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Pituitary adenomas in childhood and adolescence. Clinical analysis of 10 cases

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ABSTRACT. Pituitary adenomas in childhood and adolescence constitute 2-6% of all operated pituitary adenomas. We report the clinical features, treatment and follow-up of 10 pediatric patients affected by pituitary adenomas. All patients underwent clinical evaluation, endocrine tests, magnetic resonance imaging and visual field assessment. Follow-up ranged from 8 to 132 months (median 52.6). All patients were older than 10 years of age; 60% were males. In 50% the initial complaints were headache and/or visual impairment, all except one had clear evidence of endocrine dysfunction. Ninety percent were macroadenomas. According to hormone measurements and immunostaining 50% were prolactinomas, 20% were pure GH-secreting and 30% were non-functioning adenomas. Prolactinomas in two females were successfully treated with cabergoline. The other patients underwent surgery: three prolactinomas are still being treated with dopamine agonists and a GH-secreting adenoma is being treated with octreotide LAR and cabergoline. Two patients were also treated with conventional radiotherapy. Treatments were completely successful in 50% of patients: these have normal hormone secretion, full pubertal development, no significant tumor mass and normal visual field. Hypersecretion of prolactin persists in two cases; partial or complete hypopituitarism is present in four, relevant tumor remnant in another four and impairment of visual field is present in two cases. In conclusion, pediatric adenomas occur mostly in pubertal age, are prevalently macroadenomas and clinically functioning. Medical therapy should be preferred for secreting adenomas, but in some cases, notably prolactinomas in males, surgery and eventual radiotherapy may be needed.
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INTRODUCTION

Pituitary adenomas rarely occur in childhood and adolescence (1-6). Most data are based on case reports and only a few series of importance have been reported. Furthermore, different definitions of pediatric age and criteria of cure have been used which, in addition to incomplete follow-up, make this topic of pediatric endocrinology far from resolved (7). We report the clinical features, management and outcome of 10 pediatric patients with pituitary adenomas.

Key-words: Pituitary adenomas, adolescence, prolactinomas, gigantism, octreotide.

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MATERIALS AND METHODS

The files of all patients admitted to our hospital for pituitary adenomas since 1989 were searched. Ten patients were considered pediatric cases: all subjects were 18 years old or less at diagnosis with the exception of one patient affected by acromegaly/-gigantism. 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. Hormonal status was assessed in the basal state with dynamic tests when appropriate, generally according to standard protocols (8). Hormone measurements were made using commercial radioimmunologic Kits: IGF-I was measured by an immunoradiometric assay after ethanol extraction and the values compared with normal references after adjustment for age.

Pituitary imaging was performed by magnetic resonance before and after contrast. All patients underwent complete ophthalmologic evaluation, includ-

ing visual field measurement by Goldman-Friedman or computerized perimetry. All operations, except in patient 6, were performed by the same surgeon (D.B.). Tumor specimens were stained with specific antibodies against GH, PRL, ACTH, LH, FSH, TSH. Pituitary radiotherapy was performed using a 6 MV linear accelerator to deliver a dose of 4500 cGy via three fields in 25 fractions with the aid of computerized tomography for targeting. Clinical examination, hormonal measurements and ophthalmologic evaluation were performed at least every six months and M.R. was repeated at least yearly.

RESULTS

The results are shown in Table 1 (prolactinomas) and Table 2 (non prolactinomas). Six patients were males (60%). Age at diagnosis ranged from 11 to 19 years (median 16.5). Mean delay from onset of symptoms and diagnosis was 17 months (range 2-48). Follow-up ranged from 8 to 132 months (median 52.6).
Symptoms that primarily led to medical attention were visual defects and/or headache in five patients (50%), primary amenorrhea in two (20%), secondary amenorrhea in one (10%) and acromegaly/gigantism in two other cases (20%). At diagnosis clinical

Table 1 - *Clinical features, hormonal status, treatment and follow-up of pediatric prolactinomas.*

Case	1	2	3	4	5
Sex	F	F	M	M	M
Age at onset of symptoms and diagnosis (yr)	13 16	16 17	14 15	11 11	16 18
Follow-up (months)	51	8	60	38	11
Presenting complaints	Primary amenorrhea, galactorrhea	Secondary amenorrhea	Visual defects	Visual defects	Visual defects, headache
Other clinical findings		Galactorrhea	Compulsive behavior, epilepsy	Short stature	Gynecomastia
Pubertal stage (Tanner)	B3P2	B5P5	G3P4	G1P2	G3P3
Visual field	Normal	Reduced bitemporal field	Right temporal hemianopsia, visual loss of the left field	Bitemporal hemianopsia	Bitemporal hemianopsia
Magnetic resonance	Adenoma with sovrasellar extension (18 mm)	Adenoma (13 mm)	Giant adenoma (98 mm)	Adenoma with sovrasellar extension (33 mm)	Adenoma with sovrasellar extension (22 mm)
Hormonal findings	PRL 254 ng/ml	PRL 105 ng/ml	PRL 9400 ng/ml	PRL 787 ng/ml	PRL 2130 ng/ml
Surgery			Combined TC and TSP	TSP: two operations	TSP
Immunostaining			PRL	PRL	PRL
Radiotherapy			Conventional external		
Current treatment	Cabergoline 1.5 mg/week	Cabergoline 3 mg/week	Bromocriptine 20 mg/day, C, D, Te, T_4	Bromocriptine 15 mg/day, hrGH	Cabergoline 0.5 mg/day
Long-term results	PRL 21 ng/ml, marked tumor shrinkage (4 mm), normal visual field, B5P5, normal menses	PRL 2 ng/ml, marked tumor shrinkage (6 mm), normal visual field, normal menses	PRL 142 ng/ml, marked reduction of tumor mass, right quadrantopsia and improved vision of the left eye, G5P5	PRL 199 ng/ml, persistent tumor mass (20 mm), worsening of the bilateral hemianopsia, G1P2	PRL 10 ng/ml, significant tumor shrinkage (6 mm), improved visual field, G4P4

C: cortone acetate, D: desmopressin, hrGH: human recombinant GH, T_4: L-thyroxine, TC: transcranial surgery, Te: testosterone enanthate, TSP: transsphenoidal surgery.

Table 2 - *Clinical features, hormonal status, treatment and follow-up of pediatric pituitary GH-secreting and non-functioning adenomas.*

Case	6	7	8	9	10
Sex	M	M	F	F	M
Age at onset of symptoms and diagnosis (yr)	17 19	17 18	14 18	11 12	14 15
Follow-up (months)	66	42	95	23	132
Presenting complaints	Acromegaly, gigantism	Acromegaly, gigantism	Primary amenorrhea	Visual defects, headache	Visual defects, headache
Other clinical findings					Obesity
Pubertal stage (Tanner)	G5P5	G5P5	B3P4	B3P4	G1P1
Visual field	Normal	Normal	Normal	Left temporal hemianopsia	Left temporal hemianopsia
Magnetic resonance	Adenoma with sovrasellar extension (30 mm)	Adenoma (8 mm)	Adenoma (25 mm)	Adenoma (12 mm)	Adenoma with sovrasellar extension (24 mm) and cavernous sinus invasion
Hormonal findings	Mean basal GH 14 ng/ml, IGF-I 640 ng/ml	Mean basal GH 12 ng/ml, IGF-I 1246 ng/ml	Testosterone 1.5 ng/ml; mean basal LH 4 and FSH 3 mU/ml, reduced response to GnRH	Normal	Complete hypopituitarism
Surgery	TSP	TSP	TSP	TSP	TC
Immunostaining	Only GH	Only GH	Negative	Negative	Negative
Radiotherapy					Conventional external
Current treatment	C, D, Te, T4	Otreotide LAR 30 mg/month and cabergoline 1.5 mg/week			C, Te, T_4, hrGH
Long-term results	GH<0.5 ng/ml IGF-I 93 ng/ml, empty sella, normal visual field, P5G5	Mean GH 2.5 ng/ml IGF-I 350 ng/ml, no residual tumor, normal visual field, G5P5	No residual tumor, normal visual field, B5P5, normal menses	6 mm residual tumor, normal visual field, B5P5, normal menses	Intracavernousal remnant, normal visual field, P5G5

C: cortone acetate, D: desmopressin, hrGH: human recombinant GH, T_4: L-thyroxine, TC: transcranial surgery, Te: testosterone enanthate, TSP: transsphenoidal surgery.

evaluation disclosed that all patients but one (case 9) had signs and/or symptoms of endocrine dysfunction: delayed or arrested puberty (cases 1, 5, 8, 10) with galactorrhea or ginecomastia in three patients (cases 1, 2, 5), acromegaly/gigantism in two (cases 6, 7) and short stature in one (case 4); patient 3 had a clear hypothalamic syndrome with compulsive behavior and epilepsy.

Visual field was reduced in six cases (60%). Magnetic resonance disclosed the adenoma in all patients and the diameters were larger then 10 mm in all but one (case 7). Sovrasellar extension was present in 6 subjects, in particular patient 3 had a giant adenoma.

Adenomas were clinically functioning in 7 patients (70%). Cases 1-5 had prolactin levels ranging from 105 to 9400 ng/ml and were classified as prolactinomas. Cases 6 and 7 had mean basal GH of 14 and 12 ng/ml respectively, with paradoxic response to a standard OGTT. Their IGF-I were 640 and 1246 ng/ml respectively (age-adjusted upper normal values 450 ng/ml) and prolactin levels were normal; these adenomas were classified as pure GH-secreting. Patient 8 had inappropriately low levels of gonadotropins and impaired responsiveness to GnRH; patient 9 had normal basal and stimulated hormone values and patient 10 showed complete hypopituitarism. These three cases were considered clinically non-functioning adenomas.

Prolactinomas

Cabergoline caused a quick improvement in the two female patients (cases 1 and 2); prolactin levels are normal, tumor shrinkage has been impressive and visual fields are normal; their sexual characteristics are fully expressed and they have regular menses. In male patients the results of therapy were less successful apart from case 5. In this patient bromocriptine had not improved bilateral hemianopsia, he was operated on and then treated with cabergoline 0.5 mg/day: PRL is normal, the size of the residual tumor has decreased and the visual field has markedly improved. Patient 3 had a giant prolactinoma; a transcranial-transsphenoidal operation was performed, followed by radiotherapy. Complete hypopituitarism is present and, despite bromocriptine 20 mg/day and a decrease in the tumor size, PRL is 142 ng/ml and significant derangement of visual field is still present. Patient 4 was treated by transsphenoidal surgery followed by bromocriptine with doses up to 20 mg/day and later cabergoline 3 mg/week, but PRL did not normalize, the tumor went on growing and visual field worsened so a second transsphenoidal operation was performed. Despite bromocriptine 15 mg/day, PRL levels keep increasing, a significant tumor remnant is still present and visual field is worsening, therefore radiotherapy has been scheduled.

GH-secreting adenomas

Patient 6 was operated on by transsphenoidal route, but the operation was complicated by intrasellar hemorrhage causing complete hypopituitarism. No residual tumor is present, basal GH is less than 0.5 ng/ml and IGF-I is 93 ng/ml. Patient 7 underwent selective transsphenoidal adenomectomy. Despite no evidence of residual tumor, acromegaly was still active. He is currently treated with octreotide LAR 30 mg/month and cabergoline 1.5 mg/week: GH is 2.5 ng/ml and IGF-I is normal.

Clinically non-functioning adenomas

Two patients (cases 8 and 9) were successfully operated on by transsphenoidal approach: visual fields are normal and they both have normal sexual development with regular menses; no residual tumor was evident after surgery but in case 9 an asymptomatic recurrence was found 20 months later. Patient 10 was operated on by transcranial route, followed by radiotherapy. The patient suffers from hypopituitarism, but his visual field is normal and a small remnant in the cavernous sinus is unchanged. Therefore, treatment was completely successful in 5 patients (cases 1, 2, 5, 7, 8) (50%): they now show normal hormone secretion, have achieved complete pubertal development, no significant tumor mass is present and visual fields are intact. In the other patients hypersecretion of PRL still persists in 2 cases (cases 3 and 4), partial or complete hypopituitarism is present in 4 (cases 3, 4, 6, 10), relevant tumor remnant is evident in 4 (cases 3, 4, 9, 10) and visual field is impaired in 2 patients (cases 3, 4).

DISCUSSION

In childhood and adolescence pituitary adenomas constitute 2.1-6% of adenomas removed by surgery in all age groups (1-6). All our patients were older than 10 years of age, confirming that most pituitary adenomas in pediatric age occur in the pubertal period (2, 4-6). Males accounted for 60% of our patients. A slightly higher prevalence of males (52-60%) had been reported in a few series (2, 3, 9), while others reported a higher prevalence (70-83%) of females (4-6). The female/male ratio is higher for prolactinomas, ranging from 1.6:1 to 4.8:1 (3, 5, 6, 10, 11) but perhaps less striking than in adults; in GH and mixed GH/PRL tumors, female/male ratio is lower ranging from 1:3 to 1:4.5 (3, 5, 6, 12); clinically non-functioning adenomas are predominantly male (6, 13).

Half our patients came to medical attention for tumor mass symptoms, namely visual defects and headache. It should be emphasized that clinical evaluation at diagnosis disclosed that most of our patients had unrecognized or misinterpreted endocrine dysfunctions, in particular 40% of the patients had inappropriate pubertal development for their age: a more careful investigation of these endocrine signs would probably have allowed an earlier diagnosis. The initial complaints of pediatric patients are generally reported to be endocrine symptoms or signs, particularly failure of growth or sexual maturation (5, 6), but headache was present in 61% of patients in the series of Kane (5) and headache and/or visual defects were the presenting symptoms in half of 26 prolactinomas (11), too. Perhaps in our series the large prevalence of symptoms due to tumor mass can be accounted for by the fact that 90% were macroadenomas, sometimes of great size. In pediatric age macroadenomas encompass 54-69% of prolactinomas (4-6, 10, 11), 50-92% of GH/PRL-secreting tumors (3, 5, 6, 12) and 92-100% of clinically non-functioning adenomas (6, 13): this is in sharp contrast with ACTH-secreting adenomas which are almost always microadenomas (6, 14-16).

On the basis of clinical and immunohistochemical characteristics 50% of our cases were PRL-secreting, 20% pure GH-secreting and 30% non-func-

tioning adenomas. Clinically functioning adenomas are by far more frequent in all pediatric series. Prolactinomas are the most frequent tumors, accounting for about 50% of cases (5, 6, 17, 18); ACTH-secreting adenomas are more frequent than GH (pure and mixed) tumors, representing respectively 29-50% *vs* 9-13% (3, 5, 6, 12) of surgically resected adenomas, in contrast with what observed in adult patients. Non functioning adenomas are very rare: the incidence is about 3-6% of all pediatric pituitary adenomas (3, 6, 13, 18) and a review of the literature in 1998 encompasses only 25 cases (13).

Dopamine agonists are the treatment of choice for prolactinomas in adults and are effective both in reducing PRL levels and in tumor shrinkage also in pediatric patients (10, 11, 19, 20). Recently in a multicenter study Colao *et al*. (11) found that bromocriptine normalized PRL levels in 10/26 patients, furthermore other 12 patients resistant or intolerant to BCR normalized PRL levels with dopamine agonists quinagolide and cabergoline. Dopaminergic drugs alone were very effective in two female patients. Furthermore, cabergoline normalized PRL levels and induced shrinkage of the residual tumor in an operated patient. In the other two prolactinomas dopamine agonists only partially controlled PRL levels and tumor growth: both the patients were males, confirming that prolactinomas in males are more aggressive and less responsive than in females (3, 4, 18). The results of surgery in GH adenomas in pediatric patients are not as good as for adults (2, 3, 5, 12). Dyer *et al*. (3) reported that surgery alone cures 12% of patients; somewhat better results are those of Abe *et al*. (12) (40% of cure), who used intra-operative GH measurements and subsequent tumor exploration if indicated. Even if GH tumors in pediatric age are more likely to be locally invasive and aggressive than in adults, results are worse also for microadenomas (12). Somatostatin analogues, particularly in the form of slow-release formulations, are the drugs of choice for GH-secreting tumors; there are very few data for pediatric patients and in general octreotide has been shown to have only limited effectiveness, for istance Abe *et al.* (12) reported that 2 out of 4 patients responded to octreotide. We have found that 30 mg/month of octreotide LAR and 1.5 mg/week of cabergoline normalized IGF-I levels. In three non-functioning pituitary adenomas, operation was completely successful in only one patient. Poor results have been reported by Artese *et al.* (18), but in general the outcome of transnasal surgery does not differ from that of adults (13).

The aims of therapy for pituitary adenomas are complete ablation of the tumor and control of hormonal hypersecretion without causing deficiency of other hormones. In pediatric age an important objective is to guarantee a full sexual and linear development. These aims were completely coupled in 50% of our patients. In the other patients complete tumor removal or normalization of hypersecretion was not achieved or was achieved at the price of hypopituitarism; furthermore 2 patients still have impairment of the visual field. In the series of Mindermann *et al*. (6) only 10% of patients had tumor recurrence, but data are lacking concerning final sexual development and hypopituitarism. In the Mayo Clinic series (5) 65% of microadenomas were free of disease, but this fell to 33% for operated macroadenomas without further treatment; furthermore in 30% of patients hypopituitarism is present. In the prolactinoma series of Colao *et al.* (11), medical therapy had clearly better results in preservation and restoration of the anterior pituitary functions compared with surgery. As far as visual loss is concerned Lee *et al.* (9) reported that pediatric patients are more severely affected than adults and improvement after surgery occurs more rarely.

Review of the literature, availability of dopamine agonists and somatostatin analogues, experience derived from the present data suggest that the treatment of choice for PRL and GH-secreting adenomas in adolescence should be medical. In prolactinomas cabergoline is probably the drug of choice for its better tolerability, compliance and effectiveness. Nevertheless, we point out that some patients, particularly males with prolactinomas, do not invariably respond and a tumor may go on increasing and subsequent transsphenoidal surgery is needed. For clinically non-functioning adenomas surgery is the best initial approach. The role of radiotherapy is well established for pediatric Cushing's disease after unsuccessful surgery (21, 22), but in the case of non-ACTH-secreting adenomas we think that it should be used only for tumors which go on growing despite medical and surgical therapy. The close collaboration of pediatric and adult endocrinologists, a neurosurgeon experienced in transsphenoidal surgery and a radiotherapist make up the team necessary to give the best chance of successful long-term management of this uncommon and intriguing pediatric disease.

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