Impressive shrinkage of a giant prolactinoma treated with cabergoline in a prepubescent girl. What now?

Athanasios Christoforidis [1], Christos Tsakalides [1], Athanasia Anastasiou [2], Antigoni Pavlaki [1], Meropi Dimitriadou [1]

1 1st Paediatric Department, Aristotle University, Thessaloniki, Greece
2 Radiology Department, Ippokratio General Hospital, Thessaloniki, Greece

Correspondence to: Athanasios Christoforidis
1st Paediatric Department, Aristotle University
49, Konstantinoupoleos str, 54642 – Thessaloniki, Greece.
TEL: +30 2310892491; FAX: +30 2310992784; E-MAIL: christoforidis @doctors.org.uk

Submitted: 2013-01-24 Accepted: 2013-04-15 Published online: 2013-06-25

Key words: **prolactinoma; giant; cabergoline; prepubescent; delayed puberty**

Neuroendocrinol Lett 2013; **34**(4):275–277 **PMID:** 23803868 NEL340413C01

Abstract

Giant prolactinomas are extremely rare in the pediatric population. We describe the case of a giant prolactinoma in a girl aged 14 years and 9 months old presented with delayed puberty. Medical treatment with dopamine agonist cabergoline resulted in a rapid normalization of prolactine levels and an impressive shrinkage and liquefaction of the mass as illustrated in serial MRIs. The therapeutic dilemma regarding the type of treatment (medical versus surgical) has now been replaced by the dilemma regarding the optimal treatment strategy and duration. Initial, rather optimistic, estimations regarding the probability of treatment discontinuation without increased relapsing risk have now been replaced by guidelines with more strict criteria for selecting candidates for treatment discontinuation.

INTRODUCTION

Giant prolactinomas are characterized by huge mass size (>4 cm), massive extrasselar involvement and levels of prolactin >1000 ng/ml and represent an extreme subset of macroprolactinomas, being even more rare in the pediatric population (Shrivastava *et al.* 2002). Dopamine agonists are considered as first line treatment for macroprolactinomas, irrespectively of the size of the mass (Melmed *et al.* 2011). However, experience is limited in patients with giant prolactinomas (Corsello *et al.* 2003; Shimon *et al.* 2007; Cho *et al.* 2009) and even more limited in pediatric population, restricted in few case reports (Krassas *et al.* 1999). Further evidence is also required to clarify the optimal treatment strategy and duration. Initial optimistic reports showing satisfactory decreased risk of relapse after treatment discontinuation (Colao *et al.* 2003), were followed by studies showing not so promising results (Kharlip *et al.* 2009). Thus, the more recent guidelines published under the auspices of the Endocrine Society adopts more strict criteria for identifying patients eligible for treatment discontinuation (Melmed *et al.* 2011).

Within this article we discuss all these dilemmas based on a clinical case of a pediatric patient diagnosed with a giant prolactinoma presented with delayed puberty.

CASE REPORT

We describe the case of a girl that presented to our pediatric endocrinology outpatient clinic complaining about delayed puberty. At a chronological age of 14 years and 9 months she exhibited no signs of secondary sexual development including breast or pubic hair development and she had

CASE REPORT

not undergone menarche. At auxological evaluation, she had a height of 150.3 cm (3rd–10th percentile) and a weight of 49.2 kg (25th–50th percentile). On review of her growth chart, she appeared to be growing parallel to the 25th percentile and in accordance to familial potential until the age of 12 years when her growth decelerated. Past medical history and family history were non-contributory. Review of systems, focused especially on neurological system, was also negative for indicative symptoms. On physical examination, she appeared overall well.

Initial laboratory testing for the differential diagnosis of delayed puberty revealed normal full blood count and serum biochemical profile, normal to low basal levels of gonadotrophins/estradiol (LH: 0.2 u/L, FSH: 5.2 u/L, E2: 14 pg/ml), normal thyroid function and extremely elevated levels of serum prolactin (PRL: 1326 ng/ml, reference values: 2.8–29.2 ng/ml). Pelvic ultrasound showed normal internal genitalia, being prepubescent in size and appearance and with no apparent abnormality. A Magnetic Resonance Imaging (MRI) of the hypothalamic-pituitary area revealed a giant nodular solid mass with small cystic components with a uniform enhancement after intravenous administration of contrast material. Dimensions of the mass were 2.69 × 2.78 × 4.02 cm. The lesion extended superiorly into the suprasellar region, in proximity to the optic chiasm, posteriorly into the sphenoid sinus and laterally into the left cavernous sinus with an encirclement of the ipsilateral carotid artery (Figure 1). Further testing included a complete anterior pituitary function evaluation that showed normal levels of Thyroid-Stimulating Hormone (TSH), normal Cortisol levels, reflecting normal Adrenocorticotropic Hormone (ACTH) production and marginal levels of growth hormone (GH) after stimulation (GHmax=8.3 ng/ml). Finally, no restriction in patient's functional visual fields was recorded.

The combination of high levels of prolactin with MRI findings supported the diagnosis of a pituitary macroadenoma secreting prolactin (macroprolactinoma) as proposed by the recently published guidelines by the Endocrine Society (Melmed *et al.* 2011). The patient commenced on cabergoline, an ergot-derived, long acting, oral dopamine agonist, which is considered first line treatment for prolactinomas of any size. Initial dose was 0.25 mg given twice a week and this dose effectively normalized levels of prolactin that maintained within normal range throughout the 2-years follow up as they were checked bimonthly. Subsequent MRI was performed with the completion of 6-months

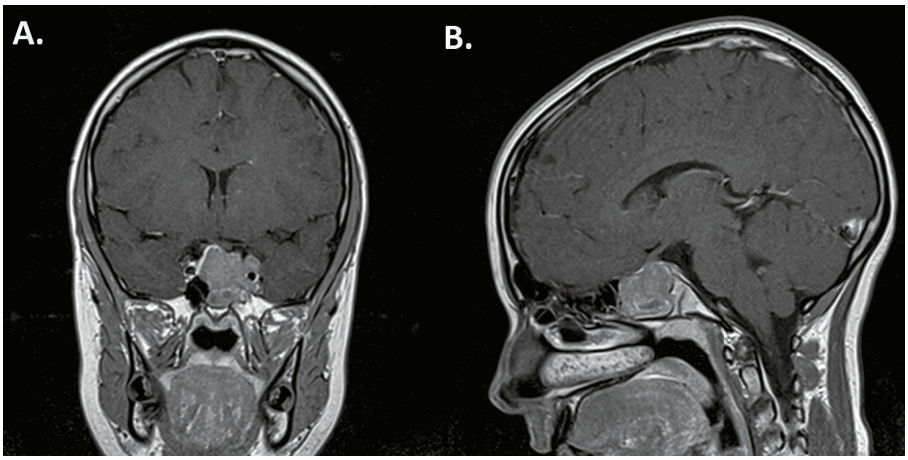

Fig. 1. Contrast-enhanced coronal (A) and sagittal (B) MRI planes of the hypothalamic-pituitary area showing a giant nodular solid mass (2.69 × 2.78 × 4.02 cm) with small cystic components. The lesion extends into the suprasellar region, in proximity to the optic chiasm, into the sphenoid sinus and into the left cavernous sinus with an encirclement of the ipsilateral carotid artery.

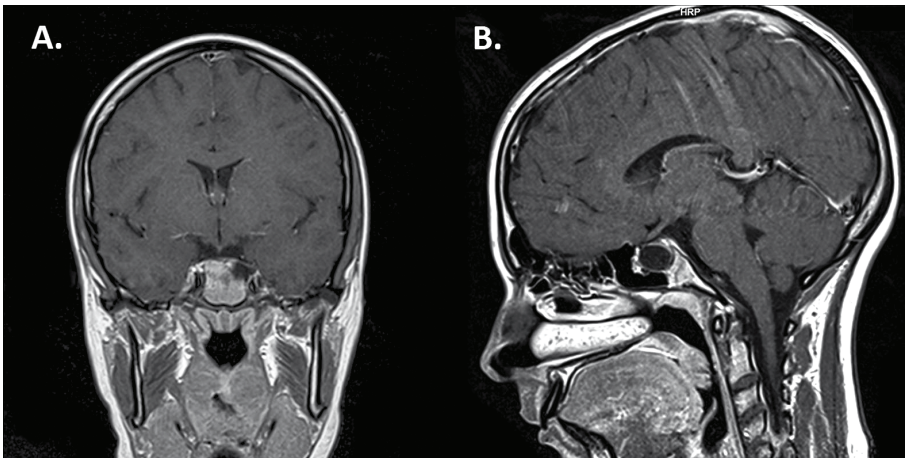

Fig. 2. After two years completion of cabergoline treatment, an impressive shrinkage with liquefaction of the mass is observed (1.43 × 2.14 × 1.93 cm) in contrast-enriched coronal (A) and sagittal (B) MRI planes.

of treatment with cabergoline. An impressive shrinkage of the mass was observed with the mass now looking heterogeneous and with dimensions that were reduced approximately by half (1.60 × 2.18 × 1.81 cm). No more encirclement of the left carotid artery was observed. Gonadal function was restored and the patient entered into puberty. Last MRI performed with the completion of 2 years on cabergoline showed further but smaller reduction of the mass that now was 1.43 × 2.14 × 1.93 cm and has undergone liquefaction (Figure 2). During these two years of treatment the patient had menarche and normal menses since.

DISCUSSION

Giant prolactinomas represents an extreme subset of macroprolactinomas characterized by huge mass size (>40 mm), massive extrasselar involvement and levels of prolactin >1000 ng/ml (Shrivastava *et al.* 2002). Despite dopamine agonists being first line treatment for macroprolactinomas of any size (Melmed *et al.* 2011), with cabergoline being particularly advantageous over other dopamine agonists, little is known regarding its efficacy in the treatment of giant prolactinomas. Relatively recent published series of giant prolactinomas treated with cabergoline have shown promising results both in normalization of prolactine levels and in tumour shrinkage (Corsello *et al.* 2003; Shimon *et al.* 2007; Cho *et al.* 2009). However, all these reports involve adult men. Experience in children with giant prolactinomas treated with cabergoline is limited only in sporadic case reports (Krassas *et al.* 1999). Despite the limited experience in pediatric population, we justified our decision to commence on cabergoline based on the promising results in adult men, the lack of serious side-effects and the absence of specific neurological complications that advocate immediate surgical intervention.

Dopamine agonists have been widespreadly used for the treatment of patients with prolactinomas for many decades. However, the optimal treatment strategy and duration of treatment is still a matter of debate. In 2006, the Pituitary Society provided guidelines for the clinical care of patients with hyperprolactinemia (Casanueva *et al.* 2006). According to these guidelines withdrawal of dopamine agonists and close follow-up is recommended when prolactin levels are normal for at least 2 years and there is a reduction in tumor size by more than 50%. These recommendations justify a withdrawal of cabergoline in our patient as both criteria are well fulfilled. However, in the first clinical study that met the above criteria for withdrawal of dopamine agonists results were not so encouraging (Kharlip *et al.* 2009). The estimated risk of recurrence of hyperprolactinemia for all patients was 63% by 18 months, whereas selectively in the macroprolactinoma group hyperprolactinemia recurred in 55% after a median period of 3 months. The 2011 guidelines on diagnosis and treatment of hyperprolactinemia of the Endocrine Society had taken a more cautious approach by stating that dopamine agonist should be tapered and perhaps discontinued in patients after 2 years of treatment, with normal prolactin levels and no visible tumor remnant on MRI (Melmed *et al.* 2011). Following these recommendations, our patient should continue on cabergoline. In 2010, a published meta-analysis of studies on persisting normoprolactinemia after withdrawal of dopamine agonists in patients with hyperprolactinemia tried to determine factors influencing a successive treatment outcome (Dekkers *et al.* 2010). Prognostic factors for a favorable outcome was idiopathic hyperprolactinemia versus both micro- and macro-prolactinoma, duration of treatment more than 25 months and the use of cabergoline over other dopamine agonists. According to this study, our patient gathers two favorable prognostic factors (duration of treatment and type of dopamine agonist used), however, initial size of the lesion contradicts a desired outcome.

In summary, we have reported a rare case of a giant prolactinoma in a prepubescent girl treated with cabergoline. The initial dilemma between medical or surgical management has been replaced now by the dilemma whether the medical treatment should continue lifelong or should be discontinued. Further evidence is required to support such a decision.

REFERENCES

1 Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, *et al.* (2006). Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) **65**: 265–273.
2 Cho EH, Lee SA, Chung JY, Koh EH, Cho YH, Kim JH, Kim CJ, Kim MS (2009). Efficacy and safety of cabergoline as first line treatment for invasive giant prolactinoma. J Korean Med Sci **24**: 874–878.
3 Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G (2003). Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med **349**: 2023–2033.
4 Corsello SM, Ubertini G, Altomare M, Lovicu RM, Migneco MG, Rota CA, Colosimo C (2003). Giant prolactinomas in men: efficacy of cabergoline treatment. Clin Endocrinol (Oxf) **58**: 662–670.
5 Dekkers OM, Lagro J, Burman P, Jorgensen JO, Romijn JA, Pereira AM (2010). Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab **95**: 43–51.
6 Kharlip J, Salvatori R, Yenokyan G, Wand GS (2009). Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. J Clin Endocrinol Metab **94**: 2428–2436.
7 Krassas GE, Pontikides N, Kaltsas T (1999). Giant prolactinoma presented as unilateral exophthalmos in a prepubertal boy: response to cabergoline. Horm Res **52**: 45–48.
8 Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine S (2011). Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab **96**: 273–288.
9 Shimon I, Benbassat C, Hadani M (2007). Effectiveness of long-term cabergoline treatment for giant prolactinoma: study of 12 men. Eur J Endocrinol **156**: 225–231.
10 Shrivastava RK, Arginteanu MS, King WA, Post KD (2002). Giant prolactinomas: clinical management and long-term follow up. J Neurosurg **97**: 299–306.