

Original Article

Cabergoline Effectively Induced Remission of Prolactinoma in a 9-year-old Japanese Boy

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Abstract. Prolactinomas are rarely diagnosed in children under the age of 10. A 9-yr-old Japanese boy complained of severe headache and progressive visual disturbance. His growth had been retarded for approximately 3 yr, and his serum PRL level was 811.6 ng/ml. Brain magnetic resonance imaging (MRI) revealed an enlarged pituitary (2.8 × 2.6 × 2.1 cm) with heterogeneous enhancement. He was diagnosed as having a macroprolactinoma accompanied by pituitary apoplexy and growth hormone deficiency. A surgical approach was initially undertaken due to the progressive visual deficits, but a residual tumor was observed, and the level of serum PRL was still high after the surgery. Cabergoline was then started, and the dose was gradually increased to 1.5 mg/wk. The serum PRL level decreased from 138.8 ng/ml to 32.5 ng/ml and 17.7 ng/ml after 5 wk and 19 wk, respectively. At 33 wk of cabergoline treatment, brain MRI demonstrated no evidence of the residual tumor. Thereafter, the serum level of PRL decreased to less than 10 ng/ml, and remission was consistently confirmed on repeated MRI. No adverse events have been observed. The present case suggests that cabergoline can be an effective treatment for prolactinomas in prepubertal children as well as in adults.

Key words: prolactinoma, cabergoline, pituitary apoplexy, growth hormone

Introduction

Prolactinomas are far less common in children than in adults and constitute less than 2% of supratentorial tumors in children (1). The average annual incidence of pituitary adenomas in childhood has been estimated to be 0.1 per million children (2), and prolactinomas represent about half of them. The

mean age at diagnosis of prolactinomas in children and adolescents is approximately 14 yr of age (3). Medical therapy with dopamine agonists is an effective first-line treatment approach for prolactinomas. Cabergoline, a selective D₂ agonist, has been recently demonstrated to be more effective and to have fewer adverse effects than other dopamine agonists (4, 5). This drug was approved in Japan in 2002. So far, only a few cases of child prolactinoma treated with cabergoline have been reported in Japan, especially in children under the age of 10. We here in present a case of prolactinoma that was found in a 9-yr-old Japanese boy. Surgical intervention was undertaken due to progressive symptoms induced by pituitary

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apoplexy, but postoperative pharmacotherapy was required for a persistent tumor. Cabergoline effectively normalized the serum PRL level and induced disappearance of the tumor mass on magnetic resonance imaging (MRI).

Case Report

A 9-yr and 10-mo-old Japanese boy was admitted to our hospital for severe headache and progressive visual disturbance. He was born by normal delivery and had previously been healthy except that his growth had been significantly stunted for approximately 3 yr (Fig. 1). He had been very well until 6 d before, when headaches suddenly developed. These stabbing headaches were located primarily in the front region and were experienced all day. During the 6 d, his left visual acuity and left peripheral vision declined progressively. His height was 126.2 cm (-1.5 SD), which had only increased by 6.7 cm in the previous 3 yr, and his body weight was 26.7 kg (-0.8 SD). His body mass index was 16.8. His bone age, assessed by TW2 for Japanese, was 7 yr and 8 mo. He was fully alert, and his physical findings were normal. His testicular size was below 4 ml. There was no sign of gynecomastia or galactorrhea. Ophthalmological examination showed significant reduction of left visual acuity and severe bilateral visual field defects with bitemporal hemianopsia. Brain MRI revealed a large pituitary tumor ($2.8 \times 2.6 \times 2.1$ cm) with heterogeneous peripheral enhancement (Fig. 2), suggesting pituitary apoplexy. T2-weighted imaging showed enhanced signaling on the left optic nerve, indicating the presence of optic neuritis due to the tumor mass effect. The results of laboratory-test results are shown in Table 1. His serum PRL level was found to be as high as 811.6 ng/ml, and his IGF-1 level was as low as 83.3 ng/ml (-2.0 SD). Since dynamic testing using gonadotropin- or thyrotropine-releasing hormones could precipitate pituitary apoplexy, GH secretion was evaluated by a stimulatory test using arginine. The peak GH

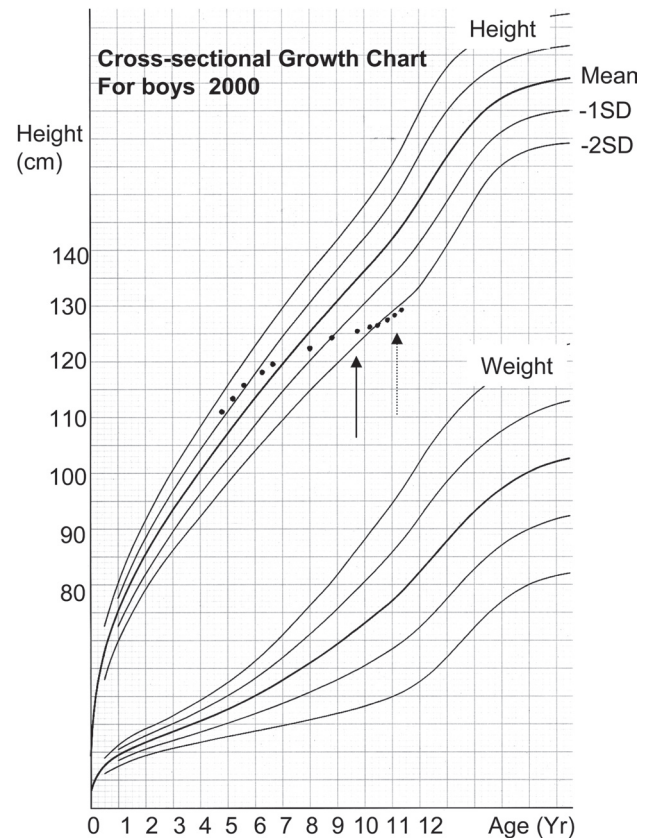


Fig. 1 Growth Curve. Prolactinoma was diagnosed when the patient was 9 yr and 10 mo old (*arrow*). GH replacement therapy was initiated after 62 wk of cabergoline treatment (*dashed arrow*).

level in response to arginine was 1.29 ng/ml, indicating GH deficiency. The levels of thyroid hormones, TSH and ACTH were within the normal ranges, and secretion of posterior pituitary hormone, ADH, appeared to be sufficient.

This patient was diagnosed as having macroprolactinoma accompanied by pituitary apoplexy and secondary GH deficiency. It was considered possible that hemorrhage into the tumor induced an abrupt increase in tumoral volume, which caused severe headache and visual loss. Since these mass effects were severe and complete surgical cure could be expected, transsphenoidal surgical resection of the tumor

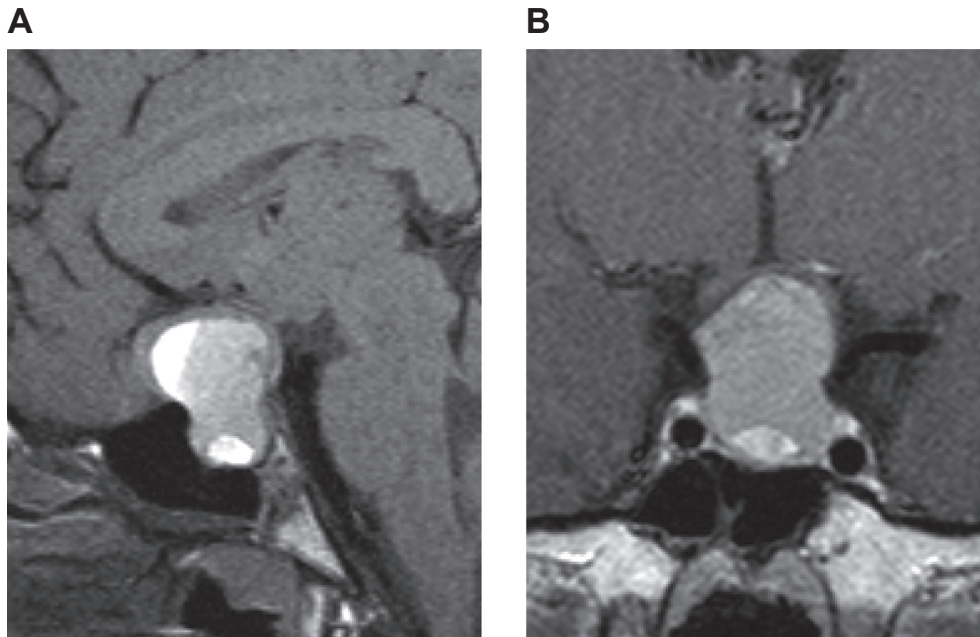


Fig. 2 Pituitary images obtained by T1-weighted MRI after gadolinium injection, midsagittal (A) and coronal (B) views, at diagnosis. An intra- and suprasellar mass (2.8 × 2.6 × 2.1 cm) was enhanced heterogeneously. A peripheral hypersignal and central hyposignal formed a mirror image-like fluid level.

Table 1 Results of laboratory tests at diagnosis

| | | | |
|----------------------|----------------------------------|------------------------------------|-----------------|
| Urinalysis | | Endocrine findings | |
| Specific gravity | 1.020 | fT3 | 2.98 pg/ml |
| Protein | (-) | fT4 | 1.10 ng/ml |
| Osmolarity | 725 mOsm/kg | TSH | 0.64 μ U/ml |
| Complete blood count | | ACTH | 22.5 pg/ml |
| WBC | 5,000 / μ l | cortisol | 9.7 μ g/dl |
| RBC | 461 × 10 ⁴ / μ l | LH | <0.1 IU/l |
| Hb | 12.5 g/dl | FSH | 0.5 IU/l |
| Plt | 19.4 × 10 ⁴ / μ l | IGF-1 | 83.3 ng/ml |
| Blood chemistry | | ADH | 3.6 pg/ml |
| AST | 20 IU/l | PRL | 811.6 ng/ml |
| ALT | 12 IU/l | GH response to arginine (0.5 g/kg) | |
| LDH | 203 IU/l | Basal | 0.37 ng/ml |
| TP | 7.1 g/dl | Peak | 1.29 ng/ml |
| TC | 188 mg/dl | | |
| UN | 12 mg/dl | | |
| Cre | 0.4 mg/dl | | |
| CRP | <0.1 mg/dl | | |
| Glu | 90 mg/dl | | |

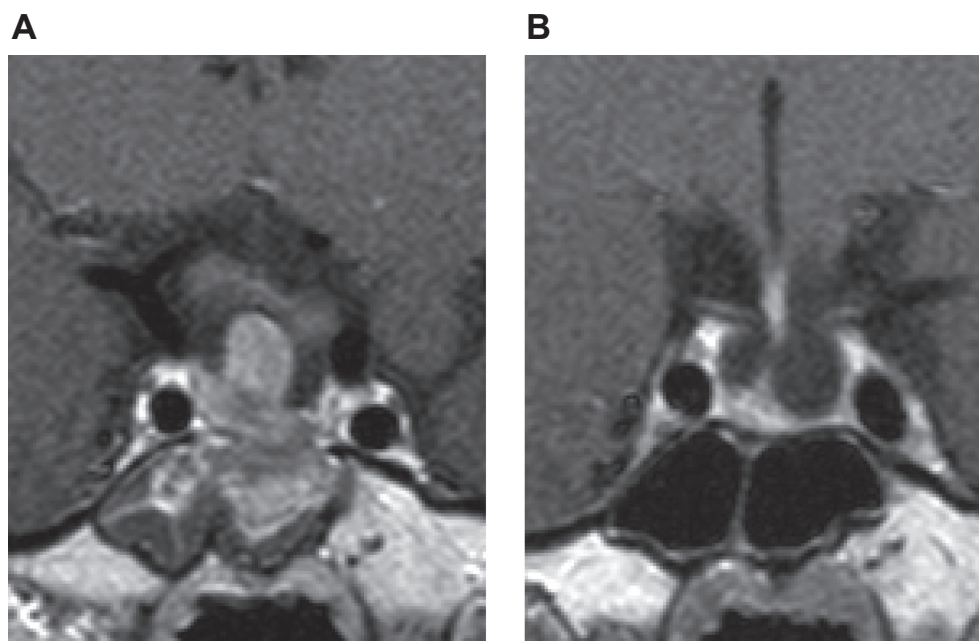


Fig. 3 Pituitary coronal images obtained by T1-weighted MRI after gadolinium injection. A tumor remnant ($0.9 \times 0.6 \times 0.7$ cm) was found after the surgery (A) but disappeared after 33 wk of cabergoline treatment (B).

was undertaken on his seventh day in the hospital. Recovery of visual field and partial improvement of left visual acuity were obtained after the surgery. However, the postoperative serum PRL level remained as high as 183.8 ng/ml, and a tumor remnant ($0.9 \times 0.6 \times 0.7$ cm) was found by brain MRI, as shown in Fig. 3A.

Cabergoline was therefore started at an initial dose of 0.125 mg once a week. The serum PRL level decreased to 86.1 ng/ml after 2 wk (Table 2). Cabergoline was then administered twice weekly, and the dose was gradually increased over 4 wk. After 19 wk of treatment, the serum level of PRL was 17.7 ng/ml under 1.25 mg/wk of cabergoline. The dose was further increased to 1.5 mg/wk and maintained thereafter. Brain MRI performed after 33 wk of treatment showed disappearance of the tumor (Fig. 3B), and a consistent result was obtained on repeated MRI at 62 wk. The level of serum PRL, examined after 73 wk of cabergoline treatment, dropped to 7.1 ng/ml and was completely within the

Table 2 Serum PRL level during treatment with cabergoline

| Treatment week | Cabergoline dose (mg/wk) | PRL (ng/ml) |
|----------------|--------------------------|-------------|
| Basal | – | 811.6 |
| 0 | – | 183.8* |
| 2 | 0.125 | 86.1 |
| 5 | 0.25 | 67.7 |
| 7 | 0.5 | 32.5 |
| 11 | 0.75 | 36.9 |
| 16 | 1.0 | 23.1 |
| 19 | 1.25 | 17.7 |
| 27 | 1.5 | 16.6 |
| 44 | 1.5 | 13.9 |
| 73 | 1.5 | 7.1 |

*After surgery.

normal range. No common adverse events involving nausea, vomiting or hypotension were recognized during the period. Echocardiographic surveillance demonstrated no evidence of

Table 3 Combined stimulatory pituitary test after 44 wk of cabergoline treatment (TRH 5 μ g/kg, Insulin 0.05 U/kg, LHRH 2 μ g/kg)

| | Glucose (mg/dl) | GH (ng/ml) | TSH (μ U/ml) | LH (IU/l) | FSH (IU/l) | PRL (ng/ml) |
|-------|--------------------|---------------|----------------------|--------------|---------------|----------------|
| Basal | 90 | 0.30 | 3.14 | <0.1 | 1.0 | 13.9 |
| Peak | 32* | 1.03 | 15.19 | 1.1 | 3.9 | 46.8 |

*Glucose nadir.

valvular insufficiency.

After 44 wk of cabergoline treatment, his height was 127.5 cm (-2.1 SD). He was 10 yr and 9 mo old at that time, but his bone age was assessed as 8 yr and 9 mo by TW2 for Japanese. He was still at Tanner 1 for puberty, and his levels of thyroid hormones were normal; fT3, fT4 and TSH were 3.72 pg/ml, 1.38 ng/dl and 1.79 μ U/ml, respectively. His serum level of IGF-1 was as low as 61.5 ng/ml (-2.9 SD), and the peak GH level responses to arginine (0.5 g/kg) and GRH (1 μ g/kg) were 1.05 and 6.68 ng/ml, respectively, indicating persistence of severe GH deficiency. The results of a combined stimulatory pituitary test (TRH, insulin, LHRH) are shown in Table 3. Consistently, GH response to insulin was significantly poor. The basal and peak levels of LH and FSH response to LHRH appeared to be lower than those in normal prepubertal boys. However, further observation and reevaluation are required to make a determination in regard to hypogonadism, since gonadotropin secretion may recover following normalization of serum PRL. As shown in Fig. 1, his growth rate appeared to be gradually improving after the tumor shrinkage. The precise mechanism of this was unclear but must be independent from GH recovery or initiation of puberty, since GH deficiency persisted and no sign of puberty was recognized in him as described above.

Brain MRI, which was repeatedly performed after 62 wk of cabergoline treatment, revealed no sign of recurrence of the tumor for 6 mo. GH replacement therapy was therefore initiated at that time (Fig. 1). The serum level of PRL was

monitored cautiously, but it continued to decrease after initiation of GH replacement therapy.

Discussion

Pituitary adenomas are becoming increasingly more common during the adolescent years, but are rarely diagnosed in children under the age of 10. Macroadenomas appear to be more likely to occur in boys than in girls (1). In the case of macroprolactinomas, headache and/or visual field defects are common first symptoms. Short stature has been found in 10–15% of young patients with prolactinomas (3, 6). Our patient's height was at -1.5 SD at the time of diagnosis, but it had only increased by 6.7 cm during the past 3 yr, indicating significant growth retardation. We therefore believed that GH secretion was already impaired when he was 6 or 7 yr old. The onset of prolactinoma in the present case may have occurred at less than 6 yr of age. Unfortunately, he had no chance to be evaluated before he presented severe headache.

Surgical treatment for prolactinomas was the mainstay until the mid-1980s, when a dopamine receptor agonist, bromocriptine, was found to be effective. Recently, indications for surgery include pituitary apoplexy, failure of medical therapy and desire for pregnancy (3). Pituitary apoplexy is a rare life-threatening condition (7). Although urgent surgery is necessary for patients with unstable apoplexy, nonsurgical treatment with careful monitoring has also been recommended for stable apoplexy

(8). Since progressive visual loss was recognized in our patient, we decided to perform the surgical procedure. Although the tumor could not be completely resected, the patient's visual disturbance recovered immediately. However, we do not know whether we should have started cabergoline treatment before surgery or whether prompt resolution could have been obtained nonsurgically.

Cabergoline, a selective D2 agonist, strongly suppresses PRL secretion and synthesis (9). A remarkable tumor-shrinking effect has been recognized in patients with not only microprolactinomas but also macroprolactinomas (10). Furthermore, cabergoline induces fewer adverse effects than other dopamine agonists, and the compliance of this drug is relatively good (11), since it is usually administered once or twice weekly due to its long elimination half-life. Recent observations indicate that cabergoline should be the first-line treatment approach for not only adults but also children, unless immediate surgery is required for complications such as visual loss, hydrocephalus or CSF leak (3). Gillam *et al.* (3) demonstrated that cabergoline, at doses from 0.5–3.5 mg/wk, induced normalization of the PRL levels or disappearance of the tumor in 94% or 24% of cases in 50 adolescents/children with prolactinomas, respectively. However, little information has been provided for pharmacologically treated prolactinomas in children under 10 yr old. Maximum therapeutic doses of cabergoline for prepubertal children have not been suggested, although high-dose treatment has been demonstrated to be effective and safe in adults with drug-resistant prolactinomas (12). The most common adverse events associated with cabergoline are nausea or vomiting followed by headache, dizziness and vertigo (11, 13). Recently, cardiac valvular insufficiency has been reported in patients with Parkinson's disease treated with high doses of cabergoline (14, 15). Pituitary apoplexy during therapy with cabergoline in a 17-yr-old male with macroprolactinoma has also

been documented (16), although it is likely a rare and severe event. In the present case, a dose of as much as 1.5 mg/wk of cabergoline appeared to be sufficient, and no adverse events were observed. We suggest that cabergoline was effective for treatment of this 9-yr-old patient with prolactinoma, but further follow-up is required to evaluate its long-lasting effect and safety.

A protocol for withdrawal of cabergoline has not been established. Colao *et al.* (17) reported recurrence of hyperprolactinemia after 5 yr of cabergoline withdrawal in 32.6% of patients with microprolactinomas and 43.3% of those with macroprolactinomas. Age, basal PRL level, nadir PRL level and nadir tumor diameter after treatment are significantly higher in patients showing recurrence compared with those achieving persistent remission (17). The highest remission rate is found in patients with prolactinomas that disappeared from MRI during cabergoline therapy (3). Gillam *et al.* (3) have proposed that cabergoline can be withdrawn from patients with normoprolactinemia after 2 yr of treatment and when MRI demonstrates complete disappearance of the tumor. No evidence of the tumoral mass was found by MRI after 33 wk of cabergoline treatment in our patient, and his nadir PRL level was 7.1 ng/ml at that time, which could indicate a biochemical cure. We intend to continue the treatment with a sufficient dose of cabergoline for at least one year after tumor disappearance and to then try to reduce the dose gradually to the lowest dose before withdrawal.

Approximately 33.3% of children and adolescents with enclosed macroadenomas presented with some degree of pituitary deficiency (3). GH deficiency develops early, whereas TSH deficiency is a relatively late complication. Resolution of GH deficiency accompanied by pituitary adenomas can be expected with pharmacotherapy-induced PRL normalization. Sakazume *et al.* (18) reported a 13-yr-old Japanese boy with prolactinoma whose growth and GH secretion returned to normal after treatment with

bromocriptine. George *et al.* (19) observed that 6 of 9 patients with macroprolactinoma complicated by GH deficiency recovered normal GH response after treatment with cabergoline. Unfortunately, GH secretion did not return to normal after normalization of the PRL level in the present case. One possible reason for this may be that GH secretion in our patient was already severely impaired at the time of diagnosis. However, we cannot exclude the possibility of surgical complication, since GH deficiency after transsphenoidal surgery has also been reported. Nelson *et al.* (20) analyzed patients with macroadenomas and found that one-third of the patients with some pituitary deficits before surgery improved and that one-third of the patients with such deficits had worsened pituitary function after surgery. Finally, we should also consider the fact that dopamine agonists may have some modulatory effects on the GHRH-GH system. Vance *et al.* (21) reported that dopamine and bromocriptine augment GHRH-stimulated GH secretion in men without pituitary deficiency. On the other hand, Nariai (22) suggested that long-term administration of methylphenidate, which increases the level of dopamine, may interfere with the dopaminergic GH response to insulin and clonidine. At present, we consider it unlikely that GH secretion in our patient was negatively affected by cabergoline; GH response to not only insulin but also GRF was significantly low, suggesting that GH secretion was impaired independently from dopaminergic control.

Initiation of GH replacement therapy should be delayed in patients with prolactinoma, since GH secretion often improves following PRL normalization. However, if the recovery from GH deficiency does not occur, GH therapy can be initiated cautiously. Although there is a theoretical risk of GH-induced tumor enlargement, Colao *et al.* (23) have demonstrated the safety of GH replacement during cabergoline treatment in patients with prolactinomas. They reported that tumors did not regrow in 12 patients with macroprolactinoma during GH

replacement but continued to decrease in size without any significant difference compared with those not requiring GH replacement. At present, a consistent result has been recognized in our patient, but further observation is required because the length of follow-up in our case is insufficient.

In conclusion, we have reported the case of a 9-yr-old boy who presented pituitary apoplexy and was diagnosed with macroprolactinoma. Remission was not achieved after an initial surgical intervention. However, successful response was obtained after treatment with cabergoline; the tumor remnant disappeared on brain MRI, and the serum PRL level returned to normal. We did not find any adverse events correlated with cabergoline. Although GH deficiency was not remedied, it was considered to be independent from cabergoline treatment. Although previously published reports have already demonstrated the effectiveness of cabergoline for prolactinomas in patients including teenagers, there is little available concerning treatment of young children with cabergoline. A treatment schedule for cabergoline in young children has not been documented in detail. The present report suggests that, as in adults and adolescents, cabergoline is an effective treatment approach for prolactinomas in children under the age of 10.

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