Pituitary (2022) 25:167–179
https://doi.org/10.1007/s11102-021-01184-x

Management of prolactinomas in children and adolescents; which factors define the response to treatment?

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Accepted: 30 August 2021 / Published online: 13 September 2021

Abstract

Purpose Prevalence, presentation and clinical outcome of prolactinomas vary in children and adults. In this study, we evaluated the clinical features and outcome of children and adolescents with prolactinoma to identify the differences from that of adults, and thus to establish the management strategies for this age group.

Methods Patients with prolactinoma diagnosed before 18 years of age from a single center in the last 20-years were included. Clinical and laboratory data, radiological findings and treatment outcome were evaluated retrospectively.

Results Twenty-eight patients (23 female; 82.1%) with prolactinoma were included. Median age at diagnosis was 15.2 years (12.6–17.7 years) in girls, 12.9 years (12.0–16.7 years) in boys. First line treatment was cabergoline in 82% of patients and normal prolactin level was achieved with maximum dose of 2 mg/week in 78%. Surgery was required in 28% of patients. Adenomas < 13.5 mm responded conventional doses of CAB. Adenomas > 30 mm were drug resistant or required surgery. Adenomas between 13.5 mm and 30 mm with invasion/extension were more likely to have drug resistance. CAB had to be continued following surgery in all patients. One macroprolactinoma had an increase in size which was accompanied with increasing prolactin level.

Conclusions All microprolactinomas responded well to DA treatment. However, all adenomas larger than 30 mm was resistant to CAB or required surgery. Probability of drug resistance and requirement of second line therapy were higher in adenomas between 13.5 mm and 30 mm with invasion/extension. Doses over 2 mg/week of CAB in drug-resistant patients may not provide additional benefit. The frequency of follow-up MRI could be determined based on prolactin levels and emergence of new neurological symptoms.

Keywords Prolactinoma · Children and adolescents · Cabergoline · Body mass index · Adenoma size · Magnetic resonance imaging

Introduction

Pituitary adenoma is extremely rare in childhood in contrast to adults [1]. The prevalence of pituitary adenomas in population based studies is between 78 and 166 cases per 100,000 [2–5]. However pediatric cases represent only ~5% of all pituitary adenomas [6–8].

Pediatric pituitary adenomas differ from adults not only in prevalence but also clinical presentation and outcome as well. Unlike adulthood, most of the adenomas in childhood are functional, secreting one or more hormones. Prolactinomas constitute approximately 50% of the pituitary adenomas [1, 9]. Microadenomas are more prevalent in adults [2] while, there is a preponderance of macroadenomas in childhood and adolescence [7, 10, 11]. In addition, remission rates of pediatric pituitary adenomas are lower and recurrence rates are higher in comparison to adults [12–14].

Surgery was the basis of prolactinoma management in the past, however complications such as cerebrospinal fluid leakage, meningitis or pituitary hormone deficiencies brought about the need for other treatment options [15]. Bromocriptine, a DA, introduced in 1970s, followed by cabergoline (CAB) in 1990s, established a medical treatment option for prolactinomas [16]. CAB, a long acting DA, offered higher efficacy in terms of normalization of prolactin level and tumor shrinkage as well as better tolerability over

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bromocriptine [17]. However, CAB as a long-term treatment option, could cause a variety of side effects. One of these complications is cardiac valvular fibrosis although no definitive conclusion could be reached so far regarding numerus studies made on hyperprolactinemic disorders that did not show any evidence of clinically significant cardiac valvulopathy [18, 19], however higher risks were observed in patients with Parkinson's disease who treated with high doses DA [20, 21]. More important complication of CAB is impulse control disorders especially in high doses, and medication can be discontinued only in a small subset of patients in the long-term [22]. Despite higher efficacy, some patients exhibit primary or rarely secondary resistance to CAB. Besides these pros/cons, dose, duration of DA treatment, as well as indications for second line treatment i.e. surgery are not well-defined especially in the pediatric age group.

The Endocrine Society Clinical Practice Guideline recommendations for hyperprolactinemia are essentially based on adult studies [23]. Evidence about long-term outcome in pediatric prolactinomas continues to accumulate, and suggests that clinical features and long-term outcome is different from of adult prolactinomas, thus guidelines specific to children and adolescent should be developed.

In this study, we evaluated the clinical features and outcome of children and adolescents with prolactinoma followed over 20 years in a single-center to identify the differences from that of adults, and thus to establish the management strategies for this age group.

Methods

Twenty-eight patients (23 females and 5 males) with prolactinomas who were followed during a 20-year period (2000–2020) at a university hospital setting were reviewed retrospectively.

Age at diagnosis and onset of symptoms, clinical history including menstrual irregularities, signs of pubertal arrest were extracted from patient files. Body weight, height, pubertal stage, presence of gynecomastia and galactorrhea were noted.

Puberty was staged according to Tanner [24]. Body mass index (BMI) and its standard deviation score (SDS) were calculated [25]. Height SDS was assessed using Centers for Disease Control and Prevention (CDC) charts [25]. Delayed puberty was defined as the absence of testicular enlargement in boys or breast development in girls at the age of 14 or 13 years [26]. Pubertal arrest was defined as the absence of menarche in girls 5 years after breast development, and failure to complete genital development within 4 years in boys following testicular enlargement [26].

Serum prolactin (normal range 5–25 ng/mL in females, 3–20 ng/mL in males) and other anterior pituitary hormones were evaluated to detect pituitary hormone deficiencies at diagnosis, and at regular intervals during follow-up, subsequently. Samples for anterior pituitary hormones were drawn at 08:00 a.m. after an overnight fast. Plasma adrenocorticotropic releasing hormone (ACTH) and cortisol levels were used to evaluate the hypothalamo-pituitary-adrenal axis. Patients with early morning cortisol less than 15 µg/dl and clinically suspected adrenal insufficiency were subjected to a low dose ACTH stimulation test using 1 mcg tetracosactide. Also, growth hormone (GH), serum IGF-1 and IGFBP-3 levels were measured to determine somatotroph function, and thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels for thyrotrope function. Growth hormone stimulation tests were performed using clonidine and L-dopa in patients who has decreased annual growth rate (below the 25th percentile for age and sex [24]) and/or short stature (height > 2 SD below the mean for age and sex), and/or a delayed bone age (BA; 2 SD below the chronological age [27]). Follicle stimulating hormone (FSH), luteinizing hormone (LH) as well as gonadal steroids were measured in patients with pubertal delay or arrest. Macroprolactin was measured following polyethylene glycol precipitation to rule out macroprolactinemia. Serum prolactin, TSH, fT4, cortisol, plasma ACTH, GH, and testosterone levels were measured with the IMMULITE 2000 System (Siemens, England) using the immunochemiluminometric (ICMA) method. Serum IGF-1 and IGFBP-3 levels were measured using the Beckman Coulter trademark assays until 2018, and with DIAsource immuno assays thereafter using the immunoradiometric assay (IRMA) method. Despite different assays, reference intervals did not change. Follicule-stimulating hormone, LH, and E2 were measured using commercial kits (ARCHITECT System, Abbott Laboratory Diagnostics, USA) with ICMA method.

Magnetic resonance imaging (MRI) of the pituitary gland was performed at baseline and at 6-12-month intervals. Maximum adenoma diameter was used to express adenoma size. Patients were divided into 3 groups according to their adenoma size at presentation; microprolactinoma (< 10 mm), macroprolactinoma (≥ 10 mm and < 40 mm) and giant prolactinoma (≥ 40 mm). Visual field was assessed using perimetry at diagnosis and yearly thereafter.

All patients except those with visual field defects and/or neurological symptoms were treated with CAB as first line therapy. The initial dose of CAB was 0.5–1 mg/week, and the dose was increased at 1–3 monthly intervals until the prolactin level normalized or the maximum dose that the patient could tolerate was reached. Patients were monitored for drug side effects, change in signs and symptoms as well as growth parameters during follow-up.

Normalization is defined as achievement of normal prolactin level while residual tumor is still detected on MRI at the latest follow-up [9]. Drug cessation was considered in patients with at least two years of CAB therapy and no remnant of adenoma on MRI [23]. DA resistance is defined as failure to achieve normal prolactin level and/or lack of reduction of adenoma size more than 50% at a CAB dose of 3.5 mg/week or more at the latest follow-up [28]. Surgery and/or radiotherapy were used in patients with either DA resistance/intolerance or compression of the optic chiasma.

In order to determine the relationship between changes in tumor size and prolactin levels, initial and last MRI and prolactin levels were evaluated. All MRI were conducted more than 3 months apart. To exclude the effects of surgery, in patients who underwent surgery as a first-line treatment, evaluation was undertaken from the first postoperative MRI. Similarly, patients in whom surgery was applied as a second line treatment were evaluated up to the last preoperative MRI. Prolactin levels obtained within 3 months of MRI were also used in the analysis. Each MRI and prolactin data set were evaluated in terms of change in size and level, respectively. We evaluated the earliest and the latest sets for patients with multiple data sets. Adenoma size was defined as increased, decreased or stable using a 30% change in the largest diameter of adenoma [11]. Changes in prolactin level relative to basal values were similarly defined as increased, decreased or stable.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences software package for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). Variables are tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean and SD. Geometric means and geometric SD are calculated for nonnormally distributed variables. Mean values of continuous variables are compared using t tests; medians are compared using the Mann-Whitney U test or the Wilcoxon test, as appropriate. The parameters affecting BMI SDS at diagnosis were investigated using Spearman/Pearson correlation test and Student's t test, where appropriate. A logarithmic regression model was used to identify independent predictors of BMI SDS at diagnosis. The annual change in BMI SDS over two years of follow-up was investigated using repeated measures analysis. A multinominal regression model was used to identify independent predictors of drug resistance and surgery requirement. A p-value < 0.05 is considered to be statistically significant.

Results

Twenty-eight patients (23 female; 82.1%) with prolactinoma were included in the study. Median age at diagnosis was 15.2 years (12.6–17.7 years) in girls and 12.9 years (12.0–16.7 years) in boys. Median duration of symptoms before the diagnosis was 12 months (1–24.9 months) in girls and 3.6 months (2.4–5.5 months) in boys ($p = 0.024$). Main complaints at diagnosis were menstrual irregularities in girls; visual disturbances and headache in boys. Nine (32%), sixteen (57%) and three (11%) of the patients had microprolactinoma, macroprolactinoma and giant prolactinoma, respectively. 88.8% of patients with microprolactinoma and 93.7% with macroprolactinoma were girls, but all of the patients with giant prolactinoma were boys. Boys had larger adenoma size compared to girls ($p = 0.0003$). Symptoms and signs regarding adenoma size and gender at the time of diagnosis are presented in Table 1.

Twenty one percent of patients were overweight and 26% were obese. BMI SDS at diagnosis correlated significantly with the adenoma size and serum prolactin concentration ($r = 0.506$, $p = 0.027$ and $r = 0.525$, $p = 0.025$, respectively). Serum prolactin concentration ($R^2 = 0.387$, $p = 0.004$), adenoma size ($R^2 = 0.354$, $p = 0.009$) and gender ($R^2 = 0.289$, $p = 0.018$) predicted BMI SDS at diagnosis in logarithmic regression analysis. BMI SDS decreased significantly at the end of the 2 years follow-up ($F = 14.386$, $p = 0.001$). Laboratory parameters, imaging results at diagnosis, and treatment outcomes are summarized in Table 2.

Microprolactinoma

Eight girls and one boy had microprolactinoma. Median prolactin level at diagnosis was 121.9 ng/ml (75–300ng/ml). Patients were followed up for median 3.6 years (0.9–6 years).

First-line and sole treatment was CAB in all patients. Normal prolactin level was achieved in all patients at a median time of one month (0.5–12 months) with a median dose of 1 mg/week (0.5–2 mg) CAB. All symptoms resolved with treatment. Fifty percent or more reduction in adenoma size was attained in all patients at a median time of 12 months (range 6–36 months); total tumor shrinkage was achieved in 3 patients (33%) at a median of 24 months (range 12–48 months). Thus, no resistance or intolerance was detected in any patient (Fig. 1). Drug cessation was tried in two of those with total tumor shrinkage. In one of these 2 patients (Patient-1) CAB was discontinued after 3.5 years of therapy, however, relapse occurred after 2 months. Another attempt to stop the medication 2 years

Table 1 Signs and sypmtoms of patients at the time of diagnosis

	Microprolactinoma ($n=9$)		Macroprolactinoma ($n=16$)		Giant prolactinoma ($n=3$)		p
Female/Male, n (%)	8 (88.8) / 1 (11.2)		15 (93.7) / 1 (6.3)		0 / 3 (100)		***0.03***
Age at diagnosis (year) median, (range)	14 (12.0–17.0)		15.2 (12.6–17.7)		14.7 (12.9–16.7)		0.76
Signs and symptoms at diagnosis n (%)	Female ($n=8$)	Male ($n=1$)	Female ($n=15$)	Male ($n=1$)	Female	Male ($n=3$)	
Headache	3 (37.5)	1 (100)	7 (46.6)	1 (100)	–	3 (100)	
Visual disturbances	0	0	2 (13)	0	–	3 (100)	
Galactorrhea	6 (75)	0	2 (13)	0	–	0	
Menstrual disturbances							
None	1 (12.5)	–	1 (6)	–	–	–	
Menorrhagia	1 (12.5)	–	0	–	–	–	
Oligomenorrhea	2 (25)	–	1 (6)	–	–	–	
Secondary amenorrhea	2 (25)	–	2 (13)	–	–	–	
Primary amenorrhea	1 (12.5)	–	11 (73)	–	–	–	
Height SDS median, (range)	−0.3 (−0.5/1.1)		0.1 (−2.6/1.4)		0.9 (−1.1/2.9)		0.88
BMI SDS median, (range)	0.8 (−1.3/1.4)		0.9 (−0.8/2.2)		2.3 (2.1/2.4)		0.07
Prolactin level at diagnosis (ng/mL) median, (range)	121.9 (75–300)		188.3 (104–2466)		3216 (3062–32,225)		***0.004***

Table 2 Laboratory parameters, imaging results at diagnosis and treatment outcomes of patients with prolactinoma

Patient	Gender (F/M)	Age at diagnosis (yr)	PRL at diagnosis (ng/mL)	Maximum diameter of adenoma (mm)	Invasion / Extension	Pituitary hormone deficiencies at diagnosis	Maximal dose of CAB (mg/week)	Prolactin at last follow-up (ng/mL)	Surgery (yes/no)	Tumor shrinkage (%)	Pituitary hormone deficiencies at last follow-up	Follow-up (yr)
1	F	13.0	100.9	4.5	No	No	0.75	13.9	No	100	No	6.3
2	F	15.4	300.1	5.0	No	No	1.5	4.1	No	>50	No	2.6
3	M	12.0	120.9	6.2	No	No	1	1.8	No	100	No	6
4	F	13.8	195.0	6.5	No	No	1	12	No	>50	No	4.2
5	F	17.0	89.2	6.0	No	No	2	23.6	No	>50	No	3
6	F	13.5	152.0	6.0	No	No	1	9.1	No	100	No	7
7	F	16.7	71.1	7.0	No	No	0.75	20.8	No	>50	No	1.5
8	F	16.8	75.6	7.0	No	No	N/A	8.1	No	>50	No	1.2
9	F	14.0	143.0	8.0	No	No	0.5	7.2	No	>50	No	1.5
10	F	15.3	301.0	10.5	No	No	1	20.1	No	>50	No	2.7
11	F	15.0	327.0	12.0	No	GH	2	6.5	No	>50	GH	3.6
12	F	12.7	187.8	12.5	No	No	0.75	19.6	No	>50	No	1.1
13	F	16.0	119.0	13.0	Extension to the suprasellar cisterna	No	1.5	15.2	No	>50	No	2
14	F	14.0	188.2	13.5	Extension to the suprasellar cisterna	N/A	6	23.3	Yes	100	GH, TSH, FSH/LH, ACTH, ADH	3.3
15	F	15.2	118.8	14.0	No	No	1	16.7	No	100	No	3.5
16	F	17.5	176.7	14.0	No	No	1	10.1	No	>50	No	0.5
17	F	12.7	138.0	16.0	Extension to the suprasellar cisterna	No	0.5	3.3	No	100	No	5.3
18	F	15.7	340.9	16.0	Extension to the suprasellar cisterna	No	5.5	134	No	<50	No	1.4
19	F	16.0	370.1	16.0	In close proximity to ICA, destructing dorsum sella	No	6	32.3	Yes	100	No	10
20	F	16.1	190.3	N/A	Extension into the left cavernous sinus and suprasellar cisterna, surrounding the left ICA, compressing the optic chiasm	No	N/A	2.1	Yes	>50	ADH	3

Table 2 (continued)

Patient	Gender (F/M)	Age at diagnosis (yr)	PRL at diagnosis (ng/mL)	Maximum diameter of adenoma (mm)	Invasion / Extension	Pituitary hormone deficiencies at diagnosis	Maximal dose of CAB (mg/week)	Prolactin at last follow-up (ng/mL)	Surgery (yes/no)	Tumor shrinkage (%)	Pituitary hormone deficiencies at last follow-up	Follow-up (yr)
21	F	14.8	169.1	17.0	Compression of the optic chiasm, extension to the cavernous sinus	No	1.0	41.7	Yes	100	GH, TSH, FSH/LH, ACTH, ADH	5
22	F	15.2	169.3	18.0	No	No	1	7.2	No	>50	No	3
23	F	16.2	470.0	20.0	Extension to the cavernous sinus	No	4.5	83	Yes	>50	N/A	1.7
24	M	12.9	3036	30.0	Extension to the left cavernous sinus, and suprasellar cisterna	No	2	8.3	No	>50	No	5.1
25	F	15.5	2466.0	35.0	Extension to the cavernous sinus, surrounding the ICA	No	4.5	202	No	>50	No	2.5
26	M	14.7	3062.0	45.0	Extension to the suprasellar cisterna	No	1	7.3	Yes	>50	GH, TSH, FSH/LH, ADH	3.3
27	M	12.9	32,225.0	50.0	Extension to the suprasellar cisterna	GH, TSH, FSH/LH	1	45	Yes	>50	GH, TSH, FSH/LH, ACTH	6
28	M	16.7	3216.0	51.0	Extension to the bilateral cavernous sinus, and suprasellar cisterna	GH, TSH, FSH/LH, ACTH, ADH	8	31.5	Yes	>50	GH, TSH, FSH/LH, ACTH, ADH	1.5

ACTH Adrenocorticotropic hormone, *ADH* Anti-diuretic hormone, *CAB* Cabergoline, *FSH* Follicle-stimulating hormone, *GH* Growth hormone, *ICA* Internal carotid artery, *LH* Luteinizing hormone, *N/A* Not applicable, *PRL* Prolactin, *TSH* Thyroid-stimulating hormone, *yr* years

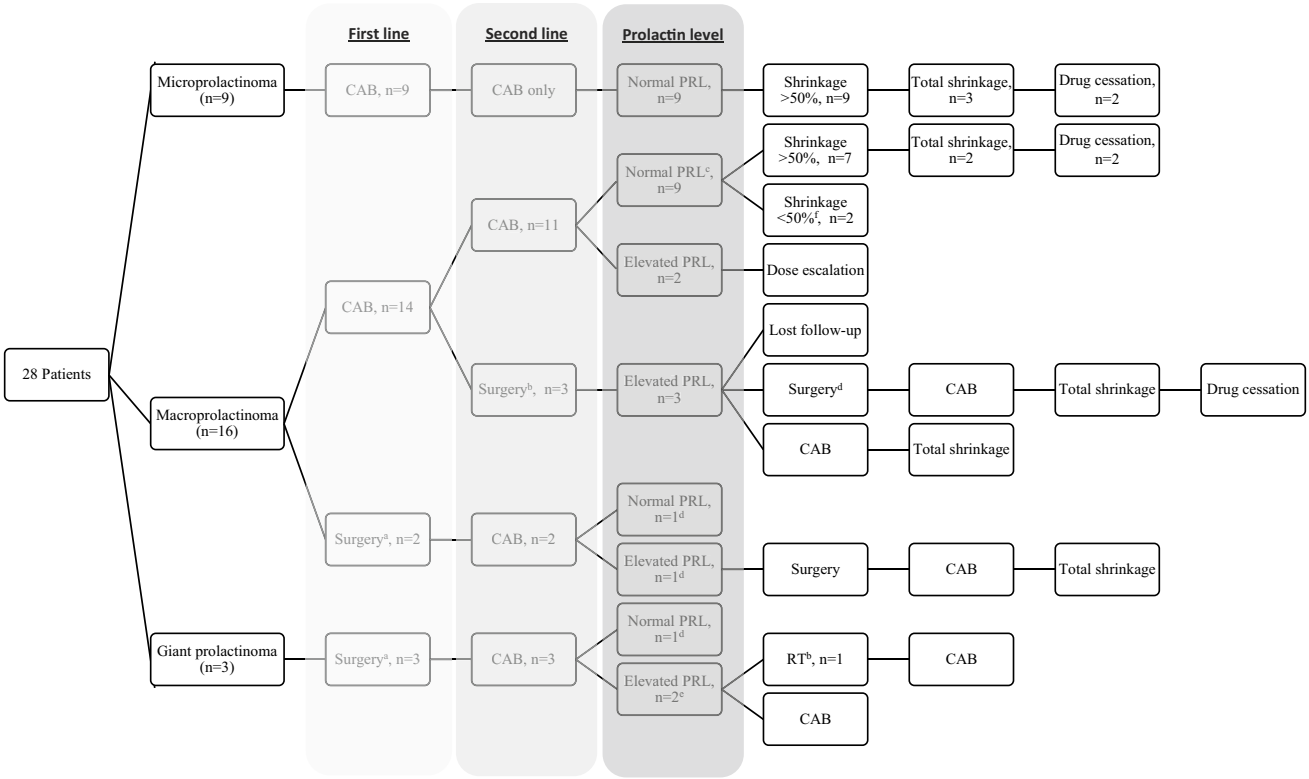

Fig. 1 Treatment modalities and outcome of patients with prolactinoma. **a** Performed due to optic chiasma compression. **b** Performed due to elevated PRL levels. **c** One of them had GH deficiency at admission. **d** Pituitary hormone deficiency was developed after surgery. **e** Pituitary hormone deficiency was present at the time of diagnosis. **f** Cabergoline dose of these patients were between 0.75 and 1 mg/week, so they were not considered as drug resistant

later was successful; there was no relapse after 6 months. In the second patient (Patient-6) treatment was stopped after six years of therapy, at the age of 20.5 years. No relapse occurred in the 8-month follow-up. The third patient with tumor shrinkage (Patient-3) after 6 years of treatment with CAB was lost to follow-up thereafter. None of the patients had any pituitary hormone deficiency.

Macroprolactinoma

Sixteen children (15 girls, 1 boy) had macroprolactinoma. First-line treatment was CAB in 14 cases, and adenomectomy in 2 cases (Patients-20, 21). Median serum prolactin concentration at diagnosis was 188.3 ng/mL (range 104–2466 ng/mL). Median follow-up was 3 years (0.5–10 years).

Normal prolactin level was achieved in 9 out of 14 patients (64.2%) with CAB as first-line treatment at a median time of 2 months (range 0.5–24 month) with a median dose of 1 mg/week (0.5–2 mg). The time until normalization and CAB dose were similar to the microprolactinoma group ($p = 0.75$, $p = 0.9$ respectively). Two of nine patients had total tumor shrinkage within 12–36 months, CAB could be discontinued after 24–48 months (Fig. 1).

Among the remaining five patients out of 14, who could not achieve normal prolactin level, CAB dose escalation was still continuing in two, and surgical excision was performed in three (Patient-14, 19, 23). In the former two patients (Patients-18 and 25) CAB was increased to 5.5 and 4.5 mg/week respectively, however prolactin levels remained high. One of them (Patient-25) had more than 50% reduction in adenoma size within 2 years (Fig. 1).

Overall five patients were operated, two as first-line (Patient-20, 21), three as second-line treatment (Patient-14, 19, 23). Two patients (Patient-14 and 21) had to be operated

Table 3 Change in adenoma size and prolactin levels during follow-up in patients with prolactinoma

	Prolactin level		
Adenoma size	Decreased	Stable	Increased
Decreased	19	4	0
Stable	2	2	0
Increased	0	0	1

more than once. Three patients (Patient-14, 19, 21) had no residual tumor on MRI during follow-up. Low dose CAB was continued after the operations in all 5 patients since prolactin levels remained high (Fig. 1). CAB therapy was discontinued in one (Patient-14), and one patient (patient 20) had normalized under CAB.

Patients with CAB treatment did not have serious side effects. Only one had transient nausea. One patient developed GH deficiency during follow-up in the CAB alone group. Among those who had undergone surgery three developed pituitary hormone deficiency (Patients-14, 20 and 21, Fig. 1; Table 2). Visual field loss improved after surgery (Patients-20 and 21).

Giant prolactinoma

Three boys with an age range of 12.9–16.7 years had giant prolactinoma. Median serum prolactin concentration at diagnosis was 3216 ng/ml (range 3062–32,225 ng/ml). All presented with visual disturbances and headache. Bitemporal hemianopsia was confirmed by perimetry in all three. They did not have short stature (height SDS range between -1.1 and 1.3), however all of them were obese (BMI SDS range between 2.1 and 2.4), and had pubertal arrest. Two of them had panhypopituitarism at the time of diagnosis. Subtotal resection was performed in all patients as the first line treatment, and the last patient also developed panhypopituitarism thereafter. Cabergoline was started after surgery. They were followed for 3 to 6 years.

Patient-26 had an adenoma extending to the suprasellar cistern. Histological examination revealed 1% of Ki67. Normalization of prolactin was achieved with CAB at a dose of 1 mg/week within 3 months following surgery. After three years of CAB therapy, he still had residue next to ICA. Patient-27, who had an adenoma filling the suprasellar cistern, extending to the lateral wall of the cavernous sinus and compressing the mesencephalon and optic chiasm, underwent incomplete resection. Postoperatively prolactin decreased from 32,225 ng/mL to 11,370 ng/mL and adenoma size from 50 mm to 40 mm. Then he was put on CAB. Within 18 months after surgery, prolactin level decreased significantly with low dose CAB. He was followed for 6 years and had elevated serum prolactin (level 41.5 ng/mL) and a minimal remnant of the tumor on MRI in the last follow-up while receiving CAB at a dose of 1 mg/week. The last patient, Patient-28, had an adenoma infiltrating the cavernous sinus. Histological examination revealed 2–3 mitosis per field and Ki67 was positive in 4% of cells. Cabergoline dose had to be increased up to 8 mg/week following surgery. He developed orthostatic hypotension, and exhibited impulse control disorder under treatment and received cyberknife radiotherapy (CR) after 12 months of CAB. Three months after the CR, adenoma size decreased from 19.6 mm to 16 mm. He went on receiving CAB at a dose of 5 mg/week, and two years after the CR he still has residue in the cavernous sinus and could not achieve a normal prolactin level .

Effect of treatment on adenoma size

At the latest follow-up 82% of patients (23/28) showed a decrease in adenoma size (19 patients with CAB and 4 also with surgery), in 14% (4/28) adenoma size was stable during follow-up (Table 3). None of the microprolactinomas had increase in adenoma size. Only one patient with macroprolactinoma had an increase in adenoma size after four years of treatment with a consistent increase in prolactin level and amenorrhea (Table 3).

All microprolactinomas achieved more than 50% tumor shrinkage by the 36th month of CAB (median 12 months [range 6–36 months]). More than 50% shrinkage occurred in eight patients (72%) with macroprolactinoma by the 48th month of CAB (median 24 months [range 12–48 months]).

Factors associated with treatment response

In regression analysis adenoma size (β [95% CI] = 1.19 [1.03, 1.41], $p = 0.035$) and invasion/extension of the adenoma (β [95% CI] = 5.53 [1.83, 16.72], $p = 0.002$) predicted either drug resistance or surgical requirement. All adenomas over 30 mm (4/28) were drug resistant or needed surgery and, all adenomas below 13.5 mm (13/28) achieved normalization with conventional doses of CAB without surgery. Eight of eleven with an adenoma size between 13.5 mm and 30 mm had either suprasellar extension or cavernous sinus invasion, and 6 out of 8 patients (75%) did not respond to conventional doses of CAB thus drug resistant or needed surgery. All patients with no invasion/extension (3/11) responded to conventional doses of CAB.

Discussion

Childhood prolactinomas may diverge from adults both in presentation as well as response to treatment and follow-up. Unlike adults, macroprolactinomas are more prevalent in children. Although in terms of female/male ratio a preponderance of females exists in all age groups until the menopause when equality is achieved [29], there is an important gender difference in adenoma size and age at diagnosis. Microprolactinoma is 2.5 times more prevalent in adult females than macro- whereas macroprolactinoma is 1.5 times more prevalent than micro- in adult males [29]. Macro-/microprolactinoma ratio for children is almost equal in girls, whereas in boys macroprolactinoma is 2–5 times more common [30, 31]. In our cohort at the time of diagnosis boys were younger than girls unlike adults [2] but similar

to results of other studies in pediatric age group [7, 30]. The adenomas ≥ 10 mm constituted the most common type of prolactinoma which makes 67% of our whole cohort. We found higher frequency of girls with a 4.6:1 ratio similar to the other studies in the pediatric age group [7, 32, 33]. On the other hand, duration of symptoms was shorter and symptoms were related to the mass effect in boys compared to girls similar to other studies in children reported so far [33–35].

Overall 47% of patients were obese or overweight on admission and we showed that higher BMI was associated with higher prolactin levels, wider diameter of adenoma and male gender. In a cohort of 77 children with macroprolactinoma, 46% were overweight or obese on admission [32]. Another cohort of children with drug resistant prolactinoma, 71% were obese or overweight and 42% were obese [33]. Increased prevalence of obesity was also observed in adults [36]. Some reports showed weight reduction and improvement in metabolic parameters such as plasma glucose, triglyceride concentrations and insulin resistance in patients with prolactinoma during dopamine agonist treatment whereas some reports did not [30, 37, 38]. Besides being an anabolic hormone, and causing an increase in the expression of transcription factors involved in adipogenesis [39] prolactin disturbs leptin and leptin receptor interaction, blocking leptin transport into the central nervous system as well as reducing expression of the leptin receptor, thus causes a reduction in anorexigenic input [39, 40]. The decrease in dopaminergic tone, which is responsible for the pathogenesis of prolactinoma and also is caused by chronic elevated prolactin level, causes a disruption in the rewarding effect of food intake in the hypothalamus [41, 42]. In conclusion changes in weight and metabolic parameters in hyperprolactinemia seem to occur due to complex interactions between gene expression, hormones and neurotransmitters.

While most of the pituitary adenomas occur sporadically, germline mutations and somatic changes have been identified in minority. Germline mutations constitutes 5–7% of pituitary adenomas [43]. *MEN1*, and *AIP* are the most common mutation in pituitary adenomas with frequency reaching 22% in pediatric patients with macroadenomas [44]. *AIP* mutation was detected in 4–9% and *MEN1* in 5–6% of young onset prolactinomas [32, 44, 45]. *PRKAR1A* mutations as a cause of Carney complex are detected less frequently [46]. Adenomas with mutations tend to be more aggressive, and resistant [32, 47, 48]. In our cohort all patients had sporadic tumors and none of them had syndromic features and family history of malignancy. There is not a clear suggestion whether patients with spontaneous prolactinomas should be screened for genetic mutations. Some reports suggest patients with macroadenomas who diagnosed before 30 years old should be screened for *MEN1* and *AIP* mutations [44]. We do not routinely perform genetic analysis, however we screen hyperparathyroidism in all patients and we have not encountered hyperparathyroidism yet.

Treatment success with DA seems to be lower in childhood prolactinoma. Normal prolactin level was achieved in 71–100% of microprolactinomas and 45–72% of macroprolactinomas in pediatric series [9, 30, 31, 34, 49]. In the current cohort 82% of patients received DA as first-line treatment, and normal prolactin level was achieved in 78% of these patients with only medical treatment (all the microprolactinomas and 64% of the macroprolactinomas). Whereas normalization of prolactin in adults was 82–92% [50, 51] in microprolactinomas, and 77–94% [52, 53] in macroprolactinomas with DA, higher than pediatric patients. Vilar et al. reported normalization rate of 91% and 83% of micro- and macroprolactinomas with CAB, respectively in 388 adult patients with prolactinoma and complete tumor shrinkage was achieved in 57.5% [53]. Success of surgery seems to be similar in children and adults. Transsphenoidal surgery can achieve normalization in 30–40% of adult patients with macroadenomas with recurrence rates of 20% over 10 years [54]. In pediatric series remission rates were between 33.3% and 69.3%, and surgical success negatively correlated to the diameter of adenoma and prolactin levels [14, 55–58]. In the current cohort 31% of macroprolactinomas and all giant prolactinomas needed surgery either as first- or second-line treatment, and all patients who underwent surgery required CAB thereafter. Normalization of prolactin was achieved in all patients with microprolactinomas under CAB, solely, suggesting a similar success to adults with microprolactinomas, however macroprolactinomas were more resistant to CAB with a normalization rate of 64% in our series, and surgery did not increase this rate (68%) significantly. Surgery alleviated mass effect of the tumor however CAB treatment was still required to normalize prolactin level after surgery in our cohort. When DA was used as either first-line or adjuvant therapy, 75% of all patients (all the microprolactinomas, 68% and 33.3% of the macroprolactinomas and giant prolactinomas, respectively) achieved normal prolactin levels. Overall CAB was discontinued in 17% within 3.3 to 10 years and 25% of patients showed drug resistance. Normalization rates of prolactin decrease with increasing adenoma size, so a second-line treatment is required in case of large adenomas [9, 30, 31, 34, 49]. Pediatric studies demonstrated that adenoma size, cavernous sinus invasion, and suprasellar extension affected treatment response [9, 32, 59] and Yang and Arya et al. showed that all children with drug resistance or surgical requirement had adenoma size of 20 mm or more [30, 31]. Size and invasion of the adenoma predicted either drug resistance or surgery requirement in our cohort, too. Patients with adenoma smaller than 13.5 mm could achieve normal prolactin levels with a maximum dose of 2 mg/week CAB. However, above this size the rate of drug resistance or surgery requirement increased, especially suprasellar

extension and cavernous sinus invasion were predictors of requirement for second-line therapies and all those above 30 mm had drug resistance or surgical requirement. Moreover, increasing the dose of CAB over 2 mg/week did not add any benefit to decrease prolactin levels.

In resistant prolactinomas management still remains a challenge. Several algorithms may be used in order to achieve normal prolactin levels and tumor shrinkage. One method is dose escalation of CAB to the maximally tolerated dose. Doses as high as 11 mg/week have been used to achieve normal prolactin level in resistant cases in the literature [60]. However, it should be kept in mind that higher doses can cause severe side effects such as neuropsychiatric disorders. In our cohort one patient with high dose CAB experienced impulse control disorder. Several studies pointed out 'maximal effective CAB dose' [51, 61]. In adult series, it was showed that intensive treatment regimen or increasing the dose above 3.5 mg/week did not contribute to normalization or tumor shrinkage [51, 52, 62]. Also, in pediatric series CAB dose of 0.5–3.5 mg/week was sufficient for achieving normal prolactin levels and increasing the dose was ineffective in cases with drug resistance [30–32, 49]. Likewise, we observed that the doses of CAB attaining normal prolactin levels in patients with micro- and macroprolactinoma were similar, and doses higher than 2 mg/week did not contribute to normalization rate in patients with macroprolactinoma.

Surgery is another option that can be used in resistant cases unresponsive to CAB dose escalation as well as patients with neurological symptoms. A recent meta-analysis in adults showed that long-term remission rates were 36% with DA after withdrawal, and 83% with surgery in micro-, and 28% with DA after withdrawal and 60% with surgery in macroprolactinomas [63]. One should keep in mind that surgery is not without its risks. In the current cohort, hypopituitarism developed following surgery in three patients, and one patient had cerebrospinal fluid leakage. Furthermore, all patients had to continue CAB following surgery. Based on the knowledge that somatostatin receptor subtypes are expressed in prolactinoma cells, several attempts had been performed with somatostatin analogs. Although somatostatin analogs showed promising results in adults there is not enough data to recommend them as an adjuvant treatment for children with drug resistance so far [64, 65].

Policy for imaging surveillance of tumor during follow-up has not been established yet, especially in children. The Endocrine Society Clinical Practice Guideline recommends repeating MRI in 1 year for micro- and in 3 months for macroprolactinomas in adults [23]. Prolactin level is correlated with adenoma size and decreasing prolactin level almost always indicates a decreasing or stable adenoma size [66]. Increase in adenoma size is accompanied by either an increase in prolactin level, visual impairment and/or neurological deterioration due to mass effect which was accompanied with drug resistance, hemorrhage or apoplexy especially in macroprolactinomas [7, 30, 31, 33]. Increase in adenoma size despite decreasing or stable prolactin level is quite rare. It was reported in a few adult patients with pituitary hemorrhage [66] or, whose imaging's were performed with low resolution methods, either with radiographs [67] or tomography [68]. To our knowledge, no case has been reported with increase in adenoma size despite stable or decreasing prolactin levels in pediatric series. We performed MRI every year in all cases with micro- and macroprolactinoma. In our cohort only one macroprolactinoma had an increase in size which was also accompanied with increasing prolactin level. Since 50% tumor shrinkage can be delayed up to 36 months in micro- and 48 months in macroprolactinomas, routine annual imaging seems to be unnecessary. Surveillance of pediatric patients with prolactinoma by prolactin levels and visual/neurological examination regularly makes more sense in the follow-up.

The current study has several limitations. First, number of patients is limited, since prolactinomas are rare in childhood and adolescence. Second, retrospective nature of this study can cause bias in terms of hormone analysis since hormone levels were measured with different assays even though the methodology and reference levels were similar. Third, only few patients were lost to follow-up.

In conclusion pediatric prolactinomas diverge from adults in terms of adenoma size, gender distribution and sensitivity to DA treatment. Macroprolactinomas are more prevalent in children and adolescents, but less sensitive to CAB treatment. All microprolactinomas responded well to DA treatment. However, all adenomas larger than 30 mm was resistant to CAB or required surgery. Probability of drug resistance and requirement of second line therapy were higher in adenomas between 13.5 mm and 30 mm with invasion/extension. Doses over 2 mg/week of CAB in drug-resistant patients may not provide additional benefit. The frequency of follow-up MRI could be determined based on prolactin levels and existence of new neurological symptoms.

Funding No funds, grants, or other support was received.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Non applicable.

Declarations

Conflict of interest All authors declare no potential conflict of interest in relation to this study.

Ethical approval The study protocol was approved by local ethics committee (Approval Number: 2019/14–24, Project Number: GO 19/476).

Consent to participate The requirement for informed consent was waived owing to the retrospective nature of the study.

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