Pediatric Pituitary Adenomas: Germline Genetic Defects

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Contents

Abstract

In childhood and adolescence pituitary tumors occur infrequently and are rarely malignant. However, these tumors may result in significant morbidity due to the essential role of the pituitary in the maintenance of homeostasis and the regulation of growth and puberty. Approximately 2–6% of surgically treated pituitary tumors occur in children and are primarily of two types, craniophayrngiomas and adenomas. The majority of pituitary tumors are sporadic; however, in children these tumors may be part of a genetic condition predisposing to pituitary and other tumors. The investigation of pituitary tumors in the context of genetic syndromes, such as MEN-1, Carney complex, familial isolated pituitary adenoma, and McCune Albright syndrome, has advanced our knowledge of the molecular basis of pituitary tumors.

Introduction

Although pituitary adenomas in children are rare, accurate data regarding their incidence and prevalence is lacking. Results of autopsy studies (primarily adults) indicate that pituitary adenomas develop in approximately 17–25% of the population(Asa and Ezzat 2002), which is consistent with results of studies of radiological imaging that report pituitary tumors in approximately 20% of the general population, with no gender predilection. Recently reported cross-sectional studies report a prevalence of one in 1064–1289 clinically relevant pituitary

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adenoma in well-defined populations(Daly et al. 2006). Approximately 3.5–8.5% of all pituitary tumors are diagnosed prior to the age of 20 years and they account for approximately 3% of all diagnosed intracranial tumors in childhood (Melmed 2011). There are two predominant types of tumors that occur within the pituitary fossa, craniopharyngiomas and adenomas. Typically pituitary tumors in children and adolescents are histologically benign; however, significant morbidity may result due to mass effect and/or interference with normal pituitary hormone function (Asa and Ezzat 2002). Sporadic lesions comprise the majority of pituitary tumors. However, in children more frequently than adults, pituitary tumors may be a manifestation of a genetic condition, such as multiple endocrine neoplasia type 1 (MEN1), Carney complex, familial isolated pituitary adenoma (FIPA), and McCune-Albright syndrome. These genetic syndromes have provided a model to help advance our knowledge of the molecular basis of pituitary tumorigenesis. In this chapter, we review recent findings on the diagnosis, evaluation, treatment, and molecular genetics of the two most common tumors of the pituitary gland in childhood, craniopharyngiomas and pituitary adenoma.

Pituitary Development

The pituitary gland has an essential role in the maintenance of homeostasis, normal growth, 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). Cell fate studies document a placodal origin of the anterior pituitary in all vertebrates. The pouch has elongated and constricts at the attachment to the oral epithelium around the 5th week of development; the adenohypophysis (pars anterior, pars intermedia, and pars tuberalis) develop from the ectoderm of the stomodeum. The neurohypophysis develops from the neuroectoderm (infundibulum)(Faglia and Spada 2001). The anterior and posterior pituitary lobes develop concurrently and continue to interact closely despite the different embryologic origin of the two tissues.

The adenohypophysis contains six different cell types that are characterized by their hormone secretion: corticotrophs secrete corticotropin (adrenocorticotropic hormone (ACTH)), somatotrophs secrete growth hormone (GH), thyrotrophs produce thyrotropin (thyroid-stimulating hormone or (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 that are surrounded by pituitocytes (astroglia). Peptide hormones (oxytocin and vasopressin) 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 secretes 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. In addition dopamine inhibits PRL secretion and TRH stimulates it; therefore a putative PRL-RH or releasing factor (PRF) has long been postulated to exist (Zhu et al. 2007).

Craniopharyngiomas

Craniopharyngiomas comprise the majority (80–90%) 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 5–14 years and rarely in the fifth decade of life (Bunin et al. 1998) and incidence does not vary with race or gender. 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 (Jagannathan et al. 2007). Histology of craniopharyngiomas identifies primarily two categories, adamantinomatous, with cyst formation (ACF, typical pediatric form) and squamous-papillary (adults), although transitional forms have been reported.

Craniopharyngiomas typically present with endocrine dysfunction, diabetes insipidus, vision problems, and intense headaches or vomiting 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 (Bunin et al. 1998). 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 (Rienstein et al. 2003). Recently, β-catenin gene mutations were found in up to 20% of the rare adamantinomatous craniopharyngiomas, and Gaston-Massuet et al. (2011) reported that craniopharyngiomas arise from activation of β-catenin in pituitary progenitors during embryogenesis. However, the more common papillary craniopharyngiomas to this date have no common genetic abnormality (Sekine et al. 2002).

At the time of diagnosis of a craniopharyngioma, endocrine dysfunction is found in about 80% of the patients. GH deficiency is the most frequent endocrine finding (75%), followed by gonadotropin deficiency (40%), corticotropin and thyrotropin deficiency (Rienstein et al. 2003). 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) is frequently a presenting symptom (in about 9–17% of the patients). The treatment of choice for craniopharyngiomas is surgical resection. Because the recurrence rate is higher than in all other pituitary tumors adjunctive radiotherapy is often indicated, except for small, entirely intrasellar lesions. Morbidity may be significant and is associated with treatment and also 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 brachytherapy with bleomycin, radioactive phosphorus, or alpha-emitting 90Yt) 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 (Sanford 1994).

Pituitary Adenomas

Among functional pituitary tumors in early childhood, ACTH-producing adenomas are probably the most common, although overall these tumors 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)(Marx et al. 1999). 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; somato- and/or mammotropinomas become significantly more frequent than corticotropinomas in late childhood, adolescence and adulthood (Stratakis et al. 2010). Hypothalamic and pituitary factors are involved in pituitary adenoma development and cell growth. In addition, other factors and genetic events appear to influence pituitary-cell clonal expansion and oncogene activation, which is necessary to propagate tumor growth (Fig. 28.1; Melmed 2011; Xekouki et al. 2010).

Corticotropinomas are the most common pituitary adenomas in prepubertal children; their

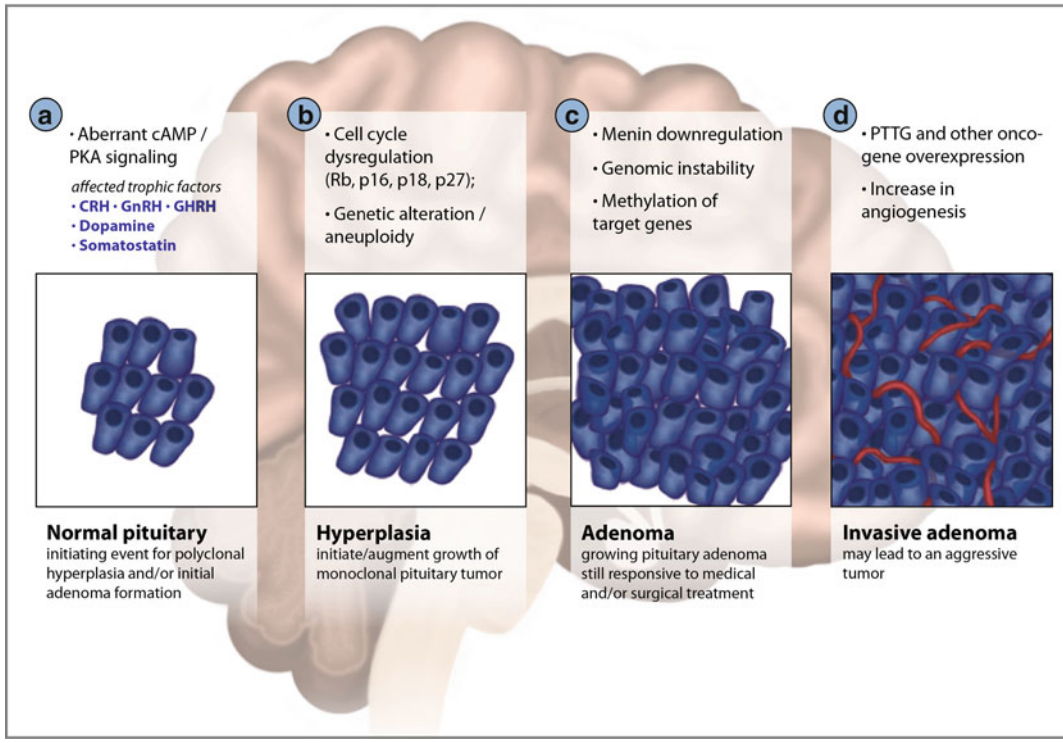


Fig. 28.1 Human molecular genetics of pituitary tumorigenesis. Possible pathways of pituitary tumorigenesis due to: (**a**) Aberrant cAMP signalling (initiating event for the polyclonal hyperplasia an/or initial formation of adenoma (i.e. *GNAS* and *PRKAR1A*); (**b**) Cell-cycle dysregulation and aneuploidy (i.e. events or genes that initiate or augment growth of a monoclonal pituitary adenoma); (**c**) *Menin* downregulation, methylation of specific target genes, aneuploidy and/or disruption of genomic integrity; (**d**) PTTG and/or other growth factor or oncogene overexpression, increased angiogenesis

frequency decreases during puberty and in adolescence, when prolactinomas become more prevalent. The cumulative incidence of ACTH-producing tumors (also known as 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. The most characteristic clinical presentation of Cushing disease is significant weight gain concomitant with failure to gain height. Other common symptoms include headaches, hypertension, glucose intolerance, and delayed pubertal development and amenorrhea despite often-significant virilization and hirsuitism. 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 may invade the cavernous sinus or wall; there are also case reports of tumors that originate in the posterior lobe (Magiakou et al. 1994). 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 (Batista et al. 2007). 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 with an expert care facility.

Radiation or gamma-knife therapy is reserved for these patients in whom surgical intervention failed (Magiakou et al. 1994). Bilateral adrenalectomy may be considered for inoperable or recurrent cases; however it is associated with a significant risk of development of Nelson's syndrome.

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 as a result of a local mass effect may occur with optic glioma seen in neurofibromatosis type-1 (NF-1) or from an ectopic GHRH-producing tumor (almost unheard of in children). 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 (Lim et al. 2004). 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 transspheniodal 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 (Lim et al. 2004).

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 (Lim et al. 2004). Suppression of insulin secretion is a side effect of treatment with long-acting somatostatin analogs, and therefore may increase the risk for development of glucose intolerance. 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 and recent studies report that combination therapy with pegvisomant and long-acting somatostatin analog offers an additional benefit since tumor suppression is combined with GH receptor blockade (Lim et al. 2004). 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 11 patients, with a higher risk for patients diagnosed with diabetes mellitus. There is limited data on pegvisomant treatment in children, mostly case studies, which report successful outcomes.

Prolactinomas are the most common pituitary adenomas in older children, accounting for approximately 50% of pituitary adenomas, with the majority occurring in adolescence with a female preponderance (Jagannathan et al. 2007). 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 (Ciccarelli et al. 2005). 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 (Stratakis et al. 2000). Clinical presentation varies depending on the age and gender of the child, although growth arrest is typically seen in children and adolescents before ephiphyseal 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, vision loss), growth or pubertal arrest and other pituitary dysfunctions. Contrary to common belief, gynecomastia is not a finding in hyperprolactinemia. Since various factors such as neurogenic (emotional stress, nipple stimulation, chest wall lesions), pharmacological (phenothiazine, metoclopramide, centrally acting antihypertensive) or mechanical processes (craniopharyngiomas, Rathke cleft cyst, non-functioning adenoma, and infiltrative processes) can lead to loss of dopaminergic suppression of pituitary lactotrophs with hyperprolactinemia as a result, the differential diagnosis of hyperprolactinemia in children and adolescents is rather large (Lafferty and Chrousos 1999).

Pharmacological 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. 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 (Schlechte 2003). In some cases treatment with dopaminergic agents can be withdrawn and prolactin levels will remain within normal limits.

Surgical intervention for prolactinomas is reserved for emergency situations such as acute threat to vision, hydrocephalus, or cerebral spinal fluid leak, or for rare tumors that grow despite exposure to increasing doses of dopamine agonists. Compliance is often a problem in long-term management of prolactimonas, 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. Treatment doses of 2.5–10 mg daily (bromocriptine) or 0.25–2 mg weekly (cabergoline) have not been associated with long-term adverse effects. However, 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 1,200 patients with Parkinson's disease (controlled and uncontrolled studies) at doses of up to 11.5 mg/day, which exceed the maximum recommended dose for treatment of hyperprolactinemic disorders. The risk of cardiac valvular disease appeared to be higher in patients treated with at least 3 mg per day of cabergoline, a dose that is 10–20 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 (Schlechte 2003).

Non-Functioning Adenomas

Non-functioning pituitary tumors in childhood and adolescence are rare; these tumors represent only 4–6% of pediatric cases while in series of adult patients, hormonally silent tumors account for approximately 33–50% of the total number of pituitary lesions (Lafferty and Chrousos 1999). 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 (Lafferty and Chrousos 1999). 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. Non-functioning pituitary adenomas may present with GH deficiency (up to 75%), LH/FSH deficiency (~40%), or ACTH and TSH deficiency (~25%) (Lafferty and Chrousos 1999; Jagannathan et al. 2007).

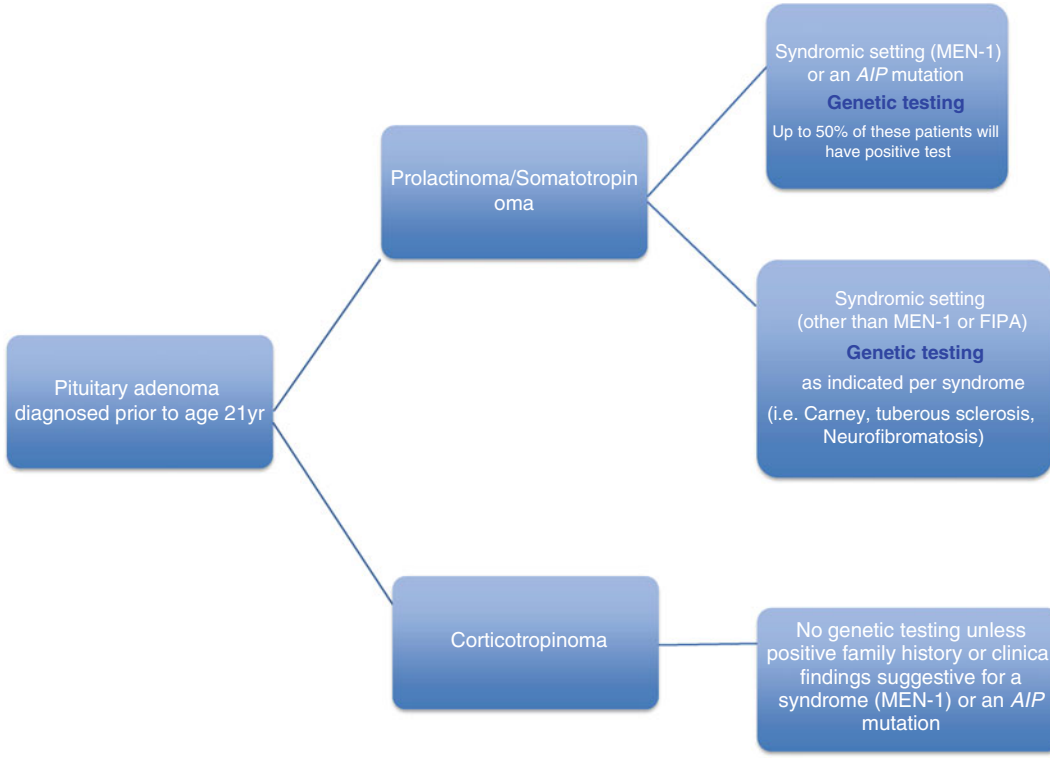
Compression of the pituitary stalk by pituitary adenoma has been reported but secondary hyperprolactinemia is typically seen in less than 20% of patients. DI is also rare (9–17%) but is more commonly seen in patients with Rathke's cleft cysts (Jagannathan et al. 2007). Recommendation for surgical excision of a hormonally silent intrasellar tumor or cyst depends on the tumor size, location, and potential for invasiveness (Freda et al. 2011).

Molecular Genetics of Pituitary Tumors

Genetic conditions associated with pituitary tumors include MEN 1, Carney complex, familial isolated pituitary adenomas (FIPA), and McCune-Albright syndrome. MEN1 is caused by germ line mutations in *menin*. Recently, a mutation in the *CDKN1B* gene (also known as p27 and KIP1) was reported to be associated with a MEN 1-like syndrome known as MEN 4 (MENX in rodents) in a rat disease model and human kindred. Genetic defects in one of the regulatory subunits of protein kinase A (PKA) (regulatory subunit type 1 alpha, *PRKAR1A*) causes Carney complex (Horvath et al. 2008). Vierimaa (2006) reported that inactivation 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 (Vierimaa et al. 2006). Somatic mutations on the adenylate cyclase-stimulating G alpha protein (GNAS complex locus, GNAS) are found in McCune-Albright syndrome (Stratakis et al. 2010). Familial growth hormone secreting pituitary adenomas may occur as an isolated autosomal dominant disorder (familial somatotropinoma) or as part of MEN 1 and Carney complex (Stratakis et al. 2010). McCune-Albright syndrome (MAS) is a genetic, but not inherited, disorder. A recent study of the prevalence of germline mutations in *MEN1*, *AIP*, *PRKAR1A*, *CDKN1B*, *and CDKN2C* reported that AIP or MEN1 mutations are frequent in pediatric patients with either GH- or PRL-secreting pituitary adenomas, however are rarely found in corticotropinomas (Stratakis et al. 2010). A proposed algorithm for genetic testing for pituitary adenomas in paediatrics is listed in Fig. 28.2 (Xekouki et al. 2010).

Carney complex(CNC), first described by Carney in the mid-1980s, is a rare autosomal dominant disorder that includes 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 (Carney et al. 1985; Stratakis et al. 2010). We recently reported that GH-producing tumors were identified in a cohort of adult patients (mean age 35.8 years) with clinical acromegaly (Boikos and Stratakis 2006). 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 Cushing 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 (Boikos and Stratakis 2006).

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 (2004). 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 (Boikos and Stratakis 2006). It is common practice to treat CNC patients with elevated IGF-1 levels with somatostatin analogues with the goal of normalizing IGF-1(Melmed 2011). For CNC patients with abnormal response to oral glucose



Adapted from: Xekouki P, Azevedo M, Stratakis, CA. Anterior pituitary adenomas: inherited syndromes, novel genes, and molecular pathways. 2010. Expert Rev Endocrinol Metab, 5, 697-709.

Fig. 28.2 Recommended algorithm for genetic testing in children with pituitary adenomas. *MEN-1* Multiple endocrine neoplasia type 1, *AIP* Aryl hydrocarbon-interacting protein

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 adenyl 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 *PRKAR1A* mutations, GH excess in MAS is frequently observed (approximately 20% of the patients) but pituitary tumors are not typically detectable by MRI (Stratakis et al. 2010).

Typical histological findings in pituitary glands of MAS patients are GH- and PRL-producing cell hyperplasia (Horvath et al. 2008); 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. 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 (Chanson et al. 2007).

MEN 1 is a genetic 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 (Marx et al. 1999). Pituitary adenomas occur in approximately 30–40% of patients with *menin* mutations (Asa and Ezzat 2002). 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 (Jagannathan et al. 2007; Marx et al. 1999). 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 (Bertolino et al. 2003). 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 (Marx et al. 1999). 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 (Asa and Ezzat 2002).

Familial isolated pituitary adenoma (FIPA) is a clinical condition that refers to kindreds with two or more pituitary adenomas that are genetically negative for mutations in *menin* or *PRKAR1A*. 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 (Beckers and Daly 2007). 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. 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 tumor FIPA specimens. AIP mutations were reported in 15% of FIPA 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 (Daly et al. 2010).A recent study of clinical characteristics and therapeutic response in 96 patients with Germ-line AIP mutations and pituitary adenomas, reported that somatotropinomas were most frequent presentation (almost 80%) and more than half of these tumors were co-secretors of GH and PRL, while prolactinomas accounted for 13.5, 7.3% nonsecreting (all tumors were macroadenomas), and a single *AIP-mut* TSH-secreting tumor. The predisposition for aggressive tumors in children and adolescents (often in a familial setting) highlights the importance of early detection to improve treatment outcomes (Daly et al. 2010).

In conclusion, 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 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 counselling 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.

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