

# Hyperprolactinemia in children and adolescents and long-term follow-up results of prolactinoma cases: a single-centre experience

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## ABSTRACT

**Background.** Hyperprolactinaemia refers to increased circulating prolactin and is divided into functional and pathological hyperprolactinaemia. Prolactinoma is the most common cause of severe hyperprolactinaemia. Prolactinomas are rare in children. Treatment outcomes and long-term follow-up data in children are insufficient. Dopamine agonists are the first step in the treatment of prolactinomas. There are no recommendations supported by a high level of evidence regarding the dose and duration of cabergoline treatment.

**Methods.** Patients with hyperprolactinaemia were evaluated for etiological, clinical, and follow-up characteristics. The case files of patients with high prolactin levels who were followed up in our clinic between 2001 and 2019 were reviewed retrospectively.

**Results.** 27 cases (20 female, 7 male) with hyperprolactinemia were detected. The median age of the cases was 15 years (0.3–17.4). Prolactinoma was detected in 40.7% of the cases (n=11). Among these cases, six were macroadenomas. The median prolactin level was 118 ng/mL (34–4340) in those with prolactinoma and 60 ng/mL (22–200) in the hyperprolactinaemia group (p=0.007). In the prolactinoma group, the median age at presentation in macroadenoma cases (13.8 years) was lower than in microadenoma cases (17 years) (p=0.06). There was a negative correlation between prolactin level and height SDS (r=-0.770, p=0.06). In all cases, the median initial cabergoline dose was 0.5 mg/week, and prolactin levels returned to normal within an average of 2.6±2.4 months. Cabergoline treatment achieved a 50% reduction in adenoma size in the first year of treatment without high doses.

**Conclusions.** Prolactinoma consists of an important group among hyperprolactinemia in children. In our study, prolactinoma was detected in 40.7% of children with hyperprolactinemia, and children with prolonged use (over 4 years) tolerated cabergoline well and prolactin levels normalized without high doses. Follow-up is required for relapse after discontinuing the treatment.

**Key words:** hyperprolactinemia, prolactinoma, cabergoline.

Prolactin (PRL) is a hormone secreted from the pituitary gland which has been shown to affect lactation, metabolism, osmoregulation, and the immune and nervous systems.<sup>1</sup> Prolactin excess is defined as hyperprolactinaemia. Hyperprolactinaemia is rare in children and

there are insufficient data on its frequency, aetiology, method, and duration of treatment and follow-up.<sup>2</sup> Hyperprolactinaemia occurs in children, adolescents, and adults for various organic and functional reasons. The frequency of prolactinoma in children with hyperprolactinaemia is also not known.<sup>3</sup> There are no high-level recommendations regarding diagnosing, treating, and monitoring hyperprolactinaemia and prolactinoma in children and adolescents. Similarly, there is not enough data on treatment duration, treatment

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cessation, and follow-up during the period without treatment. In children and adolescents, symptoms usually include functional alterations resulting from hyperprolactinaemia. The clinical manifestations of prolactinomas vary according to gender, age of onset, and tumour size.<sup>4</sup> Prolactinoma is rare in children, and there are few reports of prolactinomas in children. There are difficulties in the management of prolactinomas in children and adolescents. Dopamine agonists are the first step in the treatment of prolactinoma.<sup>5</sup> There is no strong evidence regarding the dose and duration of cabergoline treatment in children and adolescents. In this study, we aim to determine the frequency of prolactinoma among children and adolescents with hyperprolactinemia and long-term follow-up results.

## Material and Methods

The case files of 27 patients with hyperprolactinemia who were followed up in our clinic between 2000 and 2019 were evaluated retrospectively. Using two different measurements, patients with serum PRL levels above normal (<25 g/L in girls and <20 g/L in boys) were included in the study.<sup>2</sup> We recorded admission characteristics, anthropometric measurements, accompanying diseases, medications, puberty stages, and physical examination findings. Neurological examination findings, visual field examination, pituitary function, and cranial imaging results were also evaluated in prolactinoma cases. This study assessed the patients in two groups: prolactinoma (PRLO) and non-prolactinoma hyperprolactinaemia (NPRLO). The given treatment (cabergoline or surgery), treatment doses, duration of treatment, clinical and laboratory evaluation, treatment side effects, and radiological follow-up of patients with prolactinoma were recorded. We recorded echocardiography results performed before and during treatment and other drug side effects in all patients who started treatment.

The study protocol was approved by the Ankara University Ethics Committee (approval number: 15-638-15).

## Statistical analysis

Statistical analyses were performed using SPSS v.23 for Windows (IBM Inc., Chicago, IL, USA). Normality was tested using the Shapiro-Wilk test. Data are presented as mean±SD for parametric data and median (range) for non-parametric data. Student's t-test was used to compare parametric variables, and the Mann-Whitney U test was used for non-parametric data. The Chi-squared test determined significant differences in proportions between categorical variables. The Spearman rank test was used to analyse the correlation between parameters. Crosstab and Fisher's exact tests are used to display the (multivariate) frequency distribution. A  $p < 0.05$  was considered statistically significant.

## Results

Twenty-seven cases (20 girls and 7 boys) were diagnosed with hyperprolactinaemia during the study period. The median age (range) of the patients with hyperprolactinaemia was 15 (0.3–17.4) years, and 74% (n=20) were females. Presenting symptoms were headache in 33.3% (n=9), irregular periods in 11.1% (n=3), vision loss in 11.1% (n=3), galactorrhoea in 3.7% (n=1) and other symptoms (obesity, etc.) in 37% of the hyperprolactinaemia group.

Prolactinoma was detected in 40.7% (n=11) and macroadenoma in 22% (n=6). Other causes of hyperprolactinaemia were defined in 59.3% (n=16). Clinical features of the NPRLO and PRLO are in Table I. Other causes of hyperprolactinemia were sorted into rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysfunction syndrome (ROHHAD) (n=3), craniopharyngioma (n=2), polycystic ovarian syndrome (n=3), septo-optic dysplasia (n=2), drug-induced hyperprolactinemia (n=2), central

**Table I.** Presentation characteristics of cases with hyperprolactinemia.

	NPRLO (N=16)	PRLO (N=11)	P
Age (years) (median (min-max))	11 (0.3-17.4)	13.8 (12-15.5)	
Gender	%75 girl (n=12)	%72.7 girl (n=8)	( <i>p</i> >0.05)
Puberty	%57 pubertal (n=8)	%100 pubertal	
Height SDS (mean ± SDS)	-0, 77 (-4.1-0.79)	0, 67 (-2.04-1.69)	( <i>p</i> =0.005)
Prolactin level ng/mL (median (min-max))	38.7 (22.9-200)	118 (34-4340)	( <i>p</i> =0.007)

NPRLO: nonprolactinoma

PRLO: prolactinoma

neurocytoma (n=1), pituitary stalk interruption syndrome (PSIS) (n=2), and hypothyroidism (n=1).

While symptoms were observed in 89% of PRLO cases (54.5% headache, 27.3% menstrual irregularity, 9.1% galactorrhea), 37.6% of the NPRLO cases were symptomatic (headache, visual impairment). One patient presented with headache and vision loss; cranial MRI demonstrated mass lesion and PRL level was 200 ng/mL. The histopathological diagnosis was central neurocytoma (CN). Medical treatment started 3 months after surgery because PRL normalized by the third month of cabergoline treatment. Cabergoline treatment was gradually decreased and discontinued at 15 months.

The median prolactin level was 118 ng/mL (34-4340) in patients with PRLO and 38.7 (22.9-200) ng/mL in the NPRLO group (*p*=0.007). In the PRLO group, the median admission age in macroadenoma cases (13.8 years) was lower than in microadenoma cases (17 years) (*p*=0.01). In the PRLO group, there was no relationship between adenoma size and gender. The mean size of adenoma (longest axis) was 14.6±11.9 mm before treatment. Median PRL level in our study was higher in patients with macroadenoma (200 ng/mL; range 118-4340 ng/ml) than microadenoma (54.8 ng/mL; range 34-80 ng/ml) (*p*=0.006).

A statistically significant negative correlation was found between PRL level and height SDS (*r*=-0.770, *p*=0.06) in the PRLO group. Cabergoline was started as the first treatment in eight of 11 patients with PRLO. In all cases, the median initial cabergoline dose was 0.5

mg/week, and PRL levels returned to normal in an average of 2.6±2.4 months (1-9 months). The three patients with macroadenoma were treated with cabergoline with a dose of 1 mg/week. No side effects were observed at this dose. Surgery was performed as the first-line treatment in three patients with macroadenoma because of mass effect (visual impairment). Postoperative cabergoline was started in all patients due to the high PRL level. One patient received radiotherapy in addition to surgery and cabergoline treatment due to residual mass.

In patients with microadenoma (n=5), cabergoline was started at 0.5 mg/week. Normal PRL levels were achieved with this dose in all cases and no dose increment was necessary. The treatment regimen is shown in Figure 1. In our study, the PRL levels of patients were checked regularly in the first month of treatment and then at 3-month intervals. The follow-up period was 26.6±24 months (3 months-7 years) in all cases. Cabergoline treatment was discontinued in two patients who completed 4 years of therapy. One case had a 50% reduction in pituitary size (11mm to 4mm) on MRI in the 4th year of treatment and PRL level was normal in the last 2 years. The second case was a patient who underwent surgery and radiotherapy, whose MRI was normal in the 4th year of the treatment, and PRL level was normal in the last 2 years. After discontinuation of cabergoline treatment, PRL levels increased again, and cabergoline was restarted in the second month of the follow-up. One of these cases has completed 7 years in cabergoline treatment and remains on a dose of 1.5 mg/week. No side effects were observed in any case.

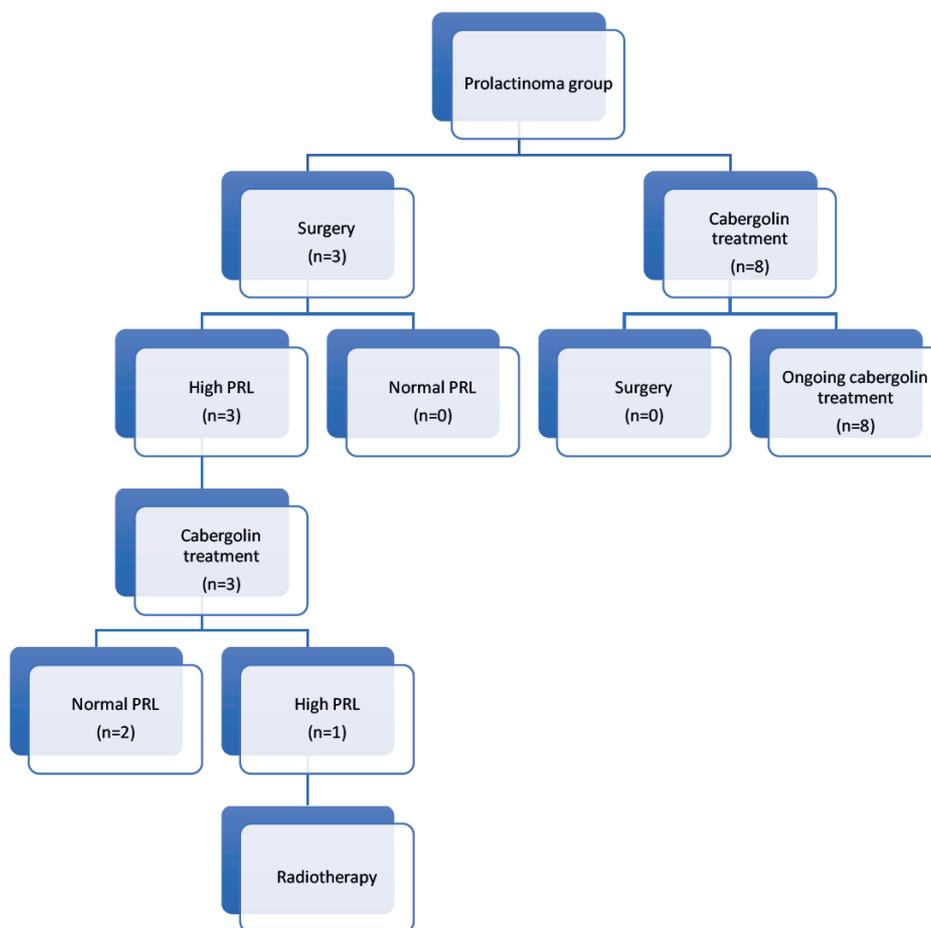


Fig. 1. Treatment regimen of prolactinoma cases.

**Discussion**

Hyperprolactinaemia refers to increased circulating prolactin and is divided into functional/physiological, analytical, and pathological hyperprolactinaemia. Functional hyperprolactinaemia is typically observed in pregnancy, during lactation, with high protein diets, stress (including venepuncture), and secondary hypoglycaemia due to medications.<sup>5,6</sup> Macroprolactinaemia is characterized by a molecular mass of PRL greater than 150 kDa as the predominant molecular form of circulating PRL.<sup>7</sup> There was no macroprolactinaemia in our study.

Pathologic hyperprolactinaemia is mainly due to sellar and parasellar lesions. Other reasons for organic hyperprolactinaemia are polycystic

ovary syndrome (PCOS), chronic renal failure, cirrhosis, hypothyroidism, Cushing disease, and adrenal insufficiency.<sup>3</sup>

Hyperprolactinaemia has been reported in 7–52% of adults with PCOS.<sup>8</sup> One report says that PCOS with a PRL level exceeding 85.2 ng/mL should undergo pituitary MRI for prolactinoma differential diagnosis, especially with lower luteinizing hormone (LH) levels.<sup>9</sup> Still, there is no cut-off level for PRL in children and adolescents with PCOS with suspected prolactinoma. We had three patients with hyperprolactinaemia in PCOS, and PRL levels are 27.8 ng/mL, 32.8 ng/mL, and 37.2 ng/mL, respectively. The second had a normal pituitary MRI. More extensive studies are required to establish cut-off values for normal PRL levels

in children and adolescents that discriminate prolactinomas from hyperprolactinaemia in PCOS.

Rapid onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) syndrome is a rare disorder. Hyperprolactinaemia can be seen in this 40.2 ng/mL, and 49.6 ng/mL, respectively. None of them have neuroendocrine tumours.

Central neurocytoma (CN) is a rare brain tumour often located in the lateral ventricular region. Extraventricular neurocytoma is very rare in the paediatric population.<sup>10</sup> One patient has an extraventricular neurocytoma that occupied the sella area mimicking macroadenoma, WHO grade 2 without signs of malignancy. Immunohistochemical analysis demonstrated a Ki-67 index of 10%, so tumour biological behaviour was thought to be more aggressive. Therefore, histopathological diagnosis is essential in applications that mimic giant adenomas.

Idiopathic hyperprolactinaemia is considered when there are no secondary causes and normal pituitary MRI. Idiopathic hyperprolactinaemia is caused by either a microadenoma <2mm, too small for MRI detection, or familial idiopathic hyperprolactinemia. Familial idiopathic hyperprolactinaemia is caused by a mutation in the prolactin receptor (PRLR) disrupting ligand binding.<sup>11</sup> There was no case with idiopathic hyperprolactinaemia in our study.

Prolactinomas are the most frequent organic cause of hyperprolactinaemia and the most common pituitary adenomas representing children and adolescents.<sup>4</sup> A microadenoma was defined as a pituitary tumour of less than 1 cm in diameter, and a macroadenoma was defined as a tumour above 1 cm in diameter. Serum PRL level increased in parallel with tumour size.<sup>12</sup>

Although they are rarely hereditary, prolactinomas can occur as part of the multiple endocrine neoplasia (MEN) type 1 syndromes, Aryl Hydrocarbon Receptor-Interacting Protein

(AIP) mutations, Carney complex, and McCune-Albright Syndrome.<sup>13,14</sup> No risk factors have been identified for sporadic prolactinomas.<sup>15</sup> Mutation analysis of the *MEN* or *AIP* genes was not performed in our study group.

The clinical manifestations of PRLO vary according to gender, age of onset, tumour size, increased prolactin level, mass effect, and another accompanying pituitary hormone deficiency. In our study, PRLO mainly occurred in females (8 of 11), similar to the literature.<sup>16</sup> Despite a small number of patients, macroadenoma was found more often in the paediatric literature, unlike in adults.<sup>13</sup> In the PRLO group, the median admission age in macroadenoma patients (13.8 years) was lower than in microadenoma cases (17 years). This age difference may be related to the early symptoms of macroadenoma due to the mass tumour effect.

The first aim of PRLO treatment is to normalize PRL levels, provide normal gonadal functions, and protect other pituitary functions. It is crucial to reduce the mass tumour effect, especially in macroadenomas. There is no need for treatment in asymptomatic microadenomas, but close follow-up is recommended regarding size increases and symptoms.<sup>17,18</sup>

When there is no need for emergency surgery, dopamine agonists are the first treatment option in PRLO as they normalize the PRL level, reduce tumour size, and improve gonadal functions.<sup>17,19</sup> Although the mechanism is not precisely known, dopamine agonists also provide a reduction in adenoma size.<sup>20</sup> The cabergoline starting dose is 0.25–0.5 mg/week and can be increased weekly to a maximum of 3.5 mg/week until normal PRL levels are reached.<sup>12,17</sup> In adult studies with dopamine agonist treatment, PRL levels were normalized in 85% of patients with macroprolactinoma and tumour size was reduced by at least 25% in 80% of cases.<sup>21</sup> Our study achieved a nearly 50% reduction in tumour size in the first year with the mean initial dose of cabergoline in three cases for whom cabergoline treatment was preferred as the initial treatment. It has

been observed that there is no need for high-dose cabergoline in microadenoma. Control was achieved with doses of 0.5 to 1.5 mg/week in all cases.

Cabergoline has fewer side effects and better patient adherence.<sup>22</sup> Cardiac evaluation of patients using cabergoline for a long time is essential to evaluate cardiac valvulopathy associated with dopamine agonists.<sup>17</sup> Echocardiographic examinations of the cases were normal.

In our study, cabergoline treatment is well tolerated and improves clinical symptoms while reducing adenoma diameter without increasing the maximum doses. While on medical treatment, the patient's serum PRL levels should be monitored regularly.<sup>17</sup> Although studies have reported that the discontinuation of cabergoline treatment is safe, relapse and tumour size enlargement is common.<sup>17</sup> In adult guidelines, the discontinuation of cabergoline may be recommended for patients with normal PRL levels, no tumour on MRI, a 50% reduction in tumour size, and no invasion of critical structures for at least 2 years.<sup>23</sup> After about 4 years of dopamine agonist therapy, an attempt may be made to withdraw the drug. Cabergoline treatment should be discontinued by gradually tapering it while maintaining normal PRL levels.<sup>17</sup> Regular follow-up is required at 3-month intervals in the first year, then annually for at least 5 years to monitor prolactin levels and tumour recurrence. Because relapse rate is higher in macroprolactinoma cases, they should be carefully monitored with an MRI 6 months after the cessation of therapy and annually thereafter.<sup>17,24</sup>

Prolactin levels increased again in the follow-up of our two patients who completed 4 years of cabergoline treatment and discontinued cabergoline per the guideline suggestions, which was restarted. A study by Barber et al.<sup>25</sup> found recurrence rates as high as 93% for macroprolactinomas and 64% for

macroprolactinomas, and hyperprolactinemia recurrence is most commonly observed during the first 6 months to 1 year following cessation. Patients with recurrence had macroadenoma and recurrence occurred in the 6th month after cabergoline discontinuation, similar to the literature. Although there is no standardization regarding the treatment dose and duration, the periods reported in the guidelines may need to be individualized.

Surgical intervention was performed in three cases. Surgical treatment is often performed for large tumours that cause a mass effect (cranial nerve palsy, visual impairment, and pituitary apoplexy), cystic tumours that do not respond to medical treatment, and intolerant patients resistant to dopamine agonists.

Radiotherapy is a tertiary treatment for prolactinomas that are not controlled by dopamine agonists or surgery, mainly to control tumour growth.<sup>26,27</sup> One patient received radiotherapy in addition to surgery and cabergoline treatment due to a residual tumour.

In conclusion, prolactinoma is the most common cause of severe hyperprolactinaemia. Prolactinomas are rare in children, causing difficulties in diagnosis and treatment management. Although there is not yet a standardization regarding the treatment dose and duration, the durations stated in the guidelines may need to be individualized. According to our observation, children tolerated cabergoline well in long-term use and did not need high doses to normalize the prolactin level. Treatment and follow-up results are needed in large series for paediatric and adolescent patients.

### **Ethical approval**

The study protocol was approved by the Ankara University Ethics Committee (approval number: 15-638-15).

### Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MB, ZŞ; TK; data collection: TK, EÖ, EB, AC, RU; analysis or interpretation of results: TK, ZŞ, MB; draft manuscript preparation: TK, ZŞ, MB.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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