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# Giant prolactinoma, a case report and review of the literature

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ABSTRACT

A 13 year old boy presented with acute onset of sudden severe headache and visual impairment following a one-year history of intermittent frontal headache. Serum prolactin level was 17532ng/ml (normal 3–24ng/ml). Magnetic resonance imaging showed a large intrasellar mass with suprasellar extension and evidence of recent hemorrhage within the mass. Cabergoline was started and laparoscopic trans sphenoidal resection of pituitary adenoma was performed. Six months post therapy, he had complete restoration of right eye vision, and partial restoration of left one. Early surgical intervention in addition to medical therapy in case of pediatric pituitary apoplexy associated with giant prolactinoma might be essential to restore vision.

## 1. Introduction

Pediatric pituitary adenomas are rare, accounting for < 3% of all childhood intracranial tumors, the majority of which (40–50%) are prolactinoma. Consequently they are often misdiagnosed as other suprasellar mass such as craniopharyngioma. Prolactinoma is a rare benign tumor that appears as a result of monoclonal expansion of the lactotrophic cell line of the adenohypophysis probably due to somatic mutation. Unlike adults, macroprolactinomas in children (mass measuring ≥1 cm in diameter) are more common (~60–80%). Giant prolactinoma is a subset of macroprolactinoma with diameter ≥4 cm, or ≥2 cm in suprasellar extension. Herein we report the case of 13-year-old male who presented with giant macroprolactinoma and acute pituitary apoplexy who responded to combination of surgery and medical therapy.

## 2. Case report

A 13-year-old refugee boy who was previously healthy presented to the emergency department (ER) with acute history of headache, visual loss, and vomiting following a one year history of intermittent frontal headache and blurred vision, no galactorrhea or gynectomastia. He was not taking any medication. His family history was unremarkable for endocrinopathies. Vital signs at the time of admission showed blood pressure 118/65 mmHg, heart rate 74/min, temperature 36.8C, anthropometric measurements showed a height of 164.5 cm (54.79 percentile) weight of 85.4kg (98.95 percentile), and body mass index of 31.55 kg/m2 (31.52 percentile). Physical examination showed a Tanner stage 4 axillary hair and pubic hair, testicular volume of 12 ml bilaterally. Fundal examination showed a pale left optic disc. Visual field examination revealed total left eye vision loss, while there was a temporal hemianopia of the right eye.

Laboratory investigations (Table 1) revealed high prolactin (PRL) level of 17532ng/ml, thyroid stimulation hormone (TSH) 0.9 mu/L and free thyroxin (F T4) 10.9 pmoL/L(0.8ng/dl) (indicating secondary hypothyroidism). Adrenocorticotrophic hormone (ACTH) 0.3 pmoL/L (1.3pg/ml), cortisol 9.9 nmoL/L (0.3 μg/dl) (indicating central adrenal insufficiency), luteinizing hormone (LH) 1.1IU/L, follicular stimulation hormone (FSH) 2.5 IU/L, and testosterone 6.3 nmoL/L (181.1ng/dl). Liver and renal function were normal with serum glucose 4.4mmol/l (79mg/dl). Serum sodium 137mmol/l with normal serum osmolality. There was no evidence of diabetes insipidus or syndrome of inappropriate anti diuretic hormone (SIADH) before or after surgery. Computed tomography scanning (CT) (Fig. 1B) showed mass measuring 4 × 2.5 × 3 cm. A magnetic resonance imaging (MRI) revealed a large interstellar mass with suprasellar extension with evidence of recent hemorrhage within the mass (Fig. 1A), with no radiological evidence of calcification. Due to acute left eye visual loss and under steroid coverage, microscopic *trans*-sphenoidal resection of the pituitary mass was performed. CT and MRI were done post surgical day 1 and day 2

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**Table 1**
Results of investigations and cabergoline doses.

| hormone (normal values) | Baseline (prior surgery) | Post surgery | 3 months | 6 months |
|---|---|---|---|---|
| Prolactin (3–24ng/ml) | 17,532 | 8681 | 2426 | 2565 |
| TSH (0.5-5Mu/L) | 0.9 | | 0.7 | 0.6 |
| F T4 (0.9–1.8 ng/dl) | 0.8 | | 0.9 | 1.1 |
| ACTH (22–68 pg/ml) | 1.3 | | | 30.9 |
| Cortisol (5–23 μg/dl) | 0.3 | | | 9.9 |
| LH (1.7–8.6IU/L) | 1.1 | | | 2.5 |
| FSH (0.8–9IU/L) | 2.5 | | | 6.5 |
| Testosterone (28–1110 ng/dl) | 181.1 | | | 129.7 |
| Cabergoline Dose (twice/week) | | 0.25mg | 2mg | 2.5mg |

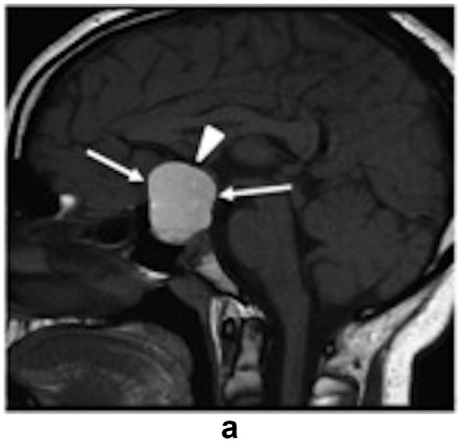


**Fig. 1.** Pituitary giant macroadenoma (1A) Mid-sagittal brain MRI (T1 weighted image without intravenous contrast: shows a large intrasellar/suprasellar mass (arrows) with homogenous high signal intensity indicating hemorrhage. The mass is compressing on optic chiasm (arrowhead). (1B) Mid-sagittal brain CT scan without intravenous contrast: shows a large hypodense intrasellar mass (arrow) with suprasellar extension. It is causing expansion of sella turcia (arrowhead).

respectively (Fig. 2A and B). Immunostaining (Fig. 3) revealed neoplastic cells with diffuse strong positively for prolactin and negative for ACTH, FSH, LH, TSH and GH. Immediately post surgery the serum prolactin regressed to 8681 ng/ml. The patient was started on Cabergoline (dopamine agonist), 0.25 mg twice a week and increased gradually in 4 weeks to reach to 2 mg twice a week. Hydrocortisone and Levothyroxine replacement therapy were started before surgery and continued thereafter. Six months post surgery, Cabergoline dose was

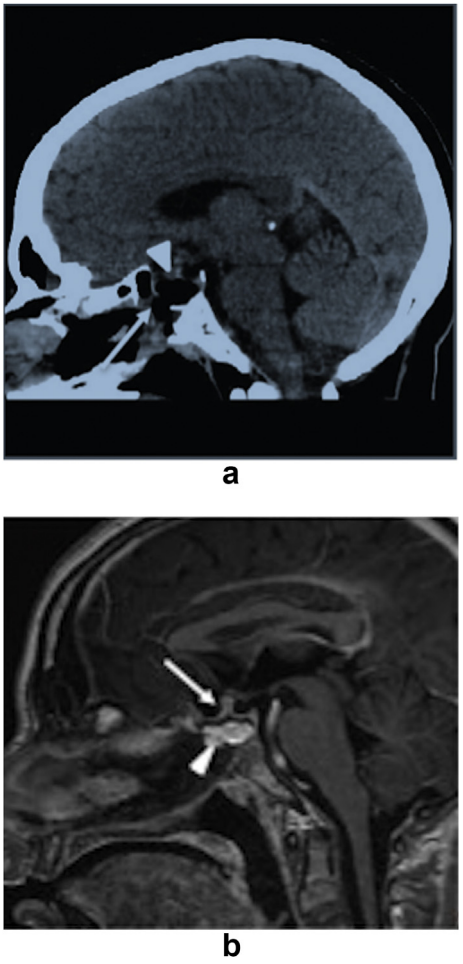


**Fig. 2.** Post transphenoidal resection of pituitary macroadenoma (2A) Mid-sagittal brain CT scan without intravenous contrast: Day one after resection shows sphenoid bone defect (arrow) and fat packing in sphenoid sinus (arrowhead). (2B) Mid-sagittal brain MRI (T1 weighted image with intravenous contrast): Day two after resection shows linear enhancement along the pituitary stalk (arrow) and fat packing in sphenoid sinus (arrowhead).

increased to 2.5mg twice a week because of increase in prolactin level (Table 1), although patient showed marked clinical and radiological improvement (Fig. 4) we increased the dose because we anticipated that this is an earlier sign for relapse. During follow up patient has no significant symptoms and sign of orthostatic hypotension, vertigo, nausea and vomiting. Importantly, the left eye vision was partially restored with remaining temporal hemianopia, and complete improvement of the right eye vision. Growth velocity and puberty continued to progress normally. Unfortunately the patient lost to follow up after the 6 months visit. The family were contacted several but they did not respond.

## 3. Discussion

Giant prolactinoma is exceptionally rare in childhood with an estimated frequency of 0.5–4.4% for all pituitary tumors [1,2]. They present with symptoms of hyperprolactinemia and tumor mass effect, such as neuro - ophthalmologic symptoms. Rarely pituitary apoplexy may occur when acute bleeding inside the tumor occurs causing a sudden headache, visual loss, double vision and pituitary failure. Females tend to present with microprolactinoma. The main manifestation is with signs and symptoms that are related to hyperprolactinemia. While males present with macroprolactinoma resulting in the presence of neuro-ophthalmologic signs like our patient [1,2]. We identified 13

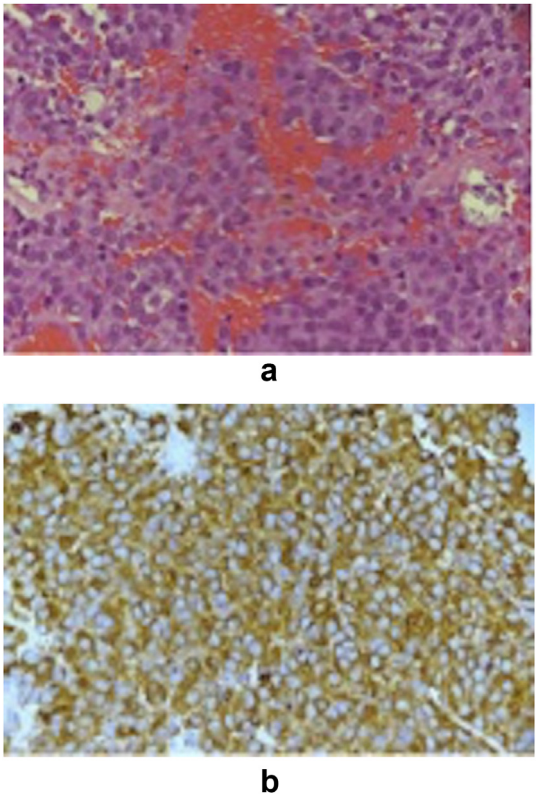


**Fig. 3.** Histopathology (3A): The photomicrograph shows a neoplasm composed of rounded monomorphic cells arranged in a diffuse pattern. The neoplastic cells are medium-sized containing moderate amounts of finely granular eosinophilic cytoplasm, round to oval nuclei and small nucleoli. There is no pleomorphism, brisk or atypical mitosis or necrosis. (Hematoxylin and eosin stain, x200 original magnification). (3B): On immunohistochemistry study the neoplastic cells show strong, diffuse cytoplasmic positivity with prolactin. The immunostains for ACTH, FSH, TSH, LH and GH were negative. (Prolactin immunostain, x400 original magnification).

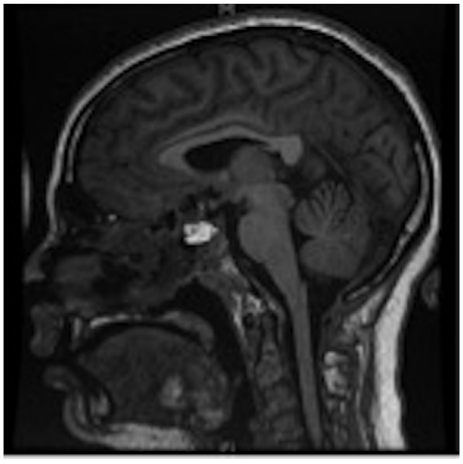

**Fig. 4.** 6 months after surgery and under Cabergoline therapy. Post transphenoidal resection of pituitary macroadenoma with interval resolution of left suprasellar enhancing focus. There is resolution of postoperative changes and fat packing.

pediatric giant prolactinomas in the literature. The youngest child presented at age 7 years. All cases had mean PRL level of 10,989.7ng/ml. The clinical presentation and management of these cases are summarized in Table 2. Serum PRL levels associated with giant prolactinoma are usually high, reaching 1000 ng/ml, and occasionally exceeding 40, 000 ng/ml. However, these level do not correlate with the tumor size [3,4]. Sometimes PRL levels are so high that they can appear in the urine in the form of nephrotic range proteinuria [5].

Dopamine agonists are the initial therapy of choice in children and adolescent because of their effectiveness and tolerance [6–9]. Therapy with Cabergoline normalizes prolactin level in 68%, reduces the tumor size in 73%, and improves of the visual field in 91% of the patients. In a 24-month prospective study, treatment with Cabergoline (0.25–3.5 mg/week) normalized PRL levels in 76% of patients, significantly reduced tumor size in all patients with a percentage reduction of the maximum tumor diameter of 84%, normalized serum testosterone in 60% and sperm alterations in > 90% of patients [25]. Cabergoline is more effective than other dopaminergic agonist because it has higher affinity for dopamine receptors binding sites, longer half life, and lower adverse effects [10,21,23]. The most common adverse events associated with cabergoline are nausea or vomiting followed by headache, dizziness and vertigo [26]. Recently cardiac valve insufficiency has been reported in patient with Parkinson's disease treated with high dose of cabergoline [27] Majority of pediatric giant prolactinomas respond well to medical treatment. However, medical therapy might be limited because of treatment side effects especially when high doses of dopamine agonists is needed to normalize the prolactin level and achieve tumor size shrinkage. Experience in children with giant prolactinomas treated with cabergoline is limited to sporadic case reports [28]. Table 2 shows the variability in management, and treatment success rate in giant pediatric prolacetinomas. Surgical management usually is reserved to children with neuro-opthalmic symptoms in combination with medical treatment. Surgery usually results in rapid resolution of neuro-opthalmic symptoms. Radiotherapy has a limited role in the treatment of giant prolactinoma due to low efficacy and risk of complications [1].

Pituitary apoplexy presenting with giant prolactinoma is extremely rare in children. Our case is the second in the literature [22]. Timely management is extremely prudent to preserve vision and reverse adverse neurological squeal. The first case of pituitary apoplexy presented with giant prolactinoma was for 9 years old child. The child presented with acute headache, visual disturbance. He underwent *trans*-sphenoidial surgical resection combined with Cabergoline. After 33 weeks of treatment the PRL levels completely normalized, his left eye vision was partially restored with remaining temporal hemianopia, and complete improvement of the right eye vision, and the tumor completely resolved. On the other hand, early surgical intervention in our case resulted in complete right eye vision restoration, and partial restoration of left eye vision. Adult systematic review and meta-analysis of 6 studies for cases of pituitary apoplexy indicated that early surgical intervention resulted in good visual recovery compared to medical management [11].

The optimal management for pediatric pituitary apoplexy remains controversial. Medical management for giant prolactinoma is considered optimal. However, when children presents with poor medication intolerance or tumor resistant to medical treatment with dopamine agonist, and when it produce a neuro-ophthalmological symptoms, loss of vision or pituitary apoplexy, or in case of malignant prolactinoma then early surgery should be considered to preserve vision [12,13].

## Statement of ethics

The authors have no ethical conflicts to disclose.

## Disclosure statement

Patient informed consent was obtained.

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None.

**Table 2**
Summary of published cases of prolactinoma in pediatric age group.

| Outcome | Surgical and radiological management | Medical management | Presentation | Age, Sex | Case no./ref. |
|---|---|---|---|---|---|
| Significant reduction in the tumor size in 5 years. | Not required | Cabergoline, 0.5 mg/week for 2 weeks prolactin level 12, 059 ng/ml then dose increased up to 12 mg/wk prolactin level 316 ng/ml. | Progressive weight gain, nasal stuffiness, snoring, and a polypoid mass in his left nostril. | 14, M | 1 [14] |
| Excellent response to medical therapy alone, with resolution of hydrocephalus, restoration of normal vision and a 98% reduction in serum prolactin after 6 months of treatment. | Not required | Quinagolide 150 μcg/day initially then added cabergoline 1 mg twice/week.<br>The dose of cabergoline was doubled to 2 mg twice/week | Left-sided proptosis, bilateral papilloedema and hydrocephalus. | 13, M | 2 [15] |
| Vision improved to 6/12. | Sublabial rhino-septal transsphenoidal approach. | Bromocriptine<br>1.25 mg twice a day, which was increased to1.25 mg three times a day after 1 month. | Visual disturbances headache and gynecomastia. | 7, M | 3 [16] |
| His visual function improved and there was no tumor recurrence at 32 months follow-up.<br>His prolactin levels were normal. | Two-stage surgery with both transcranial and transsphenoidal procedures.<br>Radiotherapy was administered to the patient after the surgery. | No medical therapy | Visual disturbance bitemporal visual-field defects. | 10, M | 4 [17] |
| Rapid improvement, with the prolactin dropping to 113 ng/ml 4 months later.<br>The vision in his left eye improved after 6 months of therapy.<br>No improvement in the function of his right eye. MRI scan has shown a marked reduction in the size of the tumor mass 6 months after commencement of treatment. | Not required. | Bromocriptine<br>5 mg twice a day. | 5-year history of headaches and deteriorating vision for 1 year. | 14, M | 5 [18] |
| Normal vision of left eye, unchanged on right eye<br>MRI scan has shown a marked decrease in the size of the tumor. | Not required. | Bromocriptine and the dose increased to a daily regimen of 5 mg, 7 mg and 5 mg. | Decrease vision, hemiparesis optic atrophy. | 13, M | 6 [18] |
| After 14 years from diagnosis, the patient presents PRL level in the normal range.<br>Residual visual disorders have been stable for several years with complete resolution of diplopia. | Due to no significant improvement of the visual deficit, the patient underwent left transmaxillosphenoidal approach through a sublabial route. After 2 years from the surgical procedure, patient underwent conventional radiotherapy. | Bromocriptine 7.5 mg daily.<br>Then After 1 year he was started on Cabergoline treatment. | Headaches and deteriorating vision. | 11, M | 7 [19] |
| Laboratory exams normal hormonal profile, and MRI demonstrated complete regression of the tumor. | After 6 weeks treatment, the patient did not experience a significant improvement of the visual deficit.<br>Therefore, a transsphenoidal procedure was done. The patient presented a new worsening of the visual acuity. The MRI showed a regrowth of the adenoma, a second transsphenoidal approach was then performed. | Cabergoline | Visual disturbance | 10, M | 8 [19] |
| | Due to multiple relapses threatening vision he required two transcranial interhemispheric debulking procedures and adjuvant proton beam irradiation, with the second debulking and radiotherapy. | Cabegoline | Headache and visual deterioration. | 11, M | 9 [20] |
| Prolactin maintained with in normal range throughout the 2-years follow up as they were checked bimonthly.<br>Gonadal function was restored and the patient entered into puberty. Last MRI performed after 2 years of cabergoline therapy showed further but smaller reduction of the mass. | Not required. | Cabergoline dose was 0.25 mg twice/week. | No signs of secondary sexual development. | 14, F | 10 [21] |
| After 72 week of treatment serum prolactin was completely normalized<br>Brain MRI after 33 weeks of treatment showed disappearance of tumor. | Transsphenoidial surgical resection. | Cabergoline with initial dose 0.125mg initial dose then the dose gradually increased 1.4mg/week. | Headache<br>Visual disturbance<br>Pituitary apoplexy. | 9, M | 11 [22] |
| Rapid normalization of serum PRL (6 weeks after initiation of treatment) and reduction of tumor size. MRI done 2.5 months after treatment, revealed tremendous improvement with a decrease in the size of the tumor. Exophthalmos, anisocoria and visual fields improved. | | Cabergoline 0.5mg once weekly, gradually increased to 3.5mg weekly. | Unilateral exophthalmos. | 7, M | 12 [23] |

(*continued on next page*)

**Table 2** (*continued*)

| Outcome | Surgical and radiological management | Medical management | Presentation | Age, Sex | Case no./ref. |
|---|---|---|---|---|---|
| In postoperative period, child developed transient diabetes insipidus. Post operative scan showed near total removal of the tumor. | Right frontotemporal craniotomy and decompression of tumor was achieved via inter-optic and carotico-optic spaces. | | Epistaxis from right nostril. Right eye progressive loss of vision. | 13, M | 13 [24] |


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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jecr.2019.100048.

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