PITUITARY TUMORS IN CHILDHOOD

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ABSTRACT

The pituitary region in childhood can be mainly affected by two kinds of neoplasia: craniopharyngiomas and pituitary adenomas. Craniopharyngiomas accounts for 1.2 to 4% of all childhood intracranial tumors, at this age adamantinomatous with cyst formation is the most common histological type. Craniopharyngiomas are benign from a histological point of view, but they can be aggressive, invading surrounding tissues and bony structures. Clinical presentation is non-specific with neurological disturbances, such as headache and visual field defects, together with manifestations of endocrine deficiency. Pituitary adenomas constitute less than 3% of supra-tentorial tumors in children, they are less common in pediatric patients than in adolescents or adults. Prolactinoma is the most frequent adenoma type in children, followed by the corticotrophinoma and the somatotrophinoma. Non-functioning pituitary adenomas, TSH-secreting, and gonadotrophin-secreting adenomas are extremely rare in children, accounting for only 3-6% of all pituitary tumors. Presenting symptoms are typically related to endocrine dysfunction, rather than to mass effects. Pituitary adenomas in childhood may have a genetic cause and, in some cases, additional manifestations can occur as part of a syndromic disease. Therapeutic options depend on the tumor type, with surgical approach often remaining the first choice.

INTRODUCTION

Pituitary function depends on the integrity of the hypothalamo-pituitary axis and the functionality of numerous differentiated cell lines in the anterior pituitary lobe that specialize in specific hormone production. The development of these cell lines is the result of events during pituitary organogenesis that are under the sequential control of transcription factors (1). Any abnormality occurring in the pituitary gland, either congenital (congenital malformations, genetic abnormalities) or acquired (perinatal insults, tumors, infections), will cause profound alterations of the whole endocrine system.

Tumors in the pituitary region can be classified on the basis of topographic criteria as intra-, supra- para- or retrosellar (2). Intrasellar tumors are mostly represented by pituitary adenomas (more than 90% of all intrasellar lesions), while dys-embryogenetic lesions such as Rathke's pouch cyst or pituitary blastomas are less frequent. The suprasellar tumors are dys-embryogenetic lesions of the midline such as craniopharyngiomas, germinomas, dermoid or epidermoid cysts, lipomas, teratomas, and hamartomas. Other tumors such as meningiomas or gliomas are uncommon during childhood or adolescence. Craniopharyngiomas, the most common cause of hypopituitarism in childhood, and adenomas are the most frequent lesions of the pituitary region in children and adolescents. Virtually all tumors of this region are benign.

This chapter aims at reviewing the most recent epidemiological, diagnostic, and therapeutic knowledge on pituitary tumors in childhood and adolescence.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are rare embryonic malformations of the sellar and parasellar area with an incidence of 0.5 to 2 cases per million persons per year, 30 to 50% of all cases presenting during childhood and adolescence (3-7). They originate from squamous rest cells of the remnant of Rathke's pouch between the adenohypophysis and

neurohypophysis in the region of the pars tuberalis. Rathke's pouch is a cystic diverticulum from the roof of the embryonic mouth that gives rise to the adenohypophysis and determines the induction of the neurohypophysis. Craniopharyngiomas represent 1.2 to 4% of all childhood intracranial tumors (8-10) and show a bimodal distribution during the first-second decade of life and then in the fifth, apparently without any gender difference (5, 7). The tumor generally originates in the suprasellar region (94-95%), purely suprasellar (20–41%) or both supra- and intrasellar (53–75%), whereas the purely intrasellar forms (5-6%) are less frequent (5). Extremely rare are forms originating in the III ventricle, in the rhinopharynx, in the sphenoid, or in other locations (5). In their pure form, the adamantinomatous form and papillary form are clinicopathologically distinct. In childhood and adolescence, its histological type is usually adamantinomatous with cyst formation (3-7).

The pathogenesis of adamantinomatous craniopharyngioma is characterized by the deregulation of the Wnt pathway, in particular by activating mutations in exon 3 of the *CTNNB1* gene encoding for β-catenin (11-13). Otherwise, most of papillary craniopharyngioma show a *BRAF* V600E mutation, resulting into activation of MAPK pathway (13, 14). Papillary forms exhibiting *BRAF* V600E mutations are rarely found in the pediatric age range (15, 16).

Craniopharyngiomas are benign from a histological evaluation but they can be aggressive, invading surrounding bony structures and tissues; they commonly have cystic components that may be multiple and generally cause compression of adjacent neurological structures (3-7). The adamantinomatous form is more locally aggressive and is characterized by a higher rate of recurrence than the papillary form (17). The molecular basis of this phenomenon is still not defined; however, a recent study showed that tissue infiltration could be favored by signaling of tyrosine kinase (18).

Clinical Presentation and Diagnosis

The diagnosis of craniopharyngioma is often made late, sometimes years after the initial appearance of symptoms. Neurological disturbances, such as headache and visual field defects, together with manifestations of endocrine deficiency such as stunted growth and delayed puberty, are the common presenting symptoms of craniopharyngiomas (3-7). Among adult-onset craniopharyngioma patients, hormonal deficits at the time of diagnosis are much more pronounced when compared with childhood-onset craniopharyngioma patients (3). At diagnosis, endocrine dysfunction is found in up to 80% of patients (3-7). Reduced GH secretion is the most frequent finding, present in up to 75% of patients, followed by FSH/LH deficiency in 40%, and ACTH and TSH deficiency in 25% (3-7). Despite the fact that the tumor is frequently large at presentation, the pituitary stalk is usually not disrupted, and hyperprolactinemia secondary to pituitary stalk compression is found in only 20% of patients (3-7). Diabetes insipidus is also relatively uncommon, occurring in ~17% of patients (3-7, 19). An increase in weight tends to occur as a later manifestation, shortly before diagnosis (3-7). Then, the clinical combination of headache, visual impairment, decreased growth rate, and/or polydipsia/polyuria would be very suggestive of childhood craniopharyngioma in the differential diagnostic process (20).

To date, magnetic resonance imaging (MRI) before and after gadolinium application is the standard imaging for the detection for craniopharyngiomas. The neuroradiological diagnosis of craniopharyngiomas is based on the features of the lesion itself and on its relations with the surrounding structures. Particularly, the diagnosis is mainly based on the three characteristic components of the tumor: cystic, solid and calcified (5, 7, 21-23). The cystic component (Fig.1 and 2) constitutes the most important neoplastic part (up to the 70-75% of the total volume), and shows a variable signal depending on the chemical-physical properties of its content (24). A fluid content will appear hypointense in T1 and hyperintense in T2 while a lipid (due to cholesterol), methemoglobin or protein content will appear as hyperintense in T1 and T2 sequences. The solid portion shows an isointense signal in T1 and a hyperintense signal in T2 with enhancement after gadolinium, at variance with the cystic component (Fig. 3 and 4). However, enhancement after paramagnetic contrast is not a consistent feature (24). Computed tomography (CT) imaging is the only way to detect or exclude calcification, which is found in approximately 90% of tumors and therefore a crucial differentiating component for diagnosis (21-23).Calcification appears as areas of low signal in all sequences (23). The radiological appearance of non-homogeneous signal or a prevalent cystic component should not be regarded as a proof of a craniopharyngioma, since macroadenomas can also sometimes be characterized by patterns resembling craniopharyngiomas.

Moreover, the craniopharyngioma, without evidence of calcification, could be confused with different neoplasms such as hypothalamic/chiasmatic astrocytomas, germ cell tumors, or Langerhans cell histiocytosis (24).

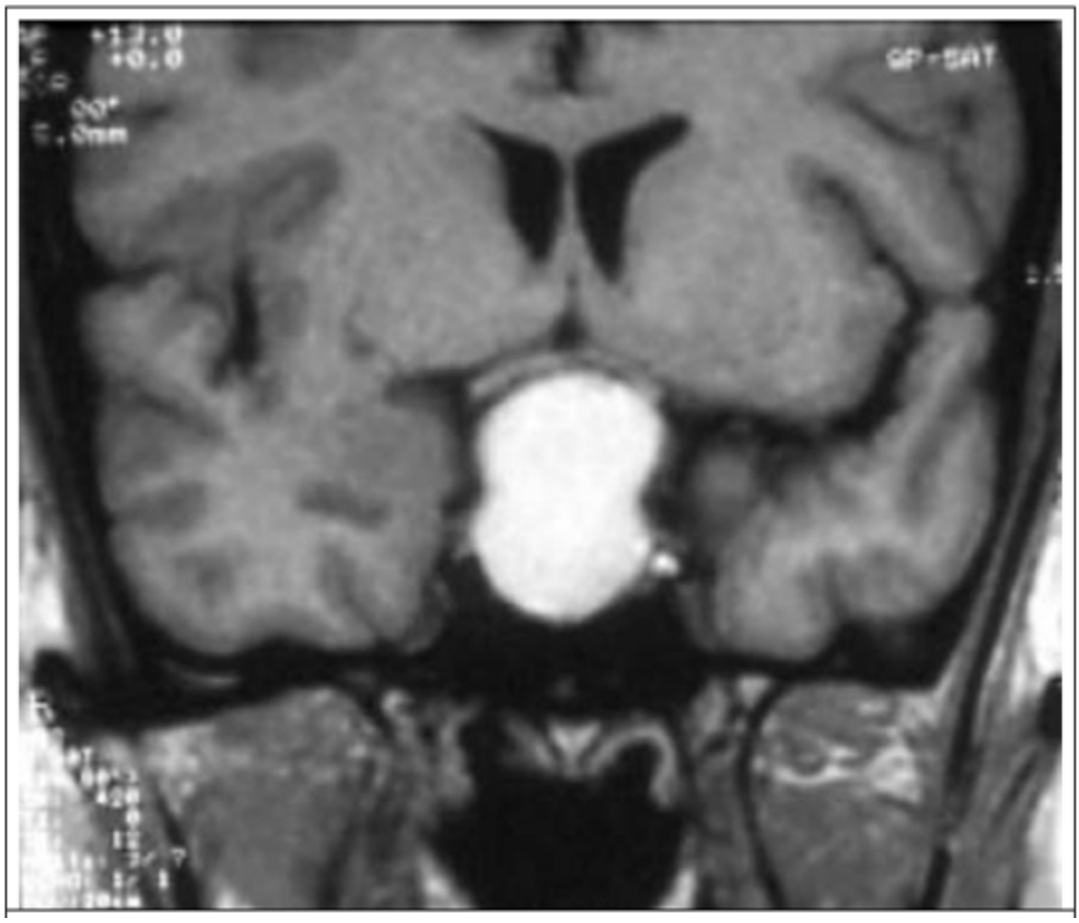

Figure 1. Resonance imaging T1-weighted sequences on coronal planes. Intra- and suprasellar craniopharyngioma in an 8-year-old boy presenting with reduced growth velocity and headache. This tumor has a total cystic component as shown by the hyper-intense spontaneous signal. (Kindly provided by S. Cirillo, II University of Naples)

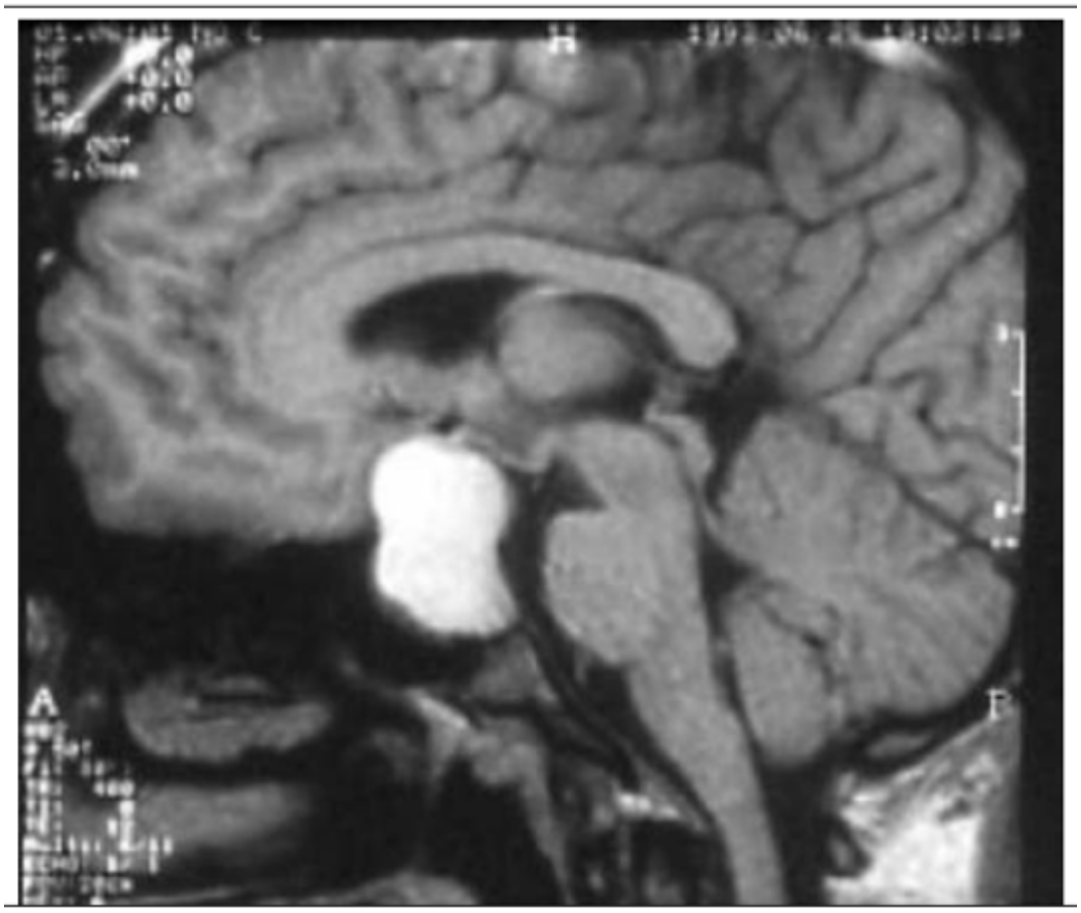

Figure 2. Resonance imaging T1-weighted sequences on sagittal planes. Intra- and suprasellar craniopharyngioma in an 8-year-old boy presenting with reduced growth velocity and headache. This tumor has a total cystic component as shown by the hyper-intense spontaneous signal. (Kindly provided by S. Cirillo, II University of Naples)

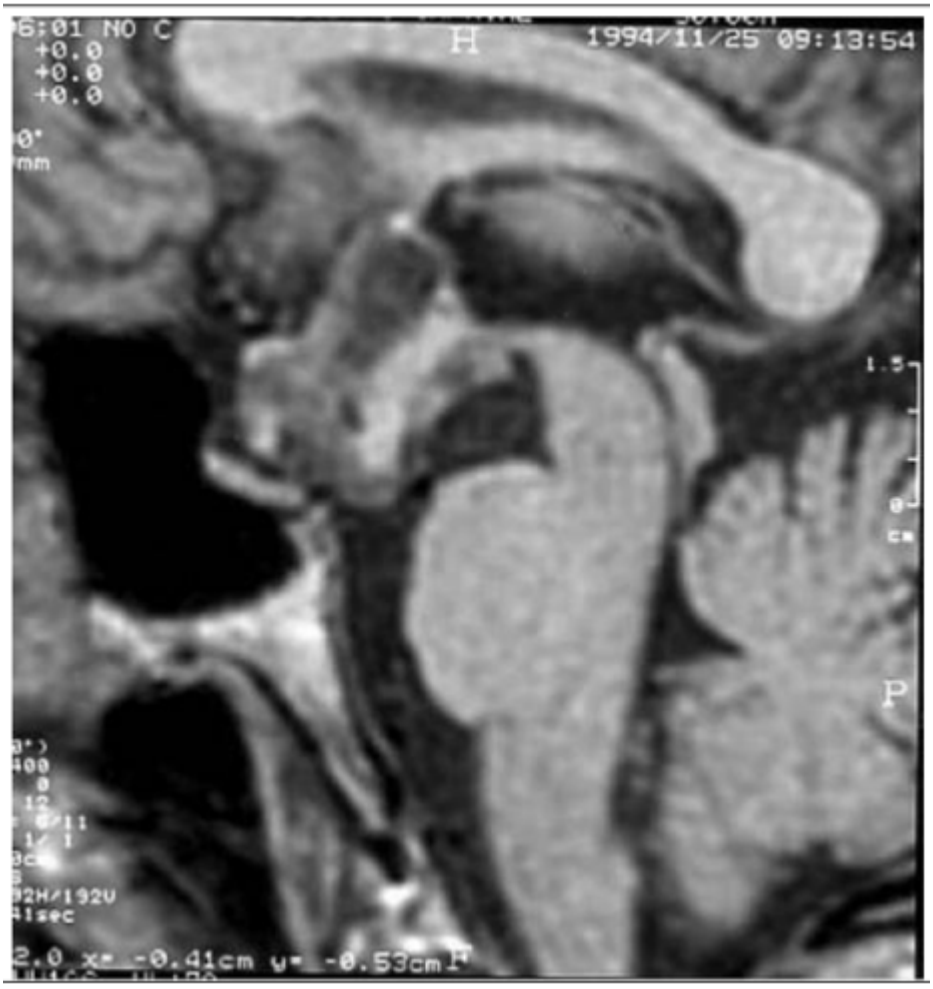

Figure 3. Resonance imaging T1-weighted sequences on sagittal plane before IV gadolinium chelate administration. Extra-axial craniopharyngioma in the intra and suprasellar space, with non-homogenous signal due to calcifications and cysts, in a 7- year-old boy presenting with reduced growth velocity, sleepiness, and visual loss. (Kindly provided by S. Cirillo, II University of Naples).

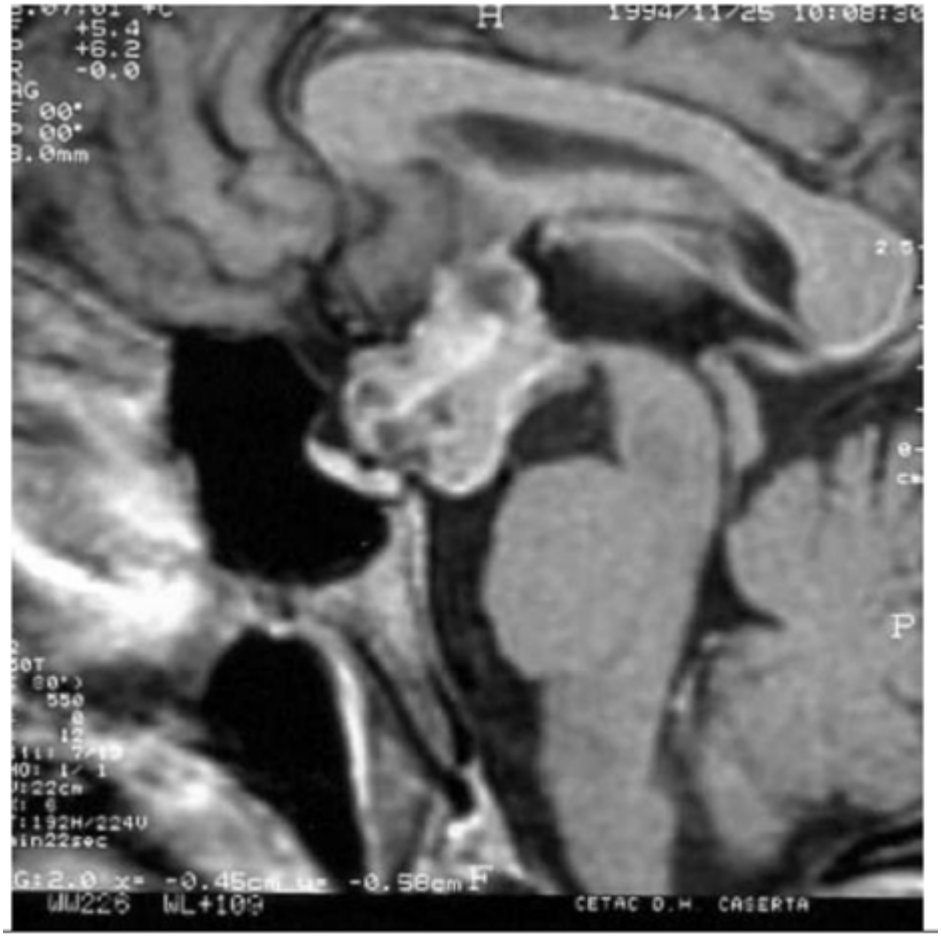

Figure 4. Resonance imaging T1-weighted sequences on sagittal plane after IV gadolinium chelate administration. Extra-axial craniopharyngioma in the intra and suprasellar space, with non-homogenous signal due to calcifications and cysts, in a 7- year-old boy presenting with reduced growth velocity, sleepiness, and visual loss. After contrast medium non-homogenous enhancement of the solid component. (Kindly provided by S. Cirillo, II University of Naples).

Treatment Strategy

The treatment of craniopharyngioma is individualized on the basis of clinical presentation and several tumoral features such as dimension, location and extension, balancing the therapeutic radicality and the consequent risk of relapse with the onset of neurologic and endocrine complications. In instances where the onset of manifestation is an emergency with symptoms of raised intracranial pressure or rapid deterioration in visual function, to relieve these symptoms and prevent further visual deterioration initial surgical treatment, for hydrocephalus or tumor cyst decompression may be necessary prior to definitive treatment of the tumor (3-7).

To date, surgery remains the first treatment option in pediatric craniopharyngiomas. Craniopharyngiomas are characterized by variability of localization and a relationship with important structures like the hypothalamus, optic chiasm, third ventricle, and vessels of the circle of Willis: for this reason, there is no paradigmatic surgical treatment (25). The main purpose of surgery is significant tumoral removal and the operative approach is generally dictated by localization and extent of the craniopharyngioma. Optimal initial localization, without involvement of the hypothalamus and optic chiasm, allows one to aim at radical resection preserving visual and hypothalamic functions; indeed, purely infra-diaphragmatic as well as supra-diaphragmatic/infra-chiasmatic tumors have a favorable surgical outcome with higher gross total resection rates in experienced hands. Otherwise, lesions extending within the

third ventricle and lesions beyond 3cm in diameter, independent of their localization, are characterized by a greater complexity of treatment and a worse therapeutic outcome. In effect, radical resection and attempting total neoplastic removal results in significantly impaired functional outcomes (26, 27) , so currently many prefer subtotal removal and subsequent radiotherapy. Aside from the traditional microscopic approach via the subfrontal or pterional craniotomy, transsphenoidal approaches and other minimal invasive surgical methods, e.g., catheter implantation into cystic formations of the tumor, have become popular (26, 27). The transsphenoidal approach is appropriate for infra-diaphragmatic lesions, whereas tumors with suprasellar extensions require a transcranial approach. Nevertheless, the extended transsphenoidal approach has been used in lesion with supradiaphragmatic extension, showing a higher frequency of endocrine and neurological complications compared to the use of the same technique for an intra-diaphragmatic one (28).

Radiotherapy is required in case of incomplete tumor removal, which is common for extra-sellar craniopharyngiomas, and can effectively be added to avoid recurrences, determining lower progression rates (21%) compared to subtotal surgery alone (71-90%) (28). In children, however, the benefit of any additional radiotherapeutic treatment should be balanced against the high risk of inducing hypopituitarism later in life. In a retrospective preliminary review aiming at evaluating the efficacy and toxicity of fractionated proton radiotherapy in the management of pediatric craniopharyngioma, local mass control was reported in 14 of 15 patients with few acute side effects and newly diagnosed panhypopituitarism, a cerebrovascular accident (from which the patient recovered), and an out-of-proton-field meningioma in a single patient who received previous radiotherapy as a long-term complications (8, 29).

Modern radiotherapy techniques allow a better conformation of the field of action, reducing the dose on the structures adjacent to the craniopharyngioma and the consequent adverse effects, particularly endocrine and visual ones. Currently, intensity modulated radiotherapy (IMRT) and proton beam therapy (PBT) have shown encouraging results in the pediatric population (25).

Further, therapeutic options for large cystic craniopharyngiomas are cyst drainage and intracystic instillation of Interferon-alpha, whereas instillation of bleomyicin is no longer used because of neurotoxicity due to leakage. Recently, a multicenter trial on the systemic use of peginterferon alpha-2b, administered subcutaneously, ended prematurely due to a lack of efficacy on the relapse prevention of the solid portion of the neoplasm (28). Relapse of craniopharyngioma occurs in about 35% of patients and the management of recurrence is influenced by previous therapy (30).

Currently, attention focuses on the potential of molecular target therapy. Agents that effect the Wnt pathway are not currently available, whereas evaluation of the use of vemurafenib and dabrafenib (BRAF inhibitors) and the combination of dabrafenib and trametinib (a MEK inhibitor) are showing encouraging results (14, 15, 31-33).

PITUITARY ADENOMAS

Pituitary adenomas are the most common cause of pituitary disease in adults but they are less common in children, becoming increasingly more frequent during the adolescent years (34-37). The estimated incidence of pituitary adenomas in childhood is still unknown since most published series included patients with onset of symptoms before the age of 20 yrs as pediatric patients. Pituitary adenomas constitute less than 3% of supra-tentorial tumors in children, and 2.3-6% of all pituitary tumors treated surgically (34, 35, 38, 39). The average annual incidence of pituitary adenomas in childhood has been estimated to be 0.1/million children (40). Among all supra-tentorial tumors treated during a 25-year period in a center, pituitary adenomas were diagnosed in only 1.2% of children (41). Pituitary carcinomas are rare in adults and extremely rare in children (42). The first, and probably unique, case of pituitary carcinoma in a child was described by Guzel *et al.* in 2008. A 9-year-old girl, with an history of hydrocephalus treated with ventriculoperitoneal shunt 3 years before, complained of progressive visual and gait disturbance, headache, and speech difficulties. Neurological examination revealed visual loss, papilledema, and dysarthria. Magnetic resonance revealed a large tumor mass in frontal region, multiple lesions in sellar-parasellar region, posterior fossa, and multiple intraspinal metastatic lesions. Gross total resection of frontal mass was performed, and the histopathological and immunohistochemical exams revealed a pituitary carcinoma. Despite of the post-operative use of temozolomide, the patient died after 2 months without

response to this therapy (43). There is no consensus on the alleged greater invasiveness of pituitary adenomas in children than in adults, while a slightly greater prevalence in females has been reported (7, 34-36, 40). However, gender distribution reflects the relative contribution of the two main groups, PRL- and ACTH- secreting adenomas, which predominate in most series reported. Prolactinoma is indeed the most frequent adenoma histological type in children, followed by the corticotrophinoma and the somatotrophinoma (44). Non-functioning pituitary adenomas, TSH-secreting, and gonadotrophin-secreting adenomas are very rare in children, accounting for only 3-6% of all pituitary tumors. ACTH-secreting adenomas have an earlier onset and predominate in the pre-pubertal period, where interestingly male cases are more frequent, while GH-secreting adenomas are very rare before puberty, except in XLAG (7). Similar to adults, presenting symptoms are generally related to the endocrine dysfunction, such as growth delay and primary amenorrhea, rather than to mass effects (41, 42, 44-48). Symptoms of pituitary tumor presentation differ according to the tumor type as shown in Table 1 and detailed in the specific sections.

Table 1. Prevalence of Clinical Symptoms and Signs in Children/Adolescents with Pituitary Adenomas. Data drawn from ref. 47-53

	PRL-secreting adenomas	ACTH-secreting adenomas	GH-secreting adenomas	TSH-secreting adenomas	Clinically non-functioning adenomas
Acne	–	+	–	–	–
Delayed/arrest growth	-/+	+	–	++	++
Delayed/Advanced bone age	–	+	+	–/+	++
Delayed puberty	++	+	+	+	++
Early sexual development	–	++	–	–	–
Erythroses	–	+	–	–	–
Fatigue or weakness	–	+	–	+	–
Galactorrhea	+++	–	–/+	–	–
Gigantism/Acromegaly	–	–	++	–	–
Glucose intolerance	–	+	+	+	–
Gynecomastia	+	–	–/+	–	–
Headache	++	+	++	+	++
High school performance	–	+	–	–	–
Hirsutism	–	+	–	–	–
Hypertension	–	+	–/+	–/+	–
Menstrual irregularities	++	+	++	+	++
Mild hyperthyroidism	–	–	–	+	–
Osteoporosis	+	+	–	+	–
Premature thelarche	++	–/+	–	–	–
Primary amenorrhea	++	+	++	+	++
Sleep disturbances	–	+	–	++	–
Striae	–	+	–	–	–
Visual field defects	+++	—/+	+++	+++	+++
Weight increase	+	+	–	–	–

– Absent; –/+ rare; —/+ very rare; + present; ++ frequent; +++ frequent in macroadenomas

PRL-SECRETING ADENOMAS

Prolactinomas are the most frequent pituitary tumors both in childhood and in adulthood, and their frequency varies with age and sex, occurring most frequently in females between 20-50 years (35, 44, 49-51). Also, pediatric prolactinomas are more frequent in girls, but earlier onset, larger adenoma volume, and higher serum prolactin levels are found in boys (52).

Clinical Presentation and Diagnosis

PRL-secreting adenomas are usually diagnosed at the time of puberty or in the post-pubertal period, and clinical manifestations vary in keeping with the age and sex of the child (34-36, 44, 50, 51). Pre-pubertal children generally present with a combination of headache, visual disturbance, growth failure, and amenorrhea (Table 1). Growth failure is not, however, a common symptom: in fact, in two different retrospective studies, 4% of 25 patients (51) and 10% of 20 patients (53) were reported to have short stature at the diagnosis of prolactinoma. Weight gain has been reported to occur in patients with hyperprolactinemia (54-56) but never described in children. In a re-evaluation of the young/adolescent patients with hyperprolactinemia admitted to the University Federico II from January 1st 1995 to December 31st 2004 (44, 57), short stature was found in 7 of 50 patients (14%), five girls and two boys, and another two patients, one girl and one boy, had their height below or at the 5th percentile and another 8 (3 girls) had their height between the 5th and 10th percentile. The height percentiles in the patients with extrasellar/invasive macroprolactinomas were lower than in those having smaller tumors (Fig. 5). Additionally, all girls presented with oligomenorrhoea or amenorrhea; most also had galactorrhea; gynecomastia was present in 12 of 21 boys (57.1%). The most common symptoms of prolactinomas in the peripubertal age are those associated with deficiency of the pituitary-gonadal axis. Menstrual irregularities in girls are common in all types of pituitary adenomas, except those causing Nelson's syndrome (58). Galactorrhea should be carefully investigated by expressing the breast, because teenagers may not spontaneously refer to it as a symptom, and frequently it is not spontaneous. Headache and visual field defects predominate in patients bearing large adenomas (Table 2).

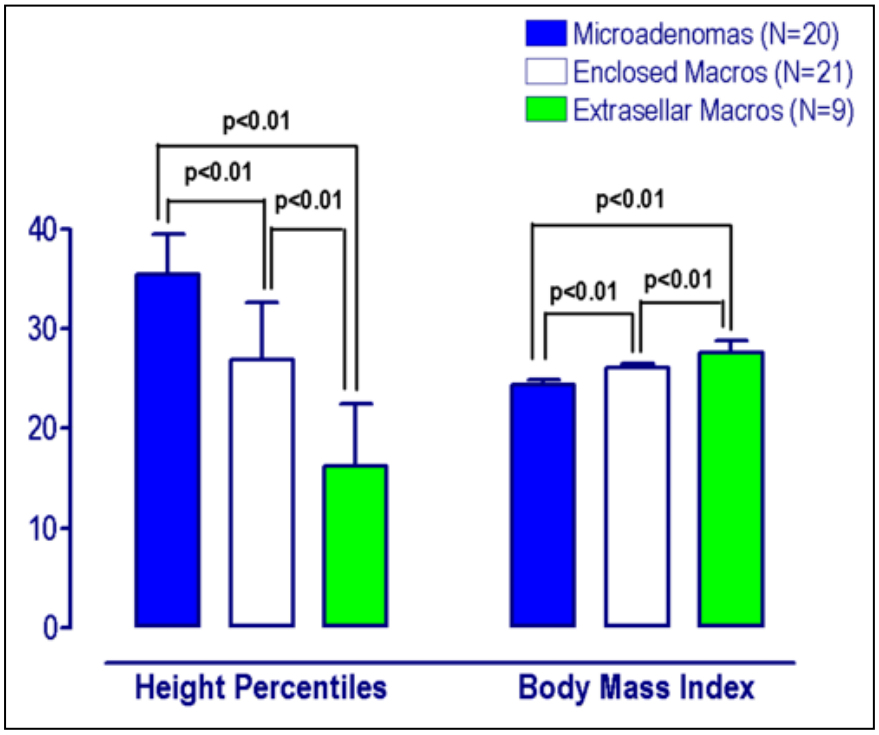

Figure 5. Height (shown as mean percentiles for age) and Body Mass Index in 50 patients with prolactinomas diagnosed before 20 years of age. Data from ref. (57).

Table 2. Presentation of Prolactinomas in Children and Adolescents: The Two-Decade Experience of the Department of Endocrinology and Oncology, University "Federico II" of Naples. Data from reference (57)

	Microadenomas	Enclosed Macroadenomas	Extrasellar and/or Invasive Macroadenomas
Number	20	21	9
Girls/Boys	15/5	11/10	3/6
Age at diagnosis (yrs)	14.4±0.5	14.8±0.4	13.8±1.1
Basal PRL levels (µg/L)	138.4±21.6	671.4±161.9	2123±279
Tumor volume on MRI (mm3)	113.0±15.1	1145±145	2826±330
Symptoms (%)			
Secondary or Primary Amenorrhea[1]	53.3%	72.7%	66.7%
Oligomenorrhea[1]	46.7%	18.2%	0%
Gynecomastia[2]	100%	60%	33.3%
Galactorrhea	42.8%	60%	33.3%
Visual field defects	0%	50%	66.7%
Headache	33.2%	80%	66.7%

Calculated only in [1]girls or [2]boys.

Impairment of other pituitary hormone secretion was reported to occur in a minority of patients at diagnosis (44, 51, 53, 58), and in some patient's hypopituitarism developed after surgery. In a more recent analysis (59), we can confirm that only a minority of patients bearing large adenomas had a severe degree of hypopituitarism, while a very few patients with either microadenomas or enclosed macroadenomas had isolated hormone deficiency (Fig. 6). Macroadenomas at presentation are more likely in boys than in girls (37, 38, 44, 53, 60). In our series (57), microprolactinoma and enclosed macroadenomas were more frequent in females with a ratio of 1.7:1 while large macroprolactinomas were 2 times more frequent in males (Table 2).

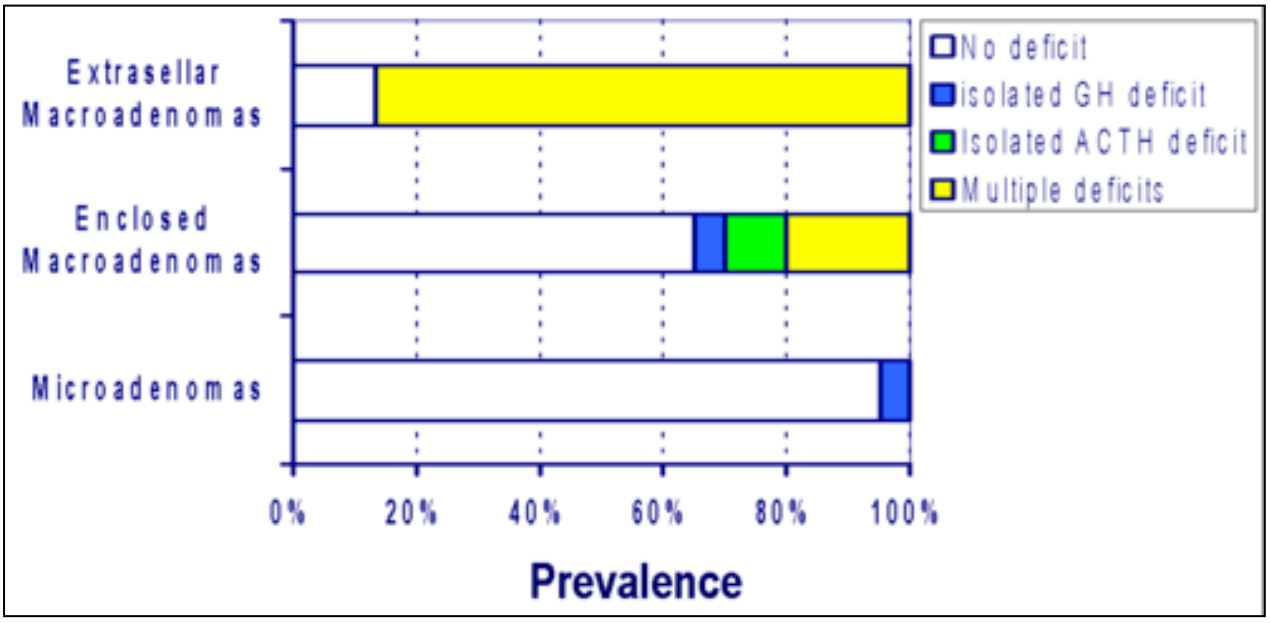

Figure 6. Prevalence of pituitary deficit according with prolactinoma size in 50 patients at diagnosis. Data from ref. (57).

Hyperprolactinemic patients have a decrease in bone mineral density (BMD), and progressive bone loss has been demonstrated in untreated patients (61). Young hyperprolactinemic men were shown to have a more severe impairment of BMD than patients in whom hyperprolactinemia occurred at an older age (62). In 20 patients with diagnosis of hyperprolactinemia during adolescence, we found (63) significantly lower BMD values in adolescents than in young adult patients with hyperprolactinemia. This finding was confirmed in a large cohort of patients (57). In 22 patients all having a diagnosis of prolactinomas before the age of 18 yrs, the bone mineral density (BMD) in the lumbar spine was significantly lower than in age-matched controls (Fig. 7). The use of drugs to increase bone mass, such as amino bisphosphonates, has not been investigated.

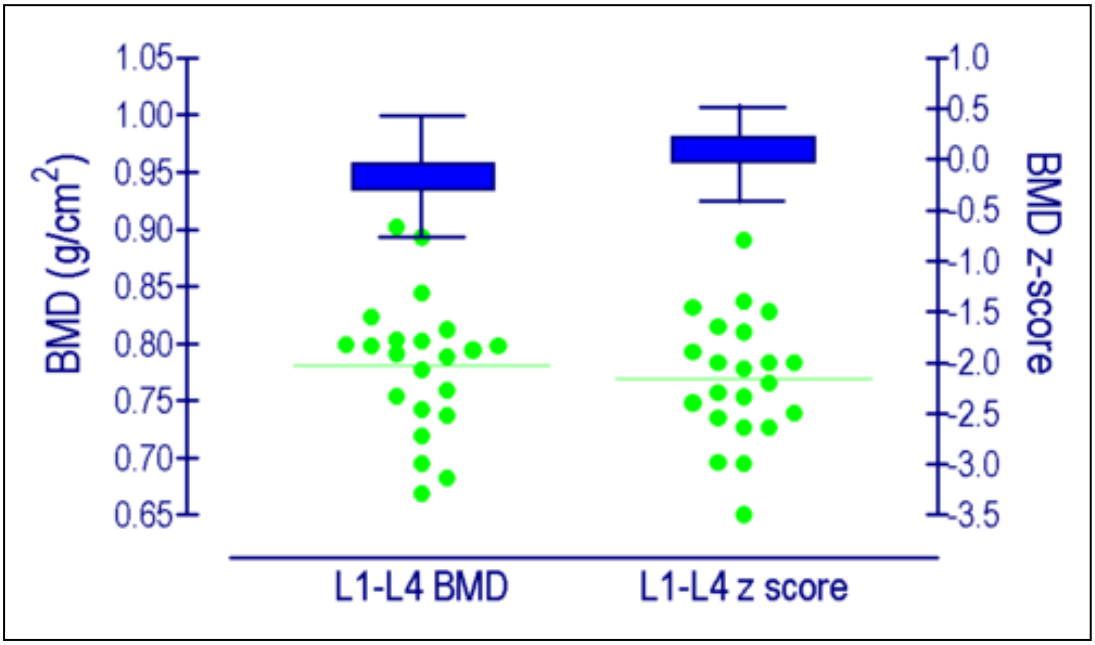

Figure 7. Bone density (BMD) measured as g/cm2 or z-score in 22 patients with prolactinoma (individual data shown as solid circles) and their sex- and age-matched controls (data shown as mean ± SD). Data from ref. 52, modified from ref. (57).

The diagnosis of prolactinoma is based on the measurement of serum PRL levels and neuroradiological imaging. The differential diagnosis of hyperprolactinemia should consider any process interfering with dopamine (DA) synthesis, its transport to the pituitary gland, or its action at lactotroph DA-receptors. A single measurement of PRL levels is unreliable since PRL secretion is markedly influenced by physical and emotional stress. Basal PRL levels greater than 200ng/l are diagnostic, whereas levels between 100 and 200ng/ml and the presence of a mass requires additional investigation to rule out mass an effect of a non-functioning adenoma versus a prolactin- secreting adenoma. Some peculiar conditions should, however, be remembered (64). Serial serum PRL measurements at 0, 30 and 60 min after the needle was inserted into an antecubital vein is a valuable and simple measure to identify stress- related hyperprolactinemia in order to avoid diagnostic pitfalls and unnecessary treatments. It is important to exclude from the assay the monomeric PRL forms, big-prolactin (b-PRL), and big big- prolactin (bb-PRL); the latter may contain immunoglobulin (IgG) (65). These molecular complexes are seldom active but may be measured by the PRL assay. The absence of a clinical syndrome of hyperprolactinemia will suggest the presence of macroprolactin. The 'high-dose hook effect' can be a serious problem in the differential diagnosis between prolactinomas and non-functioning adenomas (NFPA): it is mandatory, in these cases and in every patient with a

pituitary mass and hyperprolactinemia, to dilute PRL samples routinely (1:10 and 1:100 dilutions) or to use alternative methods to immunoradiometric assays. The difference between macroprolactinomas and 'pseudoprolactinomas' is essential to provide a correct treatment approach (66). This problem is, however, of little relevance in children and adolescents, as non-functioning macroadenomas are very rare at this age.

Treatment Strategy

The goals of prolactinoma treatment are the control of PRL excess and its clinical consequences, and the removal of pituitary adenoma. Today dopamine-agonists (e.g., bromocriptine, quinagolide, or cabergoline) should be considered the first treatment approach for pediatric prolactinomas (34, 44, 51-53, 59, 60). According to a recent study, dopamine-agonists should be started immediately at prolactinoma diagnosis even in case of severe visual impairment. If there are no improvement in visual defects and serum prolactin levels in the first 24-hours, early surgical treatment should be considered to avoid further visual deterioration and radiological signs of progression. The efficient use of dopamine-agonists reduces the necessity of surgical approach (52).

Situations requiring first-line neurosurgery typically occur in invasive macroadenomas: in these cases, the aim is resecting the tumor to relief the mass effect. Anyway, in these cases surgical cure usually cannot be obtained so medical therapy after debulking neurosurgery is required, with the benefit of a better response to anti-dopaminergic therapy due to the cytoreduction (67).

Treatment with dopamine-agonists is effective in normalizing PRL levels and shrinking tumor mass in the majority of adult patients with prolactinomas (34, 44, 51-53, 59, 60), preserving pituitary function and visual field in most cases (51). In children and adolescents, bromocriptine has been used successfully by several investigators (51, 68-71). In our series, bromocriptine at doses ranging from 2.5-20 mg/day orally normalized prolactin in 38.5% of patients (51). In the remaining patients, 10 with macro- (Fig. 8) and 6 with microprolactinoma (Fig. 9), PRL levels remained above the normal range despite a progressive increase of the dose of the drug. However, the possibility that some patients were indeed not taking bromocriptine appropriately cannot be ruled out as 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 regarding the gastrointestinal tract. Both quinagolide, at doses ranging from 0.075-0.6 mg/day, or cabergoline, at doses ranging from 0.5-3.5 mg/week orally, two selective DA receptor subtype-2 selective agonists, have been reported to be effective in reducing PRL secretion and tumor size in most adult patients with prolactinoma, even in those previously shown to be poorly responsive or intolerant to bromocriptine (57). There are now data on cabergoline, showing that it is more effective and often better tolerated than bromocriptine, due to less and milder side effects. For these reasons cabergoline should be the initial treatment of choice.

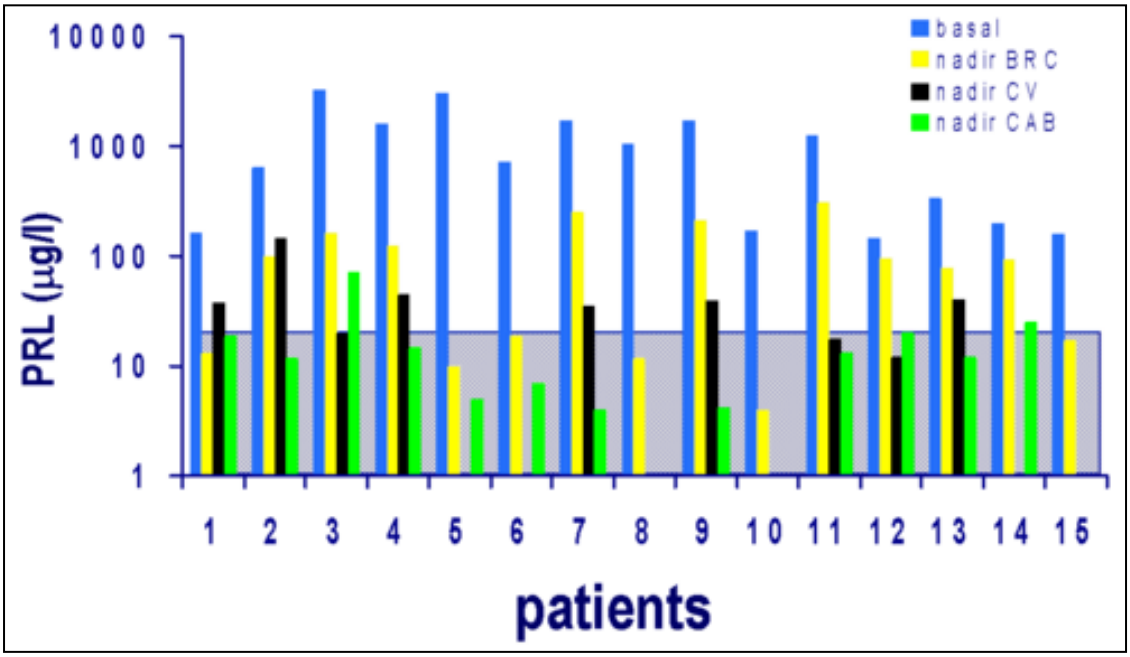

Figure 8. Serum PRL response to different dopaminergic drugs, namely bromocriptine (BRC), quinagolide (CV), and cabergoline (CAB) in 15 children with macroprolactinomas. The shaded area represents the normal PRL range. Data are shown as nadir PRL values at diagnosis and during treatment. Data from ref. 51.

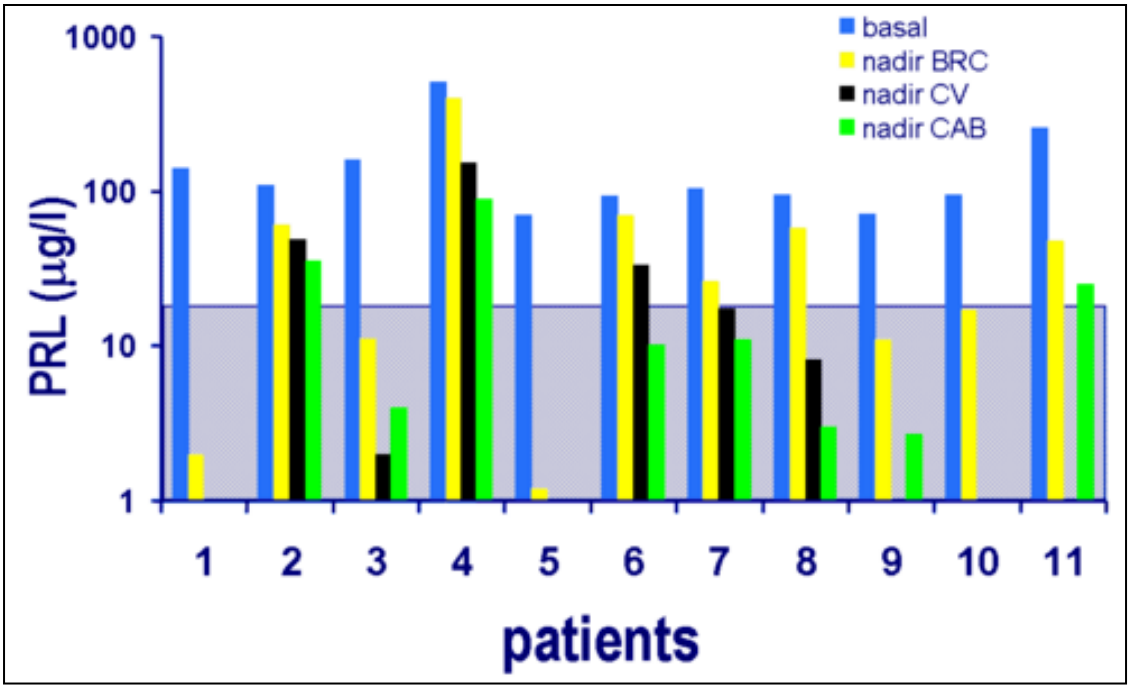

Figure 9. Serum PRL response to different dopaminergic drugs, namely bromocriptine (BRC), quinagolide (CV), and cabergoline (CAB) in 11 children with microprolactinoma. The shaded area represents the normal range. Data are shown as nadir PRL values at diagnosis and during treatment. Data from ref. (51).

Of our 50 cases (57), cabergoline induced normalization of PRL levels in all but 3 cases. Two of the three patients had large extrasellar macroprolactinomas (tumor volume of 4579 mm3 and 1983 mm3 respectively) with baseline PRL levels of 3300 µg/L and 1700 µg/L, respectively that progressively decreased but did not normalize after 2-7

years of treatment. Tumor shrinkage by 93.2% and 54.5% was seen in both patients. The third patient had a microprolactinoma (tumor volume=123.6 mm3) with a baseline PRL levels of 500 µg/L that progressively decreased to 88 µg/L at the last follow-up after 6 years of treatment and achieved tumor shrinkage by 53.9% (57). Only one case of pituitary apoplexy following cabergoline treatment in a young patient has been reported so far (72). Twelve of our 50 patients (one with enclosed macroprolactinoma and 11 with microprolactinoma) achieved the disappearance of the tumor so that they were withdrawn from treatment (57). In our former series, tumor shrinkage was observed in most patients with macroadenomas and even in some with microprolactinomas (Fig. 10). The easy weekly administration makes cabergoline an excellent therapeutic approach to children/adolescents with prolactinoma. Cabergoline has been reported to be tolerated, even at rather high doses (73). Relevant safety issues to be considered in patients treated with cabergoline are possible cardiac valve derangement (74-76) and psychiatric adverse effects (mood changes or obsessive behavior including hypersexuality). These phenomena were first described in patients with Parkinson's disease, who require higher doses of the dopamine agonists than patients with prolactinomas, but has now been documented in patients with pituitary adenomas as well. Cardiac safety of treatment with cabergoline in prolactinomas, even long-term, has been demonstrated in adults (77, 78), so use in children should also be safe, although we need to be aware of cumulative dose builds up if treatment has been started in childhood. Knowledge about psychiatric consequences of dopamine agonists used in pediatric prolactinomas is still scant. Psychotic symptoms during bromocriptine therapy were observed in a child by Hoffman *et al*. (52). Bulwer *et al*. also described a case of an adolescent male with a giant prolactinoma who developed impulsive/compulsive sexual symptoms during cabergoline treatment. These were diagnosed as an iatrogenic effect, a hypothesis supported by symptomatic improvement during a one-month trial off cabergoline (79). Despite the rarity of both pediatric prolactinomas and development of psychiatric side effects of dopamine agonists, this important aspect it needs to be further investigated.

In patients with tumors resistant to dopamine agonists as well as in those showing severe neurological symptoms at diagnosis, surgery is indicated. Radiotherapy should be limited to the cases with aggressive tumors, non-responsive to dopamine agonists, because of the risk of neurological damage, hypopituitarism, and second malignancies later in the lives of these patients (44, 51-53, 57).

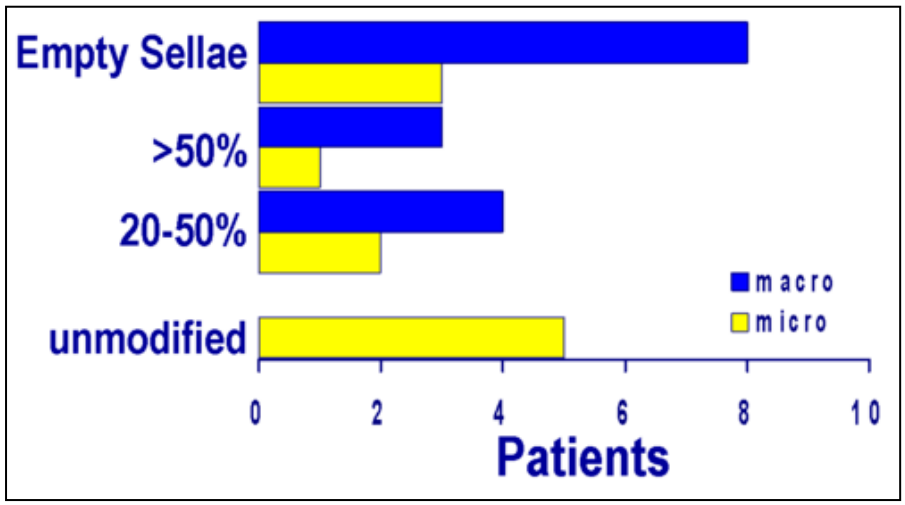

Figure 10. Tumor mass response after bromocriptine, quinagolide, or cabergoline treatment in 15 children with macro- and 11 with microprolactinoma. Data are shown as number of cases with empty sella; greater than 50% tumor shrinkage; 20-50% tumor shrinkage or less than 20% tumor shrinkage shown as unmodified tumor volume. Data from ref. (57).

ACTH-SECRETING ADENOMAS

Cushing's disease (CD), caused by an ACTH-secreting pituitary corticotroph adenoma, is the commonest cause of

Cushing's syndrome (CS) in children over 5 years of age (80, 81). CS can occur throughout childhood and adolescence; however, different etiologies are commonly associated with particular age groups with CD being the commonest cause after the pre-school years. The peak incidence of pediatric CD is during adolescence (81). A macroadenoma is rarely the cause of CD in children; pediatric CD is almost always caused by a pituitary microadenoma with diameter <5 mm with a significant predominance of males in pre-pubertal patients (80, 81).

The molecular basis of pediatric Cushing's disease is complex. Recently, pathological variants of *USP8* gene have been found in an elevated number of ACTH-secreting adenomas; in the pediatric population *USP8* mutated adenomas are clinically distinguished from wild-type adenomas for older age at diagnosis, female preponderance, and more frequent recurrence. In *USP8* wild-type adenomas, *BRAF* and *USP48* mutations have been noted. In pediatric corticotrophinomas, the presence of copy number variations, indicating chromosomal instability, has been related to larger size and more frequent invasion of the cavernous sinus (82).

There are other extremely rare germline conditions that can predispose to the development of pediatric corticotrophinoma such as *DICER1*, *CABLES1*, and *CDKN1B* mutations. DICER1 syndrome is characterized by pituitary blastomas, and manifest itself in early infancy with a highly deadly Cushing's syndrome. *CABLES1* is another potential ACTH-secreting adenoma predisposition gene, whose mutation has been found in very few pediatric cases. *CDKN1B* mutation occurs in the MEN4 syndrome, in which pituitary tumors arise usually in adults, as no gene mutations have been found analyzing children bearing a pituitary adenoma (82).

Clinical Presentation and Diagnosis

The clinical manifestations of CD are mostly the consequence of excessive cortisol production. The clinical presentation is highly variable, with signs and symptoms that can range from subtle to obvious (Table 1). The diagnosis is generally delayed since a decrease in growth rate may be the only symptom for a long time. Growth failure in CD may be due to a decrease of free IGF-I levels and/or a direct negative effects of cortisol on the growth plate (83, 84). In a series of 50 children with CD, Magiakou *et al.* (85) found that obesity and growth retardation were the most frequent symptoms (in 90 and 83% of patients, respectively). Weight gain and stunted growth were the most frequent symptoms also in the series by Weber *et al.* (86) and Devoe *et al.* (87). The skin of the face is plethoric, and atrophic striae can be found in the abdomen, legs, and arms. Muscular weakness, hypertension, and osteoporosis, especially of the spine, are common. Results on BMD or bone metabolism in children with CD have been reported only in a limited number of patients in a few studies (86, 88). Consistent with the findings in adult patients, marked osteopenia was also found in affected children. The bone loss is more evident in trabecular than in cortical bone (89). As compared to patients with adult-onset disease, those with childhood-onset CD have a similar degree of bone loss at the lumbar spine and similar increased bone resorption (90). In a study conducted in 10 patients with childhood-onset and 18 with adulthood-onset CD, BMD at the lumbar spine was significantly lower than in sex and age-matched controls (Fig. 11) (90). Osteoporosis was found in 16 patients (57.1%) (8 adolescent (80%) and 8 adult (44·4%) patients) while osteopenia was found in 12 patients (42.8%) (2 adolescent (20%) and 10 adult (55·6%) patients) (90). Additionally, we have reported that two years of cortisol normalization improved but did recover bone mass and turnover neither in children nor in adult patients with CD (91). This negative finding suggests that a longer period of time is necessary to restore bone mass after the cure of CD and, thus, other therapeutic approaches may be indicated to limit bone loss and/or accelerate bone recovery in these patients (87). In a study Lodish *et al.* (92) analyzed retrospectively, 35 children with CD; in these patients, vertebral BMD was more severely affected than femoral BMD and this effect was independent of degree or duration of hypercortisolism. BMD for the lumbar spine improved significantly after TSS; osteopenia in this group may be reversible. Complete reversal to normal BMD was not seen.

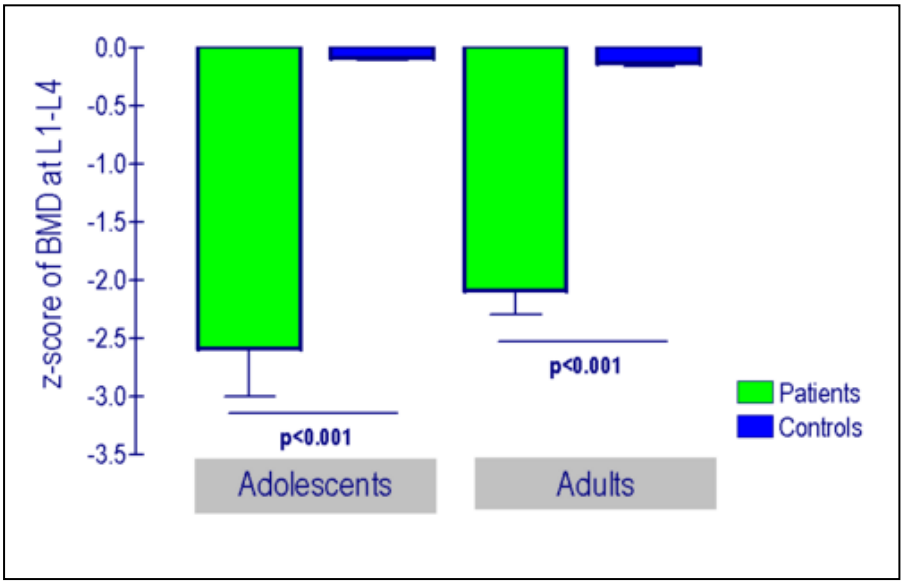

Figure 11. Z score of bone density at lumbar spine in 10 patients with childhood onset Cushing's disease compared to 10 healthy adolescents of matched sex- and age and in 18 patients with adult-onset Cushing's disease compared to 18 healthy adults matched sex- and age. Data from ref. (90).

Hypercortisolism leads to decreased bone formation through direct or indirect inhibition of osteoblast function, while bone resorption is normal or increased in patients with CD (90, 93). Hypercortisolism is known to be associated with loss of skeletal mass and can lead to increased vertebral fracture risk (94, 95). It should also be noted that in children with CD the direct negative effect of hypercortisolism on bone formation is further worsened by concomitant hypogonadism and GH deficiency, both of which are associated with decreased BMD. Children with CD often have musculoskeletal weakness and can have decreased weight-bearing activity that may contribute to impaired BMD.

Children with CD may also have impaired carbohydrate tolerance, while overt diabetes mellitus is uncommon. Excessive adrenal androgens may cause acne and excessive hair growth, or premature sexual development in the first decade of life. On the other hand, hypercortisolism may cause pubertal delay in adolescent patients. Peculiarly, young patients with CD may present neuropsychiatric symptoms which differ from those of adult patients. Frequently, they tend to be obsessive and are high performers at school.

The differential diagnosis of CD includes adrenal tumors, ectopic ACTH production, and the very rare ectopic CRH-producing tumors. However, ectopic ACTH secretion is extremely rare in the pediatric age. In a child/adolescent with suspected CD the diagnosis is based on measurement of basal and stimulated levels of cortisol and ACTH. Measurement of 24-h urinary free cortisol is elevated, and a low dose of dexamethasone (15 μg/Kg) at midnight does not induce suppression of morning serum cortisol concentrations as in normal subjects (96). Loperamide, an opioid agonist, lowers cortisol secretion and has been proposed as a reliable screening test for hypercortisolism in children and adolescents (97) , but has not achieved popular use. Suppression of the spontaneous circadian variations of serum cortisol is another feature of CD. Suppression of cortisol by more than 50% after high-dose dexamethasone (150 μg/kg) given at midnight will confirm that hypercortisolism is due to an ACTH-secreting pituitary adenoma (97). Midnight salivary cortisol measurements have been suggested as an alternative non-invasive screening test in the diagnosis of CS in adults(98), but is there is not much experience of its use in this age group.

All patients should undergo pituitary MRI with the administration of gadolinium, but since ACTH- secreting pituitary adenomas are significantly smaller than all other types of adenomas, often having a diameter of 2mm or less (99), pituitary MRI may fail to visualize the tumor. In most instances the diagnosis of CD can be made by initial clinical and laboratory data (Fig.12). Bilateral inferior petrosal sinus sampling has a high specificity, so that no patient with extra-pituitary CS runs the risk of being submitted to transsphenoidal surgery, but it carries a significant number

of false negative results (99). This procedure can also be technically difficult in children, and the risk of morbidity from surgery and/or anesthesia must be considered.

Lateralization of the adenoma can be of greater help to the surgeon than pituitary scanning (100). Therefore, bilateral venous sampling should only be performed in centers with wide experience in the technical procedure as well as in the interpretation of the results. If a patient without anomalous venous drainage patterns exhibits a lateralizing ACTH gradient of 2:1 or greater (101, 102), removal of the appropriate half of the anterior pituitary gland will be curative in 80% of cases (99). Kunwar and Wilson (99) reported that in the presence of a negative surgical exploration, a guide to the probable location of the adenoma is invaluable, and under the right circumstances, a hemi-hypophysectomy is appropriate and successful in most cases.

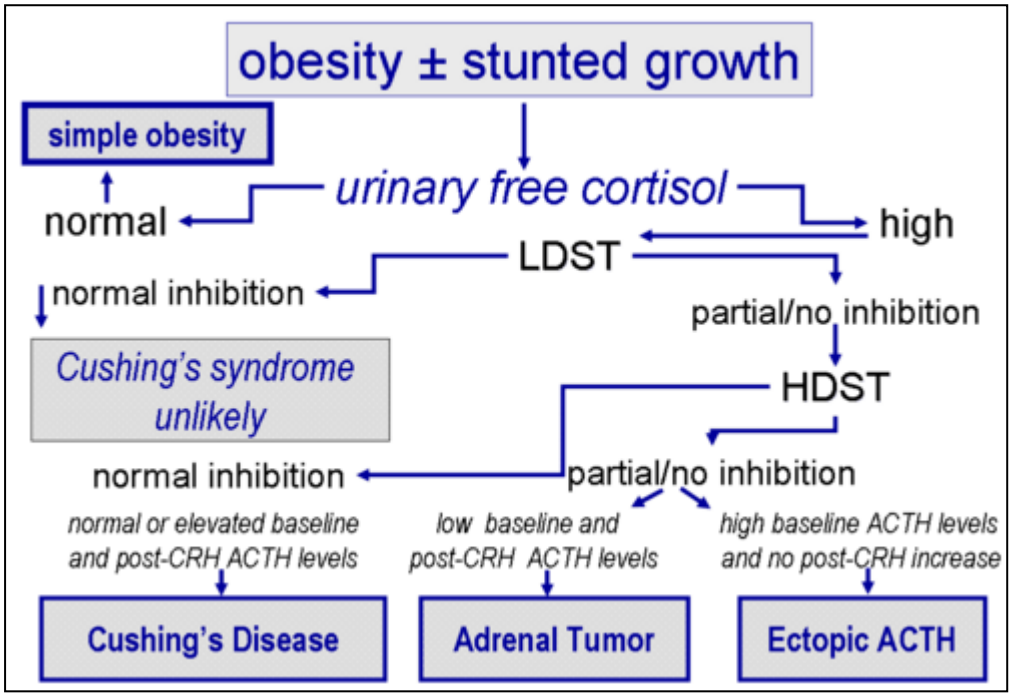

Figure 12. The diagnosis of Cushing's syndrome. LDST, low dose suppression test; HDST, high dose suppression test; CRH, corticotrophin releasing hormone. Data from ref. (36).

Treatment Strategy

The goal of the treatment of Cushing's disease are normalization of cortisol levels, reversion of hypercortisolism-related signs and symptoms, and pituitary adenoma removal. Transsphenoidal adenomectomy is the treatment of choice for ACTH-secreting adenomas in childhood and adolescence, because of the greater prevalence of microadenomas in this population that allows for total tumor removal and thus disease remission. Radiotherapy could be the first-line treatment in children with surgical contraindications (103). Transsphenoidal microsurgery is considered successful when it is followed by remission of signs and symptoms of hypercortisolism and by normalization of laboratory values. Surgical excision is successful in the majority of children, with initial remission rates of 70-98% and long-term cure of 50-98% in most studies (38, 39, 80, 81, 84, 86, 87, 104-109). The success rate decreases when the patients are followed-up for more than 5 years (84, 86, 87), and the outcome cannot be predicted either by preoperative or immediate postoperative tests (87). Surgical cure was found in 59% of 27 patients over a 21-year period, with a higher age favoring cure, as did an identifiable tumor seen at surgery and positive histology (110). Several conditions are indeed predictors of Cushing's disease recurrence in children: older age at the time of disease symptoms, younger age at the time of surgery, larger tumor diameter, and mutations in *USP8* gene in resected tumor tissue (111).The recurrence rate of Cushing's disease in children in about 40% in 10 years (67).

Noteworthy in pediatric patients there are several technical difficulties with the transsphenoidal surgical approach due to a different anatomic conformation in children compared to adults. In children, the smaller size of the sella and pituitary may interfere with surgical maneuvers, in addition to the difficult identification of surgical landmarks due to different anatomic variations of sellar region such as the shorter intercarotid distance and piriform aperture, and the low pneumatization of sphenoid bone. Furthermore, in children with skull base lesions short nasal-sellar and vomer-clivus distances and smaller transsphenoidal angles than healthy children have been noted (112).

Surgery is usually followed by adrenal insufficiency and patients require hydrocortisone replacement for 6-12 months. After normalization of cortisol levels, resumption of normal growth or even catch-up growth can be observed. Generally, final height is compromised compared to target height (68, 85). Johnston *et al.* (113) have, however, reported that some children do achieve a normal final stature. However, even if catch-up and favorable long-term growth can be achieved after treatment for Cushing's disease, post-treatment GH deficiency is frequent (114). Lebrethon *et al*. (114) demonstrated that early hGH replacement may contribute to a favorable outcome on final stature (Fig.13). A re-analysis of this series confirmed that pediatric Cushing's disease patients achieve a normal final stature provided that replacement therapy including GH is correctly performed (115). Normal body composition is more difficult to achieve. Many patients remain obese and BMI SDS was elevated at mean interval of 3.9 years after cure in 14 patients (115).

Rarely, surgery may induce panhypopituitarism, permanent diabetes insipidus, and cerebrospinal fluid leak (46); transient diabetes insipidus, and cerebrospinal fluid leak occur more frequently in pediatric patients than adults (116). Probably such a higher prevalence may be due to technical difficulties related to the anatomy of pediatric sellar region. Cure is more likely to be achieved and morbidity is low if the surgery is performed by an experienced neurosurgeon, by analogy with other studies performed in acromegaly (113).

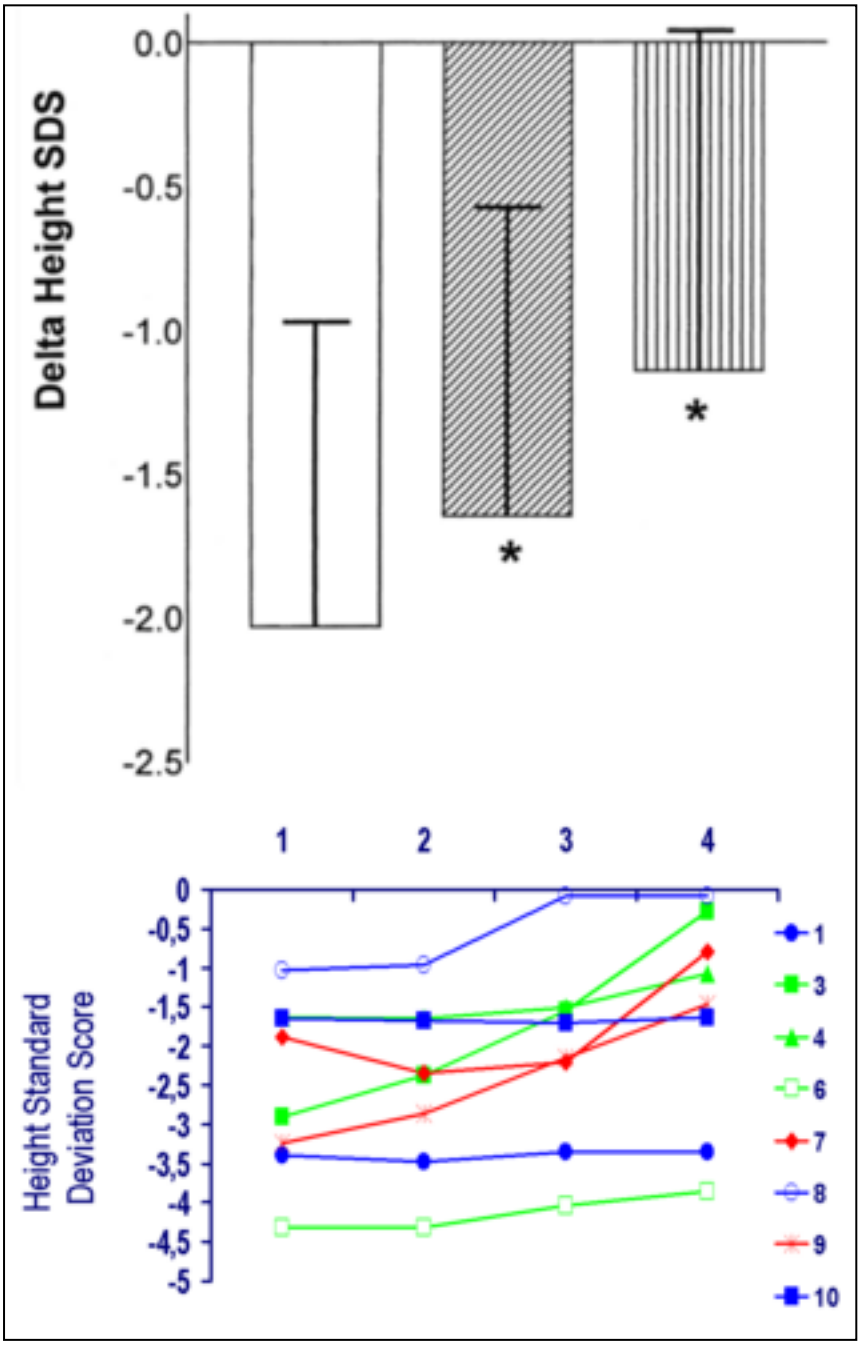

Figure 13. GH treatment in children with Cushing's disease improves the height gain. Upper graph: Evaluation of growth (change (D) in height SD score) in eight patients during hGH treatment. Bottom graph: Individual changes of height standard deviation score before and after GH replacement. 1= At diagnosis; 2= Before GH treatment; 3= After 1 year of GH treatment; 4= Final height. Data drawn from ref. (114).

In recent times, the endonasal approach, consisting in a direct access of neurosurgeon to the sellar region through the patient's nares, has also been used in pediatric Cushing's disease, usually using an endoscope aiming to improve surgical visualization. However, because of small patients' nares, an expert neurosurgeon is required (112). Nowadays, while there is little evidence of this less invasive technique are available, it seems to be an effective treatment for pediatric CD, without relapses observed in treated patients (109, 117, 118). However, no studies

comparing microscopic and endoscopic endonasal technique in pediatric pituitary adenomas are available (67).

The treatment modality in patients who have relapses after transsphenoidal adenomectomy is still controversial. Some authors recommend repeat surgery (84, 119), while others favor radiotherapy (120, 121). Transsphenoidal surgery is actually suggested as a second-line treatment in recurrent or persistent CD patients (103), and is required in case of incomplete initial tumor removal, in patients with tumor reappearance after initial complete surgical resection, or even in persistent patients in the days immediately after first TSS aiming to optimize therapeutic efficacy (116). The efficacy of a second surgical treatment in Cushing's pediatric disease is still unclear, due to the presence in literature of only single case reports, or case series. Interestingly, in one of this case series Lonser *et al.* reported an initial disease remission in 93% of patients (122).

Radiotherapy techniques currently used for pediatric corticotrophinomas are divided in two groups: conventional radiotherapy (RT) and stereotactic RT. Conventional RT, in which small, daily radiation doses are delivered to the target tumor over a 25-30 days period, and stereotactic RT, where high radiation doses are delivered to a more precisely identified target area, minimizing radiation exposure to the surrounding central nervous system structures. Stereotactic RT could be performed as a single treatment, called stereotactic radiosurgery such as gamma-knife radiosurgery, or as a fractionated treatment, called stereotactic conformal radiotherapy.

Disease remission using conventional radiotherapy is reached by about 80% of pediatric corticotrophinoma (113, 121, 123-127). Conventional RT is a safe treatment, as no nerve damage or other major complications were observed in treated patients. Compared to adults with Cushing's disease treated with Conventional RT as a second-line treatment, this seems to be slightly more effective in pediatric corticotrophinoma (116). There are only two studies concerning gamma-knife radiosurgery in the pediatric population, reporting a remission rate of 87.5 % and 79.2%, respectively (128, 129). Radiotherapy usually requires time before reaching its maximum result, and for this reason pharmacotherapy could be considered as a temporary treatment until this achievement (103, 116). Of note, hypothalamo-pituitary dysfunction is an early and frequent complication of radiation (87).

For the medical therapy of Cushing's disease, three pharmacological categories are currently available: pituitary-directed agents, adrenal-directed agents, and glucocorticoid receptor antagonists. Scientific evidence regarding their use in pediatrics is scant, and there are no data on the use of mifepristone in pediatric patients.

Data on the use of etomidate, an adrenal-directed agent, in the emergency management of severe hypercortisolemia seems to be promising. There are at least 3 case reports demonstrating that intravenous infusion of etomidate at doses ranging from 1 to 3.5 mg/h, with constant dose titration according to serum levels, adding contemporaneous hydrocortisone infusion at 0.25-0.5 mg/kg/h to prevent adrenal insufficiency is a safe and effective approach in patients with very severe Cushing's disease prior to bilateral adrenalectomy (130-132).

Moreover, experience with cabergoline for CD in childhood and adolescence is also limited (133). Bilateral adrenalectomy is actually a third-line treatment, employed in cases of surgical and radiotherapeutic failures. This therapeutic approach has gradually lost his importance in the context of pediatric corticotrophinoma treatment, due to the side effects and the growing evidence of pharmacological treatment as valid therapeutic alternative (116, 119).

It is interesting that in pediatric Cushing's disease patients, in contrast to adult ones, there does not appear to be complete recovery from cognitive function abnormalities despite rapid reversibility of cerebral atrophy (134).

GH-SECRETING ADENOMAS

GH excess derives from a GH-secreting adenoma in over 98% of cases. In adulthood, these adenomas are relatively rare with an incidence of 1.1 new cases/100,000 individuals per year, and a prevalence from 3 to >13 cases per 100,000 individuals according to the country under study (135) , while gigantism is extremely rare with a little bit more than 400 reported cases to date (136, 137). In childhood, GH-secreting adenomas account for 5-15% of all pituitary adenomas (138). In less than 2% of the cases excessive GH secretion may depend on a hypothalamic or ectopic GH releasing hormone (GHRH)-producing tumor (gangliocytoma, bronchial or pancreatic carcinoid), which causes somatotroph hyperplasia or a well-defined adenoma (139-142).

Nowadays, approximately 50% of patients with pituitary gigantism have a known genetic mutation causing the disease, so genetic counselling should be considered (143). In this genetic context, pituitary gigantism could be part of syndromic, or non-syndromic disease. Recently, non-syndromic pituitary gigantism has been described due to aryl hydrocarbon receptor-interacting protein (*AIP*) gene mutations and Xq26.3 microduplication causing X-linked acrogigantism (XLAG) (144-146). *AIP* mutations occur in about 40% of gigantism cases, sporadically or in the setting of familial isolated pituitary adenoma (FIPA)., and patients with truncating *AIP* mutation had a younger age at disease onset and diagnosis, compared to patients with non-truncating *AIP* mutation (146).

Typically, *AIP*-mutated adenomas bear several features: early disease is manifest usually in the second decade of life, the majority of the cases are GH- or mixed GH/prolactin-secreting pituitary adenomas (144, 146), the tumors are large and invasive, often with suprasellar extension, resistance to first-generation SSA treatment is common, thus require a multimodal treatment and pituitary apoplexy can often occur, especially in pediatric patients (82, 137, 146). Interestingly, *AIP*-mutated patients with GH excess had been shown to be taller than the non-mutated counterparts (147).

XLAG represents 10% of the cases of pre-pubertal gigantism (143). X-LAG is due to a submicroscopic chromosome Xq26.3 duplications that include *GPR101* gene, which is differentially overexpressed in the affected pituitary adenoma (82, 148). Duplications are germline in females and somatic in sporadic males with variable levels of mosaicism in the latter (82). Somatic mosaicism occurs in sporadic males but not in females with XLAG syndrome, although the clinical characteristics of the disease are similarly severe in both sexes (148). Three rare case of families in which the germline duplication was transmitted from the affected mother to son have been described, and all carriers of the duplication had gigantism (149). The disease often occurs during the first year of life, mostly in females and as sporadic disease.

Regarding the characteristics of the pituitary gland at diagnosis in these patients, most of them harbor macroadenomas, generally mixed GH- and PRL-secreting tumors, while a minority have hyperplasia alone (82, 137, 145). A pattern of multiple microadenomatous foci against a hyperplastic background has also been described (82). Noteworthy is the peculiar presence of acromegalic features in these pediatric patients, and a poor response to SSA treatment such as AIP-mutated somatotrophinomas (82).

Concerning syndromic pituitary gigantism, Carney Complex and McCune-Albright syndromes contribute to gigantism approximately in 1% and 5% respectively, where pituitary hyperplasia or a distinct pituitary adenoma could be found in the pituitary gland (82, 143). GH-secreting adenomas may also occur in MEN1 syndrome and cause 1% of cases of pituitary gigantism; the possibility of pituitary hyperplasia due to GHRH hypersecretion from neuroendocrine tumor should be considered in this syndromic context (143).

Somatotrophinomas could also be one of the manifestations of the MEN4 syndrome and the pheochromocytoma/paraganglioma and pituitary adenoma association (82) (151).

GH excess and consequent gigantism could be a rare manifestation of NF-1 syndrome, characterized by the presence of optic pathway gliomas but not pituitary adenomas, in addition to the characteristic syndromic manifestations. In this case it can be speculated that GH secretion could be either due to loss of somatostatinergic inhibition or presence of excessive GHRH secretion due to disrupted regulation of GHRH by the optic pathway tumor (82).

Clinical Presentation and Diagnosis

In adults, chronic GH and IGF-1 excess causes acromegaly, which is characterized by local bone overgrowth, while in children and adolescents leads to gigantism. The associated secondary hypogonadism delays epiphysial closure, thus allowing continued long-bone growth (Fig.14). However, the two disorders may be considered along a spectrum of GH excess, with principal manifestations determined by the developmental stage during which such excess originates (Table 1). Supporting this model has been the observation of clinical overlap between the two entities, with approximately 10% of acromegalics exhibiting tall stature (150), and the majority of giants eventually demonstrating features of acromegaly (151).

Gigantism predominantly affects males (78%), is generally characterized at diagnosis by the presence of a

macroadenoma, often invading surrounding structures (54.5%), and prolactin co-secretion is present in 34% of pituitary adenomas causing pituitary gigantism (143). As demonstrated, older age at diagnosis, and the consequent longer time of exposure to higher GH and IGF-1 levels than normal, is associated with an increased prevalence of many pathological signs and symptoms, particularly those related to longer-term exposure such as joint disease, facial changes, skin changes, and diabetes mellitus (136, 143). In contrast to adults where there is an increased prevalence of cardiovascular, respiratory, neoplastic, and metabolic complications (136, 141, 152), there is no report of similar complications in childhood.

In our study, we did not find any patient with hypertension, arrhythmias, diabetes or glucose intolerance; as expected, however, some degree of insulin resistance and enhanced ß-cell function was observed in our patients at diagnosis (153). In a study conducted in six patients with gigantism, Bondanelli *et al.* (154) showed that 33% of giant patients had left ventricular hypertrophy and inadequate diastolic filling, 16.7% had isolated intraventricular septum thickening and impaired glucose metabolism. In acromegaly, clinical features develop insidiously and progressively over many years and in modern epidemiological studies the average delay between the onset of symptoms and diagnosis is approximately 5 years (135), while the presentation of gigantism is usually dramatic and the diagnosis is straightforward. All growth parameters are affected although not necessarily symmetrically. Mild-to-moderate obesity occurs frequently (138), and macrocephaly has been reported to precede linear and weight acceleration in at least one patient (155). All patients also had coarse facial features, disproportionately large hands and feet with thick fingers and toes, frontal bossing and a prominent jaw (138). In girls menstrual irregularity can be present (156) while glucose intolerance and diabetes mellitus are rare. Tall stature and/or acceleration of growth velocity was observed in 10 of 13 patients. Headache, visual field defects, excessive sweating, hypogonadism, and joint disorders may also be present (143). Several cases of ketoacidosis have been reported(157, 158).

The diagnosis of acromegaly and gigantism is usually clinical, and can be readily confirmed by measuring GH levels, which in more than 90% of patients are above 10 µg/l (139-141). The oral glucose tolerance test (OGTT) is the simplest and most specific dynamic test for both the diagnosis and the evaluation of the optimal control of GH excess (139-141). In healthy subjects, the OGTT (75-100 grams) suppresses GH levels below 1 µg/l after 2 hours, while in patients with GH-secreting adenoma such suppression is lacking, and a paradoxical GH increase is frequently observed. GH excess should be confirmed by elevated circulating IGF-I concentrations for age and gender (159, 160). The assay of IGF-I binding protein-3 is conversely not useful for diagnosis nor for the follow-up of the patients (161, 162). The presence of different GH isoforms in patients with gigantism/acromegaly may represent a diagnostic problem (163). A greater sensitivity of the GH assay may facilitate the distinction between patients and normal subjects, as shown by the use of a chemiluminescent GH assay (164). It might help in demonstrating the persistence of GH hypersecretion after surgery or during medical therapy. In cases of clinical and laboratory findings suggestive of a GH-producing adenoma, pituitary MRI must be performed to localize and characterize the tumor (141-143) (Fig. 15).

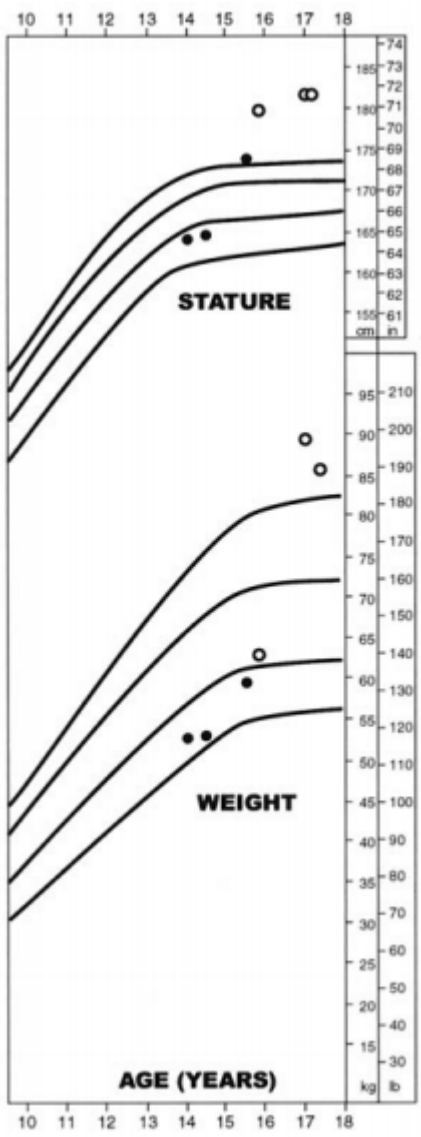

Figure 14. The patient's growth and weight chart with normal growth and weight curves (solid lines, 5th, 50th, 75th, and 95th percentile). Measurements subsequent to therapeutic intervention. Reproduced from (165), with permission.

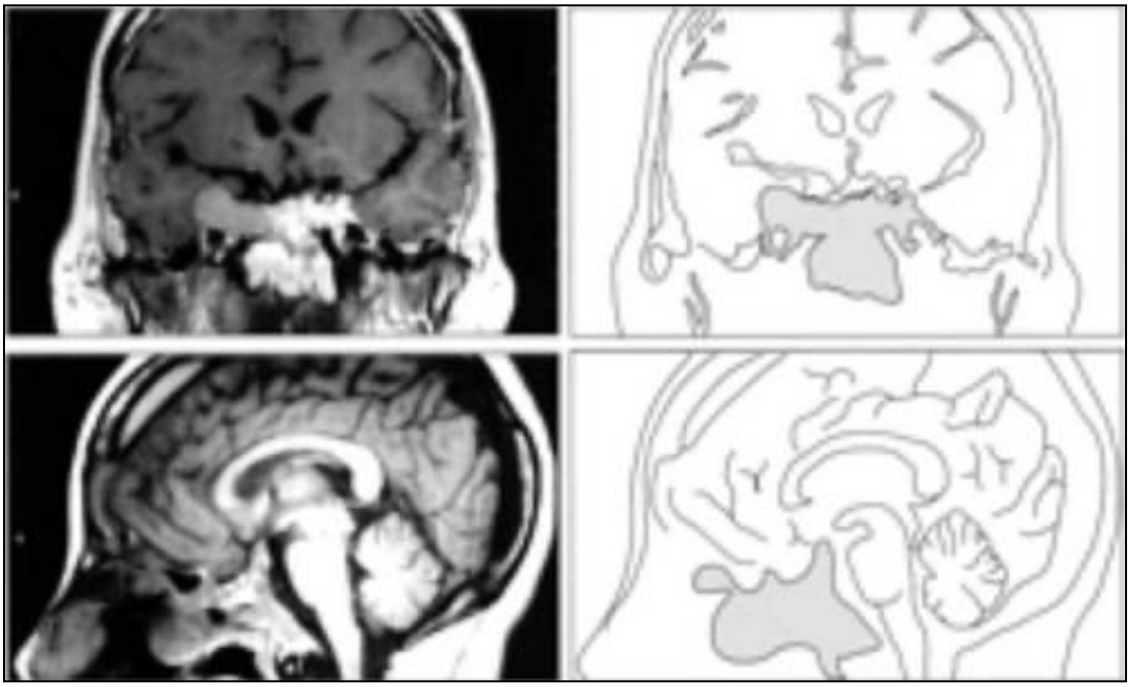

Figure 15. The extent of tumor invasion as visualized with coronal and lateral MRI views and their outlines. Reproduced from (165) with permission.

Treatment Strategy

The objectives of treatment of GH excess are tumor removal with resolution of its eventual mass effects, restoration of normal basal and stimulated GH secretion, relief of symptoms directly caused by GH and IGF-1 excess, and prevention of progressive disfigurement, bone expansion, osteoarthritis and cardiomyopathy which are disabling long-term consequences, as well as prevention of hypertension, insulin resistance, diabetes mellitus and lipid abnormalities that are risk factors for vascular damage (139-141). The currently available treatment options for pituitary gigantism include surgery, radiotherapy, and pharmaco-therapeutic suppression of GH levels.

For pituitary gigantism treatment, combination therapy is often necessary due to the aggressiveness of the disease, and the consequent low rate of primary control using both surgical and medical first approach, 26 % and 4% respectively (143). Satisfactory results are obtained in the treatment of hyperprolactinemia using dopamine agonists in prolactin co-secreting adenomas.

Transsphenoidal adenomectomy is the cornerstone in the treatment of GH-secreting tumors, and is a valid first-line therapeutic option (143). In pediatric patients with gigantism, transsphenoidal surgery was found to be as safe as in adults (166), although some technical difficulties exist due to the different anatomic conformation in children compared to adults as previously reported in the ACTH-secreting adenoma section. The surgical approach can be difficult in McCune-Albright syndrome patients due to the fibrous dysplasia in the surrounding tissue.

In patients with intrasellar microadenomas, surgical removal provides biochemical control with normalization of IGF-I in 75–95% of patients (167, 168). In case of macroadenomas, particularly when they exhibit extrasellar growth, transcranial approach might be requested, and persistent postoperative hypersecretion of GH occurs frequently. Despite this, tumor debulking contributes to improving disease control using medical therapy (143). In most surgical series, only about 60% of acromegalic patients achieve circulating GH levels below 5 µg/l (169-173), with better success score when the neurosurgeon is skilled in pituitary surgery (169, 170).

Concerning gigantism, for medical treatment it is necessary to consider that several drugs used for acromegaly are not formally studied in children, and for those employed drug-dosing is labelled for adults and might not be directly applicable in pediatric patients. Treatment with somatostatin

analogues can be effective in patients with GH excess (150, 174, 175), although limited data are available in adolescent patients. Octreotide given subcutaneously in two patients was shown to inhibit GH levels and reduce growth velocity (176, 177). Of interest, in adolescents, as in adults, we observed tumor shrinkage by 30% on average after first-line treatment with somatostatin analogues. Whether this treatment has facilitated the subsequent surgical approach in this series could not be ruled out because of the limited number of cases studied. Treatment was tolerated very well by all patients (153).

As about one third of patients had concomitant hyperprolactinemia and combined treatment with dopaminergic compounds such as cabergoline and somatostatin analogues, may be necessary.

In another case of a 15 yr-old girl with a mixed GH/PRL-secreting adenoma (165), octreotide-LAR (at the dose of 20 mg/28 days) combined with cabergoline (at the dose of 0.5 mg twice/week) normalized serum GH and IGF-I levels, and decreased growth rate from 12 cm/yr to nearly 2.5 cm/yr. This association has be proven to be effective also in an adolescent bearing a somatotropinoma in the context of McCune-Albright syndrome (178). In seven of the eight hyperprolactinemic patients included in our study, combined treatment with octreotide plus bromocriptine or octreotide-LAR or lanreotide plus cabergoline was effective and well tolerated by all patients. Only two patients (15.4%) of the entire series still presented with active acromegaly after treatment with surgery and pharmacotherapy with somatostatin analogues plus dopamine-agonists(153).

Although long-acting somatostatin analogues have been shown to be effective and safe in pediatric patients, this therapy often fails to achieve disease control especially in the most frequent genetic forms of pituitary gigantism (*AIP*-mutated adenomas and X-LAG acrogigantism), which are characterized by poor responses to first generation SSAs. Recently the successful use of pasireotide LAR has been reported in two cases of *AIP*-mutated gigantism not controlled by surgery and first-generation somatostatin analogues, respectively. Pasireotide LAR allowed not only biochemical control but also the reduction of the pituitary adenoma volume. These patients developed pasireotide-induced diabetes, controlled by drug therapy (179).

The GH receptor antagonist pegvisomant is a very potent drug which has been introduced into clinical practice. In patients with resistant acromegaly, the use of the GH-receptor antagonist pegvisomant was followed by normalization of IGF-I levels in more than 80% of patients (180-182). However, there are few data related to pediatric patients. In a 12-year-old girl with tall stature (178 cm), bearing a GH/PRL-secreting macroadenoma inoperable since tumor tissue was fibrous and adherent to the optical nerves, the GH receptor antagonist at a dose of 20 mg/day completely normalized IGF-I levels (183). In a 3.4 year-old girl with a GH/prolactin-secreting adenoma, treatment with pegvisomant and cabergoline was effective to normalize IGF-I levels and height velocity without side effects (184). Combined therapy with the addition of pegvisomant to octreotide LAR rapidly allowed biochemical control in three children with pituitary gigantism, pituitary tumor size did not change despite concomitant therapy with a somatostatin analogue (185). The main limit of pegvisomant is the eventual adenoma size increase during treatment, requiring treatment suspension. Pegvisomant was successfully used also in the youngest known patient with AIP-related pituitary adenoma, in which despite of the previously transsphenoidal surgery, and the medical treatment after surgery with temozolomide, subsequently in addition to bevacizumab, IGF-1 was normalized only after pegvisomant treatment (186).

Radiation therapy is rarely used in pediatric patients, and is generally is considered only after the failure of both primary surgical and medical therapies, because of a maximum response is achieved 10–15 years after radiotherapy is administered (187, 188), and the involvement of surrounding structures in the radiation-induced damage. Radiation-induced damage of the surrounding normal pituitary tissue results in hypogonadism, hypoadrenalism, or hypothyroidism in most patients within 10 years (187), whereas complications such as optic nerve damage, cranial nerve palsy, impaired memory, lethargy, and local tissue necrosis have been reduced thanks to improved precise isocentric simulators and accurate dosing techniques. At long term follow-up, about 43% of patients with pituitary gigantism among who undergone to secondary radiotherapy have shown controlled GH and IGF-I levels (136). Noteworthy, as a consequence of the multiple operations and radiotherapy, 64% of patients develop hypopituitarism during long-term follow-up (143).

TSH-SECRETING ADENOMAS

This tumor type is rare in adulthood and even rarer in

childhood and adolescence with only a few cases reported so far (189). Plurihormonal adenomas with GH and TSH co-secretion can also occur. It is frequently a macroadenoma presenting with mass effect symptoms such as headache, visual disturbance, together with variable symptoms and signs of hyperthyroidism (Table 1). TSH-secreting adenomas must be differentiated from the syndrome of thyroid hormone resistance (190). In most cases, the classical criteria of lack of TSH response to TRH stimulation, elevation of serum α-subunit levels, and a high α-subunit/TSH ratio along with a pituitary mass on MRI, are diagnostic of a TSH-secreting adenoma (190).

Treatment Strategy

Transsphenoidal surgery is the first treatment approach to these tumors. However, since the majority of these adenomas are macroadenomas, which tend to be locally invasive, surgery alone fails to normalize TSH and thyroid hormone levels in most cases. In adults, radiotherapy is recommended as routine adjunctive therapy when surgery has not been curative (190). However, due to the high frequency of post-radiotherapy hypopituitarism, in children pharmacotherapy is the preferred second choice. There is very little success with dopamine agonists for treatment of these tumors (191). In contrast, therapy with somatostatin analogues normalizes TSH levels in the majority of patients, and tumor shrinkage occurs in approximately half of cases (192-195) and shown be useful in children as well. Rabbiosi *et al*., first used lanreotide successfully as first-line treatment in a pediatric patient bearing a macroadenoma characterized by a low probability of complete surgical eradication due to its antero-superior extension. The response to medical treatment was optimal, with significant tumor shrinkage and development of central hypothyroidism after few months. Thus, suggesting that preoperative somatostatin analogue treatment used for tumor shrinkage may be helpful to prepare a hyperthyroid patient to surgery (189). Before this somatostatin analogue in the pediatric age had only been used in two post-pubertal boys (189). Chronic treatment with SR-lanreotide reduced plasma TSH and normalized fT4 and fT3 levels, suggesting its use in the long-term medical treatment of these adenomas (190, 195).

CLINICALLY NONFUNCTIONING ADENOMAS

Clinically non-functioning adenomas (NFAs) are extremely rare in childhood, compared with adults (196). Nonetheless, there is *in vitro* and *in vivo* evidence that almost all of these tumors synthesize glycoprotein hormones or their subunits (197, 198). In adults, NFAs represent 33-50% of all pituitary tumors, while in pediatric patients they account for less than 4-6% of cases (38, 40, 44), for this reason incidentally discovered adenomas in childhood are rare (199). In a study, 5 out of 2288 patients treated at Hamburg University between 1970-1996 were diagnosed to bear a clinically NFAs (196). In a most recent surgical series, 9 out 85 pituitary adenomas (10.6%) were NFAs in the pediatric group (107). Most silent adenomas arise from gonadotroph cells, the clinical presentation includes visual field defects, headache, and some degree of pituitary insufficiency since invariably all patients had a macroadenoma (Table 1). Recent data show that hypogonadism is the most frequent pituitary deficiency at diagnosis occurring in 71.4% of pediatric patients, followed by TSH deficiency (33.3%), and GH and ACTH deficiency (both 11.1%). No case of diabetes insipidus occurred in this pediatric series (107). Larger macroadenoma could also cause hydrocephalus due to the obstruction of foramen of Monro (199). A modest hyperprolactinemia can also be present due to pituitary stalk compression (196).

Functioning gonadotroph adenomas are tumors expressing and secreting biologically active gonadotropins. They are extremely rare, and their real prevalence is unknown due to only case reports and small case series reported in literature. Peculiar presenting manifestation in the pediatric age is isosexual precocious puberty or ovarian hyperstimulation, frequently in addition to mass effect due to the presence of a macroadenoma. To date, only three female patients aged <14 years with a clinical functioning gonadotroph adenoma have been described in literature (200-202). Biochemical findings include elevated serum FSH levels, elevated or low LH levels, and high estradiol and testosterone levels in females and in males, respectively (203). In the pediatric population, these adenomas need to be differentiated from other sellar/para-sellar masses such as cysts, craniopharyngioma, and dysgerminoma. Therefore, the MRI of the sella and parasellar structure is the basic step in the diagnosis.

Treatment Strategy

The first approach to these adenomas, silent and even functioning, is transsphenoidal surgery to remove tumor mass and decompress parasellar structures. As in the other adenoma types, surgery has a low morbidity and leads to an improvement of visual symptoms in the majority of

cases. Endoscopic endonasal unilateral transsphenoidal approach to the pituitary (204), which has the same indications as the conventional transsphenoidal microsurgery, overcomes many of the potential problems tied to the surgical route, thanks to its minimal invasiveness. This procedure involves no sublabial dissection nor any fracture of the facial bones with dental or naso-sinusal complications. Furthermore, a wider surgical vision of the operating field is obtained, which potentially improves the likelihood of a better and safer tumor removal. In addition, this procedure requires a shorter hospitalization, permits a rapid recovery of the child (205), and maintains neuroendocrine-pituitary integrity, with ensuing normal growth. This approach can also be safely used for the surgical removal of remnant pituitary tumors (206). After surgery these patients partially recover from hypopituitarism. Postoperative radiotherapy can be used in patients with subtotal tumor removal to prevent tumor re-growth and reduce residual tumors, but is burdened by a high prevalence of pan-hypopituitarism (207-209).

Medical therapy has poor effects on clinically non-functioning adenomas (197, 210), and data are from adults. A positive response to cabergoline associated with detection of dopamine receptors *in vitro* has been proven in clinically non-functioning adenomas (211). Positive effects of cabergoline were observed in some patients with α-subunit secreting adenomas, mostly in patients with tumors expressing high number of dopamine D2 receptors (212). Greenman *et al*. proved that dopamine agonists treatment in adult patients with NFAs is associated with decreased prevalence of residual adenoma growth after neurosurgery. A decrease in residual mass was observed in 38% of patients treated immediately after surgery, while a stable or enlarged residual adenoma was observed in 49% and in 13%, respectively. A significant shrinkage or stabilization of residual mass was achieved (58%) also in patients in which the administration of the same therapy was performed when residual growth was noted during the post-operative follow-up (213). *In vitro*, chimeric dopamine/SSTR agonists are effective in inhibiting cell proliferation in two-thirds of non-functioning adenomas (214). Somatostatin analogues and dopamine agonists have not been tested in children/adolescents with clinically non-functioning adenomas.

Concerning medical therapy for functioning gonadotroph adenomas, there is little published information in the literature about the use of dopamine agonists, somatostatin analogues, GnRH agonists, and antagonists in the pediatric age range (203).

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