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Pituitary Tumors in Childhood: an update in their diagnosis, treatment and molecular genetics

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Abstract

Pituitary tumors are rare in childhood and adolescence, with a reported prevalence of up to 1 per million children. Only 2 - 6% of surgically treated pituitary tumors occur in children. Although pituitary tumors in children are almost never malignant and hormonal secretion is rare, these tumors may result in significant morbidity. Tumors within the pituitary fossa are of two types mainly, craniopharyngiomas and adenomas; craniopharyngiomas cause symptoms by compressing normal pituitary, causing hormonal deficiencies and producing mass effects on surrounding tissues and the brain; adenomas produce a variety of hormonal conditions such as hyperprolactinemia, Cushing disease and acromegaly or gigantism. Little is known about the genetic causes of sporadic lesions, which comprise the majority of pituitary tumors, but in children, more frequently than in adults, pituitary tumors may be a manifestation of genetic conditions such as multiple endocrine neoplasia type 1 (MEN 1), Carney complex, familial isolated pituitary adenoma (FIPA), and McCune-Albright syndrome. The study of pituitary tumorigenesis in the context of these genetic syndromes has advanced our knowledge of the molecular basis of pituitary tumors and may lead to new therapeutic developments.

Keywords

Brain tumors; Cushing disease; Acromegaly; Multiple Endocrine Neoplasias (MEN); Prolactinoma

Introductory notes: pituitary development & physiology

The pituitary gland has an essential role in the maintenance of homeostasis and reproductive function. The pituitary gland forms around the middle of the fourth embryonic week from an invagination of the oral ectoderm (stomodeum) to the rudimentary primordium (Rathke's pouch). Fate map studies document a placodal origin of the anterior pituitary in all

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vertebrates [1]. By the fifth week, the pouch has elongated and constricts at the attachment to the oral epithelium; the adeno-hypophysis (pars anterior, pars intermedia, and pars tuberalis) develop from the ectoderm of the stomodeum. The neurohypophysis develops from the neuroectoderm (infundibulum) [2,3].

The anterior and posterior pituitary lobes form concurrently and continue to interact closely despite the different embryologic origin of the two tissues. The adeno-hypophysis contains six different cell types that are characterized by their hormone secretion: corticotrophs secrete adrenocorticotrophic hormone or corticotropin (ACTH), somatotrophs secrete growth hormone (GH), thyrotrophs produce thyroid-stimulating hormone or thyrotropin (TSH), gonadotrophs secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and lactotrophs produce prolactin (PRL). The posterior pituitary lobe contains axonal terminals from the magnocellular hypothalamic neurons which are surrounded by pituitocytes (astroglia); oxytocin and vasopressin are peptide hormones that are synthesized by the magnocellular neurons and transported to the axonal terminals in the posterior lobe from where they are secreted to the general circulation. The hypothalamus also secretes trophic factors, releasing hormones (RH), that regulate the function of the anterior pituitary through modulation of cell proliferation, hormone synthesis, and secretion: corticotropin-releasing hormone (CRH) controls ACTH, GHRH and somatostatin (SMS) regulate GH secretion, thyrotropin-RH (TRH) for TSH, and gonadotropin RH (GnRH) for LH and FSH; dopamine inhibits PRL secretion and TRH stimulates it but a putative PRL-RH or releasing factor (PRF) has long been postulated to exist [4].

In this report, we review recent findings on the two most common tumors of the pituitary gland in childhood, craniopharyngiomas and pituitary adenomas.

Craniopharyngiomas

Craniopharyngiomas comprise the majority (80 to 90%) of neoplasms found in the pituitary fossa of children: up to 15% of all intracranial tumors in childhood are craniopharyngiomas. These tumors have a bimodal age-specific incidence: they occur most frequently at age 5 to 14 years and rarely in the fifth decade of life [5]. Incidence does not vary with gender or race. Craniopharyngiomas arise from squamous rest cells left as remnants from the Rathke's pouch; these cells are located between the adeno- and neurohypophysis and this is where most craniopharyngiomas first form. By the time most craniopharyngiomas (70% of the total) give symptoms they are extended in both the intrasellar and suprasellar regions; 30% of the tumors may be either intra- or suprasellar in location [6].

Craniopharyngiomas typically present with endocrine dysfunction, decreased vision, and an intense headache or other symptoms related to increased intracranial pressure. By histology, these tumors are benign; however, craniopharyngiomas can behave aggressively through papillae that invade surrounding bony structures and tissues. In addition, they can have cystic components that may enlarge and compress adjacent structures [5]. The molecular mechanisms underlying craniopharyngiomas have not been well characterized, some studies suggest it is a monoclonal tumor. In addition, cytogenetic abnormalities have been identified in up to 50% of tumors, most commonly gains in 1q, 12q, and 17q [7,8]. Recently, β -catenin gene mutations were found in up to 20% of the rare adamantinomatous craniopharyngiomas,

whereas the more common papillary craniopharyngiomas to this date have no common genetic abnormality [9].

In about 80% of the patients, endocrine dysfunction is found at diagnosis of a craniopharyngioma. Most patients have GH deficiency (75%), followed by gonadotropin deficiency (40%), corticotropin and thyrotropin deficiency (25%) [7,8,10]. Although craniopharyngiomas are frequently large at presentation, pituitary stalk disruption is not typically seen and hyperprolactinemia secondary to pituitary stalk compression is noted only in approximately 20% of patients. Diabetes insipidus (DI) occurs in 9 to 17% of patients, but this a more frequent presentation.

Surgical resection is the treatment of choice for craniopharyngiomas. Because the recurrence rate is higher than in all other pituitary tumors adjunctive radiotherapy is often indicated, except for small, entirely intrasellar lesions. Morbidity associated with treatment is dependent on the size, location, and invasiveness of the tumor, the experience of the surgeon and the route of surgical approach. Craniopharyngiomas are generally radiosensitive and stereotactic radiosurgery has been used with success; since up to 60% of craniopharyngiomas are both solid and cystic, adjuvant treatments such as cyst aspiration or stereotactic Ommaya reservoir (for intracavity brachitherapy with bleomycin, radioactive phosphorus, or alpha-emitting ^{90}Yt) are used to avoid surgery in situations where the solid part of the tumor is small or surgery is not possible or not indicated in younger patients [11-16].

Pituitary adenomas

Accurate information regarding the prevalence and incidence of pituitary tumors is lacking, particularly for children and adolescents, because of the overall rarity of these lesions. Data from autopsy studies show that pituitary adenomas develop in approximately 17 - 25% of the population [17,18] studies with radiological imaging report a similar incidence of pituitary gland lesions in the general population (up to 20%) with no gender predilection [19]. Approximately 3.5 to 8.5% of all pituitary tumors are diagnosed prior to the age of 20 years [3,20-22].

Pituitary adenomas are extraordinarily rare in early childhood; their frequency increases during adolescence but they remain relatively rare tumors: approximately 3% of all diagnosed intracranial tumors in childhood are pituitary adenomas. The majority of these tumors are sporadic, but in children, more common than in adults, they can be part of a genetic condition predisposing to pituitary and other tumors. Nevertheless, even sporadic tumors harbor significant genetic abnormalities: most pituitary tumors are monoclonal lesions and modifications in expression of various oncogenes or tumor suppressor genes, including *GNAS*, *PTTG*, *HMGA2*, and *FGFR-4* have been identified [23,24]. Both pituitary and hypothalamic factors appear to influence pituitary tumor development and cell growth [17,25,26]. Other factors and genetic events seem to be implicated in pituitary cell clonal expansion, and oncogene activation is necessary to propagate tumor growth [23,27]. The best example of this secondary phenomenon is the widespread presence of *GNAS* activating

mutations in sporadic GH-secreting pituitary tumors (in up to 40% of all such lesions) [28]. (Figure 1).

Among functional pituitary tumors in early childhood, ACTH-producing adenomas are probably the most common although they are still considerably rare. To date, no genetic defects have been consistently associated with childhood corticotropinomas, which only rarely occur in the familial setting, and then, most commonly in the context of multiple endocrine neoplasia type 1 (MEN 1) [29-31].

GH- and/or PRL-producing are the second most frequently found functional pituitary tumors in early childhood; these tumors in children almost always occur in the familial setting or in the context of known genetic defects: *GNAS*, *menin*, *PRKAR1A*, *AIP* and p27 (*CDKN1B*) mutations [21,32-36]; somato- and/or mammotropinomas become significantly more frequent than corticotropinomas in late childhood, adolescence and adulthood [37].

There is conflicting information in the literature concerning the potential growth and invasiveness of pediatric pituitary adenomas. Some authors reported that pituitary tumors may be highly invasive in younger patients [38-43]; however, others did not report similar findings [26,44-46].

Overall, **prolactinomas** account for approximately 50% of pituitary adenomas. Prolactinomas are the most common pituitary adenomas in older children, with the majority occurring in adolescence with a female preponderance: in older children and adolescents, prolactinomas [6,47-49]. Prolactinomas arise from acidophilic cells from the same embryonic lineage as somatotropes and thyrotropes. Prolactinomas may be seen in several inherited syndromes, including MEN 1, Carney complex, and familial isolated pituitary adenomas [50]. A pituitary adenoma may be the first clinical manifestation of MEN 1, with the youngest reported case in a 5-year old boy with a pituitary somatomammotroph macroadenoma [51].

Clinical presentation varies depending on the age and gender of the child, although growth arrest is typically seen in children and adolescents before epiphyseal fusion is completed. Females may present with pubertal delay, amenorrhea, and other symptoms of hypogonadism. In males, macroprolactinomas are more frequent; accordingly, males with prolactinomas also have a higher incidence of neurological and ophthalmological abnormalities (i.e. cranial nerve compression, headaches, visual loss), growth or pubertal arrest and other pituitary dysfunctions. Contrary to common belief, gynecomastia is not a common finding. Since various factors such as neurogenic or mechanical processes (mass effects from craniopharyngiomas, Rathke cleft cyst, nonfunctioning adenomas, or due to infiltrative processes) can lead to loss of dopaminergic suppression of pituitary lactotrophs resulting in hyperprolactinemia, the differential diagnosis of the latter in children is large [52].

Medical management with dopamine agonists (e.g. bromocriptine, pergolide, or cabergoline) is typically the first line of treatment for prolactinomas. The goals of treatment include the normalization of prolactin levels and pituitary function and the reduction of tumor size. Dopamine agonists are effective in reducing tumor size and controlling prolactin levels in

approximately 80-90 % of patients with microadenomas and about 70% of macroadenomas [53]. Studies report that cabergoline, a selective D2 receptor agonist, is more effective and often better tolerated than bromocriptine. In addition, cabergoline has been shown to be effective in treatment of tumors resistant to other dopamine agonists [54]. In some cases treatment with dopaminergic agents can be withdrawn and PRL levels will remain within normal limits [55].

Surgical intervention for prolactinomas is reserved for emergency situations such as acute threat to vision, hydrocephalus, or cerebral spinal fluid leak, or for these rare tumors that grow despite exposure to increasing doses of dopamine agonists. Compliance is often a problem in long-term management of prolactinomas, since cessation of medical treatment leads to recurrence of hyperprolactinemia and tumor re-growth. At the initiation of therapy, commonly reported side effects of dopamine agonist treatment include nausea, dry mouth, dyspepsia, or dizziness [56,57]. Treatment doses of 2.5 to 10mg daily (bromocriptine) or 0.25 to 2mg weekly (cabergoline) have not been associated with long-term adverse effects.

Recent reports of cardiac valve regurgitation in patients with Parkinson's disease treated with pergolide and cabergoline raised concern about the safety of long-term treatment with dopamine agonists; the safety of cabergoline was evaluated in a study of 1200 patients with Parkinson's disease (controlled and uncontrolled studies) at doses of up to 11.5mg/day, which exceeded the maximum recommended dose for treatment of hyperprolactinemia. The risk of valvular disease appeared to be higher in patients treated with at least 3mg per day of cabergoline, a dose that is 10 to 20 times higher than the standard regimen for macroprolactinomas. Since the risk of long-term, low-dose treatment is unknown, discussion of potential risks of therapy with the patient and decision about the need for echocardiogram is advisable [58,59].

Corticotropinomas are the most common pituitary adenomas in prepubescent children; their frequency decreases during puberty and in adolescence, when prolactinomas become more prevalent. The cumulative incidence of ACTH-producing tumors or Cushing disease in children does not exceed a tenth of the annual incidence of 2-5 new cases of Cushing syndrome per million people per year [22,41,60].

The most characteristic clinical presentation of Cushing disease is that of significant weight gain concomitant with severe failure to gain in height. Other common symptoms include headaches, hypertension, glucose intolerance, and delayed pubertal development and amenorrhea despite often significant virilization and hirsutism. Compared to adults and older adolescents, children and younger adolescents do not typically report problems with sleep disruption, muscle weakness, or problems with memory or cognition.

Corticotroph adenomas are significantly smaller than other types of pituitary tumors (usually 3 mm or less). Rarely, corticotropinomas can be exophytic, growing into the subarachnoid space, or they invade the cavernous sinus or wall; there are also case reports of tumors that originate in the posterior lobe [61]. Most recently our group suggested a 3-day inpatient evaluation of a child suspected of having Cushing syndrome for confirmation of the diagnosis and investigation of a corticotropinoma [62] (Figure 2). First-line treatment for

Cushing disease in childhood is always surgical; transsphenoidal adenomectomy or hemihypophysectomy in situations where the surgical exploration is negative has been shown to be nearly 90% curative. Radiation or gamma-knife therapy is reserved for these patients in whom surgical intervention failed [41,61]. Bilateral adrenalectomy may be considered for inoperable or recurrent cases; however it is associated with a significant risk of development of Nelson's syndrome [63].

Somatotropinomas comprise approximately 5-15% of pediatric pituitary adenomas in children and adolescents before the age of 20 years. Excess GH production results from an adenoma, usually macroadenoma or, rarely, somatotroph hyperplasia which occurs in certain genetic conditions such as McCune-Albright syndrome or Carney complex. GH excess due to dysregulation of GHRH signaling may occur as a result of a local mass effect, for example with optic glioma seen in neurofibromatosis type-1 (NF-1) [64] or (almost unheard of in children) from an ectopic GHRH-producing tumor. These tumors may also stain for prolactin and thyrotropin, which is usually of no clinical significance.

Clinical presentation in children and adolescents varies depending on whether the epiphyseal growth plate is open. Prior to epiphyseal fusion, significant acceleration of growth velocity is noted, a condition also known as 'gigantism'; as epiphyseal fusion is completed, the clinical symptoms become more similar to those in acromegalic adults (coarse facial features, broadened nose, large hands and feet, obesity, organomegaly, sweating, nausea). Since somatotropinomas are often macroadenomas, headaches and visual disturbances are frequently reported [65,66].

First-line of treatment for childhood gigantism or acromegaly is transsphenoidal surgery; however, unlike Cushing disease, GH-producing tumors are often large and locally invasive. With small, well-circumscribed tumors transsphenoidal surgery may be curative, while with larger and locally invasive tumors surgery may be beneficial to decompress tumors but persistent or recurrent disease is common and adjuvant therapy is needed. Radiotherapy, either primary or post-surgical, has slow onset of treatment effect and high treatment related morbidity of panhypopituitarism [21,67-69].

Pharmacologic agents are often indicated both before and after surgery and have been shown to be effective at shrinking tumor size and improving biochemical abnormalities. Long-acting somatostatin analogs have been shown to be effective at normalizing IGF-1 levels in most patients [69-75]. Since suppression of insulin secretion is a side effect of treatment, treatment with long-acting somatostatin analogs may increase the risk for development of glucose intolerance [76,77].

Recently, pegvisomant, a GH receptor antagonist, has been shown to be effective therapy for normalization of IGF-1 levels with no detrimental effects on glucose metabolism [78]. Pegvisomant, on the other hand, requires a daily injection, an important factor to be considered when initiating this type of treatment.

Feenstra *et al.* (2005) reported that pegvisomant administered weekly in combination with long-acting somatostatin analog normalized IGF-1 levels in 95% of patient. Indeed, combination therapy offers an additional benefit because tumor suppression is combined

with GH receptor blockade: a study of the long-term efficacy and safety of combination therapy (long-acting somatostatin analog plus twice weekly pegvisomant) reported that IGF-1 levels normalized for all 32 patients; however, transient elevation in liver enzymes was observed in eleven patients, with a higher risk for patients diagnosed with diabetes mellitus [79]. There is limited data on pegvisomant treatment in children, mostly case studies, which report successful outcomes [80,81].

Incidentally discovered pituitary adenomas in childhood are rare. This is because non-functioning pituitary tumors in childhood and adolescence are rare; these tumors represent only 4 to 6% of pediatric cases while in series of adult patients, hormonally silent tumors account for approximately 33 to 50% of the total number of pituitary lesions [20,82,83]. Most silent adenomas arise from gonadotroph cells and often are macroadenomas at diagnosis; they occasionally grow and may present with headaches and visual disturbances, as well as deficient growth and/or pubertal delay [84]. Large adenomas may obstruct the foramen of Monro and cause hydrocephalus, while pituitary adenomas and sellar tumors that impinge on the optic apparatus and/or cavernous sinus can result in cranial nerve palsies, cavernous sinus syndromes, and/or additional visual disturbances. Nonfunctioning pituitary adenomas may present with GH deficiency (up to 75%), LH/FSH deficiency (~40%), or ACTH and TSH deficiency (~25%) [84]. Compression of the pituitary stalk by pituitary adenoma has been reported but secondary hyperprolactinemia is typically seen in less than 20% of patients. DI is also rare (9 to 17%) but is more commonly seen in patients with Rathke's cleft cysts [6]. Recommendation for surgical excision of a hormonally silent intrasellar tumor or cyst depends on the tumor size, location, and potential for invasiveness.

Advances in the imaging of pediatric pituitary adenomas

The most important initial imaging technique in the localization and characterization of pituitary tumors is pituitary magnetic resonance imaging (MRI) [85]. Accurate detection and localization of adenomas is an important tool to permit successful treatment. MRI should be performed in thin sections with high resolution and always with contrast enhancement (gadolinium). Only macroadenomas are detectable without contrast, whereas an otherwise normal-looking pituitary MRI may reveal a hypoenhancing lesion, a microadenoma, after administration of contrast *only*. More than 90% of ACTH-producing tumors are hypoenhancing; interestingly, approximately 5% of corticotropinomas are hyper-enhancing after contrast.

Due to limitations of imaging techniques, many institutions use petrosal sinus sampling to distinguish pituitary from ectopic source of ACTH-secreting adenomas. However, while petrosal sinus sampling has high diagnostic accuracy, it is an invasive, expensive, and not widely available test, and is associated with the risk of serious complications. Various modifications of MRI techniques have been proposed to improve the rate of pituitary tumor detection. Overall, only approximately 50% of ACTH-producing pituitary tumors were detectable with MRI, even with the use of contrast. Recent studies [86,87] report the use of post-contrast spoiled gradient-recalled acquisition (SPGR) in the steady state in addition to conventional T-1 weighted spin echo (SE) acquisition MRI. SPR-MRI was superior to

conventional MRI imaging for the diagnostic evaluation of corticotropinomas and, in general, for investigation of the pituitary gland in children and adults (Figure 3).

Intraoperative ultrasound during transsphenoidal surgery has been reported by several surgical centers to be valuable in tumor localization in patients with microadenomas and extent of tumor resection in macroadenomas [88-93]. Recently, low-field intraoperative MRI was developed to facilitate assessment of extent of tumor resection before the patient is awakened from anesthesia [94-96].

Positron emission tomography with fluorodeoxyglucose (PET) has been shown to be valuable in the differential diagnosis of pituitary adenomas, meningiomas, and skull base neuromas as well as to distinguish tumor recurrence from surgical scarring [97]. Radiolabeled receptor ligands (that are known *in vitro* to be expressed by pituitary tumors) and receptor imaging (i.e. type 2 dopamine receptor) are not widely used to localize pituitary tumors or to predict response to treatment [98].

Molecular Genetics of pituitary tumors

Genetic conditions that are associated with pituitary tumors include MEN 1, Carney complex, familial isolated pituitary adenomas (FIPA), and McCune-Albright syndrome. MEN 1 is caused by germline mutations in *menin*. Recently, a mutation in the CDKN1B gene (also known as p27/ KIP1) was reported to be associated with a MEN 1-like syndrome in a rat model and few humans [99]. Genetic defects in one of the regulatory subunits of protein kinase A (PKA) (regulatory subunit type 1 alpha, *PRKAR1A*) causes Carney complex [100]. Vierimaa (2006) reported that inactivating mutations of the gene encoding aryl hydrocarbon receptor-interacting protein (AIP) were found in patients with pituitary tumors (predominantly acromegaly) in both sporadic and familial settings [101]. Somatic mutations on the adenylate cyclase-stimulating G alpha protein (GNAS complex locus, GNAS) are found in McCune-Albright syndrome [102]. Familial growth hormone secreting pituitary adenomas may occur as an isolated autosomal dominant disorder (familial somatotropinoma,) [103,104] or as part of MEN 1 and Carney complex [32,105]. McCune-Albright syndrome (MAS) is a genetic, but not inherited, disorder [106]. In the remaining text of this report we briefly review these conditions.

Carney complex (CNC), first described by Carney in the mid-1980s, is a rare autosomal dominant disorder that includes a complex of myxomas, lentigines, endocrine overactivity, and a variety of other tumors such as schwannomas and pituitary adenomas. In approximately 60% of the patients who meet diagnostic criteria, an inactivating mutation in the gene encoding PRKAR1A has been identified and a second, as yet uncharacterized locus at 2p16 has been implicated in some families [107]. We recently reported that GH-producing tumors were identified in a cohort of adult patients (mean age 35.8 years) with clinical acromegaly. Acromegaly in CNC is characterized by a slow progressive course and aggressive pituitary tumors are not common. Of note, in many of these patients, clinically significant acromegaly did not present until after surgical treatment of their Cushing syndrome (72% of these patients were diagnosed with CS due to primary pigmented nodular adrenocortical disease). This change in clinical phenotype in patients with concurrent

Cushings syndrome and acromegaly is not surprising given the known relationship between cortisol and growth hormone metabolism, but as phenomenon deserves further investigation in patients affected with CNC or similar conditions, such as McCune Albright syndrome [34]

For patients with CNC who have elevated GH and/or IGF-1, it is important to identify clinically significant acromegaly as defined by generally applied criteria [69]. Most CNC patients will have some abnormality of GH secretion due to the underlying pituitary hyperplasia, but almost all of them will have negative imaging studies [100,108]. It is common practice to treat CNC patients with elevated IGF-1 levels with somatostatin analogues with the goal of normalizing IGF-1 [100,109]. For CNC patients with abnormal response to oral glucose tolerance tests but normal IGF-1 levels and normal pituitary imaging, evaluations should be performed annually to assess for changes that may require treatment.

McCune Albright syndrome (MAS) is characterized by polyostotic fibrous dysplasia, café-au-lait pigmented lesions, endocrine abnormalities (precocious puberty, thyrotoxicosis, pituitary gigantism, and Cushings syndrome) and rarely by other tumors. MAS is caused by mosaicism for activating mutations of the *GNAS* gene. *GNAS* maps to chromosome 20q13 and encodes the ubiquitously expressed Gs- α subunit of the G protein. The phenotype of MAS, including hypersomatotropinemia, is due to the cellular response to the activation of adenylyl cyclase signaling pathways. As mentioned above, *GNAS* mutations were also identified in sporadic GH-producing tumors. As seen with patients affected by CNC or carriers of *PRKARIA* mutations, GH excess in MAS is frequently observed (approximately 20% of the patients) but pituitary tumors are not typically detectable by MRI [110,111].

Typical histological findings in pituitary glands of MAS patients are GH- and PRL-producing cell hyperplasia [32,106,112], similar to what one sees in CNC pituitaries. Hypersomatotropinemia in MAS can be associated with significant morbidity due to exacerbation of polyostotic fibrous dysplasia in the presence of elevated GH levels [106,113]. Hypersomatotropinemia has also been implicated in sarcomatous transformation of bone tumors in a MAS patient [114]. Treatment of GH-producing tumors in MAS with cabergoline has consistently shown an inadequate response, while long-acting octreotide has demonstrated an intermediate response. Recently, GH-receptor antagonists have been proposed as effective medical intervention for patients with inoperable MAS pituitary tumors or hypersomatotropinemia without a visible tumor [72,75,115].

MEN1 is disorder inherited in an autosomal dominant manner and characterized by a predisposition to peptic ulcer disease and primary endocrine hyperactivity involving the pituitary, parathyroid, and pancreas. The disorder is due to inactivating mutations in the *menin* gene which was identified in 1997. *Menin* is a tumor suppressor, which has been localized to chromosome 11q13. Several studies have reported that menin interacts with various proteins involved with transcriptional regulation, genome stability, cell division and proliferation [29,30,116,117].

Pituitary adenomas occur in approximately 30 to 40% of patients with *menin* mutations [17]. The most common pituitary tumors are those secreting PRL (~60%) and GH (~20%), while ACTH-secreting and non-functional adenomas represent less than 15% of MEN 1-associated pituitary adenomas [6,29]. Data from studies in recently developed mouse models report similar frequency (~37 %) of PRL-producing and other pituitary tumors in heterozygote mice with one *menin* allele inactivated [118,119]. Although no genotype-phenotype correlation has been noted in *menin* mutation carriers, in familial MEN 1 the frequency of pituitary disease is significantly higher than in sporadic MEN 1 cases [29]. In addition, in MEN 1 patients with pituitary adenoma and acromegaly, an increased female-to-male ratio has been reported for both familial and sporadic cases [17].

Familial isolated pituitary adenomas (FIPA) is a clinical condition that refers to kindreds with two or more pituitary adenomas that are genetically negative for mutations in *menin* or *PRKARIA*. Homogeneous mutations refer to similar pituitary tumor type occurring within the same family and heterogeneous mutations refer to families with two or more different tumor types [36]. All pituitary tumor phenotypes have been reported in FIPA kindreds, and typically at least one prolactin- or GH-secreting adenoma is noted in each family. Predisposition genes for FIPA remain largely unknown.

Recently, a genome-wide and DNA mapping study identified inactivating mutations in the gene that encodes aryl hydrocarbon receptor-interacting protein (AIP) gene on chromosome 11q13.3. In this series, combinations of somatotropinomas, mixed GH- and PRL-secreting adenomas, and prolactinomas were noted. Lack of functional AIP was shown by loss of heterozygosity in the tumors. AIP mutations were reported in 15% of the investigated families and half of those with isolated familial somatotropinoma, which is a well-described clinical syndrome related only to patients with acrogigantism. Typically tumors in patients with AIP mutations are larger and diagnosed at a younger age than patients without AIP mutations or in sporadic tumors [120,121].

Conclusions

Although pituitary tumors are rare in childhood and adolescence, and are typically histologically benign, significant morbidity may result due to their location, mass effect, and/or interference with normal pituitary hormone functions. Advances in diagnostic testing, neuroimaging, microneurosurgery, and pharmacological interventions have resulted in significant improvements in the diagnosis and interventions for pituitary tumors in childhood and adolescence. Genetic syndromes such as MEN 1, CNC, and MAS, and familial isolated pituitary adenomas have advanced our knowledge of the molecular basis of pituitary tumors and provide a basis for future research on molecular mechanisms of genesis of endocrine tumors.

Expert opinion

Early identification of pituitary tumors in children is necessary to avoid serious adverse effects on both physiological and cognitive outcomes as a result of pituitary hormone dysregulation during the critical periods of growth in childhood and adolescence. Treatment

of rare disorders, such as pediatric pituitary tumors, requires a multidisciplinary team with expertise in the diagnosis, treatment, and long-term management of this disorder to facilitate early diagnosis and treatment and reduce morbidity. The family of a child diagnosed with a pituitary tumor as part of a genetic syndrome should be offered genetic counseling and surveillance of family members as appropriate. As ongoing studies identify gene and protein expressions, mutations, and candidate genes important for the development and function of the anterior pituitary gland, this information will facilitate earlier diagnosis and provide opportunities to develop therapeutic targets.

Five-year view

To ameliorate the permanent pituitary- related morbidities associated with pituitary adenomas in vulnerable age groups, early diagnosis and targeted intervention are essential. Significant progress in microneurosurgery, neuroimaging molecular biology, and genetics has advanced our ability to evaluate and treat pituitary tumors. Novel approaches to treating pituitary tumors continue to develop as our understanding of the relationship between structure and function of endocrine receptors develops. Although our understanding of the molecular basis of pituitary tumorigenesis has progressed rapidly, the molecular defects in a significant proportion of pituitary tumors have not been identified. Advances in our understanding of the mechanisms of pituitary oncogenesis through genetics, genomics, and molecular biology approaches will lead to the improvements in diagnostic, prognostic, and therapeutic tools in an increasing proportion of predisposed individuals.

Key Issues

- Pituitary tumors are rare in childhood and adolescence and histologically almost always benign; however they are associated with significant morbidity due to the interference with endocrine function during a vulnerable period of development.
- Early identification of pituitary tumors in children is necessary to avoid serious adverse effects (on both physiologic and cognitive outcomes) of pituitary hormone dysregulation during the critical periods of growth in childhood and adolescence. Common presenting signs are headache, visual disturbances, growth failure, or disturbances of pubertal development.
- Two main types of tumors occur within the pituitary fossa, craniopharyngiomas and adenomas.
- The majority of pituitary tumors are sporadic; however they are sometimes seen in association with genetic conditions such as MEN 1, Carney complex, familial acromegaly, and McCune- Albright syndrome.
- Surgical intervention is the treatment of choice for craniopharyngiomas, corticotropinomas, and somatotropinomas, while medical management is usually first line of treatment for prolactinomas.

- Novel approaches to treating pituitary tumors continue to develop as our understanding of the relationship between structure and function of endocrine receptors develops.

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FIGURE 1. Human molecular genetics of pituitary tumorigenesis

Proposed pathways to pituitary tumorigenesis due to:

- aberrant cAMP signaling (primary initiating event for the polyclonal hyperplasia and/or initial adenoma formation, as evidenced by *GNAS* and *PRKAR1A* involvement)
- cell-cycle dysregulation and aneuploidy (may initiate or augment growth of a monoclonal pituitary tumor)
- *menin* downregulation, methylation of certain target genes, aneuploidy and/or disruption of genomic integrity in a greater scale (may lead to a growing pituitary adenoma still responsive to medical and/or surgical treatment, depending on the type)
- *PTTG* overexpression and/or additional growth factor upregulation and increased angiogenesis (may lead to aggressive tumors).

FIGURE 2.
Algorithm for evaluation of Cushing syndrome in children

FIGURE 3.

MRI studies of a patient with a corticotropinoma detected by both SE- and SPGR-MRI in postcontrast studies. This is one of the largest microadenomas encountered in this series. A, Coronal precontrast SE images revealed no abnormality. B, Coronal postcontrast SE images demonstrated a homogeneously hypoenhancing area in the right side of the anterior pituitary lobe. C, Coronal postcontrast SPGR images identified an adenoma in approximately the same location as the enhanced SE scan. Although the adenoma was identified by both studies, the contrast between normal and abnormal tissues is superior on the SPGR images. The tumor location was confirmed at surgery.