

Clinical, hormonal and radiological features, and treatment outcomes of prolactinomas in a pediatric population

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ABSTRACT

OBJECTIVE: Prolactinoma is the most common hormone-secreting pituitary tumor in the pediatric population. Although it is less common in children and adolescents than in adults, it accounts for 50% of childhood pituitary adenomas. Data on prolactinomas in the pediatric population are still limited. In this study, the symptoms, laboratory data, radiological findings, and therapeutic outcomes of prolactinomas in children and adolescents were assessed.

METHODS: This retrospective study included pediatric patients diagnosed with prolactinomas before 18 years of age, who presented at Istanbul Medeniyet University, Professor Doctor Suleyman Yalcin City Hospital during an 8-year period (August 2015 to November 2023).

RESULTS: Seventeen patients (13 female; 76.4%) with prolactinoma were included. Median age at diagnosis was 14.7 years (12.2–16.1 years) in girls, 11.8 years (6.8–16.2) years in boys. All boys and most girls (62%) had macroadenomas (≥ 1 cm). The most common presenting symptom was amenorrhea/oligomenorrhea in girls and, mass effects and gynecomastia in boys. The median prolactin (PRL) level was significantly higher in the macroprolactinoma group than in the microprolactinoma group (262.5 vs. 178 ng/mL; $p=0.035$). Cabergoline was introduced to all patients as first-line treatment and normal PRL level was achieved in 88.3% of them after a two-year treatment. One male and one female patient were unresponsive to 2 mg/week cabergoline treatment and therefore underwent transsphenoidal surgery. PRL elevation recurred in six of seven patients (86%) after the withdrawal of cabergoline treatment.

CONCLUSION: A macroprolactinoma is more common in children and adolescents than a microprolactinoma in adults. Increased PRL levels, male gender and the presence of mass effects at the time of diagnosis are associated with macroprolactinomas diagnosed during childhood and adolescence. Cabergoline was highly effective in the treatment of pediatric prolactinomas. However, due to the high recurrence rate of hyperprolactinemia after withdrawal of a 2-year treatment, use of cabergoline for a longer duration (≥ 3 years) before the first withdrawal attempt might be beneficial to reduce the risk of recurrence in selected pediatric cases with macroprolactinoma.

Keywords: Adolescents; cabergoline; characteristics, children; dopamine agonists; management; prolactinoma; treatment.

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In children and adolescents, prolactinomas are rare as compared to adults and account for only 1% of pediatric intracranial masses, but, they represent approximately 50% of all pediatric pituitary adenomas. They originate from prolactin (PRL)-secreting lactotroph cells in the anterior pituitary. They are classified as micropro-

lactinomas (< 10 mm) and macroprolactinomas (≥ 10 mm). Serum PRL level correlates positively with tumor size. Prolactinomas tend to be larger in boys (≥ 10 mm), because most of these tumors have more aggressive behaviour and also they are discovered later due to their subtle clinical manifestations in male gender [1–11].

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Prolactinomas are more common in adolescent girls. Thereby clinical manifestations in this gender are mainly those of hypogonadism. Accordingly, girls usually present with amenorrhea, irregular menses, pubertal arrest and galactorrhea. As macroprolactinomas are more prevalent in boys, their presenting symptoms in this gender are usually associated with the pressure effects of the tumor on optic chiasm and normal hypophysis, including headache, visual loss, and growth or pubertal arrest followed by gynecomastia, and other signs of hypopituitarism [12].

Medical monotherapy with dopamine agonists is recommended as first-line treatment for all prolactinomas due to their excellent efficacy, probable preservation of residual hypothalamo-pituitary function and low side effect profile, cabergoline at doses of up to 2 mg/week being favoured over bromocriptine [1]. Surgery via transsphenoidal route is a reasonable option for patients in whom medical therapy fails [1, 2].

The guideline recommendations for hyperprolactinemia are essentially based on adult studies [1]. There is still limited data in literature on characteristics, treatment outcomes and follow-up of prolactinomas in children and adolescents. In this study, clinical manifestations, treatment response, and follow-up of 17 pediatric cases with prolactinoma were reported.

MATERIALS AND METHODS

This study included 17 pediatric patients (13 girls and 4 boys) with prolactinomas who were followed during an 8-year period (2015–2023) at Istanbul Medeniyet University, Professor Doctor Suleyman Yalcin City Hospital. The diagnosis of a prolactinoma was based on typical clinical signs and symptoms, brain magnetic resonance imaging (MRI) findings and a PRL level >25 ng/mL in girls and >20 ng/mL in boys [13]. Age at diagnosis, anthropometric measurements, symptoms, menstrual history (primary or secondary amenorrhea), presence of galactorrhea (or gynecomastia in males), accompanying diseases, medications, tanner stages of puberty, physical examination findings, presence of mass effects with headaches and/or visual disturbances and/or hypopituitarism and laboratory test results were collected retrospectively. Children with primary hypothyroidism, a psychiatric history, iatrogenic hyperprolactinemia, macroprolactinemia and polycystic ovary were excluded.

The treatment administered (cabergoline±surgery), cabergoline doses, treatment duration, clinical and laboratory assessments, medication side effects, and radiolog-

Highlight key points

- Prolactinomas are the most common pituitary tumors in children and adolescents.
- Prolactinomas are more common in girls than in boys. Macroprolactinomas are more prevalent in boys than in girls. While prolactinomas mostly present with signs of hypogonadism in girls, they usually present with clinical symptoms related to mass effects of the tumor in boys.
- Cabergoline is highly effective and safe in the treatment of pediatric prolactinomas.
- In pediatric cases with cabergoline-responsive macroprolactinoma, treatment duration ≥3 years might reduce the risk of recurrence.

ical follow-up of children and adolescents with prolactinoma were recorded. Puberty was staged according to Marshall and Tanner [14]. Z-scores for weight, height, and body mass index (BMI) were calculated using the reference values for Turkish children [15].

For the detection of hypopituitarism due to mass effect or additional hyperpituitarism, the functions of all anterior pituitary cells (somatotroph, adrenotroph, thyrotroph and gonadotroph) were assessed by measuring their respective hormones at the time of diagnosis and during follow-up in patients with prolactinoma. Somatotroph functions were assessed by measuring serum growth hormone (GH), insulin-like growth hormone-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels. GH stimulation tests were performed by using L-dopa and clonidine in patients whose serum IGF-1 and IFGBP-3 levels were <-2 SDS, whose height was <3rd percentile and/or whose annual growth velocity was <25th percentile for age and gender. Patients with peak GH levels <7.5 ng/ml in both stimulation tests were considered to be GH deficient [16]. In patients with accelerated growth and elevated serum IGF-1±IGFBP-3 levels (>+2 SDS) for age-, gender-adjusted and Tanner stage-matched normal range, GH suppression test by oral glucose load (1.75 gr/kg) was performed to rule out GH excess. Failure to suppress GH levels below 1 µg/dl after oral glucose loading, was considered growth hormone excess [17]. Adrenotroph functions were assessed by measuring serum adrenocorticotrophic hormone (ACTH) and cortisol levels regardless of clinical symptoms. Adrenal insufficiency was excluded in patients with cortisol levels >10 µg/dl [18]. On the other hand, patients with early morning cortisol levels >25 µg/dl were subjected to a 1 mg dexamethasone suppression test. Patients with unsuppressed early morning cortisol

levels (≥ 1.8 $\mu\text{g}/\text{dl}$) were hospitalized and their 24-hour urine and salivary cortisol levels were measured. Patients with elevated 24-hour urine and salivary cortisol levels in at least two of the three samples were considered to have Cushing's disease [19]. Thyrotroph functions were assessed in all patients by measuring serum-free T4 and thyrotropin (TSH) levels. Follicle-stimulating hormone (FSH), luteinizing hormone (LH) and sex steroids were measured in all patients to evaluate gonadotroph functions. Macroprolactin was measured following polyethylene glycol precipitation to rule out macroprolactinemia.

Cabergoline was the first-line treatment in all patients. The initial dose of cabergoline was 0.5–1 mg/week, and dose was increased at 1–3 monthly intervals until the PRL level returned to normal or the maximum dose that the patient could tolerate was reached. If there was no response despite increasing the dose up to 3.5 mg/week, cabergoline medication was stopped. Drug cessation was considered in patients with at least two years of cabergoline therapy and no remnant of adenoma on MRI (1). Cabergoline resistance is defined as lack of normalization of serum PRL levels or lack of relevant mass shrinkage ($\geq 30\%$ reduction in maximum diameter) when treated with standard cabergoline doses (2.0 mg per week of cabergoline) for at least 6 months (1). Transsphenoidal surgery (TSS) was performed in patients with cabergoline resistance and/or intolerance (1).

Magnetic resonance imaging (MRI) of the pituitary gland was performed at baseline and at least six-month intervals. Based on adenoma size, patients were divided into two groups as microprolactinoma (< 10 mm) and macroprolactinoma (≥ 10 mm) groups. In order to determine the relationship between alterations in tumor size and PRL levels, initial and last MRI and PRL levels were compared.

The study protocol was approved by Istanbul Medeniyet University, Professor Doctor Suleyman Yalcin City Hospital Clinical Research Ethics Committee, Turkiye (2023/0088, 08.02.2023) and was consistent with the ethical guidelines of the Declaration of Helsinki (2013).

Statistical Analysis

In our study, the IBM SPSS statistics 26 package program (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Quantitative data are given as mean [standard deviation (SD)] and median [interquartile range (IQR) 25–75] and quantitative data, mean and percentage. Test of normality was assessed by the Shapiro-Wilk test. The chi-square and Fisher's exact test were used in the evaluation of

qualitative data whereas the Student's *t*-test and the Mann-Whitney U test were used in the comparison of quantitative data. Spearman analysis test was used for correlation analysis. A *p*-value of < 0.05 is judged as significant.

RESULTS

A total of 17 patients (13 girls and 4 boys) were included in this study (Table 1). The median age at diagnosis was 14.6 years (range 6.8–16.2) for overall cohort. It was 14.7 years for girls and 11.8 years for boys. The prevalent manifestations of prolactinomas at diagnosis were amenorrhea/oligomenorrhea (9/13, 70%) and galactorrhea (7/13, 54%) in girls whereas mass effects (3/4, 75%) including short stature due to GH deficiency (2/4, 50%), blurred vision (1/4, 25%) and headache (1/4, 25%), and gynecomastia (2/4, 50%) in boys (Table 1). Two patients developed prolactinoma in the prepubertal period. Both were male.

Out of the 17 patients, 12 (71%) had macroadenomas and 5 (29%) had microadenomas. Eight female patients (8/13, 62%) and all male patients (4/4, 100%) had macroprolactinomas. The median PRL level at diagnosis was 248 (IQR 175–393.3; range 89–1,688) ng/mL. It was significantly higher in the macroprolactinoma group than in the microprolactinoma group (262.5 vs. 178 ng/mL; $p=0.035$). The maximum adenoma diameter ranged from 3 mm to 24 mm. It was larger in male patients [18.5 mm; (IQR 14–21.5 mm)] than in female patients [10 mm; (IQR 8.3–14 mm)] ($p=0.047$).

The mean follow-up period of the patients was 2.5 ± 1.9 years. The initial treatment in all patients was cabergoline and normal PRL levels were achieved until the maximum dose of 2 mg/week in 88.3% (15/17). No significant drug-related adverse events were observed. One male (patient no: 15) and one female patient (patient no: 5) (11.7%) underwent TSS because of their cabergoline-resistant adenomas. Additionally, the adenoma was secreting both ACTH and PRL in patient no: 5 (mixed macroadenoma) (Table 1). The male patient developed central hypothyroidism after TSS and thyroid hormone replacement was introduced. After surgery, the female patient's ACTH level returned to normal but required cabergoline treatment one year after the surgery. One prepubertal male patient (patient no:17) was recently diagnosed with a mixed hormone-secreting macroadenoma (PRL+GH). PRL level normalized two months after the introduction of 1 mg/week cabergoline treatment. Because of the GH-secreting component of his macroadenoma, TSS schedule was set.

TABLE 1. Anthropometric measurements, clinical symptoms, imaging findings, treatments and outcomes

N	Sex	Age at diagnosis (year)	Height (m)	Height SDS ^a	Weight (kg)	BMI	BMI SDS ^b	Basal PRL (ng/ml)	Maximum diameter (mm)	Manifestations at diagnosis	Visual field defect	Cabergoline treatment duration (total year) ^c	TSS	Tumor shrinkage (%)	Additional hormone secretion
1	F	12.2	139	-2.35	32.0	16.5	-1.1	245	5.5	SS ^e	-	2.75	-	100	-
2	F	14.0	157	-0.57	50.4	20.4	-0.1	172	17	G	+	2.08	-	>70	-
3	F	15.9	158	-0.73	65.0	26.0	1.7	213	16	AO, G	-	0.58	-	<30	-
4	F	16.1	167	0.08	70.5	25.0	1.4	377	10	H	-	0.66	-	<50	-
5	F	12.8	160	0.54	72.0	28.0	2.3	256	10	H, AO	-	2.66	+	100 ^d	ACTH
6	F	14.6	164	0.52	69.0	25.8	1.6	89	9	AO	-	7.50	-	100	-
7	F	15.9	152	-1.76	52.0	22.0	0.5	248	7	G, H, AO	-	2.00	-	100	-
8	F	15.8	167	0.81	74.0	26.0	1.8	832	14	G, AO	-	4.75	-	100	-
9	F	15.0	162	0.05	60.0	22.8	0.7	178	3	G, H, AO	-	3.58	-	100	-
10	F	13.3	160	0.24	54.0	21.0	0.4	269	24	G, H, AO	+	1.66	-	>70	-
11	F	14.4	164	0.52	68.0	25.0	1.5	117	8.3	AO	-	1.58	-	100	-
12	F	15.9	157	-0.83	62.0	24.9	1.4	143	11	G, AO	-	3.00	-	100	-
13	F	14.7	157	-0.73	47.0	19.0	-0.8	467	10	AO	-	5.00	-	100	-
14	M	16.2	158	-2.38	65.5	26.0	1.2	1688	21	SS ^e , GY, H	-	1.10	-	<50	-
15	M	9.8	138	0.32	44.4	23.0	1.9	179	16	BV	+	2.75	+	100 ^d	-
16	M	13.8	149	-1.81	33.0	14.8	-2.3	250	12	SS ^e	+	0.58	-	<30	-
17	M	6.8	133	-2.35	35.0	19.8	1.9	410	22	GY	-	0.20	-	N/A	GH

N: Number; SDS: Standard deviation score; PRL: Prolactin; BMI: Body mass index; G: Galactorrhea; H: Headache; AO: Amenorrhea/oligomenorrhea; BV: Blurred vision; SS: Short stature; GY: Gynecomastia; TSS: Transphenoidal surgery; ACTH: Adrenocorticotropic hormone; GH: Growth hormone; N/A: Not applicable; a: Refers to height and weight standardized growth charts for Turkish children and adolescents aged 0 to 18 years; b: Refers to body mass index centiles for Turkish children and adolescents aged 0 to 18 years; c: Refers to duration of initial cabergoline treatment after the relapse of hyperprolactinemia; d: 100% tumor shrinkage after TSS; e: SS due to GH deficiency.

All four patients with visual field defects had macroadenomas. It improved in three cases after cabergoline treatment and in one case after surgery (Table 1).

There were a total of 8 patients (4 microadenoma and 4 macroadenoma) whose cabergoline treatment could be withdrawn after two years of treatment. Among the three patients with microadenoma, one patient (patient no: 7) lost to follow-up after withdrawal, one (patient no: 9) was in remission for 1.6 years and two (patient no: 1, 6) had recurrence of hyperprolactinemia (67%) within 9 months after cabergoline withdrawal. Recurrence was observed within 6 months after cabergoline withdrawal in 3 patients with macroadenoma (patient no: 8, 12, 13). One patient with macroadenoma (patient no: 2) could not be assessed for recurrence because it had been just 1 month since her cabergoline medication was withdrawn (Table 1). Overall, PRL elevation recurred in six of seven patients (86%) after the cabergoline withdrawal.

Adenoma disappeared totally in all 5 patients with microprolactinoma (100%, patient no: 1, 6, 7, 9, 11) at a median duration of 18 months (range 6–24 months) with a median dose of 1 mg/week (0.5–2 mg).

Adenoma disappeared totally in 4 of 6 patients with macroprolactinoma who were under cabergoline treatment for at least two years (67%, patient no: 2, 8, 12, 13, 15). No tumor remained at a median duration of 24 months (range 21–36 months) with a median dose of 1 mg/week (0.5–2 mg). Two patients underwent TSS due to cabergoline resistance±mixed adenoma and no tumor remnants were visualized in their control MRIs after the intervention.

DISCUSSION

In our study, a higher rate of prolactinoma was observed in girls, which supports previous studies showing gender-related differences in prolactinomas [5, 20–22]. These pituitary tumors are uncommon during childhood [23]. Consistent with the literature, all patients except two boys were diagnosed during adolescence. As is known, estrogen stimulates lactotroph cells via its receptors and it augments the effect of GH on lactotroph cells [1, 24]. Thereby, estrogen levels, which begin to increase with the onset of puberty, may have contributed to the occurrence of prolactinomas more common in girls than in boys during adolescence.

Comparison of prolactinomas with respect to their sizes showed that macroprolactinomas (71% of patients) were more common than microprolactinomas in chil-

dren and adolescents which contrasts with the higher prevalence of microprolactinomas in adults [25, 26]. In certain studies, the mean age at diagnosis was reported to be around 15 years in female patients [10, 27]. Likewise, we found this age as 14.7 years in our study. The fact that estrogen begins to reach its highest level in girls at the age of 14–15 years [28] might have contributed to this finding. Consistent with the previous studies the mean age at diagnosis was lower in boys than in girls [2, 5, 10, 22].

Serum PRL concentrations tend to vary with adenoma size [13]. Microprolactinomas are usually associated with serum PRL levels below 200 ng/mL whereas macroprolactinomas are almost always diagnosed when serum PRL levels exceed 500 ng/mL [29]. We did not find a correlation between adenoma size and PRL level. This result might be associated with the small size of our cohort. The median PRL level was significantly higher in the macroprolactinoma group than in the microprolactinoma group (262.5 vs. 178 ng/mL) which is consistent with the prior studies [7, 8, 10, 20–22].

The clinical manifestations of prolactinoma vary according to gender, age of onset, tumor size, PRL level, type (mixed cell-type adenoma) and mass effects [1, 7, 8, 10, 20–22]. The common presenting symptoms of our patients at diagnosis were amenorrhea/oligomenorrhea (70%) and galactorrhea (54%) in girls, and mass effects (75%) and gynecomastia (50%) in boys. In girls with prolactinoma, because the prevalence of hypopituitarism is low and growth disorders develop less frequently than pubertal disorders, the adverse effects of prolactinomas on gonadotroph functions ensue because of hyperprolactinemia rather than their mass effects on normal pituitary cells [5]. In boys, as macroprolactinomas are more common than in girls, clinical findings related to mass effects are more prominent [2–7]. Accordingly, we observed headaches, visual field defects, and short stature due to GH deficiency more common in boys than in girls. Another common presenting symptom in boys is gynecomastia. Boys with prepubertal breast enlargement and advanced breast enlargement at puberty should be assessed for prolactinomas, as well. Aguilar Riera et al. [6] found visual field defects in 42% of children with prolactinoma. Likewise, 33% of our patients with macroprolactinoma (2 girls and 2 boys) had visual field defects at the time of diagnosis. Visual compromise improved in girls within 3 months after the introduction of cabergoline treatment. One male patient with macroprolactinoma underwent TSS due to cabergoline resistance, and his visual defect recovered after the intervention.

The majority of prolactinomas secrete only PRL. However, since the GH-secreting cells (somatotrophs) in the adenohypophysis originate from the same progenitor cells (mammosomatotroph progenitors) with PRL-secreting cells, mixed cell-type adenomas secreting both PRL and GH can evolve from the adenohypophysis [1]. Rarely, PRL and ACTH can be secreted together from a pituitary adenoma [1]. In our study, mixed cell-type adenomas secreting GH, or ACTH, along with PRL were diagnosed in two patients with macroadenoma. At the other end of the clinical spectrum, hypopituitarism manifested by short stature due to GH deficiency was diagnosed in two other patients with macroprolactinoma. Hence, as part of the diagnostic examination, comprehensive evaluation of pituitary hormones in children and adolescents with symptoms suggesting prolactinoma is vital to exclude the existence of mixed-pituitary hormone-secreting adenomas as well as hypopituitarism due to mass effect.

Dopamine agonists, bromocriptine and cabergoline, are the first-line treatment for prolactinomas [1]. They reduce both PRL level and tumor volume. Over the years, demonstration of superiority of cabergoline over bromocriptine in terms of both efficacy and tolerability has made cabergoline the first choice in the treatment of prolactinomas in both children and adults [1]. Accordingly, all the patients in our study received cabergoline medication. It was well tolerated, and no significant drug-induced side effects (such as valvular heart disease, GI complaints or orthostatic hypotension) were observed.

Several predictors of cabergoline response have been described. These are low pretreatment PRL level and small adenoma at diagnosis, as well as normalization of serum PRL levels with a low dopamine agonist dose (cabergoline, ≤ 2 mg/week) [1, 30]. Despite some controversy, several studies revealed that the success rate of cabergoline treatment in childhood prolactinomas, particularly in macro-ones, is slightly lower. PRL level was found to be normalized in 71–100% of microprolactinomas and 45–72% of macroprolactinomas in pediatric series [4, 7, 8]. In our study, PRL level was normalized in 88% (15/17) of the entire cohort after 3–6 months of cabergoline treatment (≤ 2 mg/week). Success rate of cabergoline in normalizing PRL levels in our patients with microadenoma is 100% which is consistent with the finding of Alikasifoglu et al. [8]. Whereas we found this rate 83% in patients with macroadenoma. Considering the inverse relationship between adenoma diameter and cabergoline response, the borderline sizes (10–11 mm) in 33% of our patients with macroadenoma might have contributed to the high success rate of cabergoline in the macroadenoma group.

'Cabergoline resistance' has been defined as lack of normalization of serum prolactin levels or lack of relevant mass shrinkage ($\geq 30\%$ reduction in maximum diameter) when treated with 2.0 mg/week of cabergoline for at least 6 months [1]. It was more common in macroadenomas than in microadenomas and in children than in adults [4, 7, 8]. Maiter reported that cabergoline fails to normalize PRL levels in 17% of adult patients with macroprolactinoma and fails to lead to tumor shrinkage in 29% [31]. Data specific to pediatric patients is limited. In a few studies, normalization of PRL level has been reported as 18%, 25% and 36% in the pediatric age group [4, 5, 8]. Cabergoline-resistant macroprolactinomas were observed in 17% of our patients. This rate is similar to that in the study by Arya et al. (18%) [4].

Most children with macroprolactinomas respond to standard doses of cabergoline, ranging from 0.5 mg/week to 2 mg/week. The dose of 3.5 mg/week was suggested as the maximum dose that might be effective in the treatment of prolactinomas [1]. Numerous studies showed that increasing the cabergoline dose above 3.5 mg/week was not able to normalize PRL levels or tumor shrinkage in pediatric cases with drug resistance [4, 5, 7, 8]. Moreover, high doses may increase the risk of valvular heart disease as a side effect [1]. In line with the literature, standard doses of cabergoline (< 2 mg/week) were able to normalize PRL levels in 83% of our patients with macroprolactinomas. The remaining two patients (17%) were unresponsive to the maximum dose of cabergoline (3.5 mg/week). The choice of treatment in such patients is TSS [1]. Success of TSS seems to be similar in children and adults. In pediatric series remission rates were reported between 31% and 69.3%, and surgical success was found to be negatively correlated with the maximum adenoma size and PRL levels [8]. In our study, two patients underwent TSS and one patient required cabergoline treatment after surgery.

TSS is a safe surgical procedure in the hands of an experienced neurosurgeon, however, sometimes associated with certain complications including cerebrospinal fluid leakage, diabetes insipidus, infection, hyponatremia, and hypopituitarism. Amongst, hypopituitarism was reported to be the most common complication [7, 32]. Accordingly, one patient in our study developed central hypothyroidism, as a manifestation of hypopituitarism and his thyroid hormone levels normalized after the introduction of L-T4 replacement treatment. Particularly, in macroadenomas causing severe neurological deficit and unresponding to maximum FDA-approved dose

of cabergoline treatment (2 mg/week), TSS can be performed without delay to avoid permanent neurological deficits and drug-induced side effects, rather than gradually elevating the cabergoline dose up to 3.5 mg/week and waiting for a response.

Recurrence rate of hyperprolactinemia after cabergoline withdrawal ranges widely from 36 to 80% in adult series [33]. However, data on pediatric series is limited. Almutlaq et al. [11] reported that the overall recurrence rate of hyperprolactinemia in children with prolactinoma was 79%. The poor outcome was linked to higher PRL levels and larger adenoma size at the time of diagnosis. In our study, there were a total of 8 patients (4 microadenoma and 4 macroadenoma) in whom cabergoline medication could be withdrawn after a two-year treatment and who could then be followed up for at least 9 months. The recurrence rate of hyperprolactinemia was 67%, 100% and 86%, in the microadenoma group (n=3), in the macroadenoma group (n=4) and in the entire group (n=7), respectively. These findings were similar to those of Almutlaq et al. [11]. Taken together, it may be suggested that the overall recurrence rate of hyperprolactinemia in pediatric patients seems to be higher than those reported in adults.

There were some limitations in our study. Firstly, our sample size was small. Secondly, the follow-up period of our patients was relatively short. Thirdly, the design of our study was retrospective. Fourthly, not all patients could be evaluated for rare genetic causes of prolactinoma (MEN1, AIP, PRKAR1A). Despite these limitations, our findings might still contribute to the literature because of the rarity of pediatric prolactinomas and the lack of sufficient research on pediatric series. As known, a pediatric guideline providing recommendations regarding the dose and duration of cabergoline treatment in the management of pediatric prolactinomas still could not be established.

Conclusion

Our data are compatible with the findings of previous studies. Likewise in adults, cabergoline is effective in the treatment of childhood and adolescence prolactinomas as well. Consistent with earlier studies, macroprolactinomas are more common in children and adolescents than microprolactinomas in adults. The use of cabergoline for a longer duration (≥ 3 years) has been recommended in adult cases with cabergoline-responsive prolactinomas (1). Since we found a high recurrence rate after a 2-year cabergoline

treatment, we suggest that using cabergoline for a longer period of time before the first withdrawal attempt might be beneficial to reduce the risk of recurrence in selected pediatric cases with macroprolactinoma. In cases with macroprolactinomas resistant to 2 mg/week of cabergoline dose (FDA-approved maximum dose), TSS could be performed without delay to avoid permanent neurological complications and dose-related significant side effects, rather than gradually increasing the dose up to 3.5 mg/week and waiting for a response. Further large-scale and prospective studies are needed to clarify the characteristics of pediatric prolactinomas and to reveal the factors affecting the success of medical and surgical treatments in children and adolescents with prolactinomas.

Ethics Committee Approval: The Istanbul Medeniyet University, Professor Doctor Suleyman Yalcin City Hospital Clinical Research Ethics Committee granted approval for this study (date: 08.02.2023, number: 2023/0088).

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