

# Giant Prolactinoma: Case Report and Review of Literature

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**Abstract** Prolactin (PRL) secreting adenomas are the most common secreting pituitary tumors, accounting for approximately 45% of all pituitary tumours. Giant prolactinomas are a rare subset of macroadenomas, characterized by large size (more than 40 mm in diameter (an arbitrary size), high aggressiveness and massive extrasellar involvement. We describe an unusual giant prolactin producing macroadenoma of pituitary gland in female patients with type 2 diabetes mellitus and its response to cabergoline.

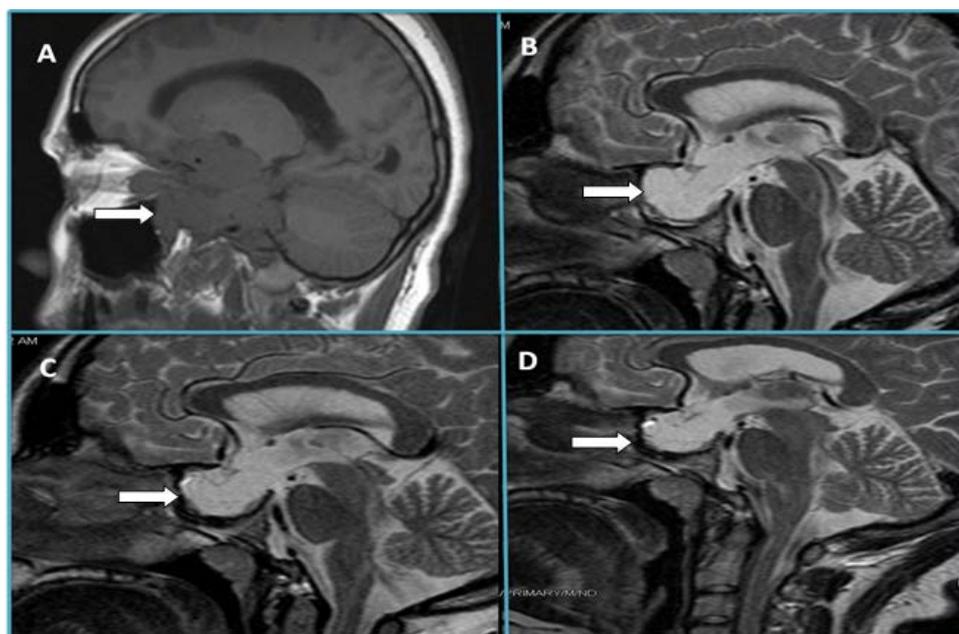
**Keywords:** giant prolactinoma, dopamine agonist

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## 1. Introduction

Prolactin (PRL) secreting adenomas are the most common secreting pituitary tumors, accounting for approximately 45% of all pituitary tumors [1]. Microprolactinomas are more common than macroprolactinomas. In general, prolactinomas have a female predominance, and microadenomas occur more often in female, whereas macroadenomas are common in male [2,3]. Giant prolactinomas are a rare subset of macroadenomas, characterized by large size (more than 40 mm in diameter (an arbitrary size), high aggressiveness

and massive extrasellar involvement [4,5]. They are usually associated with very high serum PRL levels (>1000 ng/ml). Patients harboring a giant prolactinoma typically respond to dopamine agonist (DA) therapy, despite the large tumor size and invasion of adjacent structures [6,7]. Complete surgical removal of giant tumor is difficult and biochemical cure is rare [8,9]. Medical therapy with DA is the first-line treatment for giant prolactinomas. In the present report we describe an unusual giant prolactin producing macroadenoma of pituitary in female patient with type 2 diabetes mellitus and its response to cabergoline (DA).



**Figure 1.** Pituitary macroadenoma (white arrow) at various times of presentation and follow up: A: At time of diagnosis, B: 2 years post Dopamine agonist therapy, C: 4 years post Dopamine agonist therapy, D: 6 years post Dopamine agonist therapy

## 2. Case Report

A 35 years old single female patient was referred to Endocrinology clinic with headache, blurred vision, galactorrhea and oligomenorrhea for 6 years. Physical examination showed bilateral optic disc pallor and atrophy and bitemporal hemianopia which was confirmed by digital central field exam. Other systems examinations were unremarkable. Initial laboratory work up revealed normal complete blood count, electrolytes and renal profile and liver enzymes. Serum prolactin 10000 mIU/l (normal<360 mIU/l) , Thyroid stimulating hormone 1.52 mIU/l (normal=0.4-4.2), FT4 19.4 pmol/l 9 (normal=10-23), Luteinizing hormone 1.5IU/l , Follicular stimulating hormone 3.4IU/l, Estradiol 217 pmol/l, early morning serum cortisol 439 nmol/l (normal=138-635) , ACTH 5.6 pmol/l (normal<15) and Insulin like growth factor-1 162 ng/ml (normal= 117-321). Cabergoline (DA) 0.5 mg twice weekly was started orally. MRI of pituitary fossa showed

giant prolactinoma (Figure 1), patient was initially strictly compliant to cabergoline dosage. Six months later, she started to experience worsening visual acuity and her fundal examination showed bilateral optic atrophy. She was referred to neurosurgery for possible surgical resection of the tumor but unfortunately the patient father refused the surgical management and the patient had missed her appointments at the endocrine clinic. Two years later, she was presented with diabetic ketoacidosis and diagnosed with type 2 diabetes mellitus based on negative Antibodies to glutamic acid decarboxylase and Islet cell antibodies. She showed no compliance to cabergoline for almost 12 months and she was restarted the therapy again with her last serum prolactin 562 mIU/l (Figure 2). Thyroid stimulating hormone 0.4 mIU/l, FT4 21 pmol/l, Luteinizing hormone 0.3 IU/l, Follicular stimulating hormone 0.6 IU/l Estradiol 239 pmol/l, early morning serum Cortisol 323, ACTH 27 pmol/l, Insulin like growth factor-1 191ng/ml (normal= 117-321).

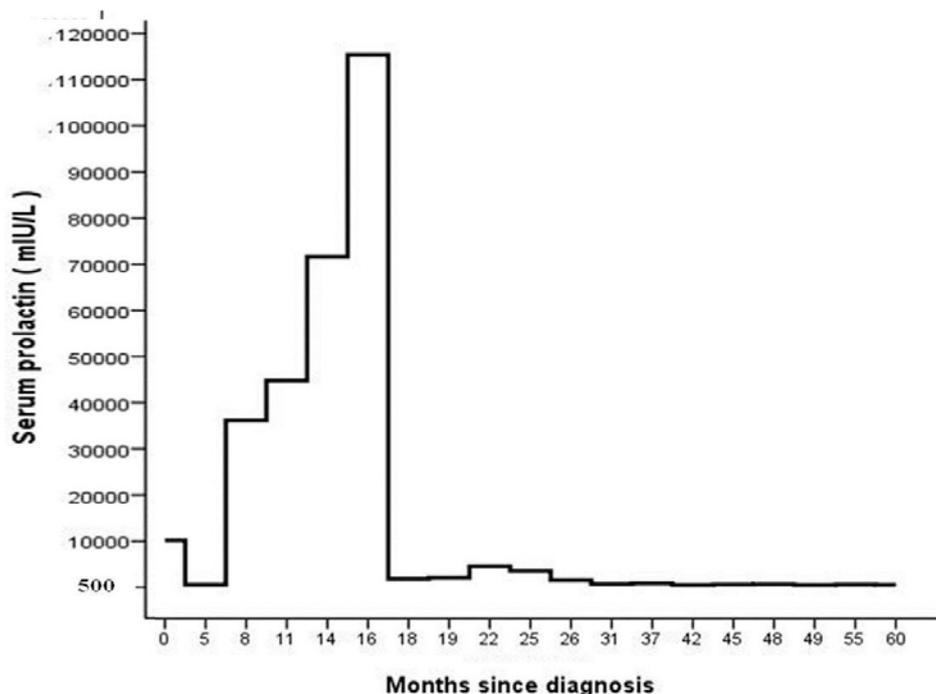


Figure 2. Serum prolactin and response to dopamine agonist

## 3. Discussion

The prevalence of giant prolactinomas is not well established. There are no data regarding the prevalence of giant prolactinomas among prolactinomas, but based on retrospective analyses, it may be estimated to range from 0.5 to 4.4% of all pituitary tumors [2,5,9]. The majority of patients included in the largest published series of giant prolactinomas are men, with a male/female ratio of 6.5/1 [10]. In women, when considering a large series of micro- and macroprolactinomas (no 709), a marked peak occurrence is observed in the third and fourth decades of life [11]. Delgrange et al reported the distribution of giant prolactinomas is different with only one case of 34 women diagnosed during the fourth decade while other cases seem to be distributed in two age groups: a small group with early onset that may reflect a stronger hereditary

pathogenesis and a larger late-onset group where a number of genetic or epigenetic events are probably required to reach a giant size [12]. In non-surgical series, due to the absence of histological confirmation of the diagnosis, diagnostic criteria for giant prolactinomas include not only tumor extension but also serum prolactin levels, which generally parallel tumors size. As in most patients, there is an association between serum PRL level and tumors volume and large invasive prolactinomas. Therefore, patients with giant prolactinomas often have been characterised by very high serum PRL levels >1000 mg/l [13], and a similar figure is used in most recent series to define giant prolactinomas [2,5,14]. However, this association is not always consistent, and tumour mass and PRL level may be dissociated. The hook effect is a possible cause for this discrepancy and has been reported to occur in 20% of giant prolactinomas [15].

In general, giant prolactinomas cause clinical symptoms as a result of mass effect and/or hyperprolactinaemia. These tumors' often cause visual field defects and/or ophthalmoplegia due to compression of the optic chiasm and/or cranial nerves, respectively, as well as headaches. Although the most common site of extrasellar extension is into the suprasellar cistern, large tumors can also extend inferiorly into the sphenoid sinus or laterally into the cavernous sinuses. Hyperprolactinaemia typically presents with symptoms and signs such as decreased libido, impotence, infertility, galactorrhoea, oligomenorrhoea or amenorrhoea and gynaecomastia.

Different therapeutic approaches, such as DA alone or in combination with surgery (or early surgery, as indicated for patients exhibiting apoplexy with severe clinical symptoms or intracranial hypertension) and radiotherapy, may be necessary to reach the therapeutic goals in patients with giant prolactinomas, which include control of tumor volume, normalization of PRL level and restoration of eugonadism [2]. It is important to emphasize that, due to large tumor volume and commonly invasive behaviour, control of mass effect should be a priority in the management of patients with giant prolactinomas [16]. Surgical debulking may be employed to induce rapid optic decompression and visual improvement, or to prevent pituitary apoplexy in patients refractory to DA [9]. However, complete surgical removal of giant tumors that extend into the suprasellar, parasellar, and infrasellar areas is difficult, and biochemical cure is rare even after extensive tumor removal [7,8,17].

Medical therapy with DA is the first-line treatment for giant prolactinomas, even in patients with visual field defects, because DAs are able to induce tumor shrinkage within a few days after initiating therapy [6,18,19]. However, close monitoring of patients with visual field disturbances is advisable. It is important to mention that caution should be used when comparing efficacy rates among the different DAs due to variability in study design and data quality. There were studies evaluating cabergoline (DA) in management of giant prolactinoma. All of these studies showed that cabergoline is safe and well-tolerated and also suggested that cabergoline should be the first line of treatment for giant aggressive macroprolactinomas. In one study, cabergoline normalized prolactin levels in ten out of twelve patients and decreased significantly in the other two significantly. Visual field defect was present in nine patients at diagnosis which returned to normal in three of patients and improved in five after treatment. Tumor diameter responded to treatment with decrease of 21-47% in size [6,14,20]. In a review of seven series of a total of 49 patients with giant prolactinomas treated with bromocriptine (no =35) or cabergoline (no = 14), Gillam et al. reported a 65% rate of PRL normalization. Saeki et al. found bromocriptine therapy (5–15 mg/day) effective in controlling PRL levels in six out of ten patients with giant prolactinomas, and Shrivastava et al. , who treated ten men with bromocriptine (10 mg/day), noted PRL uppression to normal in two cases, and a dramatic reduction to 30–100 ng/ml (99.9% suppression) in the remainder [2,16,21].

Complications of medical treatment with high-dose DA for large invasive prolactinomas are uncommon. They may include cerebrospinal fluid leakage, chiasmal

herniation, and pituitary apoplexy. Some DA doses used are beyond those recommended in the package insert, but large doses are sometimes needed for certain patients with large tumors [22]. The dose can be safely increased as long as the patient tolerates it without adverse effects. In Parkinson's disease, far larger doses of cabergoline are used, approximately 4 mg/day, and sometimes up to 20 mg/day, and these doses are usually well tolerated [23]. Recently, the association between mitral valve insufficiency and high-dose cabergoline prescribed for Parkinson's disease was reported [23]. Thus, patients using high-dose cabergoline should be monitored by echocardiography for this rare adverse effect.

In summary, the present case report demonstrates that cabergoline is as safe and effective for the treatment of giant prolactinomas.

## Consent

Written informed consent was obtained from the patient for publication of this case report.

## Competing Interests

The authors declare that they have no competing interest.

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