

NOTE

Normal Growth and Pubertal Development During Bromocriptine Therapy in Two Patients with Prolactinoma

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Abstract. The cases of two boys, a 14 years 10 months old and an 18-year-old, with delayed puberty are presented. The first patient also had a short stature. Both patients had a pituitary adenoma, as shown by computed tomography, with high prolactin levels. After bromocriptine therapy was started, there was a spontaneous progression of normal puberty. The first patient used a synthetic growth hormone together with bromocriptine, however, even after the growth hormone was stopped progression in puberty and gain in height continued. The favorable response obtained in these patients implies that bromocriptine can be an effective therapy for adolescent patients with prolactinoma.

Key words: Bromocriptine, Puberty, Prolactinoma

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HYPERPROLACTINAEMIA in adult males causes impotence and hypogonadism [1–5]. Although prolactinoma is known as the commonest pituitary tumor found in adults, it is rarely detected in childhood or in adolescent males [1, 2, 4–18]. In the adolescent, it has been reported as a cause of delayed puberty, pubertal arrest, or very rarely as a cause of precocious puberty [1, 2, 8, 17]. In addition, growth hormone (GH) insufficiency is also a common presentation of prolactinomas in childhood [5, 7].

We now report the cases of two males, a 14 years 10 months old and 18-year-old, with prolactinoma and pubertal arrest. The first patient was treated with bromocriptine (BC) and a synthetic GH in combination, and later with BC as a sole agent. The second patient was treated only with BC. The

BC treatment appeared to be effective and free of complications.

Case Report

Case 1

A 14 years 10 months old boy was seen in July 1988 for evaluation of his short stature and delayed puberty. It had been noticed by his parents that he was lagging in height when compared with his peers for the last three years. There was no family history of short stature or head trauma during childhood. He had no systemic illness and he did not describe any ejaculation.

On physical examination, he was an early pubertal-appearing male with a height of 147 cm (<3 percentile, SD score -2.88) and weight of 49 kg (25 percentile). His arm span was 151 cm and his upper segment to lower segment ratio was 0.99, the upper segment being 73 cm and the lower segment being 74 cm. He had no axillary or pubic

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hair, and he had neither gynecomastia, nor galactorrhea. His right and left testes were 4 and 5 ml respectively, and his stretched penile length was 5 cm.

At presentation the patient's hormonal evaluation was serum LH 3.9 mIU/ml, FSH 12.6 mIU/ml, total testosterone 189.2 ng/dl and prolactin (PRL) 169.3 and 200.0 ng/ml. His thyroid function and cortisol reserve (after stimulation with 0.1 U/kg insulin) were normal, but his GH reserve was found grossly subnormal, the peak GH responses after stimulation with insulin (0.1 U/kg) and with levodopa (500 mg) being 1.1 and 5.9 ng/ml respectively, and during strenuous exercise, the highest GH level was 0.6 ng/ml. All the tests involving the evaluation of GH response were performed three days after 50 mg testosterone was administered intramuscularly. The patient's testosterone level was found to be 553 ng/dl following four daily intramuscular injections of 4000 U human chorionic gonadotropin. The buccal smear showed no X chromatin and his bone age was equivalent to 10 years. A high resolution computed tomographic (CT) evaluation of the patient's sella, revealed a 7 mm hypodense intrasellar mass suggesting a microadenoma of the pituitary. The patient's visual field examination was normal.

A diet providing 1400 kcal/day and BC therapy (2.5 mg/day) was started, the BC dose being gradually increased to 10 mg/day. Later, since the serum PRL levels were still high at this dose, the daily BC dose was increased to 15 mg/day. Treatment with synthetic human growth hormone given subcutaneously at a daily dose of 4 U, six days a week was begun at the same time as BC. Within four months of this treatment the patient's serum PRL level descended to 8 ng/ml. By the sixth month of treatment, his height was 150.5 cm, his weight was 52 kg, and his right and left testicular

volumes were 6 and 8 ml respectively. He had also acquired scanty axillary and pubic hair, and his breasts had begun to enlarge and they were tender. At the end of nine months, the adenoma could not be detected by sella CT, and the patient's testicular volumes were 12 ml bilaterally. At this stage, after GH therapy had been stopped for ten days, the provocative tests for GH secretion were repeated. The peak GH responses were 9.4 ng/ml with insulin hypoglycemia, 22.2 ng/ml with levo dopa stimulation and 6.0 ng/ml with strenuous exercise. Having thus obtained some GH response to stimuli, GH treatment was stopped and the patient continued on BC alone. Three months later, the GH provocative tests were repeated with somewhat better responses (peak GH 8.5 ng/ml with insulin, 21.4 ng/ml with levo dopa, 20.3 ng/ml with strenuous exercise). In the following period, the BC dose was decreased first to 10 mg/day, and later to 5 mg/day without causing a rise in serum PRL levels. The dramatic decline in PRL levels and the increase in testosterone concentrations were followed by pubertal progress and an accelerated growth rate, sperm count being 98 millions/ml (liquefaction 2.2 min, volume 1 cc, pH 8, 60% sperm motility, 70% normal sperm morphology). The features of the patient and the hormonal evaluation during treatment are summarized in Tables 1, 2 and 3. In Table 3 the decline in prolactin and the increase in testosterone levels can be seen, however at 12 months there was a markedly high PRL level. This value was obtained at the end of a 2 month period when the patient was unable to obtain and use BC.

In the patient's last examination in November 1993, his sperm count was 58 millions/ml and his sella CT was normal. His case is still being followed and he is being treated with a BC dose of 5 mg/day.

Table 1. Growth hormone provocative tests of case 1 during treatment

Months under treatment	Tests			Treatment	
	insulin	levodopa	exercise	BC	GH
	GH (peak, ng/ml)			(mg/day)	(6×4 U/week)
0	1.1	5.9	0.6	10–15	+
9	9.4	22.2	6.0	15	+
12	8.5	21.4	20.3	10	–

GH, growth hormone treatment; BC, bromocriptine treatment.

Table 2. Clinical features of case 1 during treatment

Months under treatment	Age (years, months)	Height (cm)	SD score	Bone age	Testis (ml) right/left
0	14.10	147	-2.88	10	4/5
6	15.4	150.5	-2.88		6/8
9	15.7	155	-2.29	13	12/12
12	15.10	156	-2.15		12/15
24	16.10	161	-2.06	15	15/15
36	17.10	168	-1.32		15/15
48	18.10	170	-1.16		15/15

Table 3. Hormonal evaluation of case 1 during treatment

Months under treatment	Serum hormone levels				Treatment	
	FSH mIU/ml	LH mIU/ml	PRL ng/ml	T ng/dl	BC mg/day	GH 6×4U/week
0	12.6	3.9	200.0	189.2	10	+
6			12.0		15	+
9	23.8	8.4	33.0	333.3	15	+
12	8.5	8.7	140.3	632.0	10	-
24	13.2	5.7	2.0	356.0	5	-
36	9.6	11.0	23.0	861.0	5	-
48			5.4		5	-

GH, growth hormone therapy; BC, bromocriptine therapy; PRL, prolactin; T, testosterone.

Case 2

A 18-year-old boy was seen in November 1989, for evaluation of hypogonadism. He had complaints regarding his sexual development, such as inadequacy of penile length and beard. He had noticed that he was lagging behind his peers in those respects for the previous 4 years. The patient was from a rural part of Turkey where he has given a short period of therapy two years earlier for the same complaints, and it is probable that he used androgenic preparations.

On physical examination, his height was 164 cm (<3 percentile), his weight was 67.5 kg and his body mass index was 26. He was noted to have minimal axillary hair and his right and left testes were measured as 3 and 4 ml respectively. His stretched penile length was 3.5 cm. He had an arm span of 172 cm, and his upper segment/lower segment ratio was 0.86, the upper segment being 76 cm and the lower segment being 88 cm. He was rather on the short side with a SD score of -1.98, but his

bone age was however 18. He had no X chromatin on buccal smear. The patient had normal serum free T3 (6.0 pmol/L), free T4 (20.0 pmol/L) and TSH (1.4 U/ml) levels. The TSH response to TRH, 400 µg (iv) was normal, and his serum LH was 6.1 mU/ml, FSH 1.6 mU/ml, and testosterone 52 ng/dl at presentation. His serum PRL level was 187.5 and 200.7 ng/ml on two examinations. The patient showed a subnormal response to iv 100 µg bolus LHRH test, and after 0.1 U/kg iv insulin was given, his peak GH level was 7.3 ng/ml and peak cortisol level was 44.0 µg/dl. After four daily im injections of 4000 U human chorionic gonadotropin were given his testosterone level increased to 1710 ng/dl. The CT examination of the patient's sella revealed a sellar mass of 12 mm with suprasellar extension suggesting a pituitary macroadenoma. The patient's visual fields were shown to be normal.

BC therapy was begun at a dose of 2.5 mg/day and was gradually increased to 10 mg/day during the following months together with a calorie restricted diet. After three months of therapy the

Table 4. Hormonal evaluation of case 2 during treatment

Months under treatment	Serum hormone levels				Treatment bromocriptine mg/day
	FSH mIU/ml	LH mIU/ml	PRL ng/ml	T ng/dl	
0	1.6	6.1	187.5	52.0	—
3	10.9	3.8	68.7	249.7	5
6	11.3	5.7	144.1*	321.1	7.5
9				369.4	10
12	2.7	9.7	24.1	292.9	10
36	7.3	18.4	11.2	520.3	10

PRL, prolactin; T, testosterone.

*The transient elevation in PRL levels were thought to be due to non-compliance with drug therapy.

patient's PRL level decreased to 68.7 ng/ml. Six months later his testes began to enlarge bilaterally with mild gynecomastia. At the end of nine months a near normal sperm analysis (50 millions/ml, volume 3 cc, 60% sperm motility, 70% normal sperm morphology) was noted. The decline in PRL levels was followed by an increase in testosterone levels and pubertal progress. Unfortunately, in serial computerized tomographic investigations no regression was observed in the adenoma. The patient's case is still being followed, and he is receiving BC treatment as indicated in Table 4. In the last physical examination, 36 months from the beginning of BC therapy, his height was 165 cm, his respective right and left testes volumes were 15 and 20 ml and he described normal sexual functions.

Discussion

Prolactinomas, probably due to the inhibitory effect of PRL on GnRH, are one of the major causes of hypogonadism in adult males [2, 4, 5]. They are detected rarely in childhood and in adolescent males, but when present are frequently associated with delayed puberty and short stature [2, 4, 5–8, 19]. As with adults, BC therapy has also been reported as safe and without adverse reaction in the adolescent [2, 5–8, 19–23]. Our first patient was a 14 years 10 months old boy, who had a pituitary microadenoma, delayed puberty and short stature. During treatment with BC, a gradual decline in serum PRL levels was detected, the tumor disappeared and no adverse reactions were seen. An

increase in serum testosterone levels was noted, together with the decrease of serum PRL concentrations. In addition, GH responses to provocative stimuli which were subnormal on the patient's first presentation markedly improved at the end of nine months of combined therapy with BC and synthetic GH. There was also spontaneous progression of normal puberty and height, with BC therapy alone, after the synthetic GH treatment was discontinued. Short stature in adolescent patients having prolactinoma is probably due to two mechanisms: (a) abnormality in GH secretion as a result of either direct pituitary damage caused by a tumor or dopaminergic insufficiency caused by high PRL levels [5, 8, 19]; (b) absence of pubertal growth spurt due to either the inhibition of gonadotropin secretion by high PRL levels or by direct tumoral effect on pituitary gonadotrophs [2, 5, 7].

In our second patient there was a decrease in serum PRL levels in parallel with the clinical responses in the form of accelerated pubertal development. There was no regression observed in the tumor size in repeated tomographic examinations. In some previous reports, tumor regression was not observed in every case of prolactinoma with BC treatment [3, 8, 25]. In fact, BC treatment has been shown to have no effect on tumor size in 1/3 of the cases studied in some reports, although in such cases PRL levels can be decreased by the drug [3, 8, 25]. Whilst this patient has a macroadenoma, we have found it appropriate to follow him for a while under BC treatment without surgery in consideration of his favourable clinical response.

At presentation, this patient had eunuchoid ap-

pearance and hypogonadism. His bone age was however 18. This was probably due to the treatment he had used before, which he described in his history. These preparations were probably androgenic which might cause the advance in his bone age, and he certainly had only 1 cm increase in his height during BC treatment.

The adequate growth velocity and pubertal development seen in the first case with BC therapy (even after synthetic GH treatment had been stopped), and the initiation and progression of puberty observed in the second patient with only BC suggest BC could be the first line of therapy in adolescents as it is in adults. Transsphenoidal surgery should be preferred for patients who are intolerant or insensitive to treatment with dopamine agonists [3]. Such surgical therapy is successful in 80–85% patients with microadenoma, and in macroadenomas the success rate is even more [3].

Although surgery has the opportunity for rapid decompression of an adenoma and potential cure,

the incidence of hyperprolactinemia and tumor recurrence must be considered [24]. Prior to the advent of medical therapy surgical resection and/or radiotherapy had been the preferred treatment of choice, however irradiation does not effect a rapid reduction in serum PRL, but it does appear to be effective in the longterm prevention of hyperprolactinemia. Further more, development of pituitary insufficiency occurs in patients given radiotherapy and requires careful follow up [24].

We think that although prolactinomas are rare in the adolescent, they must still be considered in the diagnosis of children with delayed puberty, and be treated because of their serious clinical consequences. In other adolescent prolactinoma cases too, BC treatment may prove to be an easy and effective form of treatment as it did in the cases presented here. Other dopamine agonists may be effective like BC in this treatment, but there is little experience with them in the adolescent group.

References

- Slonim A, Glick AD, Island DP, Kasselberg AG (1982) Hyperprolactinemia associated with advanced puberty in male. *J Pediatr* 101: 236–239.
- Patton ML, Woolf PD (1983) Hyperprolactinemia and delayed puberty: A report of three cases and their response to therapy. *Pediatrics* 71: 572–574.
- Grossman A, Besser GM (1985) Prolactinomas. *Br Med J* 290: 182–184.
- Howlett TA, Wass AH, Grossman A, Plowman PN, Charlesworth M, Touzel R, Rees LH, Savage MO, Besser GM (1989) Prolactinomas presented as primary amenorrhea and delayed or arrested puberty: response to medical therapy. *Clin Endocrinol* 30: 131–140.
- Sack J, Friedman E, Tadmor R, Sahar A, Katznelson D (1984) Growth and puberty arrest due to prolactinoma. *Acta Paediatr Scand* 73: 863–867.
- Triwary C (1989) Prolactinoma in an adolescent girl: Unusual response to bromocriptine therapy. *Am J Dis Child* 143: 521–523.
- Ross RJM, Mc Eniery JM, Grossman A, Doniach I, Besser GM, Savage MO (1989) Massive prolactinoma with galactorrhea in a prepubertal boy. *Postgrad Med J* 65: 403–406.
- Oberfield SE, Nino M, Riddick, Pang S, Nagel M, Khandji A, Kairam R, Levine LS (1992) Combined bromocriptine and growth hormone treatment in GH-deficient children with macroprolactinoma *in situ*. *J Clin Endocrinol* 75: 87–90.
- Rohn RD (1984) Galactorrhea in the adolescent. *J Adolesc Health Care* 5 (1): 37–49.
- Dandona P, Mohiuddin J, Lindsay KW (1984) Galactorrhea following hypophysectomy in a boy with a prolactinoma. *Postgrad Med J* 60 (706): 540–541.
- Perani D, Colombo N, Scotti G, Tonon C (1984) Rapid size reduction of giant prolactinoma following medical treatment. *J Comput Assist Tomogr* 8 (1): 131–133.
- Miyanochara D, Kusumoto K, Asakura T, Kodama S, Kawasaki T (1993) A juvenile male prolactinoma: a case report. *No Shinkei Geka* 21 (4): 361–366.
- Fideleff HL, Boquete HR, Orlandi AM, Wainstein L, Holland ME (1991) The course of prolactinomas in adolescents. *Medicina B Aires* 51 (2): 121–126.
- Angyal EA, Lee HJ, Wolansky LJ, Koenigsberger MR, Nathanson D, Zimmer AE (1993) Prolactinoma invasion of superior orbital vein: CT and MR findings. *J Comput Assist Tomogr* 17(6): 964–966.
- La Selve H, Paris A, Morel Y, Grisoli F, Lucas C, Jaquet P, David M (1985) Prolactin adenoma in a 14-year-old boy. *Pediatric* 40(6): 469–473.
- Schroffner WG (1976) Prolactin-secreting pituitary tumor in early adolescence. *Arch Intern Med* 136: 1164–1168.
- Faggiano M, Criscuolo T, Perrone L, Quarto C, Sinisi

- AA (1980) Sexual precocity in a boy due to hypersecretion of LH and prolactin by a pituitary adenoma. *Acta Endocrinol* 102: 167–172.
18. Beck W, Stubbe P, Lüdecke D (1979) Prolactin producing pituitary adenoma in a 9 year old boy. *Eur J Pediatr* 130: 193–198.
 19. Dalzell GW, Atkinson AB, Carson DJ, Sherldan B (1987) Normal growth and pubertal development during bromocriptine treatment for a prolactin-secreting pituitary macroadenoma. *Clin Endocrinol* 26: 169–172.
 20. Molitch ME, Elton RL, Blackwell RE, Caldwell RE, Chang RJ, Jaffe R, Joplin G, Robbins R, Tyson J, Thorner MO BCSG (1985) Bromocriptine as primary therapy for prolactin secreting macroadenomas: Results of a prospective multicenter study. *J Clin Endocrinol Metab* 60: 698–705.
 21. Huseman CA, Rizk G, Hahn F (1986) Long term bromocriptine treatment for prolactin-secreting macroadenoma. *Am J Dis Child* 140: 1216–1217.
 22. Blackwell RE, Younger JB (1986) Long term medical therapy and follow up of pediatric-adolescent patients with prolactin secreting macroadenoma. *Fertil Steril* 45: 713–716.
 23. De Schepper J, Smitz J, Loeb H (1989) Normalization of Growth hormone deficiency during bromocriptine treatment for hyperprolactinemia. *J Pediatr Endocrinol* 3: 273–276.
 24. Vance ML, Thorner MO (1987) Prolactinomas. *Endocrinol Metab Clin* 16(3): 731–737.
 25. Mori H, Mori S, Saitoh Y, Arita N, Aono T, Uozumi T, Mogami H, Matsumoto K (1985) Effects of bromocriptine on prolactin secreting pituitary adenomas. *Cancer* 56: 230–238.