Paediatric pituitary disorders

Background

IT is now 30 years since Drs Wett-...
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 hypothyroid,蝶形 rash, central adenopathy, patchy pinhead syphilis, absent pituitary stalk and anterior pituitary hypoplasia. Photo used with permission from Stephen McDonald, John Hunter Hospital.

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

Precocious 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 that is pulsatile (figure 2). They contain GnRH neurones. 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.

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. TSHomas 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 hypercortisolism. 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 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 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.

Various imaging techniques can be used to diagnose Cushing’s disease. Below is a detailed explanation of each:

- **Magnetic Resonance Imaging (MRI)**: MRI is the next diagnostic step, after endocrine results have been obtained. MRI of the pituitary is the most sensitive test for detecting pituitary adenomas. MRI can detect adenomas as small as 1 mm.
- **Computed Tomography (CT)**: CT is less sensitive than MRI and is not as widely available. However, it is more accessible and may be used when MRI is not available.
- **Endocrine Tests**: Endocrine tests are used to confirm the diagnosis of Cushing’s disease and to rule out other causes of hypercortisolism. The tests include:
  - **24-hour Urinary Free Cortisol**: This test measures the amount of cortisol excreted in the urine over a 24-hour period. Normal values range from 30 to 100 µg/24 hours in adults and 10 to 40 µg/24 hours in children.
  - **Morning Plasma ACTH**: This test measures the level of ACTH in the blood. Normal values range from 5 to 50 pg/mL in adults and 1 to 10 pg/mL in children.
  - **Dexamethasone Suppression Test**: This test measures the response of the pituitary gland to a small dose of dexamethasone, a synthetic cortisol analogue. Normal values are less than 1 µg/dL in adults and less than 0.5 µg/dL in children.

Depending on the results of these tests, further investigations may be required, such as:

- **Gonadotrophin Suppression Test**: This test measures the response of the pituitary gland to a large dose of luteinising hormone-releasing hormone (LHRH). Normal values are less than 15 µg/dL in adults and less than 5 µg/dL in children.
- **Gonadotrophin Suppression Test with Corticotrophin**: This test measures the response of the pituitary gland to a combination of LHRH and ACTH. Normal values are less than 20 µg/dL in adults and less than 10 µg/dL in children.

If the diagnosis of Cushing’s disease is confirmed, the next step is to identify the source of the excess cortisol. This is typically done using a combination of MRI and endocrine tests.

**Treatment**

The treatment of Cushing’s disease depends on the underlying cause. The most common cause is an adenoma of the pituitary gland, which can be surgically removed. Other causes, such as ectopic ACTH production, are treated with medical therapy, such as adrenocorticotropic hormone (ACTH) inhibitors. In severe cases, surgery may be necessary.

Precocious puberty is managed with medical therapy, such as GnRH analogues, to suppress the pituitary gland and reduce the production of sex hormones. Surgery may be considered in cases where medical therapy fails or is not suitable.

**Conclusion**

Cushing’s disease is a severe metabolic disease with cortisol excess caused by an ACTH-secreting (corticotroph) pituitary adenoma. Precocious puberty is defined as signs of sexual maturation before the age of eight years in girls or nine years in boys. Pituitary adenomas can arise from any of the six pituitary cell types. Cushing’s disease is treated with surgery or medical therapy, depending on the underlying cause.
Pharmacology and hypothalamicpituitary axis

- Endocrine investigations include Marfan syndrome and Sotos' syndrome.
- Testing for acromegaly and gigantism usually involves growth hormone levels and other pituitary functions.
- Treatment for gigantism includes dopamine agonist therapy.
- Pregnancy, lactation, and breast stimulation are contraindications to dopamine agonist therapy.
- Dopamine agonist therapy may be used to decrease tumour size before surgery.
- Trans-sphenoidal surgery is another option but with a high risk of postoperative hypopituitarism.

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. Somatic hypertrophy 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. 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. 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 variable, unlike GH, which is pulsatile. A single high serum IGF-1 level may be diagnostic, but levels need to be interpreted against 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 and the symptoms of prolactinomas are most commonly seen 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 prolactinomas are the most common tumour in adolescents. 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.

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 prolactinomas

The differential diagnosis is hyperprolactinaemia (extensive Table 1). It includes all causes of loss of dopamine 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 functions (LH and FSH are suppressed by 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.

Tumours, irradiation, histiocytosis

Hypothyroidism, polycystic ovary adenomas, pituitary stalk lesions

Renal and liver failure

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.

Therapy

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

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

Figure 5: Boy, 10, with gigantism two days after selective trans-sphenoidal microsurgery of a 12mm invasive adenoma. Complete remission of GH excess and growth but late appearance of facial features

Figure 6: Nineteen-year-old woman with gigantism and acromegaly, with her mother, after trans-sphenoidal trans-sphenoidal microsurgery of a large, invasive (dopamine-agonist secreting) pituitary adenoma (blue arrow 4mm) – partially resectable. Insert: 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 deficient leading to TSH-cell hyperplasia with compression of the chiasm (right).

<table>
<thead>
<tr>
<th>Table 1: Causes of hyperprolactinaemia</th>
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<tr>
<td><strong>Hypothalamic</strong></td>
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<tr>
<td>Tumours, irradiation, histiocytosis</td>
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<tr>
<td>Drugs with antipsychomimetic action (e.g., antipsychotics, metoclopramide)</td>
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<tr>
<td>Immune complex with IgG (assay artefact, not a true high prolactin)</td>
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<tr>
<td>Lipid abnormalities</td>
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Unusual presentations have been reported. Valvular cardiac problems have been reported with the much higher doses (>20) 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.
from previous page

with persistent hyperprolacti-
noma and/or increasing tumour growth. Complica-
tions of dopamine agonist treatment that may precip-
tate 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 ther-

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 27). The differential diag-

craniopharyngiomas

CRANIOPHARYNGIOMAS are the most common cause (80-90%) of a mass in the pituitary region in chil-
dren. 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 histologi-

cranial and parasellar growth, tran-}

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craniopharyngiomas often impact

The typical clinical presentation

CRANIOPHARYNGIOMAS

 Cranio-

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

Cranio-

Figure 10: Suprasellar craniopharyngioma (asunder) with partial invasion into the hypothalamus and compression of the optic chiasm. Transcranial approach. Schematic drawing by Dr Mark Read.

Hypothalamic tumours

THESE include hamartomas (see ‘Precocious puberty’ section, page 26), germino-
momas (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 spe-

Further reading, references, online resources and relevant

Available on request from

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Cont’d page 32
Case study
MISJ 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 included tumescence for obstructive tonsillitis at age 4½. Immunisation was complete. No allergies were noted and childhood milestones were unre- markable.

There was no family history of early puberty or tall stature, and academic performance was normal. Pubertal Tanner stage was BR P1 on presentation (B1: prepubertal breasts; B2: areola observed). The high peak for age was noted.

Questions for the author
Is it reasonable to continue to observe developments clinically?
Although “true” or gonadotropin-dependent puberty may start with pubic hair alone, the history here is more suggestive of adrenarche as stated. Androgens may be oestrogen 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 premature 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 no real 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 quality 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 JRV’s parents are of discrepant heights (mother >185cm; father about 180cm), could this be purely a genetic issue?
Yes. Her tall stature is probably from her mother, hence 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 or two years of life.

The youngest pregnancy recorded was at age five years in the Andes. A study in Sweden showed early menarche (<10 years) was associated with shorter stature, excess weight as an adult, earlier sexual experiences and disrup- tion to academic pursuits. Parents need to be informed, but the child should be given age-appropriate explanations.

1. Johansson T, Ritzèn EM. Very early menarche - an adolescent disease? 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. Parents need to be informed, but the child should be given age-appropriate explanations.

2. Julian McAllan
3. La Presse Medicale 1939; 47/74.

References

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