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Prolactinomas in Children and Adolescents. Clinical Presentation and Long-Term Follow-Up

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ABSTRACT

In this study, we report the clinical presentation, response to medical treatment, and long-term follow-up of 26 patients with prolactinoma (15 macro- and 11 micro-adenomas) diagnosed at the age of 7–17 yr. All patients were first treated with bromocriptine (BRC) at doses ranging from 2.5–20 mg/day orally. BRC was discontinued for intolerance and/or resistance to the drug and was replaced by quinagolide (CV) at doses ranging from 0.075–0.6 mg/day or by cabergoline at doses ranging from 0.5–3.5 mg/week orally. Two patients received external conventional radiotherapy after surgery.

In 7 prepubertal males and 6 females with macroprolactinoma, headache and/or visual defects were the first symptoms. All females presented with primary or secondary amenorrhea. Growth arrest was observed in a male patient with microadenoma, whereas all the remaining patients had normal heights, and pubertal development was appropriate for their age. Spontaneous or provocative galactorrhea was observed in 12 patients (3 males and 9 females) and gynecomastia in 4 males. Mean serum PRL concentration (±SE) at the time of diagnosis was 1080 ± 267 μg/L in patients with macroadenoma and 155 ± 38 μg/L in patients with microadenoma. In 10 patients, BRC normalized PRL levels and caused variable, but significant, tumor shrinkage. CV normalized PRL concentrations and reduced tumor size in 5 patients. Cabergoline normalized PRL concentrations in 7 of 10 patients resistant to CV. Pregnancy occurred in 2 patients while on treatment. Pregnancies were uncomplicated, and the patients delivered normal newborns at term. Only 4 patients are still moderately hyperprolactinemic. Impairment of other pituitary hormone secretion was documented at the time of diagnosis in 7 patients, 5 of whom underwent surgery. Four patients became GH deficient in adult age.

In conclusion, the medical treatment with dopaminergic compounds is effective and safe in patients with prolactinoma with onset in childhood, allowing preservation of the anterior pituitary function. (*J Clin Endocrinol Metab* **83:** 2777–2780, 1998)

PROLACTINOMAS are the most frequent pituitary tumors, and their frequency varies with age and sex, occurring most frequently in females between 20–50 yr old. In the pediatric/adolescent age, prolactinomas are rare, representing about half of all pituitary adenomas (which, overall, account for less than 2% of intracranial tumors) (1, 2). Therefore, the clinical presentation, response to medical treatment, and long-term outcome of children and adolescents with prolactinoma have been reported in only small series (3, 4) and in a number of isolated case reports (reviewed in Refs. 5 and 6). It has been estimated that only 26 patients less than 18 yr old at diagnosis had been described between 1982 and 1991 (5, 6). In this study, we report the clinical presentation, response to medical treatment, and long-term follow-up of 26 patients with prolactinoma seen in our Institutions in the last 15 yr and whose age at diagnosis was less than 18 yr.

Subjects and Methods

Twenty-six patients (9 males and 17 females, age 7–17 yr) were referred to our Institutions for suspected pituitary tumor or for persistence of hyperprolactinemia after surgery between 1980 and 1996. Their main clinical, hormonal, and radiological findings are summarized in Table 1. Assessment of clinical history, physical examination (including pubertal staging according to Tanner), and complete evaluation of hypothalamic-pituitary function were carried out in all patients. Gonadotropin, TSH, and PRL secretion was evaluated at baseline and after GnRH (100 μg, iv) and TRH (200 μg, iv) tests in all patients except those with compression of optic chiasm documented by computed tomography (CT) or magnetic resonance imaging (MRI), to avoid the risk of sudden impairment of visual field and acuity. Somatotropic function was evaluated by means of oral clonidine test (150 mg/m^2, per os) and/or measurement of serum insulin-like growth factor-I performed at baseline and then at yearly intervals. Evaluation of adrenal, gonadal, and thyroid functions was also performed at baseline and then at yearly intervals. At diagnosis, CT and/or MRI showed the presence of a macroadenoma in 15 patients and of a microadenoma in 11 patients (Table 1). Six patients (nos. 2, 4, 8, 10, and 23) came to our observation after surgery that did not lead to PRL normalization (normal values: 5–25 μg/L in females and 5–15 μg/L in males).

All patients were first treated with bromocriptine (BRC) at doses of 2.5–20 mg/day orally. BRC was discontinued when the patients were intolerant and/or resistant to the drug and was replaced by quinagolide (CV) at doses of 0.075–0.6 mg/day or cabergoline (CAB) at doses of 0.5–3.5 mg/week orally. Resistance to BRC or CV, administered in daily doses of 15 or 0.6 mg for at least 3 months, respectively, was defined by the lack of normalization of PRL concentration and/or of tumor mass shrinkage (7). Two patients received conventional radiotherapy immediately after surgery (no. 8) and 2 yr later (no. 9) because of persistence of hyperprolactinemia and evidence of tumor remnant at MRI.

Circulating PRL, FSH, LH, GH, ACTH, and cortisol (serum and urinary) levels were assayed by commercially available RIA, whereas

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TABLE 1. Patients' profile, clinical findings, and effect of treatment on tumor size

Patient (sex)	Age at diagnosis (yr)	Present age (yr)	Serum PRL levels (ng/mL)	Presenting complaints	Surgery	Associated hormone deficiency	Radiological findings	
							Before	After treatment
1. m	7	18	165	G, Gy, H	no	none	MA	Empty sella
2. m	14	27	640	Gy, H	yes	none	MA	Empty sella, right RM
3. m	16	21	3300	H, VFD	yes	FSH,LH,TSH,GH	MA	Empty sella, left RM
4. m	15	18	1600	VFD	yes	ACTH,ADH,TSH,GH	MA	Intrasellar RM
5. m	12	21	3065	G,Gy,VFD,H	no	none	MA	30% shrinkage
6. m	14	17	720	G,Gy,VFD,H	no	none	MA	40% shrinkage
7. m	15	16	142	Gy,SS	no	GH	ma	Empty sella
8. m	17	23	1700	H	yes	ACTH,TSH,GH	MA	Empty sella, right RM
9. m	15	16	1048	VFD,H	no	ACTH,TSH	MA	20% shrinkage
10. f	17	26	1700	A1,H	yes	ACTH,TSH,GH	MA	Empty sella, right RM
11. f	14	26	110	O	no	none	ma	Negative
12. f	15	30	171	A1,G,H	no	none	MA	50% shrinkage
13. f	17	32	1246	A2,G,H	no	none	MA	Empty sella
14. f	13	36	160	A2	yes	none	ma	Unchanged
15. f	15	40	500	A1	yes	none	ma	30% shrinkage
16. f	15	17	70	A2,G	no	none	ma	50% shrinkage
17. f	14	26	93	O,G	no	none	ma	Unchanged
18. f	15	22	105	O	no	none	ma	Unchanged
19. f	17	30	145	O,G,H	no	none	MA	30% shrinkage
20. f	14	19	94	A2	no	none	ma	20% shrinkage
21. f	15	27	71	O,G	no	none	ma	Unchanged
22. f	15	23	94	A2	no	none	ma	Unchanged
23. f	14	27	336	A1,G	yes	none	MA	Empty sella
24. f	14	18	200	A1,G,VFD,H	yes	ACTH	MA	Empty sella
25. f	14	25	160	A1,G,VFD,H	no	none	MA	50% shrinkage
26. f	17	27	259	A1	no	none	ma	Empty sella

G, galactorrhea; Gy, gynecomastia; H, headache; VFD, visual field defects; A1, primary amenorrhea; A2, secondary amenorrhea; O, oligomenorrhea; MA, macroadenoma; ma, microadenoma; RM, residual mass.

TSH and insulin-like growth factor-I (after ethanol extraction) levels were assayed by immunoradiometric assay.

Visual field was assessed by Goldmann-Friedmann perimetry and was performed at diagnosis and yearly during the follow-up in patients with visual field defects. CT and/or MRI were carried out at diagnosis and every 6–12 months. A greater than 30% decrease in tumor mass after treatment was considered significant shrinkage.

Results

Clinical presentation

Headache and/or visual field defects were the first symptoms in 7 males and 6 females with macroadenoma (in the latter, associated with primary or secondary amenorrhea). Menstrual disturbances were the first symptom in females with microprolactinoma (Table 1). Growth arrest was observed in a male patient with microprolactinoma (no. 7), whereas all the remaining patients had normal heights, and pubertal development was appropriate for their age. Galactorrhea was observed in 12 patients (3 males and 9 females).

Radiological and hormonal findings

Five patients (nos. 2, 4, 8, 10, and 23) with macro- and 1 patient (no. 14) with microadenoma were investigated for tumor relapse after surgery. At diagnosis, serum PRL concentrations ranged from 145–3.300 μg/L in macro- and 70–500 μg/L in microadenomas. Impairment of other pituitary hormone secretion was documented in 7 patients, 5 of whom had undergone surgery (Table 1). Patients no. 3, 4, 8, and 10 became GH deficient in adult age.

Follow-up (Table 2)

In 10 patients (nos. 1, 5, 7, 9, 12, 14, 16, 21, 22, and 25), BRC normalized serum PRL levels within 6–12 months and caused a variable, but significant, tumor shrinkage. The remaining patients were regarded as resistant or partially resistant to BRC. In 5 patients (nos. 1, 5, 14, 21, and 22), BRC caused intolerable side effects (Table 2) and had to be discontinued. CV treatment induced PRL normalization and tumor shrinkage only in 5 patients (nos. 13, 14, and 18–20). Ten patients (nos. 1–4, 8, 10, 11, 15, 17, and 23) were partially resistant also to CV and were given CAB, which normalized PRL concentrations in 6 of them (Table 2). Pregnancy occurred in patients no. 13 (once) and no. 17 (twice) while on treatment. Pregnancies were uncomplicated, and the patients delivered normal newborns at term. All patients are still on treatment. Only 4 patients (nos. 1, 3, 11, and 15) are presently moderately hyperprolactinemic and are symptomatic.

Discussion

Prolactinomas are rare in children and adolescents. In this report, we describe the clinical presentation, response to medical treatment, and follow-up in a large series of patients diagnosed as having a prolactinoma before the age of 18 yr. As reported in adults, also in children, prolactinomas occurred mostly in females (17/26). At the time of diagnosis, symptoms of tumor expansion were consistently present in all patients with macroadenoma, whereas menstrual disturbances were the first complaint in females with microadenoma. Impairment of other pituitary hormone secretion was found only in a minority of patients (7/26); and in 5 of them,

TABLE 2. Effect of treatment with bromocriptine, quinagolide, and cabergoline in the 26 patients with prolactinoma

Patient no.	Treatment with bromocriptine				Treatment with quinagolide				Treatment with cabergoline				Current therapy
	Dose (mg/day)	Duration (years)	Nadir PRL (ng/ml)	Side effects	Dose (mg/day)	Duration (years)	Nadir PRL (ng/ml)	Side effects	Dose (mg/week)	Duration (years)	Nadir PRL (ng/ml)	Side effects	
1.	7.5	6	13	N,V	0.3	4	37	no, PC	1.5	3	18.5	no	CAB
2.	2.5	8	100	N,AP,V	0.3	3	146	N	2.5	3	11.7	no	CAB
3.	5	1	163	V,H	0.6	5	19.4	no	1.5	2	72	no	[a]CAB, T_4
4.	2.5	1	124	AP,PH	0.3	1	45	PH,PC	1	2	14.5	no	CAB,AVP,T_4
5.	7.5	9	10	PH					2	2	5	no	CAB
6.	7.5	4	18.9	N					2	2	7	no	CAB
7.	5	1	2.0	no									BRC
8.	10	1	250	N,PH	0.6	1	35	no	1	4	4	no	CAB,H,T_4,T,AVP
9.	5	2	11.6	no									BRC,H,T_4
10.	15	3	215	no	0.6	4	39	no	1	2	4.2	no	CAB,H,T_4
11.	15	9	60	no	0.6	1	48.5	no	3.5	2	35	no	CAB
12.	7.5	15	4	no									BRC
13.	5	9	305	PH	0.15	4	17.3	no	1	2	13	no	CAB
14.	5	17	11.2	V,H	0.075	4	2	no	1	2	4	no	CAB
15.	20	18	400	no	0.6	4	150.2	no	2.5	2	88	no	CAB
16.	7.5	2	1.2	no									BRC
17.	2.5	5	70	N	0.075	4	33	N	0.5	2	10	no	CAB
18.	7.5	3	26	AP,H	0.15	2	17.6	no	1	2	11	no	CAB
19.	2.5	8	96	N,H	0.075	4	12	no	1	1	20	no	CAB,T_4
20.	2.5	2	58.4	V	0.075	2	8.1	no	1	2	3	no	CAB
21.	5	9	11	H,AP					1	2	2.7	no	CAB
22.	2.5	7	17.1	D,V					1	2	0.9	no	CAB
23.	20	7	78	no	0.15	4	40	no	1	2	12	no	CAB
24.	5	3	94	N,V					1	2	25	no	CAB,H
25.	5	9	17	no									BRC
26.	10	8	48	no					1.5	2	25	no	CAB

N, nausea; V, vomiting; H, headache; AP, abdominal pain; PH, postural hypotension; D, dizziness; PC, poor compliance; T4, levo-thyroxine; H, hydrocortisone; AVP, arginine vasopressin; T, testosterone.

[a] At present, quinagolide is not available in Italy.

pituitary insufficiency developed after surgery. Stunted growth was recorded only in 1 male patient with microadenoma, who also had GH deficiency and is currently being treated with GH. GH deficiency developed later in another 4 patients. Our data indicate that GH deficiency is not a common finding in young patients with prolactinoma, in partial disagreement with other reports (reviewed in Refs. 5 and 6). Normalization of GH secretion after BRC therapy has also been reported (6, 8, 9). These differences could be explained by the observation that, in the patients previously described, arrested growth was one of the presenting symptoms; whereas, in our patients, impairment of gonadal function or symptoms of tumor expansion were more frequently observed at the time of diagnosis. Prolactinomas in children are frequently associated with delayed puberty (4), because hyperprolactinemia reportedly affects hypothalamic-gonadotropic activity. This makes difficult the diagnosis of prolactinoma in young children, which is commonly suspected only when symptoms of tumor expansion occur. The low frequency of prolactinoma in childhood might therefore be underestimated by the late occurrence of symptoms, even in the presence of hyperprolactinemia for many years.

Treatment with dopamine-agonists is effective in normalizing PRL levels and in shrinking tumor mass in the majority of adult patients with prolactinoma (10). In children and adolescents, BRC has been used successfully be several investigators (3–6, 8, 9). In our series, BRC induced normoprolactinemia in 10 of 26 patients. The poorly responsive patients were regarded as resistant or partially resistant to the drug. We recognize that many of them did not meet the criteria for being considered truly resistant, and we suspect that some of them were indeed not taking BRC appropriately. Poor compliance to any chronic treatment is a well-known phenomenon in children and adolescents. In addition, some patients required drug discontinuation for intolerable side effects, overall, regarding the gastrointestinal tract. All these patients were given CV or CAB, which were effective in reducing PRL secretion and tumor size in most of them.

In up to one third of women with microadenoma, hyperprolactinemia will prove self-limiting, and pregnancy might be one factor that triggers a return to normal function (11). However, all of our patients are still on treatment, and two of them became pregnant but remained hyperprolactinemic. We cannot predict whether some of our patients will be cured, but we believe that, for most (if not all) of them, dopamine-agonist treatment will be life-long (10).

Seven patients came to our observation immediately after surgery for persistence of hyperprolactinemia. They were first seen by the neurosurgeon for symptoms related to tumor expansion and then operated. As in adults (10), therapy with dopamine-agonists has been shown to be effective also in adolescent patients with large tumors and symptoms of tumor expansion (3, 5, 6). It is possible, therefore, that some of our patients could have avoided surgery if appropriately treated with dopaminergic drugs. Furthermore, none of the

patients who underwent surgical resection of the adenoma as first treatment (with or without external radiotherapy) was cured, and many of them also developed associated pituitary hormone deficiencies. The high recurrence rate of prolactinomas after surgery compares favorably with that reported in the literature (1, 12). Thus, treatment with dopamine-agonists should be the first therapeutic option also in young patients with prolactinomas. Surgery should be reserved for those patients with large tumors not responsive to dopamine-agonist therapy. In particular, CAB has recently received attention for its better tolerability and compliance (13) and is effective also in patients poorly responsive or resistant to BRC and/or CV (7). CAB has a longer half-life than BRC, needs to be administered only once or twice a week, and causes normalization of serum PRL levels and restoration of gonadal function in the majority of patients with microprolactinoma (13). Low-dose CAB treatment produced marked tumor shrinkage in most macroprolactinoma patients (14, 15). We suggest that CAB should be the first-line treatment also in young patients with prolactinoma.

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