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Paediatric Pituitary Adenomas: A Decade of Change

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Abstract

Pituitary adenomas, although rare in the paediatric age range and mostly benign, represent very challenging disorders for diagnosis and management. The recent identification of genetic alterations in young individuals with pituitary adenomas has broadened the scope of molecular investigations and contributed to the understanding of mechanisms of tumorigenesis. Recent identification of causative mutations of genes such as *GNAS*, *PRKAR1A*, *MEN1* and *AIP* has introduced the concept of molecular screening of young apparently healthy family members. Population-based studies have reported a significantly higher number of affected subjects and genetic variations than expected. Radiological techniques have advanced, yet many microadenomas remain undetectable on scanning. However, experience with transsphenoidal and endoscopic pituitary surgery has led to higher rates of cure. Prolactinomas, corticotroph and somatotroph adenomas remain the most prevalent, with each diagnosis presenting its own challenges. As paediatric pituitary adenomas occur very infrequently within the paediatric age range, paediatric endocrine units cannot provide expert management in isolation. Consequently, close co-operation with adult endocrinology colleagues with experience of pituitary disease is strongly recommended.

Introduction

Paediatric pituitary adenomas (PPAs) comprise rare but challenging pathologies in children and adolescents related to their endocrine and neurological characteristics. In the last decade important advances have been made in the diagnosis of PPAs and in both medical and surgical therapy. The identification of significant molecular defects in young individuals with pituitary adenomas has advanced the understanding of pathogenesis in these patients and introduced the concept of genetic screening in family members. The analysis of safety and efficacy data from studies on larger paediatric cohorts has also contributed to improved clinical outcome.

This mini-review will discuss new clinical and scientific developments and concentrate on recent advances in management. We present general aspects of epidemiology, molecular pathogenesis, diagnosis and therapy, and then describe individually advances in the management of the three most prevalent PPAs, namely prolactinomas, corticotroph and somatotroph adenomas. As these disorders are very rare in the paediatric age range, paediatric endocrinologists do not have the experience to manage such patients in isolation. We will therefore emphasize the importance of paediatric and adult collaboration in their diagnosis and treatment.

Classification and Epidemiology

In early childhood, PPAs account for <3% of paediatric brain tumours and 2.6-8.5% of pituitary tumours in the general population [8]. It should be remembered however that many adenomas presenting in early adult life probably originated in childhood. In comparison to adenomas in adults, they are more frequently functioning (80-97%), with adrenocorticotropin (ACTH)-secreting adenomas being the most common in early childhood, followed by prolactin (PRL)- and growth hormone (GH)-secreting adenomas [1]. Prolactinomas predominate in older children and adolescents [2,6,8]. Although almost invariably benign, PPAs present with symptoms of hormone hypersecretion or neurological disturbances secondary to mass effect, most typical in functioning macroadenomas [2,8]. Except for corticotroph adenomas, the majority of PPAs are macroadenomas (diameter >1 cm) and are frequently invasive. Table 1 outlines the epidemiology, clinical and tumour features, genetics and treatment of different PPAs

Adenoma type [Ref.]	Epidemiology	Adenoma features	Clinical features	Genetics	Treatment
Prolactinoma (PRL-secreting) [1, 6, 8–14, 17, 28, 33–35]	48–68% of PPAs	Typically microadenomas in females, macroadenomas in males	Oligo-amenorrhoea, delayed puberty, gynaecomastia, galactorrhoea, neuro-ophthalmological signs and symptoms	Association with FIPA, <i>AIP</i> and <i>MEN1</i> mutations <i>AIP</i> mutation-positive tumours are typically large and aggressive	I. D2-agonists II. TSS III. Combination D2, TSS, RT
Somatotroph adenoma (GH-secreting) [2, 8, 9, 14, 22, 50–52]	5–15% of PPAs Males > females	~90% macroadenomas; 30–60% invasive ~ 50% co-secreting PRL	Before epiphyseal fusion: rapid and significant growth acceleration, crossing percentiles to height >+2 SDs After epiphyseal fusion: features of acromegaly Neuro-ophthalmological signs, hyperprolactinaemia	30% of FIPA adenomas, ~60% of <i>AIP</i> mutated adenomas, typically affecting males <i>AIP</i> mutation-positive are aggressive macroadenomas with high GH ± PRL levels, association with <i>MEN1</i> and <i>MAS</i>	I. TSS II. SSA ± D2 agonists III. Combination TSS, RT, SSA/pegvisomant
Corticotroph adenoma (ACTH-secreting) [1, 37–39, 41–49]	Males > females (prepubertal); males = females (pubertal) Mean age at diagnosis: 14.1 years, 75–80% of Cushing's syndrome cases 55% of PPAs 0–11 years; 30% 12–17 years	Typically microadenomas (>90%)	CD: facial changes, weight gain, growth failure, virilisation, acne, striae, fatigue, emotional lability/depression, headache, hypertension	Rarely associated with <i>MEN-1</i> and FIPA	I. TSS II. 2nd TSS/RT III. Bilateral adrenalectomy
Gonadotroph adenoma (LH/FSH-secreting) [2, 57]	3–6% of PPAs	Mainly FSH-secreting	Neuro-ophthalmological signs and symptoms, partial/complete hypopituitarism; macro-orchidism, ovarian cysts, precocious puberty	Rarely associated with FIPA, genetic defects	I. TSS ± neo-adjuvant SSA II. SSA ± D2 agonists III. 2nd TSS/RT
Thyrotroph adenoma (TSH-secreting) [2, 55, 56]	0.5–2.8% of PPAs	Macroadenomas in 90% of cases	Clinical hyperthyroidism, goitre, neuro-ophthalmological signs	Rarely associated with FIPA, genetic defects	I. TSS II. SSA III. 2nd TSS/RT
Non-functioning adenoma (non-secreting) [2, 54, 55]	4–6% of PPAs	Macroadenomas invasive	Neuro-ophthalmological signs and symptoms, signs/symptoms suggestive of partial/complete hypopituitarism	Rarely associated with <i>MEN-1</i> or FIPA	I. TSS II. 2nd TSS/RT

Table 1. Epidemiology, clinical and tumour features, genetics and treatment of different PPAs

Molecular Pathogenesis

In recent years genetic defects have been identified in genes regulating pituitary tumorigenesis. The genes involved related to cell signalling are GNAS, PRKAR1A and SDHx, and related to cell growth and proliferation are MEN1, CDKN1B, AIP, PTTG, TGF- α , FGFR4 and BMPs [2,8,9]. These defects can affect both sporadic and familial cases, the latter accounting for about 5% of PPAs [2,9,10]. It is intriguing that the genetic associations of PPAs, present since birth, can lead to clinical presentation either in childhood or adult life depending on the rapidity of tumour growth and the degree of hormone hypersecretion.

Individual Gene Defects

GNAS Mutations

The GNAS oncogene (20q13) encodes for the Gs- α subunit of the G protein. Somatic mutations cause activation of adenylcyclase signalling pathways and cell hyperfunction characterizing the McCune Albright Syndrome (MAS) [10]. GH excess occurs in approximately 20% of patients secondary to GH- and PRL-producing cell hyperplasia or GH-secreting pituitary adenoma, and usually presents before the age of 20 years [9,11]. Fibrous dysplasia can complicate pituitary surgery. GNAS mutations also occur in 30-40% of sporadic GH-secreting adenomas, which are usually smaller and more sensitive to SSA, and 6-10% of non-functioning and ACTH-secreting adenomas [8,9].

PRKAR1A Mutations

Inactivating mutations in the tumour suppressor gene PRKAR1A (17q21-24), encoding for the regulatory subunit 1 α of protein kinase A, are reported in approximately 60% of patients with Carney Complex (CNC) [8,9]. Patients may rarely present with GH- and/or PRL-hypersecretion secondary to pituitary hyperplasia, however adenomas are very rare.

MEN1 Mutations

Inactivating mutations of the tumour-suppressor gene MEN1 (11q13), which codes for the nuclear protein menin involved in transcriptional regulation, genome stability, cell division and proliferation, are responsible for the MEN-1 syndrome [9]. MEN-1 is characterized by peptic ulcer disease and endocrine hyperactivity involving the pituitary, parathyroid and pancreas. Pituitary adenomas, which are typically large and aggressive, may occur in approximately 40% of patients [9]. Prolactinomas are the most frequent (60%), followed by GH-secreting (20%), ACTH-secreting and non-secreting adenomas (<10%) [12]. MEN1 mutations occur in <2% of sporadic pituitary adenomas [9,13].

AIP Mutations and Familial Isolated Pituitary Adenoma

In 1999, a novel autosomal dominant disease, characterized by the occurrence of pituitary adenomas, of the same or different cell types in two or more family members, was identified and termed familial isolated pituitary adenoma (FIPA) [10]. Approximately 20% of FIPA families harbour an inactivating heterozygous germline mutation of the AIP gene (11q13) [5]. The loss of the second normal allele of AIP in tumour tissue supports the role of AIP as a tumour suppressor, although its role in pituitary tumorigenesis is still obscure. To date, 211 families have been genetically characterized with the identification of 70 different AIP

mutations [14]. Characteristic features include low penetrance, female prevalence (62%), macroadenomas and predominance of prolactinomas (41%), followed by somatotroph adenomas (30%), non-secreting tumours (13%), somatotroph/mammotroph adenomas (7%), gonadotropinomas (4%), ACTH-secreting adenomas (4%) and thyrotropinomas (1%) [14]. Age at diagnosis is usually <30 years (78%) [8,9,10,14].

Screening for Genetic Disorders

Although no specific guidelines exist for genetic screening and management of mutation carriers with or without clinical disease, some concepts have to be kept in mind. First, the aim of screening is to identify affected subjects in order to provide early treatment and to rule out disease and avoid unnecessary investigations. Secondly, the prevalence of genetic mutations is significantly higher in children than in adults. Thirdly, patients with genetic mutations typically present with macroadenomas developing before the age of 30 years [5]. Finally, PPAs could be the presenting manifestation in patients with MEN-1 and CNC, but rarely remain isolated without other cardinal manifestations. Due to the high costs related to genetic analysis, screening should be addressed in young patients with suggestive features. At the same time, other clinical and biochemical features associated with multiple endocrine neoplasia syndromes should be considered [10,14].

Diagnostic Techniques

The diagnosis of PPAs depends initially on clinical examination for signs of pituitary hormone hypersecretion or deficiency together with CNS examination including visual fields, followed by basal hormonal evaluation and dynamic tests as indicated. This is followed by high-resolution contrast-enhanced magnetic resonance imaging (MRI) [2,8,15,16]. Dual-energy X-ray absorptiometry is recommended in females with amenorrhea or in hypogonadal males [17]. A diagnostic algorithm is shown in figure 1.

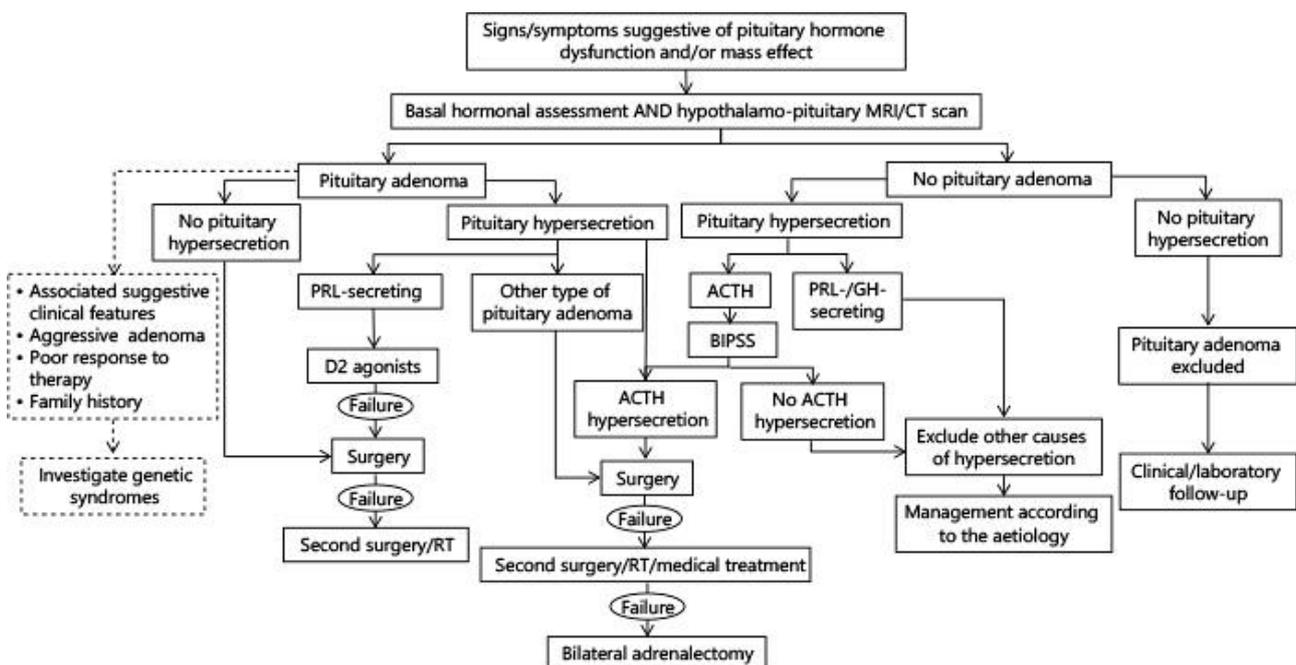


Fig. 1. Algorithm for the diagnosis and treatment of PPAs.

Radiological Imaging

MRI has superseded previous techniques for pituitary visualisation. MRI scanners currently use 3-tesla magnetic field strengths to improve signal-to-noise ratios, therefore further improving image quality [7,8,18,19]. T2-weighted imaging offers additional identification of cystic components, with post-contrast sequences improving the conspicuity of small lesions, 2- to 3-mm-thin imaging slices being optimal for their detection. Sagittal plane imaging demonstrates the anterior and posterior lobes and the infundibulum, whereas coronal imaging evaluates the relationship between the pituitary gland and adjacent cavernous sinuses, sphenoid sinus and the suprasellar cistern, the upper contour of the gland and any displacement of the infundibulum. PPAs are generally hypointense compared to the adjacent gland and take up contrast less avidly and in a more delayed fashion, and fail to enhance with gadolinium. CT imaging can be helpful in evaluating bony anatomy, the position of the carotid artery and the presence of intratumoral haemorrhage or calcification [18,19].

[goto top of outline Management of PPAs](#)

[goto top of outline Paediatric and Adult Co-operation](#)

PPAs are extremely rare in the paediatric age range. An experienced paediatric endocrine unit may see a handful of cases during a 20-year period. Consequently, paediatric endocrinologists do not acquire the experience to manage these patients with expertise. For this reason, co-operation with a specialised adult endocrinology unit with experience of pituitary disease is essential. Expertise in medical management, pituitary surgery and, if indicated, pituitary radiotherapy (RT) will stem from this collaboration and be significantly beneficial for the patient.

[goto top of outline Transsphenoidal Pituitary Surgery](#)

Transsphenoidal surgery (TSS) has been considered the first-line treatment for pituitary adenomas in adults and children for the past 20 years [1,7,20]. It has been used for the identification and selective removal of microadenomas and macroadenomas, and for the debulking of lesions invading the cavernous sinuses or

anterior skull base [1]. In children, TSS is particularly challenging due to anatomical and technical reasons and the surgeon's experience is a predictor of success [21,22]. Several large series of TSS in PPAs have been published, demonstrating highly variable rates of cure depending on the type, size and extension of the tumour [1,6,22].

[goto top of outline Endoscopic Pituitary Surgery](#)

More recently the less invasive technique of endonasal endoscopic transsphenoidal pituitary surgery (ETES) has been used in some centres and has shown equivalent rates of complete tumour resection, shorter hospital stays, decreased patient discomfort and reduced or equivalent surgical complications in adults [23,24]. In children, ETES may be preferable as the first-line treatment and for recurrent lesions, being advantageous in terms of efficacy and safety with reduction of surgical trauma, pain perception, paediatric intensive care unit admissions, need for blood transfusions, anterior pituitary deficiencies and incidence of diabetes insipidus [21,25,26].

[goto top of outline Medical Therapy](#)

The importance of medical therapy in children with PPAs has been progressively defined thanks to data derived from larger cohort studies showing its efficacy as the first- or second-line treatment, safety and low toxicity, especially when compared to pituitary RT in operated patients requiring adjuvant therapies.

Somatostatin Analogues

Pituitary tumours express hormone receptors, which in most cases are responsive to agonist and antagonist ligands. Somatostatin suppresses pituitary GH secretion by inhibiting cellular adenylcyclase through binding to 5 types of selective receptors (SSTR1-5), the expression profile of which varies among pituitary adenomas [27]. Synthetic long-acting somatostatin analogues (SSA) show a 10-fold higher receptor affinity and secretion-inhibiting potency and longer half-life compared to native somatostatin [15]. As SSTRs are expressed in the gastrointestinal tract, nausea, diarrhoea and abdominal discomfort are common side effects [15,16,22].

Dopamine Receptor Agonists

The dopamine receptor (D2) is a G protein-coupled receptor expressed by PRL- and GH-secreting pituitary cells. D2 agonists such as cabergoline, bromocriptine, pergolide and quinagolide are the most popular, potent and safe inhibitors of PRL and, to a lesser extent, GH secretion and somatotroph proliferation, representing the gold standard for treatment of prolactinomas and a second-line therapy for GH hypersecretion [28]. Side effects include nausea, vomiting, hypotension, fatigue, vertigo and, rarely, psychosis [17].

goto top of outline Pituitary RT

RT is used where surgery is contraindicated and for recurrence or progression of non-secreting adenomas or hormonally uncontrolled tumours after maximal surgical and medical therapy [29,30]. Over the past decade, stereotactic radiosurgery (SRS), delivering a large single dose of highly collimated radiation and fractionated stereotactic RT (FRST) delivered over 5-6 weeks, with higher precision and less tissue damage but requiring a longer period to achieve biochemical normalisation, has emerged [29,30]. Radiation doses are usually 18 Gy by SRS and 45-50.4 Gy by FRST (delivered at 1.8-Gy daily fractions) for non-functioning adenomas, and 20 Gy by SRS and 50.4-54 Gy by FRST (delivered at 1.8-Gy daily fractions) in functioning adenomas [31].

Based on the tumour size and proximity of the optic nerves, chiasm and brain stem, a selected type of RT is delivered. SRS is indicated when the tumour target is at least 3-5 mm removed from the chiasm and less than 3 cm in diameter, while FRST is suitable if the other conditions required for SRS are not satisfied [29,30]. More recently, hypofractionated stereotactic RT, fractionated proton therapy and intensity-modulated RT have been proposed but experience in children is limited [29,30]. Delayed pituitary hormonal deficiency is the most common complication after pituitary RT with a prevalence of approximately 10-12%, often requiring long-term replacement therapy and follow-up [29,30,32].

Individual Adenomas

Prolactinomas

Epidemiology

Prolactinomas are the most common functional pituitary adenomas, typically occurring in late childhood and adolescence with a mean age at onset of symptoms of 14.5 years, and accounting for 48-68% of PPAs [33]. In children <12 years of age, prolactinomas are the second most common pituitary adenoma after corticotroph adenomas [1,6]. Girls are more affected than boys, with a ratio varying from 1.9:1 to 4.5:1 depending on age. In boys the tumours are usually large and aggressive [1,34,35].

Molecular Pathogenesis

Patients with CNC or MAS may exhibit hyperprolactinaemia associated with excess GH secretion secondary to pituitary hyperplasia, although prolactinomas are very rare [9,33]. More frequently, prolactinomas occur in the context of MEN-1 and FIPA, accounting for 37.5% of all FIPA tumours and 22% of AIP-mutated tumours. AIP mutation-positive prolactinomas and somatotroph adenomas are typically large and invasive, and poorly responsive to medical treatment [9,14,33].

Diagnosis

Prolactinoma is diagnosed from persistent hyperprolactinaemia compared to established gender and age standards, associated with an adenoma identified on MRI or CT scanning. Physiologic, iatrogenic and pathologic causes of hyperprolactinaemia and macroprolactinaemia need to be excluded [28]. Basal PRL measurement has a high diagnostic value and correlates with the size of the tumour [1,34,36]. As secretion is pulsatile, at least two determinations on different days and 2-3 samples separated by 20 min should be obtained [17,28].

Clinical Features

These can be divided into two categories. First, neuro-ophthalmological signs, most commonly headache, visual field defects and, rarely, exophthalmos, may be the mass effects of an invasive macroadenoma, occurring almost exclusively in boys [1]. Secondly, the effects of hyperprolactinaemia include oligo- or amenorrhoea, galactorrhoea, gynecomastia, delayed puberty and hypogonadotropic hypogonadism [17,28,36].

Management

The objectives are to normalise PRL levels and decrease the diameter of the adenoma, thus improving and controlling symptoms secondary to hormonal and neurological alterations. D2 agonists can achieve control of PRL in 80-90% of patients in the majority of cases in the first 6 months of therapy [28,36]. Tumour shrinkage is observed in 80% of microadenomas and 25% of macroadenomas, often in the first year of treatment. Choice of medication consists of either cabergoline (0.5-3.5 mg/week) or bromocriptine (2.5-15 mg/day). Once normoprolactinaemia is established and the adenoma is undetectable on MRI, the dose of D2 agonist can be tapered down after at least 2 years of treatment [15,17].

Resistance to medical treatment is defined as persistence of hyperprolactinaemia after 3 months of maximal-dose treatment and shrinkage to <50% of the original adenoma size. Pituitary surgery should be considered in patients with macroadenomas unresponsive to maximum tolerable D2 agonist therapy or persistence of neuro-ophthalmological symptoms. Pituitary RT is considered to be the third-line therapy when pharmacological and surgical approaches have failed [17,28].

Corticotroph (ACTH-Secreting) Adenomas, Cushing's Disease

Epidemiology

In the paediatric age-range, ACTH-secreting corticotroph adenomas causing Cushing's disease (CD) account for 54.8% of adenomas from age 0 to 11 years, and 29.4% from 12 to 17 years [1]. The mean age at presentation is 12.3 ± 3.5 years (range 5.7-17.8) [37]. Male predominance is observed in prepubertal subjects [38,39], with an overall prevalence of males (63%) compared to females (79%) in paediatric and adult series, respectively [37]. At all ages, microadenomas are the most common cause of CD [40], accounting for 98% of paediatric cases [37], with the adenoma diameter being frequently 2 mm or less [1]. On pituitary post-contrast MR scanning, 63 and 55% of the adenomas were identified in two large paediatric series [37,41].

Molecular Pathogenesis

The majority of cases of paediatric CD do not have genetic mutations [42]. Only 1 out of 73 paediatric CD subjects had an AIP mutation [12]. An ACTH-secreting adenoma may rarely occur with a MEN1 gene mutation in the context of a family history of genetically confirmed MEN-1 [43].

Diagnosis

The diagnosis of an ACTH-secreting adenoma follows from the investigation of suspected Cushing's syndrome and the demonstration of ACTH-dependent hypercortisolaemia of pituitary origin. The protocol for diagnosis of CD is shown in table 2. Key biochemical features are loss of serum cortisol circadian rhythm with detectable cortisol at midnight, increased urinary-free cortisol excretion, failure of suppression of cortisol during the low-dose dexamethasone suppression test combined with a decrease in cortisol by approximately 30% and an increased cortisol response to IV CRH infusion. Because pituitary MRI is a relatively poor indicator of the size and position of the microadenoma, bilateral inferior petrosal sinus sampling (BIPSS) for ACTH should be performed by an experienced radiologist to localise the tumour and confirm increased central ACTH secretion following CRH stimulation [37].

Type of test	Diagnostic cut-off	Sensitivity, % ^a	Specificity, % ^a
I Confirmation of Cushing's syndrome			
1 Urinary-free cortisol excretion (24 h urine collection) for 3 days	>70 µg/m ² (193 nmol/24 h)	88	90
2 Serum cortisol circadian rhythm study [09.00, 18.00 h, midnight (sleeping)]	≥1.8 µg/dl (50 nmol/l) ^b	100 ^b	60 ^b
3 Low-dose dexamethasone suppression test a. Dose 0.5 mg 6 hourly (09.00, 15.00, 21.00, 03.00 h) for 48 h b. Dose for patients weighing <40 kg; 30 µg/kg/day c. Serum cortisol measured at 0, 24 and 48 h	≥1.8 µg/dl (50 nmol/l)	95	80
II Confirmation of CD			
1 Plasma ACTH (09.00 h)	>5 pg/ml (1.1 pmol/l)	68	100
2 CRH test (1.0 µg/kg IV)	Cortisol increase 14–22%	74–91	88–100
3 Pituitary MRI scan	Adenoma detection	63	92
4 BIPSS for ACTH (with IV CRH)	Central:peripheral ACTH ratio >3 (after IV CRH?)	100	
^a Data from references [58–60].			
^b Diagnostic cut-offs refer to midnight serum cortisol values.			

Table 2. Protocol for diagnosis of paediatric CD (ACTH-secreting adenomas)

Clinical Features

The features of paediatric CD are well documented [44] and have shown some interesting differences compared with adult patients [37] (table 3). Growth failure and short stature were frequent features with growth velocity noted to be subnormal, and height SDs being below and BMI SDs above the mean [44].

Type of test	Diagnostic cut-off	Sensitivity, % ^a	Specificity, % ^a
I Confirmation of Cushing's syndrome			
1 Urinary-free cortisol excretion (24 h urine collection) for 3 days	>70 µg/m ² (193 nmol/24 h)	88	90
2 Serum cortisol circadian rhythm study [09.00, 18.00 h, midnight (sleeping)]	≥1.8 µg/dl (50 nmol/l) ^b	100 ^b	60 ^b
3 Low-dose dexamethasone suppression test	≥1.8 µg/dl (50 nmol/l)	95	80
a. Dose 0.5 mg 6 hourly (09.00, 15.00, 21.00, 03.00 h) for 48 h			
b. Dose for patients weighing <40 kg; 30 µg/kg/day			
c. Serum cortisol measured at 0, 24 and 48 h			
II Confirmation of CD			
1 Plasma ACTH (09.00 h)	>5 pg/ml (1.1 pmol/l)	68	100
2 CRH test (1.0 µg/kg IV)	Cortisol increase 14–22%	74–91	88–100
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4 BIPSS for ACTH (with IV CRH)	Central:peripheral ACTH ratio >3 (after IV CRH?)	100	
^a Data from references [58–60].			
^b Diagnostic cut-offs refer to midnight serum cortisol values.			

Table 2. Protocol for diagnosis of paediatric CD (ACTH-secreting adenomas)

Management

Pituitary Surgery: Selective Microadenomectomy. In patients with ACTH-secreting adenomas, the small size of the adenoma and the pituitary fossa and absent aeration of the sphenoid bone in young patients adds to the technical difficulty of TSS. The results of TSS depend on the definition of post-operative 'cure' or remission. In a recent report of outcome from TSS in 200 cases of paediatric CD, 98% were in remission post-surgery [7] and 97% of the subjects who were in biochemical remission had hypocortisolaemia.

In all the published series where 'remission' is described, recurrences of post-TSS hypercortisolaemia have occurred which were treated either by pituitary re-operation or by pituitary RT. In the two series where 'cure' was defined as post-operative serum cortisol of <1 µg/dl (28 nmol/l) [38] or <1.8 µg/dl (50 nmol/l) [37] 'cure' rates were 100 and 69%, respectively. Follow-up data suggest that recurrence rates of CD in these patients were very low [37,41]. Initial post-operative remission was associated with identification of the adenoma at surgery and long-term remission correlated with younger age, smaller adenoma and morning serum cortisol of <1 µg/dl (28 nmol/l) after surgery [7]. As described above, paediatric experience with endonasal ETES is limited, but preliminary results in children with CD have recently been reported and showed an excellent outcome [21].

Pituitary RT. Historically, 20-40% of paediatric patients who undergo TSS for CD have not achieved post-operative cure or remission [34,45]. The options for second-line therapy are repeat TSS, pituitary RT, long-term medical therapy to control hypercortisolaemia and bilateral adrenalectomy. External pituitary RT is known to be effective in children with CD with a more rapid mode of action than in adult patients. Centres using RT have administered irradiation from a 4- to 15-MeV linear accelerator, via a three-field technique (two lateral, one frontal) to deliver a total dose of 45 Gy in 25 fractions over 35 days [31]. The rapid onset of this therapy was confirmed in two small series. In the first, 7 children were treated and all were cured with a mean interval from RT to cure of 0.94 years (range 0.25-2.86) [31]. In the second series, 8 subjects were treated and 4 were cured in 9-18 months after RT [45]. In a further series, 8 children were treated with stereotactic external RT using ⁶⁰Co gamma radiation. Seven of the 8 subjects were cured during the first year after completion of therapy [46].

Anterior pituitary function after RT was studied and GH deficiency was present in 5 out of 6 subjects tested with peak GH <6 ng/ml at a mean interval after RT of 1.0 years (range 0.11-2.54) [32]. On retesting at an

interval of 9.3 years (range 7.6-11.3) in 3 out of 4 subjects, GH secretion had recovered (peak GH 6.4-16.5 ng/ml). Thyroid function, PRL and testicular volume were normal. GH deficiency and hypogonadism were also documented in 7 children successfully treated with higher doses of 50-70 Gy [45,46]. Children receiving pituitary RT for CD require regular assessment of anterior pituitary function post-therapy.

Bilateral Adrenalectomy and Medical Therapy. Bilateral adrenalectomy remains a therapeutic option for CD in life-threatening situations or where TSS is not possible or available. Nelson's syndrome represents a potentially life-threatening complication more frequent in children than adults, often requiring pituitary surgery or RT [47]. Intravenous administration of etomidate has successfully controlled hypercortisolaemia in children with CD who were either too unwell for TSS or presented with acute unmanageable symptoms such as respiratory failure or severe psychosis [48,49].

Somatotroph (GH-Secreting) Adenomas

Epidemiology

Somatotroph GH-secreting adenomas account for 5-15% of PPAs with a higher prevalence of 59% in males, and median ages at symptom onset of 9 years (range 0.2-17) and at diagnosis of 14 years (range 0.8-18) [22]. Approximately 90% of cases are macroadenomas, 30-60% being invasive [8].

Molecular Pathogenesis

Somatotroph (61%) and somatotroph-lactotroph (8%) adenomas are the predominant types among AIP-mutated adenomas, typically affecting males and occurring in childhood or adolescence [50]. Gigantism (36% of cases) is the predominant presenting feature. Most AIP mutation-positive adenomas occur in males (70%), and are aggressive macroadenomas with high GH levels and increased prevalence of hyperprolactinaemia. Typically, they are poorly responsive to SSA therapy and require surgery, often combined with medical therapy and RT [14,51]. GH-secreting adenomas have also been reported in 40% of patients with MEN-1 and, more rarely, in association with MAS and CNC [9].

Diagnosis

Diagnosis is based on the detection of increased IGF-I and IGFBP-3 levels for age and gender, unsuppressed GH levels during oral glucose tolerance test (OGTT) and identification of a pituitary adenoma on MRI scan [15,52].

Clinical Features

Symptoms related to GH hypersecretion depend on the degree of epiphysial fusion. Children show rapid growth acceleration with height deviating progressively above +2 SDs. After epiphyseal fusion, excessive GH secretion leads to the features of acromegaly. Hyperprolactinaemia is common due to co-secretion of PRL with tumour immunohistochemistry being positive for both GH and PRL, or due to loss of dopaminergic tone from pituitary stalk involvement [2,22,52]. Weight gain, delayed puberty and neurological symptoms due to mass effect (23% of cases) can also occur [2,8,22]. Aggressive tumours can invade the optic chiasm or cavernous sinuses, erode the clivus, or grow inferiorly into the paranasal sinuses [2].

Management

To date, no guidelines exist for the treatment of paediatric GH-secreting adenomas. In adults, TSS is the first-line treatment for intrasellar microadenomas and non-invasive macroadenomas with biochemical control reported in 70 and 50% of cases, respectively [15,22,52]. Invasive macroadenomas often require medical therapy and/or RT after surgical debulking. Neo-adjuvant treatment with SSA is recommended when surgical cure is unlikely or when surgery fails to achieve biochemical control [8,15,22,52]. D2 agonists can be used in patients with associated hyperprolactinaemia, or as adjuvant therapy if the disease is not controlled by high doses of SSA [8,15,22,52].

More recently, pegvisomant, a pegylated GH-receptor antagonist has been used in paediatric GH-secreting adenomas inducing normalisation of IGF-I and symptomatic improvement [52,53]. Pituitary RT is considered to be the third-line therapy because of the complications of post-RT hypopituitarism, occurring in 30-50% of patients [15,22,52]. Measurement of IGF-I and post-oral glucose tolerance test GH levels together with MRI evaluation are necessary for post-operative assessment and long-term monitoring [15,22,52].

Less Common Pituitary Adenomas

Non-Functioning Adenomas

Non-functioning adenomas represent 4-6% of PPAs, and are typically invasive macroadenomas. Patients usually present with visual defects or headache, or symptoms of hyperprolactinaemia or hypogonadism, especially in young females [54,55].

Thyrotropin (TSH-Secreting) Adenomas

These account for 0.5-2.8% of PPAs [2,56]. Typical presentation includes symptoms of hyperthyroidism, goitre and neurological signs due to mass effect, as almost 90% of the cases are macroadenomas. Diagnosis is based on the detection of increased free fractions of thyroid hormones with inappropriately detectable or increased TSH [55]. They may be rarely associated with MEN-1 [2].

Gonadotroph (FSH-, LH-Secreting) Adenomas

These are extremely rare in children, with 7 biopsy-proven cases reported. Most are FSH-secreting adenomas [2,57]. The diagnosis is typically delayed until the appearance of symptoms related to tumour mass or pituitary hormone deficiency. Patients may present with macro-orchidism, ovarian cysts or precocious puberty due to FSH hyperstimulation [2,57]. Diagnosis is based on increased levels of FSH and inhibin B, with normal or low luteinising hormone and testosterone, an increased FSH response to gonadotropin-releasing hormone stimulation, detection of a pituitary mass on MRI, and immunohistochemical confirmation of the surgical specimen [57].

Conclusions and Future Perspectives

In recent years, rapidly advancing scientific knowledge in the fields of genetics and molecular biology has contributed to the understanding of mechanisms underlying pituitary tumorigenesis. However, much remains unknown, such as the influence of genetic abnormalities on the rapidity of tumour growth and the degree of hormone hypersecretion. Diagnostic techniques for PPAs have developed and therapy has advanced and become less invasive. These changes have improved patient prognosis and reduced detrimental long-term effects. Nevertheless, the management of PPAs continues to deserve special attention and a highly specialised multidisciplinary approach. Moreover, further clinical and laboratory studies are warranted to identify novel genetic alterations causative for pituitary tumorigenesis. Therapeutic outcomes and the efficacy of new therapies, both medical and surgical, also warrant further study. This field of rare pituitary pathology occurring in the paediatric age range is a prime example of the importance of multidisciplinary collaboration between paediatricians and adult specialists, which will lead to advances in basic and clinical research and improved patient care.

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