

Advances in the Diagnosis, Treatment and Molecular Genetics of Pituitary Adenomas in Childhood

a report by

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DOI:10.17925/EE.2008.04.02.81

The pituitary gland has an essential role in the maintenance of homeostasis, normal growth and reproductive function. Although pituitary tumours 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.¹ The early identification of pituitary tumours 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. In this report, we review recent findings on the diagnosis, evaluation, treatment and molecular genetics of pituitary adenomas presenting in childhood.

Pituitary Adenomas

Due to the rarity of pituitary tumours in children and adolescents, accurate information regarding the prevalence and incidence of these tumours is lacking. Data from autopsy studies (primarily concerned with adults) show that pituitary adenomas develop in approximately 17–25% of the population.^{1,2} In addition, studies using radiological imaging report a similar incidence of pituitary gland lesions in the general population (up to 20%) with no gender predilection.³ Approximately 3.5–8.5% of all pituitary tumours are diagnosed before 20 years of age and they account for approximately 3% of all diagnosed intracranial tumours in childhood.^{4–8}

The majority of pituitary tumours are sporadic; however, in children more commonly than in adults they can be part of a genetic condition predisposing the sufferer to pituitary and other tumours. Even sporadic tumours may harbour significant genetic abnormalities. Most pituitary tumours are monoclonal lesions and modifications in expression of various oncogenes or tumour suppressor genes, including *GNAS*, pituitary tumour transforming gene (*PTTG*), *HMG2A2* and *FGFR-4*, have been identified.^{9,10} Pituitary tumour development and cell growth are probably influenced by both pituitary and hypothalamic factors.^{1,11,12} Other factors and genetic events seem to be implicated in pituitary cell clonal expansion, and oncogene activation is necessary to propagate tumour growth.^{9,13} An example of this secondary phenomenon is the widespread presence of *GNAS*-activating mutations in sporadic growth hormone (GH)-secreting pituitary tumours (in up to 40% of all such lesions).¹⁴

Adrenal corticotrophic hormone (ACTH)-producing adenomas are the most common functional pituitary tumours in early childhood, although they are still considerably rare. No genetic defects have been consistently associated with childhood corticotropinomas, which only rarely occur in the familial setting, and even then occur most commonly in the context of multiple endocrine neoplasia type 1 (MEN1).^{15–17}

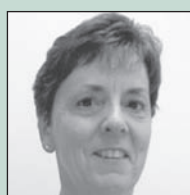
The second most frequently found functional pituitary tumours in early childhood are GH- and/or prolactin (PRL)-secreting, and in children these tumours almost always occur in the familial setting or in the context of known genetic defects, i.e. *GNAS*, *menin*, *PRKAR1A*, *AIP* and *p27 (CDKN1B)* mutations.^{5,18–23} In late childhood, adolescence and adulthood, somato- and/or mammatropinomas are significantly more frequent than corticotropinomas.²⁴

Corticotropinomas

The most common type of pituitary adenoma in pre-pubescent children is corticotropinomas; however, their frequency decreases during puberty and in late adolescence, when prolactinomas become more prevalent. The cumulative incidence of corticotropinomas (Cushing's disease) in children does not exceed one-tenth of the annual incidence of two to five new cases of Cushing's syndrome per million people per year.^{7,24,25} Typically, corticotroph adenomas are significantly smaller than other types of pituitary tumour (usually 3mm or less). Rarely, they can be exophytic, growing into the subarachnoid space, or invade the cavernous sinus or wall. In addition, there are case reports of tumours that originate in the posterior lobe.^{26,27}

Clinical Presentation, Evaluation and Treatment

In children, the most characteristic clinical presentation of Cushing's disease is significant weight gain concomitant with a decrease in linear height velocity. Other typical symptoms include headaches, delayed pubertal development and amenorrhoea (despite significant virilisation and hirsutism), hypertension and glucose intolerance. Children and



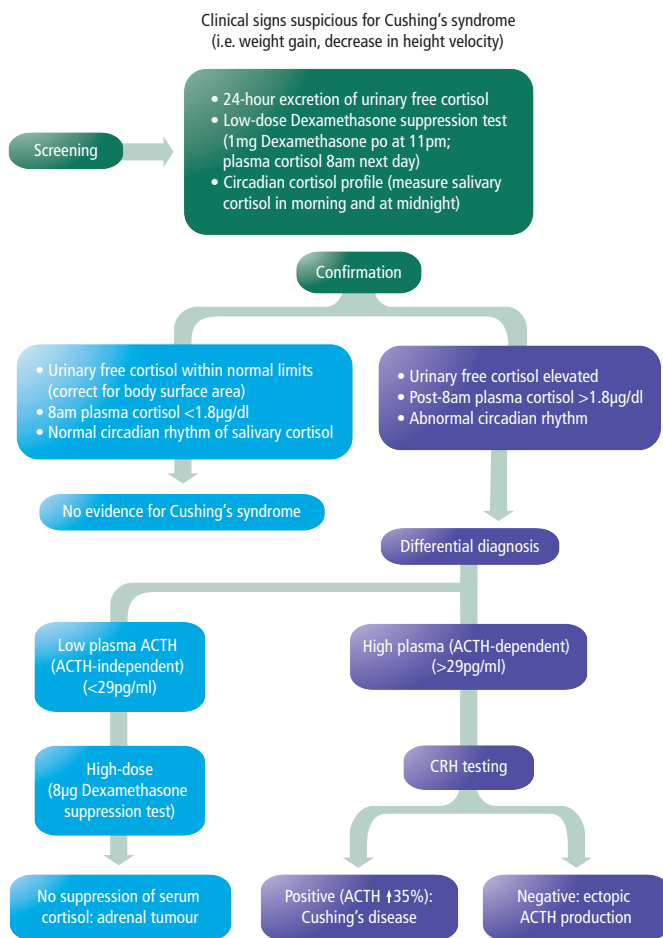
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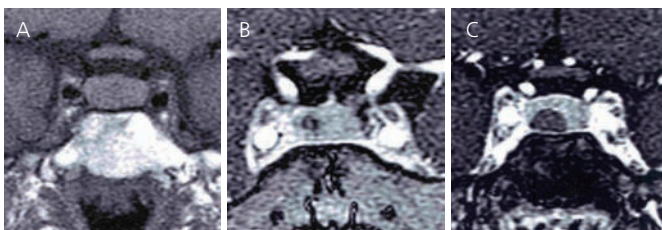
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Figure 1: Algorithm for Evaluation of Cushing's Syndrome in Children



ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone.

Figure 2: Magnetic Resonance Imaging (MRI) Studies of a Patient with a Corticotropinoma Detected by Both Spin Echo and Spoiled Gradient-recalled MRI in Post-contrast Studies



This is one of the largest microadenomas encountered in this series. A: Coronal pre-contrast spin echo (SE) images revealed no abnormality; B: Coronal post-contrast SE images demonstrated a homogeneously hypoenhancing area in the right side of the anterior pituitary lobe; C: Coronal post-contrast spoiled gradient-recalled (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. Reprinted with permission from Batista et al., MRI for Cushing's Disease in Children and Adolescents, J Clin Endocrinol Metab, 2005;90(9):5134-40.

younger adolescents usually do not report problems with sleep disruption, muscle weakness or memory or cognition compared with older adolescents and adults with Cushing's disease.²⁸

Our group recently suggested a three-day inpatient evaluation of children suspected to have Cushing's syndrome for confirmation of the diagnosis and investigation of corticotropinoma.²⁹ A midnight serum cortisol value of $\geq 4.4\mu\text{g/dl}$ confirmed the diagnosis of Cushing's

syndrome in all children (with a sensitivity of 99% and specificity of 100%). Morning corticotropin levels were elevated in patients with Cushing's disease (median 18pg/ml); a cut-off value of 29pg/ml had 100% specificity and 70% sensitivity. A decrease in morning cortisol of $\geq 20\%$ with the high-dose overnight dexamethasone suppression test (120ug/kg, maximum dose 8ug) provided the highest sensitivity (97.5%) in differentiating between Cushing's disease and primary adrenal disorders (see Figure 1). Magnetic resonance imaging (MRI) of the pituitary gland identified a lesion in 63% of patients, and CT imaging of the adrenals showed bilateral adrenal hyperplasia in 53% of children with Cushing's disease. Bilateral inferior petrosal sinus sampling is usually reserved for patients with confirmed ACTH-dependent Cushing's syndrome and a negative pituitary MRI, or, in situations where there is inconsistency in biochemical data, to exclude an ectopic source of ACTH production. Our group recently reported that in an experienced centre, bilateral inferior petrosal venous sampling (BIPSS) was safe; however, lateralisation of the ACTH gradient during BIPSS is a poor predictor of lateralisation of the tumour.³⁰

Recent studies report the use of post-contrast spoiled gradient-recalled (SPGR) acquisition in the steady state in addition to conventional T1-weighted spin echo (SE) acquisition MRI.^{31,32} SPGR-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 (see Figure 2).

Transphenoidal adenomectomy, or hemihypophysectomy, is considered to be the first-line treatment for Cushing's disease in childhood and adolescence. Hemihypophysectomy has been shown to be nearly 90% curative in situations where surgical exploration is negative. In situations where surgical intervention has not been successful, radiation or gamma-knife therapy is the next line of treatment.^{24,28} An option for inoperable or recurrent Cushing's disease is bilateral adrenalectomy; however, this is associated with a significant risk of the development of Nelson's syndrome.^{33,34}

Prolactinomas

Prolactinomas account for approximately 50% of pituitary adenomas overall and are the most common pituitary adenomas in adolescents, with a female preponderance.³⁵⁻³⁸ Prolactinomas may be seen in several inherited syndromes, including MEN1, Carney complex, and familial isolated pituitary adenomas (FIPAs).³⁹

Clinical Presentation, Evaluation and Treatment

The clinical presentation of prolactinomas varies depending on the age and gender of the child. Growth arrest is typically noted in children and adolescents prior to ephiphyseal fusion. Macroprolactinomas are found more frequently in males, perhaps due to lower detection rates during the initial phase of tumour development. Consistent with a later diagnosis and larger tumour size, 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. Gynecomastia is not a common finding. Females may present with pubertal delay, amenorrhoea, and other symptoms of hypogonadism. The differential diagnosis includes various factors such as neurogenic or mechanical processes that can result in the loss of dopaminergic suppression of pituitary lactotrophs and resultant hyperprolactinaemia,

such as mass effects from craniopharyngiomas, Rathke cleft cysts, non-functioning adenomas or an infiltrative process.⁴⁰

The diagnosis of prolactinoma is based on the measurement of serum prolactin levels (indwelling line, patient resting and fasting for an hour) and neuroradiological imaging. Basal prolactin levels greater than 200ug/l are diagnostic, whereas levels between 100 and 200ng/ml and the presence of a mass requires additional investigation to rule out mass effect versus a prolactinoma. In 2006, Waas reported that all but one patient in a series of 223 with non-functioning adenomas had prolactin levels less than 100ng/ml, which provides a well-defined cut-off value for clinical management.⁴¹

The first-line treatment for prolactinomas is medical management with dopamine agonists (e.g. bromocriptine, pergolide or cabergoline), with the goals of normalisation of prolactin levels and pituitary function and the reduction of tumour size. Dopamine agonists have demonstrated effectiveness in reducing tumour size and controlling prolactin levels in approximately 80–90% of patients with microadenomas and about 70% of macroadenomas.⁴² Cabergoline, a selective dopamine 2 (D2) receptor agonist, is more effective and often better tolerated than bromocriptine, and has been shown to be effective in treatment of tumours resistant to other dopamine agonists.⁴³ For some patients, dopaminergic agents can be withdrawn and PRL levels will remain within normal limits.⁴⁴ Patient compliance is often a problem in the long-term management of prolactinomas. Commonly reported side effects of dopamine agonist treatment include nausea, dry mouth, dyspepsia or dizziness at the initiation of therapy.^{45,46} The cessation of medical treatment prior to the disappearance of the tumour on MRI leads to the recurrence of hyperprolactinaemia and tumour re-growth. Bromocriptine 2.5–10mg daily or cabergoline 0.25–2mg weekly have not been associated with long-term adverse effects.

Recent reports in the *New England Journal of Medicine*^{47–49} of cardiac valve regurgitation in patients treated with long-acting dopamine agonists have raised concerns about the safety of these medications. The safety of cabergoline was evaluated in a nested case-control study of patients in the UK general practice database and a study of 1,200 patients with Parkinson's disease (controlled and uncontrolled studies at doses of up to 11.5mg/day, which exceed the maximum recommended dose for treatment of hyperprolactinaemic disorders). The risk of valvular disease appeared to be higher in patients treated with at least 3mg per day of cabergoline, a dose that is 10–20 times higher than the standard regimen for macro-prolactinomas. Discussion of potential risks involved in therapy with the patient and the decision about the need for echocardiogram is advisable.

Recently, Kars et al. reported a cross-sectional study of patients with prolactinomas who received cabergoline treatment (mean 5.2±0.4 years, range one to 10.3 years) and noted an increased prevalence of aortic valve calcification with mild tricuspid regurgitation, but not clinically relevant valvular heart disease.⁵⁰ Discussion of the potential risks of therapy with the patient and the decision about the need for an echocardiogram is advisable. Urgent situations, such as acute threat to vision, hydrocephalus or cerebral spinal fluid leak, or for the rare tumours that grow despite exposure to increasing doses of dopamine agonists, may require surgical intervention.^{51,52}

Somatotropinomas

Before 20 years of age, somatotropinomas account for approximately 5–15% of paediatric pituitary adenomas. Excess GH production typically results from an adenoma (usually macroadenoma); however, somatotroph hyperplasia may be a (rare) cause of excess GH that occurs in certain genetic conditions such as McCune–Albright syndrome (MAS) or Carney complex. Dysregulation of growth-hormone-releasing hormone (GHRH) signalling may occur as a result of a local mass effect, for example with optic glioma seen in neurofibromatosis type-1 (NF-1), and result in GH excess,⁵³ or from an ectopic GHRH-producing tumour, which is almost unheard of in children.

Clinical Presentation, Evaluation and Treatment

The clinical presentation of somatotropinomas 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'. When epiphyseal fusion nears completion, the clinical symptoms become similar to those in acromegalic adults (coarse facial features, broadened nose, large hands and feet, obesity, organomegaly, sweating, nausea). Since somatotropinomas are often macroadenomas, mass effect, such as headaches and visual disturbances, are frequently reported.^{54,55} Diagnosis is confirmed by elevated insulin-like growth factor (IGF)-1 level, failure to suppress GH during oral glucose tolerance test (1.75g/kg), elevated IGFBP3 level and neuroradiological imaging (with MRI). The assessment of pituitary function should include cosyntropin stimulation test, thyroid panel, gonadotropin and prolactin measurement.

Trans-sphenoidal surgery is the first-line treatment for childhood gigantism or acromegaly; however, unlike Cushing's disease, GH-producing tumours are often large and locally invasive. Trans-sphenoidal surgery may be curative of small, well-circumscribed tumours, while larger and locally invasive tumours may benefit from surgical decompression; however, persistent or recurrent disease is common and adjuvant therapy is needed. Radiotherapy, either primary or post-surgical, has a slow onset of treatment effect and a high treatment-related morbidity of panhypopituitarism.^{6,56–58}

Pharmacological agents are often indicated before and after surgery, and have been shown to be effective at shrinking tumour size and improving biochemical abnormalities. Long-acting somatostatin analogues have been shown to be effective at normalising IGF-1 levels in most patients.^{58–64} However, since treatment with long-acting somatostatin analogues suppresses insulin secretion, this may increase the risk of the development of glucose intolerance.^{65,66}

A GH receptor antagonist, pegvisomant, has demonstrated effectiveness for the normalisation of IGF-1 levels with no detrimental effects on glucose metabolism.^{67,68} However, pegvisomant requires a daily injection, an important factor to be considered when initiating this type of treatment. A study of the long-term efficacy and safety of combination therapy (long-acting somatostatin analogue plus twice-weekly pegvisomant) reported that IGF-1 levels normalised for all patients (n=32); however, transient elevation in liver enzymes was observed in 11 patients, with a higher risk for patients diagnosed with diabetes. Combination therapy can offer an additional benefit since tumour suppression activity is combined with GH receptor blockade.⁶⁸

There are limited data on pegvisomant treatment in children, and these mostly come from case studies that report successful outcome.^{69,70}

Incidentally discovered pituitary adenomas in childhood are rare, since overall non-functioning pituitary tumours in childhood and adolescence are uncommon. Hormonally silent tumours represent only 4–6% of paediatric cases, while in series of adult patients they account for approximately 33–50% of the total number of pituitary lesions.^{5,71,72} Most non-functioning adenomas arise from gonadotroph cells and are often macroadenomas at diagnosis; they may present with headaches and visual disturbances, as well as growth and/or pubertal delay.⁷³ Large adenomas may cause hydrocephalus, while pituitary adenomas and sellar tumours that impinge on the optic apparatus and/or cavernous sinus can result in cranial nerve palsies, cavernous sinus syndromes and/or additional visual disturbances. Hormonally silent adenomas may present with GH deficiency (up to 75%), luteinising hormone (LH)/follicle-stimulating hormone (FSH) deficiency (~40%) or ACTH and thyroid-stimulating hormone (TSH) deficiency (~25%).⁷³ Although compression of the pituitary stalk by pituitary adenoma has been reported, secondary hyperprolactinaemia is seen in fewer than 20% of patients. Diabetes insipidus is also rare (9–17%), but is more commonly seen in patients with Rathke's cleft cysts.³⁶ Recommendation for surgical excision of a hormonally silent intrasellar tumour or cyst depends on the tumour size, location and potential for invasiveness.

Molecular Genetics of Pituitary Tumours

Four genetic conditions associated with pituitary tumours (namely Carney complex, MAS, MEN1 and familial isolated pituitary adenomas [FIPA]) provide useful models to advance our knowledge of the molecular basis of pituitary tumours. In the remainder of this article we will briefly review these conditions.

Carney Complex

First described by Carney in the mid-1980s, Carney complex is a rare autosomal dominant disorder that includes a complex of endocrine overactivity, lentiginosities, myxomas and other tumours such as schwannomas and/or pituitary adenomas. Genetic defects in one of the regulatory subunits of protein kinase A (PKA) (regulatory subunit type 1 alpha [*PRKAR1A*]) causes Carney complex.⁷⁴ An inactivating mutation in the gene encoding *PRKAR1A* has been identified in approximately 60% of patients who met the diagnostic criteria, and a second as yet uncharacterised locus at 2p16 has been implicated in some families.⁷⁵ Pituitary pathology has been described in a number of studies of patients with Carney complex and includes hypersomatotropinaemia and hyperprolactinaemia, which often begin in adolescence. Acromegaly in Carney complex is characterised by a slow progressive course, and aggressive pituitary tumours are uncommon. However, in many patients, clinically significant acromegaly did not manifest until after surgical treatment of their Cushing's syndrome (72% of these patients were diagnosed with Cushing's syndrome due to primary pigmented nodular adrenocortical disease), which is not surprising given the known relationship between cortisol and growth hormone.²⁰

It is important to identify clinically significant acromegaly as defined by generally applied criteria for patients with Carney complex who have elevated GH and/or IGF-1.⁵⁸ It is not uncommon for Carney complex patients to have an abnormality of GH secretion due to the underlying

pituitary hyperplasia; however, almost all will have negative imaging studies.^{74,76} For Carney complex patients with elevated IGF-1 levels, treatment with somatostatin analogues with the goal of normalising IGF-1 is recommended.^{74,77} For Carney complex patients with normal IGF-1 levels and normal pituitary imaging, but with abnormal response to oral glucose tolerance test, evaluations should be performed annually to assess for changes that may require treatment.

McCune–Albright Syndrome

MAS is a genetic (but not inherited) disorder characterised by polyostotic fibrous dysplasia, café-au-lait pigmented lesions, endocrine abnormalities (precocious puberty, thyrotoxicosis, pituitary gigantism and Cushing's syndrome) and, in rare cases, other tumours. Somatic mutations on the adenylate cyclase-stimulating G alpha protein (*GNAS* complex locus) are found in MAS.⁷⁸ *GNAS* maps to chromosome 20q13 and encodes the ubiquitously expressed Gs- α subunit of the G protein. The activation of adenylyl cyclase signalling pathways results in the phenotype of MAS including hypersomatotropinaemia. *GNAS* mutations have also been identified in sporadic GH-producing tumours.

Similar to patients affected by Carney complex or carriers of *PRKAR1A* mutations, GH excess in MAS is commonly found (in approximately 20% of patients), but pituitary tumours are not typically detectable by MRI.^{79,80} However, elevated GH levels in patients with MAS may be associated with significant morbidity due to the exacerbation of polyostotic fibrous dysplasia.^{81,82} Hypersomatotropinaemia has also been implicated in sarcomatous transformations of bone tumours in MAS patients.⁸³ Similar to patients with Carney complex, GH- and PRL-producing cell hyperplasia are common histological findings in the pituitary.^{18,81,84}

The treatment of GH-producing tumours 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 tumours or hypersomatotropinaemia without a visible tumour.^{61,64,85}

Multiple Endocrine Neoplasia Type 1

MEN1 is a disorder characterised by a predisposition to peptic ulcer disease and primary endocrine hyperactivity involving the pituitary, parathyroid and pancreas, which is inherited in an autosomal-dominant manner. The disorder is due to inactivating mutations in the *menin* gene, a tumour suppressor that has been localised to chromosome 11q13. Studies report that *menin* interacts with various proteins involved with transcriptional regulation, genome stability and cell division and proliferation.^{15,16,86,87}

Pituitary adenomas are found in approximately 30–40% of patients with *menin* mutations, most commonly PRL- (~60%) and GH- (~20%) secreting, while ACTH-secreting and non-functional adenomas represent less than 15% of MEN1-associated pituitary adenomas.^{15,36} The frequency of pituitary disease is significantly higher in familial versus sporadic MEN1 cases, although no genotype–phenotype correlation has been noted in *menin* mutation carriers.¹⁵ In addition, an increased female-to-male ratio has been reported in MEN1 patients with pituitary adenoma and acromegaly for both familial and sporadic cases.¹ A pituitary adenoma may be the first clinical manifestation of

MEN1, with the youngest reported case in a five-year-old boy with a pituitary somatomammotroph macroadenoma.⁸⁸

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 *PRKAR1A*. Homogeneous mutations refer to a similar pituitary tumour type occurring within the same family and heterogeneous mutations refer to families with two or more different tumour types.²² All pituitary tumour phenotypes have been reported in FIPA kindreds, and typically at least one prolactin- or GH-secreting adenoma is noted in each family.

In 2006, Vierimaa reported that inactivating mutations of the gene encoding aryl hydrocarbon receptor-interacting protein (AIP) were found in patients with pituitary tumours (typically acromegaly) in both sporadic and familial settings.⁸⁹ A genome-wide and DNA mapping study recently identified inactivating mutations in the AIP gene on chromosome 11q13.3. In this series, combinations of somatotropinomas, prolactinomas and mixed GH- and PRL-secreting adenomas were reported. A lack of functional AIP was shown by a loss of heterozygosity in the tumour FIPA specimens. AIP mutations were noted 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. Tumours in patients with AIP mutations are usually larger and diagnosed at a younger age than patients without AIP mutations or sporadic tumours.^{90,91} Familial growth hormone-secreting pituitary adenomas may occur as an isolated

autosomal dominant disorder (familial somatotropinoma)^{92,93} or as part of MEN1 and Carney complex.^{18,94}

Conclusions

Significant improvements in the diagnosis and treatment of pituitary tumours in childhood and adolescence have resulted from advances in diagnostic testing, neuroimaging, microneurosurgery and pharmacological interventions. Genetic syndromes such as Carney complex, MAS, MEN1 and FIPAs provide insight into the molecular basis of pituitary tumours and afford a basis for future research on the molecular mechanisms of genesis of endocrine tumours. The treatment of rare disorders such as paediatric pituitary tumours 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 tumour 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. ■

Acknowledgements

This work was supported by the US National Institutes of Health (NIH), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) intramural project Z01-HD-000642-04 to Dr Constantine A Stratakis.

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