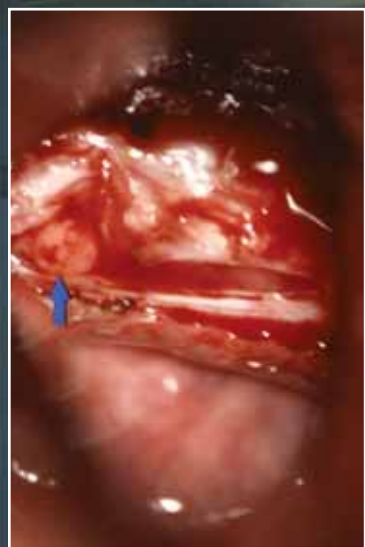
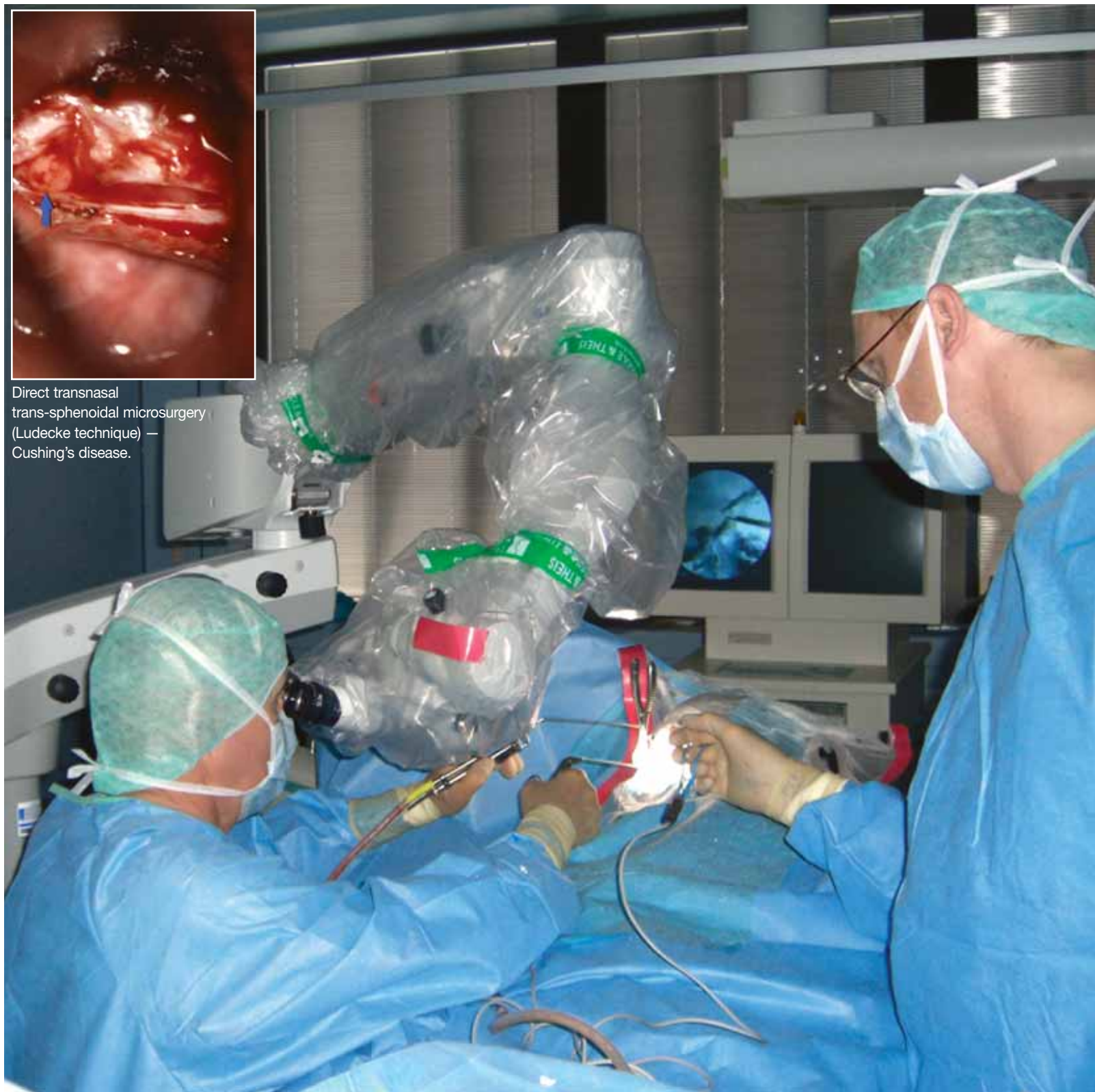


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Direct transnasal trans-sphenoidal microsurgery (Ludecke technique) — Cushing's disease.



Paediatric pituitary disorders

Background

It is now 30 years since Drs Wettenhall and Vines formed the Australasian Paediatric Endocrine Group. In the past three decades the diagnosis of pituitary conditions has improved significantly, with the availability of new, sensitive hormonal assays and MRI. The molecular basis for congenital hypopituitarism and pituitary tumorigenesis is being unravelled and therapeutic growth hormone is no longer derived from autopsy pituitaries. Trans-sphenoidal pituitary neurosurgery (also referred to as transnasal trans-sphenoidal neurosurgery) performed in specialist centres achieves high rates of remission if the tumours are diagnosed as microadenomas (<1cm) or at a resectable stage.

There are new medications to control some of these tumours.

Pituitary problems in paediatrics are rare in general practice, but if diagnosed in time, significant morbidity and life-threatening situations can be avoided. Accurate height and weight measurements taken regularly over time are critical to decision making. An orchidometer for pubertal staging in boys is also helpful. We outline the important clinical signs and symptoms, including laboratory tests and imaging and how to interpret them.

Imaging of the pituitary gland and hypothalamus

Today, MRI provides pictures of the brain and pituitary in exquisite

detail, and CT, with its lower resolution, is often unnecessary radiation.

The range of scan abnormalities in a child with hypopituitarism includes a normal or hypoplastic pituitary gland. Small glands are particularly seen in children with panhypopituitarism or with GH deficiency, as GH-producing cells make up almost two-thirds of the gland. A mere rim of tissue is called CSF sella (CSF occupies the empty sella) or empty sella syndrome, which paradoxically may not be associated with glandular hypofunction.

Pituitary stalk interruption syndrome is also known as ectopic

posterior pituitary syndrome and is a disorder of neuronal migration. Common midline anomalies include:

- Absence of the corpus callosum.
- Absence of the septum pellucidum.
- Optic nerve hypoplasia.
- Arnold–Chiari malformation.

Incidental pituitary lesions on MRI are found in about 16% of adults without clinical symptoms. The incidence in children is unknown and follow-up is as for adults. The range of pathologies is similar to that for adults, but some are found more frequently in children.

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The authors



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Congenital hypopituitarism

THE incidence of congenital hypopituitarism has been difficult to estimate. The incidence of growth hormone deficiency is about 3.5 per 100,000 children and can be seen in isolation or in combination with other hormone deficiencies. Optic nerve hypoplasia has an incidence of 6.3 per 100,000 and is frequently associated with hypopituitarism.¹

Symptoms and signs in the newborn period

Babies with hypopituitarism usually have a normal birth-weight and length because their own growth hormone is not essential for growth in utero. Growth hormone (GH), thyroid hormone and cortisol are all necessary for the maturation of hepatic enzymes. Therefore, these babies tend to develop hypoglycaemia and jaundice. Male babies may have small genitalia, as both testosterone and growth hormone contribute to phallic growth. Hypogonadism also causes cryptorchidism. Female babies do not have these extra clinical clues. The triad of hypoglycaemia, jaundice and micropenis is pathognomonic of congenital hypopituitarism.

Central adrenal insufficiency due to ACTH deficiency

Babies with cortisol deficiency are particularly prone to hypoglycaemia; this is the most potentially life-threatening of the hormone deficiencies. The babies may appear pale and jittery and then become lethargic, mottled and feed poorly. Vomiting and excessive drowsiness with high fevers (above 39°C) can also be signs of low cortisol levels. It may lead to loss of consciousness and seizures.

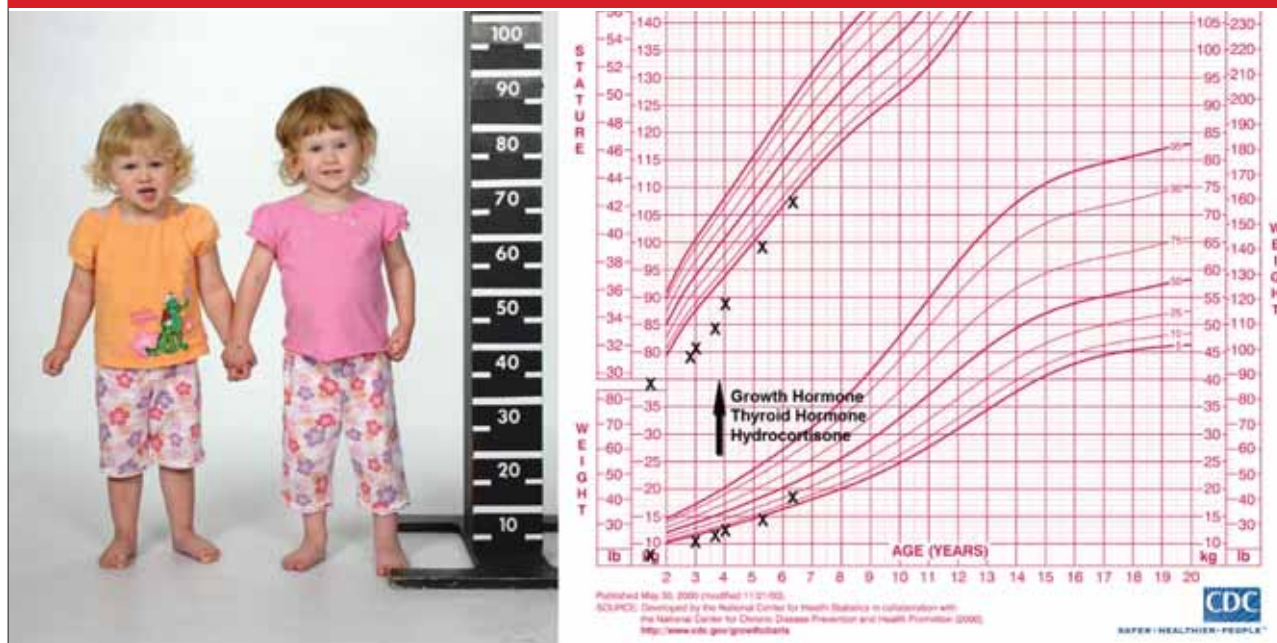
The diagnosis is confirmed by finding low ACTH and cortisol levels at the time of hypoglycaemia. The hypoglycaemia responds quickly to relatively low doses of IV glucose and frequent feeds, but ultimately appropriate hormone replacement is essential — of cortisol, and of growth hormone and/or thyroxine if these are also deficient. Jaundice may be prolonged but usually resolves, even without hormone replacement. Occasionally liver function is quite disturbed and biopsy shows giant cell hepatitis.

Treatment is oral hydrocortisone given three times daily with dose increases for intercurrent illness. Intramuscular hydrocortisone is given in emergency situations, and parents instructed in its use. A medic-alert should be worn.

Central hypothyroidism due to TSH deficiency

In Australia, the Newborn Screening Program for congenital hypothyroidism is based on TSH measurements alone. High levels indicate a primary thyroid problem

Figure 1: Growth hormone deficiency: A five-year-old girl (R) with progressive growth failure and her 2.5-year-old sister. Presentation was a hypoglycaemic episode with gastroenteritis. Free T4 low. MRI showed ectopic posterior pituitary syndrome, absent pituitary stalk and anterior pituitary hypoplasia. Photo used with permission from Stephen McNally, John Hunter Hospital.



and are promptly reported. However, TSH levels in central hypothyroidism may be low or in the normal range with a matching free T4 level that is also low or low normal. As low TSH levels are not reported and free T4 levels not measured, congenital hypopituitarism will be missed in our system and has to be diagnosed by aware GPs or paediatricians.

Symptoms of central hypothyroidism include neonatal jaundice, lethargy, hypoglycaemia and hypothermia, but are often more subtle than in primary hypothyroidism. Fontanelles may be large and slow to close.

Free T4 must be specifically requested if pituitary disease or hypothalamic disease are suspected. Mildly elevated TSH (eg, 5-6 mIU/L) can be seen in hypothalamic disease. TSH is glycosylated, and in hypothalamic disease there is a different pattern of glycosylation that makes the TSH less biologically active and increases its half-life, thus increasing TSH levels somewhat. It is common in this clinical context yet tends to be dismissed, which means that these children are missed.

Mildly elevated TSH can also indicate coexistent central hypoadrenalism, as cortisol suppresses TSH. Adrenal insufficiency should be excluded before thyroxine therapy is started, as thyroxine can precipitate an adrenal crisis.

Thyroxine replacement is extremely important for normal brain development and the aim is free T4 levels in the upper normal range. The dose cannot be adjusted based on TSH levels, as the problem is TSH insufficiency.

Hypogonadism caused by deficiency of LH or FSH (hypogonadotrophic hypogonadism)

Male babies present with micropenis with or without

cryptorchidism. Testosterone therapy is most effective in the first three months of life, as this corresponds to the physiological period of 'mini-puberty' in males. Children with Kallmann's syndrome often have anosmia (loss of smell), which occurs due to abnormalities in neural migration that affect both the olfactory bulb and the GnRH neurons in the hypothalamus.

Evidence of a midline syndrome — 'the face predicts the brain'

The developmental problems associated with congenital hypopituitarism are called midline syndromes. The greater the severity of the anomaly, the greater is the likelihood of pituitary involvement. Common associations are:

- Cleft palate (not cleft lip alone).
- Single central incisor syndrome.
- Optic nerve hypoplasia (septo-optic dysplasia).
- Absent septum pellucidum (the midline brain structure below the corpus callosum).
- Agenesis of the corpus callosum.

Optic nerve hypoplasia presents in the first few weeks after birth with failure to fix and follow, and with nystagmus (often roving). Referral to a paediatric ophthalmologist is important.

Diabetes insipidus

Excessive thirst and urination may indicate antidiuretic hormone (ADH) deficiency. Many children with septo-optic dysplasia have partial or complete diabetes insipidus. This may be masked by co-incident cortisol and thyroid hormone deficiencies because both these deficiencies impair free water clearance in the kidney. Hypernatraemia and dehydration will occur if the

baby cannot drink enough.

Diagnosis is confirmed with high plasma osmolality in the face of inappropriately low urine osmolality. Neonatal diabetes insipidus is difficult to manage, and referral to a paediatric endocrinologist is important. Infants may be more safely treated with a low renal solute load formula (that reduces obligatory urinary water losses) and hydrochlorothiazide (which concentrates the urine) than with oral desmopressin solution.

Symptoms and signs in infancy and childhood

If hypopituitarism is not diagnosed neonatally, the most common reason to suspect it is poor postnatal growth.

Growth hormone deficiency

Children with growth hormone (GH) deficiency progressively lose height relative to their peers (figure 1). At the time of diagnosis their height is usually under the third centile, unless they have tall parents, when the child's height centile is well below the centile for their mid-parental height.

Mid-parental height = (mother's height + father's height)/2 ± 6.5cm (+ for a boy, - for a girl). It is the genetic adult height target for the offspring.

The second feature is a relative excess of weight for height, carried as abdominal fat that may look like cellulite (called fat dimpling). Central hypothyroidism exacerbates this central adiposity. In contrast, in children who also have cortisol deficiency, excess abdominal fat may not be a feature. Some children may continue to be at risk of hypoglycaemia beyond the neonatal period, especially if they are fasting or vomiting. This was the presentation of the child shown in figure 1.

As skeletal growth is retarded, the child's body proportions resemble those of a

younger child. Their facial growth is also slowed and so their facial appearance is 'cherubic'. The forehead is prominent, the bridge of the nose depressed, the voice high-pitched and anterior fontanelle slow to close. Baby teeth may be slow to appear, termed delayed dental eruption. There may be irregular development and setting of permanent teeth. Bone age is delayed.

The diagnosis is made if GH levels are low at the time of hypoglycaemia and insulin-like growth factor 1 (IGF-1) levels are low or low normal. (IGF-1 is synthesised in the liver in response to GH and is the effector molecule for GH in the tissues.) If the child is not hypoglycaemic, formal growth hormone stimulation testing may be needed. Random GH levels are not diagnostic, as normal children can have undetectable levels. Treatment is with daily growth hormone injections. Initiation of GH therapy may unmask central hypothyroidism and even central hypoadrenalism.

Midline syndromes

Any child with a cleft palate, significant hypotelorism or hypertelorism (facial features too close or too far apart, respectively), and short stature should be assessed for GH deficiency. More subtle forms of cleft palate are only obvious when the child starts to speak. Children with a submucous cleft of the soft palate have symptoms such as 'nasal' speech and regurgitation of liquids out of the nose.

Symptoms and signs in adolescence

The two issues in this age group are the delayed onset of puberty and the development of further pituitary hormone deficiencies.

Delayed puberty and hypogonadotrophic hypogonadism

Delayed puberty is defined as no signs of puberty by 13

If hypopituitarism is not diagnosed neonatally, the most common reason to suspect it is poor postnatal growth.

years in girls or 14 years in boys. Bone age is delayed and bone mineral density may be already subnormal.

Spontaneous onset of puberty is less likely in a child who had signs of sex hormone deficiency in the neonatal period or has multiple pituitary hormone deficiencies. Patients may also have anosmia (Kallmann's syndrome).

Induction of puberty with sex hormones at an appropriate age is important for psychological as well as physical health and to optimise bone mineral density.

Progressive hypopituitarism

In children with certain genetic causes for hypopituitarism such as *PROP1* defects, there is progressive loss of pituitary cells, the last to fail being the ACTH-secreting cell (corticotrophs).

If patients who have previously coped well with intercurrent illness start vomiting, have high fevers and are more lethargic than expected, one must consider that these could be symptoms of cortisol deficiency. Cortisol deficiency can mimic gastroenteritis. Respiratory distress and 'air hunger' can also be a feature of cortisol deficiency and be incorrectly diagnosed as an asthma crisis.

Progressive hypopituitarism, including diabetes insipidus, occurs in patients with optic nerve hypoplasia.

Hypopituitarism and late effects in oncology patients

Hypopituitarism may develop after cranial or total body irradiation and/or high-dose chemotherapy. This is an expanding field and space restrictions do not allow us to do it justice. An excellent monograph from Dr M Zacharin is available from the Royal Children's Hospital, Melbourne.

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Precocious puberty

PUBERTY occurs when an area of the hypothalamus called the gonadostat begins to secrete gonadotrophin-releasing hormone (GnRH) in pulses of increasing frequency and magnitude. In turn, increasing LH and FSH pulses from the pituitary stimulate the gonads. A genetic or structural problem at any point in this pathway can affect puberty. Precocious puberty is defined as signs of sexual maturation before the age of eight years in girls or nine years in boys.

Hypothalamic hamartomas

Hypothalamic hamartomas cause central, gonadotrophin-dependent precocious puberty. They are a congenital malformation that consists of heterotopic neural tissue attached to the floor of the third ventricle or that is pedunculated (figure 2). They contain GnRH neurons. Intrahypothalamic lesions cause gelastic seizures (seizures characterised by laughing or crying).

Precocious puberty is far more common in girls. It may begin as early as the first or second year of life and is successfully treated by long-acting GnRH analogues. (Sustained high levels of GnRH analogues inhibit LH and FSH secretion from the pituitary, whereas pulsatile GnRH is stimulatory.)

Figure 2: Hypothalamic hamartoma (blue arrow) in a four-year-old girl with central precocious puberty and normal anterior and posterior pituitary (yellow arrow) and stalk on sagittal MRI. Coronal MRI at level of normal pituitary. Treatment with gonadotrophin-releasing hormone analogue. Images used with permission from Stephen McNally, John Hunter Hospital.



Pituitary adenomas

PITUITARY adenomas can arise from any of the six pituitary cell types (secreting prolactin, ACTH, GH, LH, FSH or TSH). They are nearly always benign. They are classified according to their diameter as micro- and macroadenomas (>10mm). If diagnosed late as large invasive tumours, they are not completely resectable, even with the best surgical techniques.

In adolescents, particularly girls, prolactinomas predominate, but are nearly always managed with medical therapy. In surgical series, corticotroph adenomas causing Cushing's disease are the most common in children, followed by somatotroph (GH) adenomas causing gigantism and acromegaly. Non-functioning adenomas are rare, in contrast to the situation in adults, where they make up nearly 50% of tumours. TSH-omas are exceedingly rare.

A family history of pituitary tumours may indicate there is an underlying genetic condition, such as multiple endocrine neoplasia type 1 (MEN1).

Cushing's disease

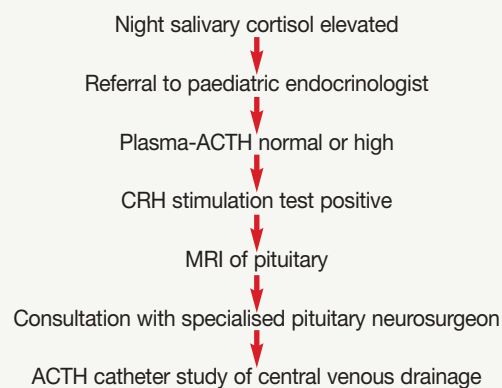
Cushing's disease is a severe metabolic disease with cortisol excess caused by an ACTH-secreting (corticotroph) pituitary adenoma. Cushing's syndrome, by contrast applies to any cause of hypercortisolaemia that is not ACTH-dependent (figure 4). It is 100 years since Harvey Cushing described the first case — a young woman with secondary amenorrhoea at age 16, with severe headache, facial plethora and hirsutism, central obesity and severe hypertension. Her disease spontaneously remitted, presumably from bleeding into the tumour. All Cushing's descriptions of pituitary cases were autopsy based, not surgical.

In children ACTH-secreting pituitary adenomas account

Figure 3: Girl with Cushing's disease three days after transnasal trans-sphenoidal microsurgery, showing the classic 'moon face' and short stature next to her normal younger sister.



Diagnostic path of Cushing's disease



for 90% of operated adenomas, and more often occur in pre-pubertal boys than in girls. In contrast, in adults they represent only 10% of all diagnosed pituitary tumours and occur predominantly in women.

The first cases described by Cushing already showed the main difficulty in diagnosis and management, namely, the minute size of pituitary adenomas, often <4mm. Despite modern MRI, these lesions may not be detected in up to 50% of cases. Advanced MRI techniques with 3 Tesla, available in some centres in Australia, could improve the detection rate.

The main clinical signs and problems in children include:

- So called 'moon face' with plethora (figure 3).

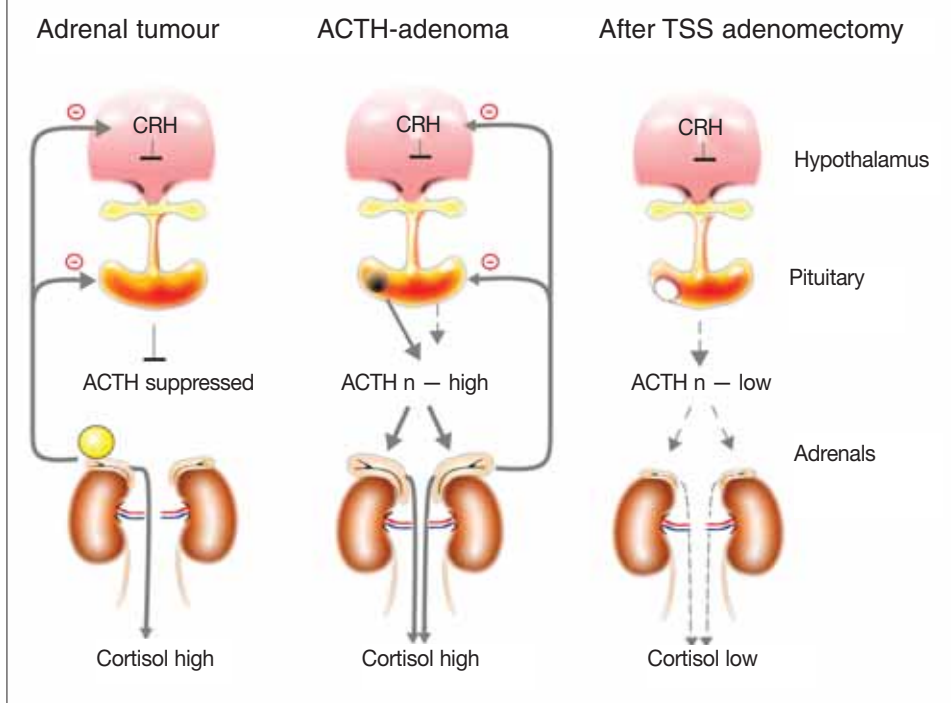
- Weight gain, which, unlike in adults, may be more generalised than central.
- Proximal myopathy, which is less evident than in adults.
- Growth failure (crossing the centiles downward).
- Signs of androgenisation occurring at the same time as delayed puberty and amenorrhoea.
- Hypertension, headaches, impaired glucose tolerance or diabetes and osteoporosis possibly also developing.

The average time from symptoms to diagnosis is two and a half years, compared with about five years in adults.

Endocrine investigations

With hypercortisolism there is a loss of diurnal rhythm, which can be easily confirmed by the measurement of free

Figure 4: Pathophysiology of (i) adrenal adenoma with low ACTH due to autonomous cortisol hypersecretion from a unilateral lesion (left); (ii) an ACTH-secreting pituitary adenoma inducing bilateral adrenal hyperplasia (middle); (iii) after selective removal of the ACTH-adenoma (right), with suppressed ACTH-secretion from the anterior lobe. Schematic drawing by Dr Mark Read.



cortisol in the saliva after 10pm. Elevated night salivary cortisol differentiates children with Cushing's syndrome from children with obesity. Obesity is almost reaching epidemic proportions yet Cushing's disease is rare. Beware the short, fat child! Most obese children are tall for their age and may have an advanced bone age. Importantly, their growth is normal. The obese child who is not growing should have a night salivary cortisol level done and see a paediatric endocrinologist. Morning cortisol levels alone are not diagnostic.

Measurement of 24-hour urinary free cortisol and low-dose dexamethasone suppression testing (1mg or 30µg/kg/day in children <40kg) are still used. Urinary free cortisol levels may be falsely low if collection is incomplete. The high sensitivity, non-invasiveness and ease of use in outpatients support

the use of the salivary cortisol technique, especially in children. If the result is pathological, referral to a paediatric endocrinologist is advised.

Polycystic ovary syndrome often presents with obesity, oligo-amenorrhoea and hirsutism, so it is reasonable to screen for Cushing's disease in this clinical setting.

Differential diagnosis is the next step to be done by the specialist.

Normal or slightly elevated ACTH levels exclude an adrenal pathology and exogenous steroid use (oral, inhaled or topical). In these latter cases ACTH is undetectable.

Significant suppression of cortisol in the low-dose dexamethasone test, and ACTH or cortisol stimulated by corticotrophin-releasing hormone are the generally accepted ways to differentiate pituitary-dependent from ectopic Cushing's syndrome (neither of adrenal nor pituitary origin). If both tests are positive, an

ectopic source is ruled out. Ectopic disease is exceedingly rare in paediatric Cushing's syndrome (thymoma, carcinoids).

For a summary of the investigation algorithm see box, left.

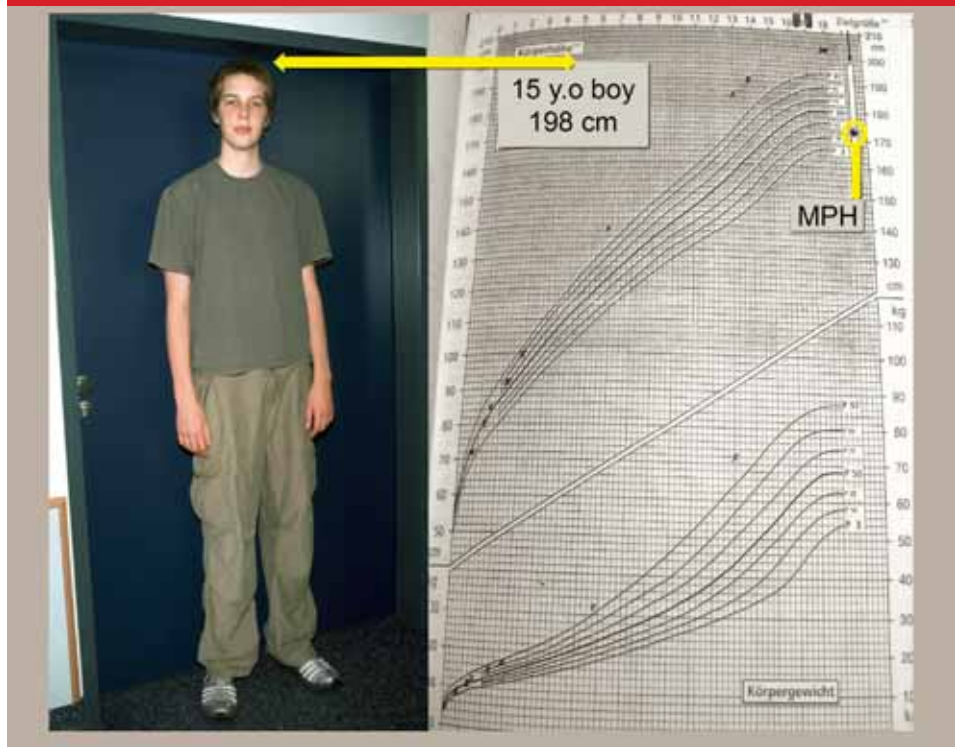
MRI of the pituitary

MRI is the next diagnostic step, after endocrine results indicate pituitary-dependent Cushing's disease. T1WI coronal and sagittal sequences, with and without gadolinium-DTPA enhancement and thin slices, have to be performed.

Invasive catheter techniques with venous blood sampling

The role of these techniques is unclear at present and not widely available. Blood sampling from the inferior petrosal sinus has been developed to distinguish between pituitary and ectopic Cushing's syndrome. Cavernous sinus sampling, as initiated

Figure 5: Boy, 15, with gigantism two days after selective transnasal trans-sphenoidal microsurgery of a 12mm GH-secreting adenoma. Complete remission.



by one of the authors (Dieter Ludecke) in 1989, is gaining wider acceptance as a more precise localisation aid for minute adenomas within the pituitary, according to Teramoto.²

Therapy

Primary therapy of Cushing's disease in children is trans-sphenoidal surgery (figure 3). Selective removal of microadenomas by experienced microsurgeons achieves remission in more than 90% of cases. A postoperative decline of ACTH and cortisol levels in the subnormal range persists for about a year (shorter than in adults) and needs adequate replacement and retesting by the endocrinologist. In 10% of cases, some pituitary deficits occur.

In case of failure of first surgery or recurrence of the adenoma, pituitary re-operation is an option but with a higher risk of pituitary deficits. Radiotherapy or medical therapies have also been used. Bilateral adrenalectomy is another option but this may stimulate growth of residual pituitary adenoma tissue (Nelson's syndrome).

Pituitary gigantism and acromegaly

Gigantism is usually due to excessive production of growth hormone from a somatotroph adenoma before the closure of epiphyseal growth plates at puberty. These tumours tend to be macroadenomas. Familial acromegaly occurs. Somatotroph hyperplasia can occur in McCune-Albright syndrome or Carney complex.

The acceleration in growth in these children crosses growth centiles upwards and predicted final height is well above their mid-parental height (figure 5). As children grow proportionately, they do not have the classic signs of acromegaly until after puberty, when, if untreated, they will develop the features seen in adults of large hands

and feet and coarsening of facial features (figure 6). Sweating is often a prominent symptom, as is headache. Visual symptoms due to optic chiasm compression may be relatively late to appear.

Differential diagnosis of tall stature and rapid growth

Rapid growth in children may be due to sex steroids, either from precocious puberty or androgen excess such as in late-onset congenital adrenal hyperplasia. Signs of sexual development will be present and bone age significantly advanced. Thyrotoxicosis also accelerates growth. Genetic causes of tall stature include Marfan syndrome and Sotos' syndrome.

Endocrine investigations

IGF-1 is synthesised under GH stimulation, mainly in the liver, and levels are stable, unlike GH, which is pulsatile. A single high serum IGF-1 level may be diagnostic but levels need to be interpreted using age- and puberty-adjusted normal ranges.

For evaluation of GH levels, an oral glucose tolerance test usually needs to be performed. If GH levels do not fall in response to the glucose load, this indicates gigantism. Unfortunately, studies in normal tall adolescents have shown that up to 30% will not show complete suppression of GH. It is also important to measure prolactin, as tumours may be mixed somato-lactotroph and may respond to dopamine-agonist therapy.

Imaging

MRI shows a pituitary adenoma in nearly every case.

Therapy for gigantism

Trans-sphenoidal surgery is first-line therapy and cure rates are high for microadenomas with an experienced pituitary neurosurgeon. Increasingly, preoperative treatment with long-acting somatostatin analogue (SSA)

injections every 4-6 weeks is being used to shrink the larger tumours.

If IGF-1 levels do not normalise after surgery, postoperative SSA is started. Somatostatin suppresses insulin secretion, so it may cause glucose intolerance or precipitate diabetes. Other side effects include gastrointestinal symptoms and gallstone formation requiring cholecystectomy.

Large and locally invasive tumours may require a multi-pronged approach including preoperative SSA, surgical reduction of the accessible tumour and postoperative SSA or the new GH-receptor antagonist, pegvisomant. Pegvisomant has to be given daily and reduces IGF-1 levels by blocking hepatic production. It does not block tumour growth. Radiation may be needed in some cases but often leads to pan-hypopituitarism.

Prolactinoma

Lactotroph adenomas or prolactinomas are the most common tumour in adolescents. They are mainly seen in girls, who tend to present with microadenomas causing primary or secondary amenorrhoea and galactorrhoea (spontaneous or provoked in up to 75% of cases). Boys nearly always present with a macroadenoma and the symptoms of mass effect, namely headache, optic chiasm compression, visual loss and hypopituitarism. Gynaecomastia is not obligatory. The size of prolactinomas correlates well with the baseline level of prolactin.

Family history is important. Prolactinomas may be part of an inherited syndrome such as MEN1, familial isolated pituitary adenomas or Carney complex.

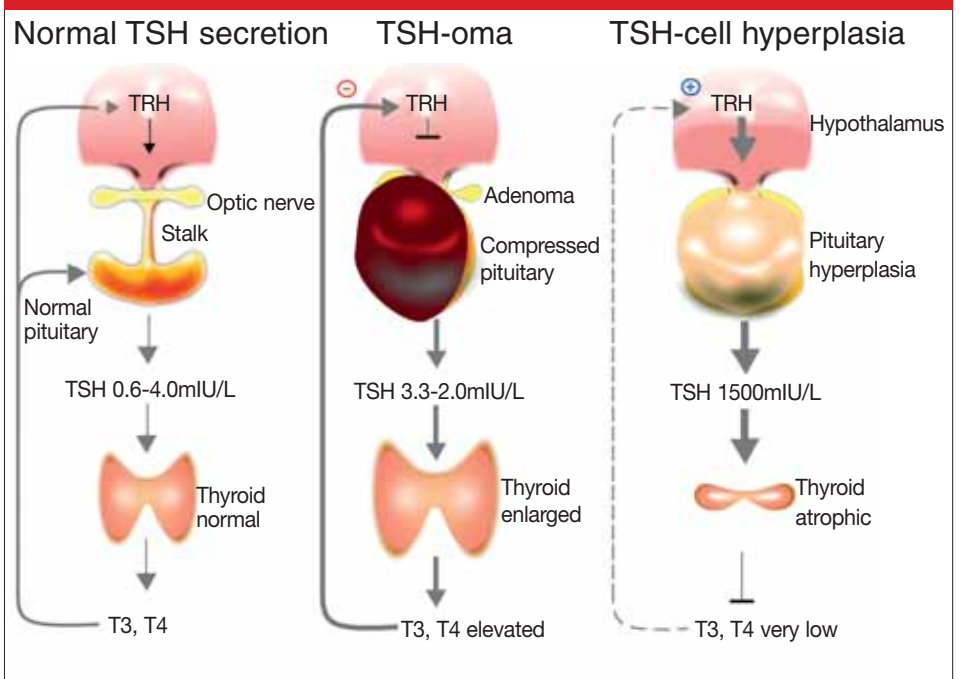
Differential diagnosis of prolactinaemia

The differential diagnosis of hyperprolactinaemia is extensive (table 1). It includes

Figure 6: Nineteen-year-old woman with gigantism and acromegaly, with her mother, after transnasal trans-sphenoidal microsurgery of a large, invasive GH-secreting pituitary adenoma (blue arrow 45mm) — partially resectable. Inset: preoperative MRI.



Figure 7: Physiological TSH secretion (left). Pathophysiology of autonomous TSH secretion from a TSH-oma without suppression by high thyroid hormone levels (middle). Primary thyroid insufficiency leading to TSH-cell hyperplasia with compression of the chiasm (right). Schematic drawing by Dr Mark Read.



all causes of loss of dopaminergic suppression. High levels of prolactin are pathognomonic of a prolactinoma and even in children on antipsychotic therapy, the cause should be clarified by an MRI.

Treatment

First-line management in prolactinomas is medical, with dopamine agonists — bromocriptine, cabergoline or quinagolide. The aim of therapy is to normalise prolactin levels and other pituitary function (LH and FSH are suppressed by high prolactin), and to decrease the tumour size.

In older children and adolescents, restoring or maintaining gonadal function will mean resumption of normal pubertal development, attainment of peak bone mass and potential fertility. In older adolescents and young women with amenorrhoea, it is important to consider the need for contraception once dopamine agonist therapy is started. Medical therapy is successful in 70-90% of patients.

Carbergoline and quina-

Table 1: Causes of hyperprolactinaemia	
Hypothalamic	Tumours, irradiation, histiocytosis
Pituitary	Adenomas, pituitary stalk lesions
Endocrine	Hypothyroidism, polycystic ovary syndrome, breast stimulation, pregnancy, lactation
Drug induced	Drugs with antidopaminergic action (eg, antipsychotics, metoclopramide)
Neurological/neurogenic	Seizures, raised intracranial pressure, chest trauma
Systemic	Renal and liver failure
Macro-prolactinaemia	Immune complex with IgG (assay artefact, not a true high prolactin)

golide (selective dopamine receptor 2 [D2] agonists), are better tolerated and more effective than bromocriptine. Gentle dose titration is important to minimise side effects. The most common are GI symptoms such as nausea, vomiting and abdominal pain. Non-specific symptoms include headache, tiredness, drowsiness and weakness. Behavioural and mood changes may also occur with exacerbation of underlying psychiatric disease.

Dizziness due to orthostatic

hypotension has been reported. Valvular cardiac problems have been reported with the much higher doses (>10) used to treat Parkinson's disease. Since the cardiac risk of long-term low-dose therapy in a young person is unknown, an echocardiogram is probably advisable.

Indications for surgery in prolactinomas include acute threat to vision and intolerance and/or resistance to dopamine agonist therapy

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with persistent hyperprolactinaemia and/or increasing tumour growth. Complications of dopamine agonist treatment that may precipitate surgery include rapid tumour shrinkage, leading to CSF rhinorrhoea, or bleeding into an adenoma, causing visual disturbance, headache and pituitary deficits. Patient preference to avoid long-term medical therapy, especially when dopamine agonist therapy is not well tolerated, is also a valid reason.

TSH-secreting pituitary adenomas

'TSH-omas' are extremely rare and nearly always overlooked in both adults and children. Even when the tumour is relatively large, the TSH level is only 3.3-20.0mIU/L with free T4 levels above the upper limit of normal (figure 7, page 27). The differential diag-

nosis is thyroid hormone resistance syndrome, also a rare entity. Very high TSH levels with low free T4 levels from longstanding primary hypothyroidism are due to TSH cell hyperplasia and can mimic an adenoma on MRI scan (figure 7). Careful interpretation of thyroid hormone test results is the key to early diagnosis and treatment.

MRI scan often shows a TSH macroadenoma, and first-line therapy in children and adolescents is neurosurgical. In adults, somatostatin analogues may be used first line.

Non-functioning (non-secreting) pituitary adenomas

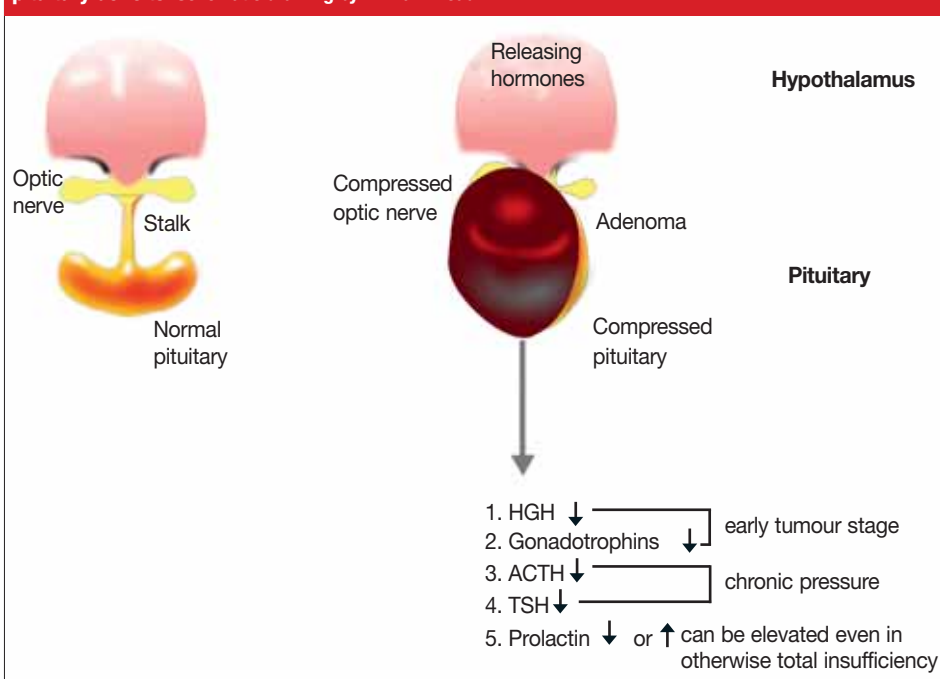
Hormonally silent pituitary tumours represent only 5% of cases in children, whereas they represent up to 50% of pituitary lesions in adults. Most present with symp-

toms of mass effect, including headache and visual disturbances with temporal field defects. Hypopituitarism due to compression of the normal pituitary may result in GH deficiency, delayed puberty or central adrenal insufficiency (figure 8). Prolactin levels may be elevated due to stalk compression, but initiating dopamine agonist therapy will have no effect on the adenoma.

Trans-sphenoidal microsurgical removal with preservation of the compressed pituitary is the first treatment option. Rarely, in cases of excessive supra- and parasellar growth, transcranial surgery and radiotherapy become necessary.

Since there is no serum marker and residual tumour may grow slowly, long-term follow-up with MRI has to be performed for more than five years, even if MRI is

Figure 8: Non-functioning pituitary macro-adenoma with asymmetrical upward pressure on the right optic nerve and compression of the anterior lobe of the pituitary to the left, resulting in pituitary deficits. Schematic drawing by Dr Mark Read.



negative postoperatively.

Incidental small tumours, without neurological or

hormonal impairment, may be monitored by endocrine observation and MRI.

Craniopharyngiomas

CRANIOPHARYNGIOMAS are the most common cause (80-90%) of a mass in the pituitary region in children. They arise from embryonic remnants of Rathke's pouch, the invagination of oral ectoderm from which the anterior pituitary develops. The incidence is 0.5-2.0 cases per million persons per year, with a bimodal peak at 5-15 years and at about 60 years. Half of all cases present in childhood. There is an equal sex distribution.

There are two different histological types. Predominant in the paediatric age is the adamantinomatous variant, which tends to be cystic.

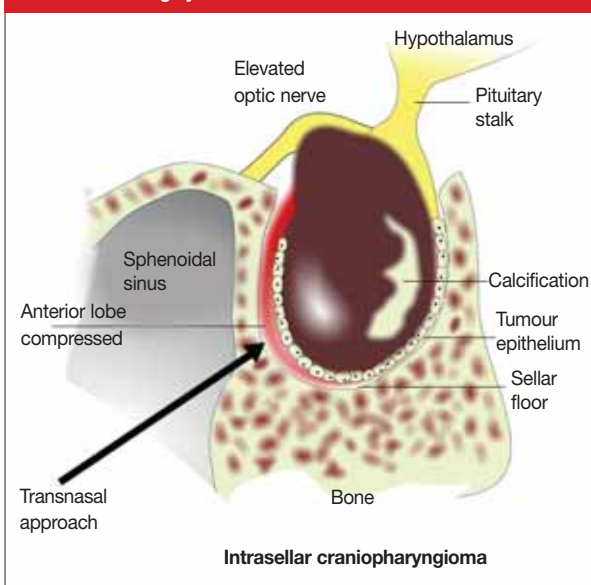
Craniopharyngiomas often impair pituitary function. Intracellular tumours develop between the adeno- and neuro-hypophyseal parts of the pituitary, so as they enlarge they displace the pituitary anteriorly. This has implications for surgery via the transnasal route (figure 9). Craniopharyngiomas often contain calcification that is best seen on CT scan.

As they expand above the sella they first impinge on the optic chiasm, then go into the hypothalamus and to the third ventricle, causing hydrocephalus (figure 10). Extension laterally into the cavernous sinus may affect ocular movements. Strabismus due to a sixth nerve palsy can also be a false localising sign of raised intracranial pressure.

The typical clinical presentation is headache and visual loss, but symptoms of hypopituitarism such as growth failure, fatigue and delayed puberty are common. Visual loss in a child may be profound before it is diagnosed, as the loss is gradual and may affect one eye more than the other. However, optic nerves that are already atrophic may decompensate acutely, with complete loss of vision within hours. In this sight-threatening situation surgical decompression is an emergency procedure.

GH deficiency is seen in 75% of patients, gonadotrophin deficiency in 40%, and hypothyroidism and hypoadrenalism in one-quarter. Dia-

Figure 9: Intracellular craniopharyngioma. Cystic and partially calcified craniopharyngioma impinging on the optic nerve. Arrow indicates transnasal surgical approach. Schematic drawing by Dr Mark Read.



betes insipidus is found in about 15% of patients. Any given patient will have their own particular 'cocktail' of pituitary hormone problems that can interact in a complex fashion, as discussed under 'Congenital hypopituitarism' (page 24).

Treatment

Observation with close follow-up by MRI may be the choice in a subgroup of paediatric patients with small cystic tumours. Some may not grow or even spontaneously regress, such as cysts due to *PROP1* mutations.

Surgery

In most cases of craniopharyngioma, microsurgical resection is the treatment of choice. Tumours with predominant suprasellar extension (about 70%) have to be operated on by the transcranial route, mainly sub-fronto-temporal (see figure 10). There are risks of damage to the chiasm, hypothalamus and pituitary stalk. This can be avoided in cases of sellar enlargement, when transnasal trans-sphenoidal surgery with its low complication rate can be chosen. Effectiveness and morbidity of surgical treatment depends

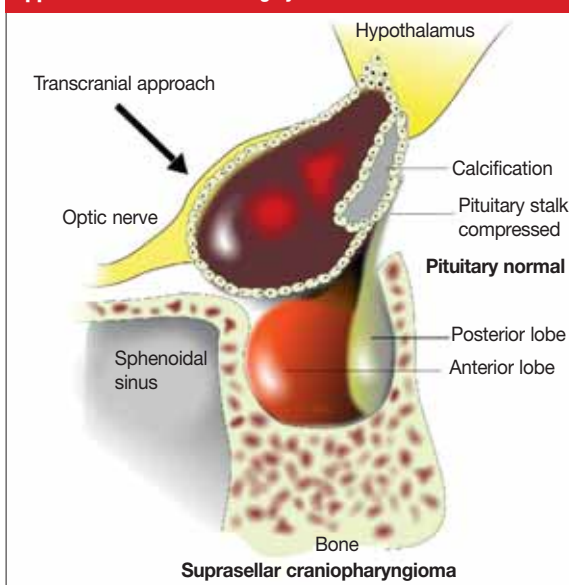
on the extension of the tumour, the equipment and the skill of the surgeon. Endoscopic approaches can achieve more radical tumor removal, eventually resulting in more function loss.

CSF fistulas are a major problem and have to be differentiated from rhinitis by beta-transferrin measurement. Frequently, reoperation is needed. Additional pituitary deficits are quite common. Postoperative adiposity occurs in about 40%, especially with hypothalamic extension, but rarely after transnasal surgery.

Radiotherapy

Since craniopharyngiomas are radiosensitive, postoperative radiotherapy has to be considered when a tumour rest (residual tissue) is present or a small rest increases during the mandatory MRI follow-ups. We suggest MRI scans at six months then yearly postoperatively unless there are other postoperative indications. Localised recurrences with distance from the optic system may be treated with stereotactic radiation. The most modern form (CyberKnife) is not yet available in Australia. This

Figure 10: Suprasellar craniopharyngioma (aubergine) with partial invasion into the hypothalamus and compression of the pituitary stalk. Arrow indicates transcranial surgical approach. Schematic drawing by Dr Mark Read.



is also applicable to adenomas if medical treatment is not effective. Most centres use gamma-knife or fractionated radiation by linear accelerator.

Hypothalamic syndrome

Tumour infiltration of the hypothalamus and damage to the hypothalamus after surgery or radiotherapy may lead to a number of problems. The most distressing is hyperphagia, which may be extreme and lead to morbid obesity. Emotional lability and rage attacks often result from attempts by parents to restrict food. Obesity may lead to sleep apnoea and daytime somnolence. There is no generally accepted pharmacological therapy. Gastric banding surgery and laparoscopic truncal vagotomy have shown immediate normalisation of the food craving.

Abnormal thirst (excessive or absent) may cause major electrolyte problems, with either hypo- or hypernatraemia. Abnormal temperature control may lead to problems of hyperthermia in summer and hypothermia in winter. Memory and intellectual impairment may compound the problems outlined above.

Hypothalamic tumours

THESE include hamartomas (see 'Precocious puberty' section, page 26), germinomas (see below), Langerhans' cell histiocytosis, and hypothalamic and optic nerve gliomas.

Germinomas

Germinomas are relatively slow-growing germ cell tumours occurring between three and 21 years of age. In one-third of patients with intracranial lesions they are localised in the pituitary stalk with the early clinical sign of diabetes insipidus. The main localisation is at the pineal gland. Serum markers such as beta-HCG are often negative. The specific marker human placental alkaline phosphatase in CSF or serum may be negative for a long time. Germinomas are highly radiosensitive and have a good prognosis with irradiation alone. Even in advanced stages, chemotherapy alone is also successful in the long term. Monitoring by experienced neuro-oncologists is essential.

Further reading, references, online resources and relevant PubMed search strategies

Available on request from
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GP's contribution

DR ROSS WILSON
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Case study

MISS JR presented at age six with premature adrenarche. Her parents had noted the appearance of pubic hair three months prior, with no axillary hair, no vaginal discharge and no facial acne. Increased sweating and body odour were also noted. From birth her growth had always been on the 90th centile for height and weight. No headache or visual disturbance were present.

Past medical history include tonsillectomy for obstructive tonsillitis at age 4½. Immunisation was complete. No allergies were noted and childhood milestones were unremarkable.

There was no family history of early puberty or tall stature, and academic performance was normal. Pubertal Tanner stage was B1 P3 on presentation (B1: prepubertal breasts; no glandular tissue, areola follows the skin contours of the chest with only the nipple

raised. P3: pubic hair becomes more coarse and curly, and begins to extend laterally). JR was normotensive. Neurological and ocular exams were normal. All tests (EUC, FSH, LH, oestradiol, 17-OH progesterone, testosterone, androstenedione and DHEAS) as well as bone age (wrist) were normal for age. Short synacthen test was also normal.

On discussion with the parents I raised the strong possibility of this being precocious puberty.

Questions for the author
Is it reasonable to continue to observe developments clinically?

Although “true” or gonadotrophin-dependent puberty may start with pubic hair alone, the history here is more suggestive of adrenarche as stated. Androgens may be adrenal or ovarian. Breast budding, ovarian and uterine enlargement on ultrasound and vaginal discharge are all signs of oestrogen action from “true” puberty. In early adrenarche, there is often a history of prematurity or



family history of polycystic ovarian disease. Bone age reports are dependent on the paediatric experience of the reporter, so re-read it, if clinically you would expect bone age to be accelerated.

Should I arrange CT brain with or without contrast?

There is really no role for brain imaging in a girl with adrenarche, but imaging of the adrenals and ovaries may be considered. If the child had gonadotrophin-dependent precocious puberty, it would be reasonable to do an MRI of the hypothalamic–pituitary

area. There is a diminishing role for CT brain scans due to the considerable radiation in a child and the lack of high definition images.

What should the management involve if further Tanner development occurs medically and psychologically?

Tanner 3 pubic hair is usually associated with axillary hair, so I wonder if this child's Tanner staging is closer to 2. To reach stage 3 in three months is quite dramatic and exclusion of an adrenal tumour would be warranted. If signs of true puberty emerge and progress quickly, then consideration would be given to suppression of puberty with GnRH analogue therapy. Early adrenarche does not necessarily imply puberty will be early too.

Given JR's parents are of discrepant heights (mother >185cm; father about 168cm), could this be purely a genetic issue?

Yes. Her tall stature is probably from her mother, but this does not explain

her early adrenarche.

General question for the author

At what age with precocious puberty does one discuss eventual height of the patient and the outlook for sensitive issues such as contraception?

Estimated mature height predictions are only available for bone ages above six years. Puberty may start even in the first one or two years of life! The youngest pregnancy recorded was at age five years in the Andes.¹ A study in Sweden showed early menarche (<10 years) was associated with shorter stature, excess weight as an adult, earlier sexual experiences and disruption to academic pursuits.² Parents need to be informed, but the child should be given age-appropriate explanations.

1. *La Presse Medicale* 1939; 47:744.
2. Johansson T, Ritzén EM. Very long-term follow-up of girls with early and late menarche, In: Delemarre-van de Waal HA (editor). *Abnormalities in Puberty. Scientific and Clinical Advances*. Karger, Basel, 2005.



How to Treat Quiz

Paediatric pituitary disorders
— 18 February 2011

1. Which TWO statements are correct?

- a) Regular and accurate height and weight measurements are critical for the detection and management of pituitary disease in children
- b) Babies with hypopituitarism with growth hormone deficiency are usually small and underweight at birth
- c) Hypoglycaemia and jaundice in infants may be due to deficiency of growth hormone, thyroid hormone or cortisol
- d) Cortisol deficiency in infants is usually a mild sub-clinical condition

2. Which TWO statements are correct?

- a) Central adrenal insufficiency is confirmed by finding high ACTH and low cortisol levels at the time of hypoglycaemia
- b) The Australian Newborn TSH Screening Program reliably detects primary hypothyroidism
- c) The Australian Newborn TSH Screening Program reliably detects central (pituitary) hypothyroidism
- d) Symptoms of central hypothyroidism include neonatal jaundice, lethargy, hypoglycaemia and hypothermia

3. Which TWO statements are correct?

- a) Both TSH and free T4 are needed to diagnose pituitary or hypothalamic hypothyroidism

- b) Mildly elevated TSH excludes hypothalamic hypothyroidism.
- c) In an infant with hypothyroidism, thyroxine replacement is essential for normal brain development
- d) In central hypothyroidism, thyroxine replacement dosage is adjusted according to TSH levels

4. Which TWO statements are correct?

- a) Male babies with a deficiency of LH or FSH usually have normal genitalia
- b) In male babies with a deficiency of LH or FSH, testosterone therapy is most effective if started in the pre-pubertal period
- c) ‘Midline syndromes’ associated with congenital hypopituitarism include cleft palate, single central incisor syndrome, or optic nerve hypoplasia
- d) Optic nerve hypoplasia presents in the first few weeks after birth with failure to fix and follow, and with nystagmus

5. Which TWO statements are correct regarding GH deficiency in children?

- a) For a child of tall parents, the height centile is well below the centile for their mid-parental height
- b) There is a relative excess of weight for height, carried as abdominal fat
- c) The child's body is small and the proportions resemble those of an adult

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY

www.australiandoctor.com.au/cpd/ for immediate feedback

- d) Low random GH levels are diagnostic

6. Which THREE statements are correct?

- a) Delayed puberty is defined as no signs of puberty by 13 years in girls or 14 years in boys
- b) Induction of puberty with sex hormones is important for psychological and physical health and to optimise bone mineral density
- c) Precocious puberty is defined as signs of sexual maturation before the age of eight years in girls or nine years in boys
- d) Cushing's disease in children can mimic both gastroenteritis and asthma crises

7. Which TWO statements are correct regarding Cushing's disease in children?

- a) In Cushing's disease the cortisol excess is caused by an ACTH-secreting pituitary adenoma
- b) Macroadenomas (>10mm) are the most common pituitary lesions in Cushing's disease and are easily detectable with imaging
- c) Weight gain in children may be more generalised than central
- d) Height is unaffected

8. Which TWO statements are correct regarding Cushing's disease in children?

- a) Androgenisation occurs as well as delayed puberty and amenorrhoea

- b) Night salivary free cortisol level is low
- c) Low ACTH levels exclude an adrenal pathology and exogenous steroid use
- d) Elevated night salivary cortisol level differentiates children with Cushing's syndrome from those with obesity

9. Which TWO statements are correct regarding gigantism and acromegaly?

- a) Sweating and headache are common symptoms
- b) Differential diagnosis of rapid growth in children includes sex steroid excess and thyrotoxicosis
- c) Random elevated GH levels are always diagnostic
- d) Medical therapy for GH-secreting adenomas involves somatostatin inhibitors

10. Which TWO statements are correct?

- a) First-line management in prolactinomas is surgery
- b) Indications for surgery in prolactinomas include acute threat to vision and intolerance and/or resistance to dopamine agonist therapy
- c) Non-secreting pituitary adenomas are never associated with endocrine dysfunction
- d) Craniopharyngiomas may present with headache, visual loss and symptoms of hypopituitarism

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at www.australiandoctor.com.au. Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

NEXT WEEK The next How to Treat looks at blistering skin disorders. The authors are **Dr Adrian Lim**, dermatologist and phlebologist, director of training, NSW Faculty of the Australasian College of Dermatologists, and in private practice, Bondi Junction and Sydney CBD, NSW; and **Dr Patricia Lowe**, staff specialist, Royal Prince Alfred Hospital, Camperdown, and dermatologist in private practice, Drummoyne and Sydney CBD, NSW.

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