref: 300-1080 ng/dl) with free testosterone of 10 pg/ml (ref: 47-224 pg/ml), which was consistent with hypogonadotropic hypogonadism. Hemoglobin A1c was 5.6%. His basic metabolic panel revealed only mild hyponatremia with a serum sodium of 133 mmol/L.

The patient was diagnosed with a giant prolactinoma and was managed by a multidisciplinary team, including endocrinology, ophthalmology, and neurosurgery. Given his very high prolactin level, he was started on high dose cabergoline, 0.5 mg daily, with close monitoring by neurosurgery and ophthalmology. After being on cabergoline 0.5 mg daily for a week, there was a 74% reduction in his serum prolactin level to 3515 ng/ml. Repeat MRI showed stability of the pituitary mass after one week and cabergoline dose was decreased to every other day after two weeks of the treatment as the prolactin level began to decline further. Repeat MRI of the brain six weeks after initiation of dopamine agonist therapy, showed a significant reduction (57%) in the tumor size to 60mm x 38mm x 47mm, and volume (decreased from 247cm³ to 107cm³) (volume calculated using equation V=abc using the three-dimensional MRI measurements [anteroposterior, transverse, and craniocaudal]. The left-sided weakness and facial asymmetry resolved a few months after treatment initiation, followed by resolution of the visual field deficits. At the 7-month follow-up visit, the patient reported full resolution of symptoms with normal neurological and visual function. He resumed normal erections, although testosterone level was still below normal. The prolactinoma size decreased to 63mm x 13mm x 38mm (31 cm³), corresponding to an 87.5% total volume reduction after 12 months. The gonadotropin axis
remained suppressed, although consistent recovery was noted, with total testosterone levels of 185 ng/dl (from 42 ng/dl) and free testosterone of 42 ng/dl (from 18 ng/dl) at his 15-month follow-up (Fig. 2). Simultaneously, follow-up MRI revealed approximately 91% total volume mass reduction since the diagnosis, with 57mm x 11mm x 35mm measurements (Fig. 3). Subsequent labs at 22 months showed further improvement of total testosterone to 214 ng/dl and free testosterone of 45 ng/dl, while prolactin levels decreased to 649 ng/ml on continued dopamine agonist therapy (cabergoline 0.5mg every other day) (Fig. 2).

Discussion

Giant prolactinomas are relatively rare pituitary tumors and management of these patients can be quite challenging. Clinical presentation can be misleading, mimicking other intracranial tumors or neurological disorders. Giant prolactinomas usually cause mass-effect, compressing surrounding tissues and the optic chiasm [6]. The most common symptoms are vision changes (54.9%), and headaches (42.3%). Hormonal derangements are frequent, the most common one being low testosterone levels with hypogonadotropic hypogonadism, causing decreased libido and erectile dysfunction [6-9]. Less common presentations include cranial nerve palsy, seizures, cognitive decline, and psychiatric disturbances and pituitary apoplexy has been described in up to 9.8% of cases [6]. These patients have been reported to present with cranial nerves III, IV, V, and VI palsies [4]. Our patient is unique in that he presented with facial nerve palsy that reversed after cabergoline was started. Hemiparesis has rarely been reported with large pituitary adenomas in the setting of concurrent stroke or apoplexy was diagnosed [10]. In our case, we suspect that the enormous prolactinoma and its mass-effect resulted in
distortion of critical brain motor pathways and the corticobulbar fibers of the VII nerve, causing impaired motor function and weakness. These findings resolved with the reduction in size of the tumor with cabergoline therapy.

Giant prolactinoma can present with very high prolactin level [6,7,9]. However, no consistent correlation has been reported between PRL level and tumor size [5,6,9,11,12]. Dopamine agonists, including bromocriptine and cabergoline, are effective first-line therapy and generally well-tolerated. Cabergoline, a long-acting D2-agonists, is favored over bromocriptine as it causes a greater decline in prolactin levels [8,13]. Surgical management is sometimes needed to rapidly decompress the optic chiasm due to visual impairment [14,15] or can be a part of multimodal therapy due to continued growth and worsening symptoms despite dopamine agonist therapy or medication intolerance [6,15]. Long term dopamine agonist therapy is usually necessary for management [14-16]. Due to concern about the neurological symptoms at presentation, the treating team decided to start the patient on a higher dose of cabergoline to see if the neurological symptoms improve and surgical intervention can be avoided. This was done with close observation and understanding that such large tumors have increased risk of apoplexy because of their large size, which can sometimes be precipitated by cabergoline treatment. The patient was followed closely and a follow up MRI of the brain a week after starting cabergoline, confirmed tumor shrinkage and lack of apoplexy. Hence, cabergoline dose was reduced to 0.5 mg every other day, on which he has been maintained.

Giant prolactinomas are very sensitive to dopamine agonists [17-18]. Acute symptoms arising from mass-effect improve dramatically within days [5, 8]. Other symptoms may resolve later during therapy, which often occurs before prolactin levels normalize [5]. Gonadal dysfunction is reversed in
67% to 80% of men in the literature [5,8]. Cabergoline dosage should be adjusted individually to avoid adverse effects and doses varying from 1.5 mg to 17.5 mg/week have been reported in various series [6,8]. In resistant giant prolactinomas, prolactin level may not normalize despite a fairly high weekly dose of cabergoline (2.0 mg/d) or bromocriptine (15 mg/d) [19]. Prolactin level may stay elevated in 20-40% of patients despite therapy and the nadir of prolactin level seen between 10-20 months of therapy [5,6,16,19]. Patients with higher initial levels of prolactin demonstrated a more significant response to dopamine agonist, suggesting that highly active tumors are more likely to respond to dopamine agonist monotherapy. The biochemical response does not correlate with tumor size and initial prolactin level [6]. Our patient had an excellent response with a significant drop in prolactin level just two days after starting cabergoline suggesting high activity of lactotrophs. Dopamine agonists also facilitate tumor shrinkage and several studies have reported 60% to 80% reduction in tumor size over time [6,8,17,19], with shrinkage in size usually reported at 6 to 20 months after starting treatment [5,8,11,16]. Although our patient has had an incomplete prolactin response at 22 months of follow-up, he continues to show gradual improvement in PRL level and gradual shrinkage in the tumor size. Therefore, CAB dose has not yet been increased due to concern about side effects from higher CAB therapy.

Giant prolactinoma require long-term follow-up to monitor for structural response and for possible complications. Prolactin level, pituitary function tests, visual fields, and tumor size need to be followed regularly. Cohort study of massive (larger than 60 mm) and aggressive prolactinomas revealed that 39% of patients did not reach full resolution of hyperprolactinemia (17% reached partial response [PRL< 3x ULN]) although most patients reported disappearance or improvement of their symptoms [16]. In our patient, given resolution of symptoms and successive decline in prolactin and increase in testosterone, patient was observed clinically with frequent hormonal evaluation and repeat imaging.
Novel pharmacological regimens like pasireotide, a new somatostatin receptor ligand, and temozolomide, an alkylating agent, have been used successfully for aggressive and resistant prolactinomas and may become promising adjuncts [20-21]. Aggressive giant prolactinomas have been also linked to familial germline mutations including MEN (multiple endocrine neoplasia) type 1, MEN4, Carney complex, familial isolated pituitary adenoma, and mutations in genes encoding succinate dehydrogenase, thus genetic testing may be pursued when there is high clinical suspicion or suggestive family history [22-23]. Our patient has continued to show gradual improvement both in tumor size and PRL levels. Hormonal testing for calcium level, parathyroid and thyroid function has been normal and testosterone level continues to improve with full resolution of erectile dysfunction. We are planning to up-titrate CAB therapy as the next step and to pursue genetic evaluation. If the adenoma starts to behave more aggressively, surgical intervention, pasireotide or temozolamide treatments may also be considered.

Dopamine agonists may not prevent tumor re-expansion once they were discontinued [24]. Hence, patients with giant prolactinomas may never be a candidate for dopamine agonist withdrawal [25-26]. The most important predictors for prolactinoma recurrence are maximum tumor diameter and baseline prolactin levels [26]. Cabergoline up-titration should be managed cautiously as rapid shrinkage of the invasive tumor may cause unplugging of the eroded area and induce cerebrospinal fluid leakage [27] and can cause pituitary apoplexy or chiasmal herniation [8, 26]. In our patient, initially high dose cabergoline (0.5mg daily) was used due to urgency of the presentation, however patient was monitored closely by Neurosurgery and had repeat brain imaging to assure none of the complications have occurred. Patients on high dose cabergoline or long-term therapy should be monitored by
echocardiography for a possible valvular adverse effect [28].

Conclusions

Giant prolactinoma is a rare entity that occurs mostly in men and presents with a significant mass effect on surrounding tissue. At diagnosis, clinical features may be mistaken for other neurological conditions like stroke. Giant prolactinoma may present with unique symptoms of facial nerve palsy and hemiparesis. Most giant prolactinomas are sensitive to dopamine agonists; however, prolactin normalization may not happen and although the adenoma may shrink in size, it may not disappear. Long-term therapy and surveillance are required to monitor symptoms, decline in prolactin, tumor shrinkage, and complications from dopamine agonist therapy.
Data availability

All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.
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**Figure Legend:**

**Figure 1.** Initial MRI of the brain: sagittal T1 pre-contrast (1), sagittal T1 post-contrast (2), and coronal T1 post-contrast view (3) demonstrating enormous sellar mass.

**Figure 2.** Trend line of prolactin (nanogram/millimeter, ng/ml) and total testosterone (nanogram/deciliter, ng/dl) level from the diagnosis until 22-months follow-up.

**Figure 3.** MRI of the brain at 15-month follow-up: sagittal T1 pre-contrast (1), sagittal T1 post-contrast (2), and coronal T1 post-contrast view (3) demonstrating significant reduction in the size of the tumor.
Figure 2
