Brief Communication

Growth hormone deficiency, secondary hypothyroidism, and empty sella following treatment of childhood macroprolactinoma

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ABSTRACT

Macroprolactinoma are rare in childhood, especially in the first decade. A 9-year-old girl presented with headache, vomiting, and decreased vision for 8 months. A diagnosis of macroprolactinoma was made following documentation of elevated serum prolactin (958 ng/ml) with a contrast enhancing macroadenoma (30 × 27 × 28 mm) on magnetic resonance imaging of pituitary. Anterior pituitary function was normal. Cabergoline therapy resulted in resolution of all symptoms in 2-8 months. Revaluation at 10 months of cabergoline therapy revealed normal serum prolactin (14 ng/ml), normal pituitary function, with 91% decrease in adenoma size (11.5 × 13.6 × 12.7 mm). Evaluation at 36 months of cabergoline therapy for growth arrest and weight gain for past 6 months revealed low serum prolactin, growth hormone deficiency, and secondary hypothyroidism with empty sella. She had biochemical as well as structural resolution of prolactinoma. This report highlights the development of multiple pituitary hormone deficiency with empty sella, an uncommon side effect of cabergoline therapy for macroprolactinoma.

Key words: Cabergoline, empty sella, macroprolactinoma, pituitary hormone deficiency

Introduction

Pituitary adenomas are rare in childhood and constitute 4% of all pituitary adenomas. As compared with adults, they are more likely to be functioning (95% vs. 33%) and tend to be larger (70% have suprasellar extension).[1] Although prolactinomas are the most common pediatric and adolescent pituitary tumors (50%), they are uncommon in the first decade, with ACTH secreting tumors being the most common type (71%).[2]

Dopaminergic agonists (DA) are the primary therapy for prolactinomas. These drugs, especially cabergoline are well tolerated and side effects are uncommon. Empty sella (partial or complete) is a rare complication of DA therapy.[3,4] We present a child with macroprolactinoma who responded to cabergoline with resolution of symptoms and a complete regression of macroadenoma, but subsequently developed growth hormone deficiency and secondary hypothyroidism with empty sella.

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Case Report

A 9-year-old girl presented with headache, nausea, vomiting, and decreased vision of 8 months duration. Automated perimetry revealed bitemporal hemianopia. Evaluation of anterior pituitary function revealed elevated serum prolactin (958 ng/ml), normal cortisol, thyroid function, and insulin-like growth factor 1 (IGF-1) [Table 1]. Magnetic resonance imaging (MRI) brain (February 2009) showed 30 × 27 × 28 mm sellar mass with predominant suprasellar extension compressing the optic chiasma [Figure 1a]. Cabergoline was initiated, initially at 0.5 mg/week increased to 1.5 mg/week over 6 months and continued. There was rapid improvement of symptoms with resolution

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of headache followed by resolution of nausea and vomiting by 2 months, vision became normal by 8 months of therapy. Revaluation after 10 months of initial diagnosis revealed normal serum prolactin with normal anterior pituitary function [Table 1]. MRI brain that time (November 2009) showed a 91% reduction in tumor size, now measuring 11.5 × 13.6 × 12.7 mm.

Complaints of lack of height gain, along with increased weight for 6 months, lead to revaluation in January 2012 (after 3 years of cabergoline therapy). Her height was 131 cm (<3rd percentile, height standard deviation score (SDS): −2.06; target height SDS: −1.4), height velocity 4 cm/year and body mass index (BMI) was 21.9 kg/m^2 (85th percentile). Sexual maturity rating was prepubertal. Perimetry was normal this time. Hormonal evaluation revealed, low serum prolactin, secondary hypothyroidism, and growth hormone deficiency [Table 1]. MRI brain showed complete resolution of pituitary adenoma with empty sella and absent posterior pituitary signal [Figure 1b].

A diagnosis of complete regression of macroprolactinoma with growth hormone deficiency and secondary hypothyroidism with empty sella was made in an overweight adolescent girl who had received cabergoline for 3 years for macroprolactinoma. Cabergoline was stopped. Levothyroxine was initiated at 50 μg/day. She could not afford growth hormone replacement [Figures 2 and 3].

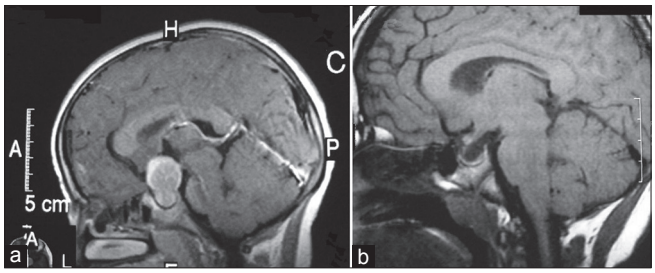

Figure 1: (a) (February 2009) T1W MRI brain showing pituitary macroadenoma with predominant suprasellar extension. (b) (January 2012) T1W MRI brain showing empty sella with absent posterior pituitary signal

Discussion

Cabergoline is the most commonly used DA for treating prolactinomas. DA act not only by inhibiting the synthesis and release of prolactin, but also have a direct cytocidal effect on the tumor.[5] Long-term remission after 2-3 years of cabergoline therapy is 30-40% for microprolactinomas, but lower and not well

Table 1: Changes in hormonal status of patient over 3 years

Parameter	Baseline (February 2009)	Follow-up	
		(November 2009)	Current status (January 2012)
Prolactin (ng/ml)	958	14	1.11
fT3 (pg/ml) (1.5-4.1)	1.6	1.4	1.3
fT4 (ng/dl) (0.8-1.9)	1.34 (0.9-1.8)	1.21	0.8
TSH (μIU/ml) (0.4-4)	2.1	2.29	4.58
8 am cortisol (μg/dl) (5-25)	17	19.4	20.4
LH* (μIU/ml) (0.8-7.6)	0.12	1.42	1.17
FSH* (μIU/ml) (0.7-11.1)	3.14	5.2	4.12
IGF-1 (ng/ml)	172 (74-388)	196 (88-452)	133 (143-693)#
GH (baseline) (ng/ml)	-	-	2.3#
30 min GH (ITT) (ng/ml)	-	-	1.9#
60 min GH (ITT) (ng/ml)	-	-	1.6#
90 min GH (ITT) (ng/ml)	-	-	0.9#
120 min GH (ITT) (ng/ml)	-	-	0.9#

fT3: Free tri-iodothyronine, fT4: Free tetra-iodothyronine (thyroxine), TSH: Thyroid stimulating hormone, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, *LH and FSH estimated at 40 minutes after giving injection triptorelin 100 μg sc., IGF: Insulin like growth factor, GH: Growth hormone, ITT: Insulin tolerance test was done with 0.15 U/kg regular insulin (7 U) given iv. when blood sugar of 37 mg/dl was documented at 90 min, initial ITT with 0.1 U/kg insulin (3.7 U) did not produce hypoglycaemia, #IGF-1 assay as well as ITT was done after normalization of serum fT4 using levothyroxine 50 mcg/day, Priming before ITT was done using ethinyl estradiol 50 m/cg/day given for 3 days before the test, Estimations were done using chemiluminiscence (CLIA) assay (Immulite-1000, USA)

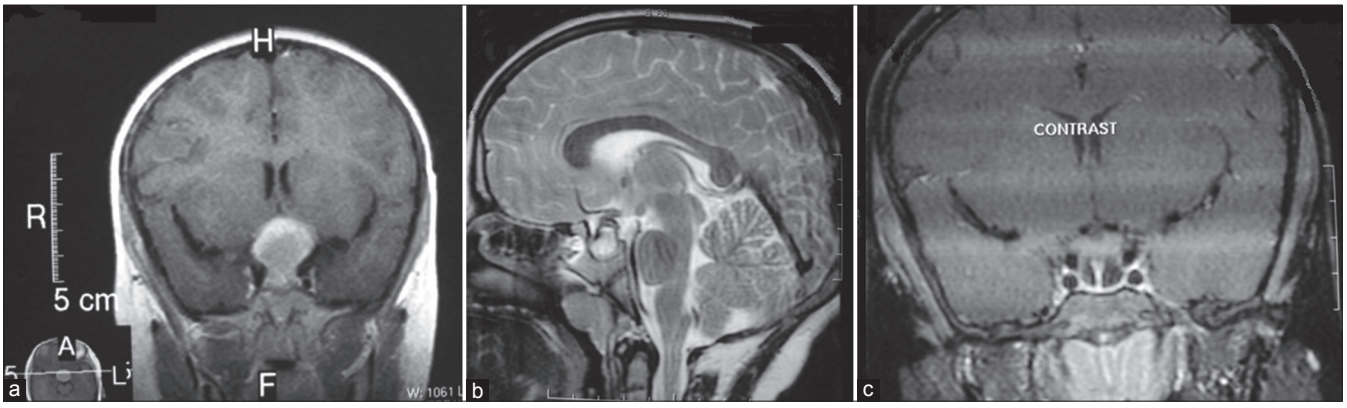

Figure 2: (a) Coronal section of MRI brain showing pituitary macroadenoma with predominant suprasellar component (February 2009), (b) MRI brain showing significant reduction in macroadenoma size after 10 months of cabergoline therapy (November 2009) (c) MRI brain coronal section showing empty sella with stalk traced till the floor of sella after 3 years of cabergoline therapy (January 2012)

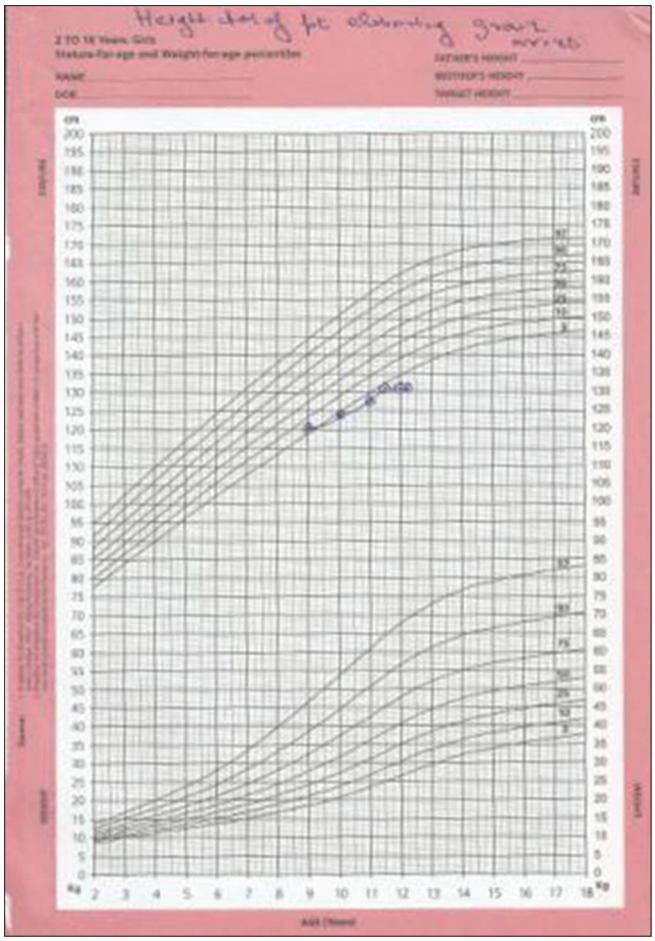

Figure 3: Growth chart

documented for macroprolactinomas.[6] Side effects are uncommon with cabergoline with a study showing only 3% patients stopping cabergoline as compared with 12% on bromocriptine as a result of adverse events.[7] The most common adverse event is nausea or vomiting, followed by headache and dizziness.[7] Rare side effects include cerebrospinal fluid (CSF) rhinorrhea, intratumoral hemorrhage, and cystic transformation; the last two may be associated with deterioration in visual acuity.[3] There has been a report of visual deterioration due to herniation of optic chaisma into the partial empty sella, a consequence of rapid regression of tumor size following bromocriptine therapy, which improved on cessation of bromocriptine.[4]

Hypopituitarism is a common associated presenting feature of prolactinomas with a study reporting 53% of prolactinomas having this problem during clinical presentation.[8] Recovery of pituitary function was reported in that study following cabergoline therapy, with GH and ACTH secretion recovering in 62.5% and 60% of the patients, respectively.[8] However, hypopituitarism following DA therapy for prolactinoma is unusual.

Our patient had macroprolactinoma, which responded remarkably to cabergoline therapy, with resolution of all symptoms, normalization of vision, biochemical remission, and reduction of tumor size. Presence of normal pituitary function at diagnosis goes against the hypothesis of macroprolactinoma damaging surrounding normal pituitary cells thus causing hypopituitarism. Absence of sudden clinical worsening with lack of features of increased intracranial tension makes pituitary apoplexy or infarction an unlikely cause for this empty sella. Presence of a huge macroadenoma at baseline with rapid response to cabergoline (91% reduction in tumor size in 10 months) may explain the increased susceptibility of tumor cells to shrinkage and apoptosis and thus leading to empty sella after 3 years. A rapid reduction of tumor size following DA therapy may thus increase the risk of empty sella in the long run.

Hypopituitarism following cabergoline therapy for macroprolactinoma in the absence of pituitary apoplexy is uncommon, and may represent a direct effect of cabergoline on pituitary cells. Pituitary function should be evaluated in patients on long-term DA therapy, especially in those who are symptomatic or have rapid reduction in tumor size or empty sella on imaging.

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