Investigating precocious puberty in boys

ERIN SHARWOOD BSc/BA, MB BS, DCH
JENNIFER BATCH MB BS, MD, FRACP

Case scenarios are used in this section to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

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Dr Sharwood is an Endocrinology Fellow at the Lady Cilento Children's Hospital, Brisbane. Professor Batch is a Paediatric Endocrinologist at the Lady Cilento Children's Hospital, Brisbane and in private practice at Greenslopes Specialist Centre, Greenslopes, Qld.

SERIES EDITOR: Dr Bernard Champion BEc, MB BS, BSc(Med)(Hon 1), FRACP, MMedEd is a Lecturer at Sydney Medical School Nepean and The University of Sydney; and Head of Department – Endocrinology and Diabetes, Nepean Blue Mountains Local Health District, Penrith, NSW.

Pubertal changes in boys typically occur between the ages of 9 and 14 years. True precocious puberty in boys is rare and can be easy to miss. Puberty is considered precocious in boys when it occurs before the age of 9 years, representing more than two standard deviations below the mean age of 11.5 years. Although precocious puberty in girls (before the age of 8 years) is usually benign, early puberty in boys is much less common and much more worrying. Signs of puberty, including testicular enlargement, presence of pubic hair, adult body odour and voice changes, in boys younger than 9 years should be investigated promptly, because precocious puberty in a boy is frequently a sign of serious underlying pathology.

Case 1. James

James is a 6-year-old boy with cerebral palsy and hydrocephalus. He has a ventriculoperitoneal shunt in situ, which is working well. While attending their GP for his yearly flu vaccine, his mother mentions that she has noticed a moderate amount of thickened pubic hair when helping James with toileting. He has mild facial acne and his mother feels he has been more irritable lately. She has not noted any change in his voice.

James's height is tracking along the 25th percentile (Figure 1). Pubertal examination reveals growth of long, slightly curly hair at the base of his penis. His scrotum is not pigmented and his testes do not appear to be enlarged, measuring 1 cm along the long axis (2 mL, i.e. prepubertal).

Is James in early puberty?

James's history of hydrocephalus puts him at risk of precocious puberty, and he now has signs of androgen activity with oily skin and early pubic hair development. His testes, however, remain small. It is helpful to determine whether his physical changes are related to true, pituitary-driven precocious puberty or increased secretion of adrenal androgens.

What investigations should be performed?

Baseline blood tests from James will help determine the source of his androgens. Tests include measurement of levels of follicle-stimulating hormone (FSH), luteinising hormone (LH) and testosterone, as well as dehydroepiandrosterone sulfate (DHEAS) and 17-hydroxyprogesterone (17-OHP). Rarely, congenital adrenal hyperplasia can present late with gonadotrophin-independent precocious puberty. A bone age x-ray of James's left wrist and hand should also be requested.

The results of these investigations are discussed later in this article.

Case 2. Chris

Chris is a 7-year-old boy who presents to his local GP with a history of extreme lethargy. He has not been himself since having his tonsils removed two months ago, and his voice remains croaky. Chris's father also mentions that over the past six months, Chris has developed some pubic hair, but no underarm hair. He is surprised by this, because he did not enter puberty himself until age 13 years. Aside from recurrent tonsillitis, Chris has no other medical history.

Chris is sleeping more than usual, and prefers to curl up under a blanket in front of the TV after school rather than playing outside. He has not been eating well since the operation, although his throat is not sore. He looks thin, and has become taller in the past few months. Chris drinks from his water bottle regularly throughout the consultation, and his father remarks that

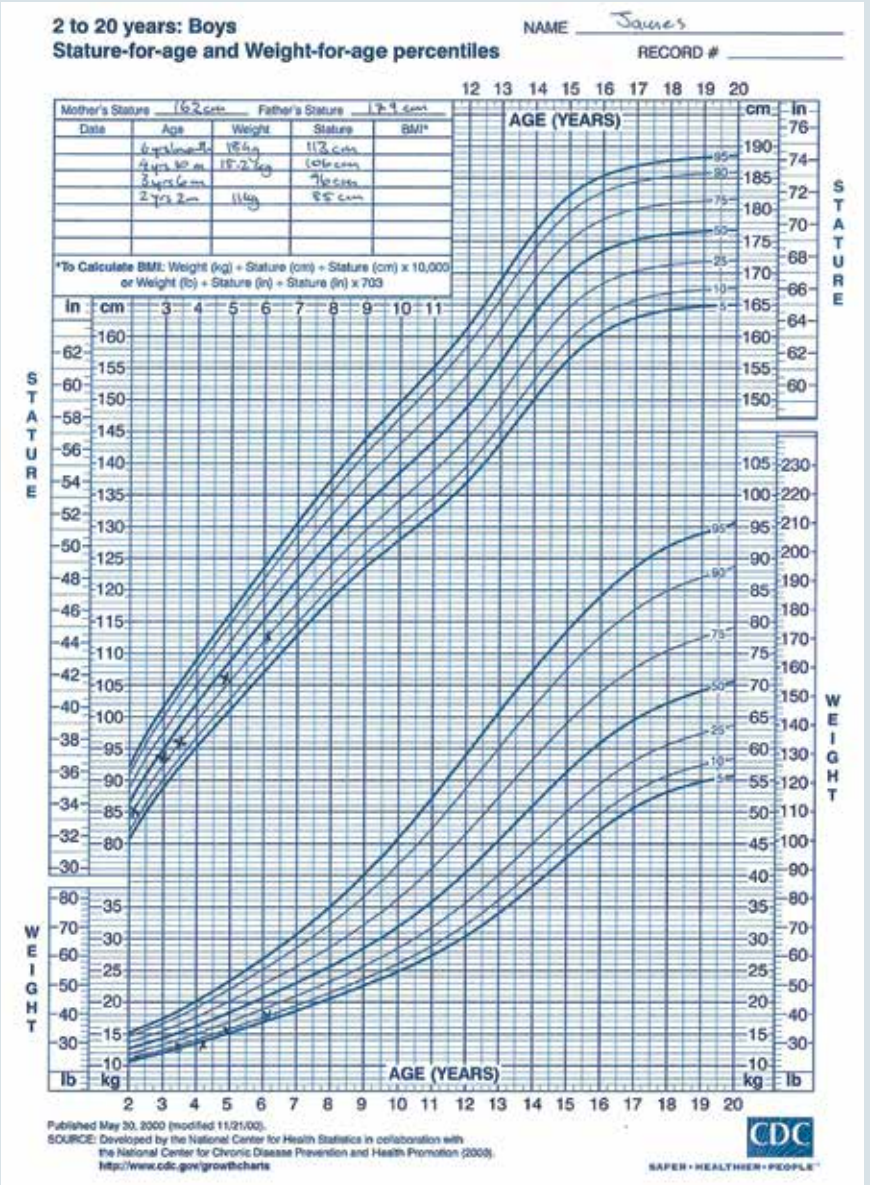

Figure 1. Growth charts for James (case 1) showing his height tracking along the 25th percentile.

Chris is always thirsty. He wonders if Chris is tired because he is waking up multiple times during the night to pass urine.

What should be looked for on examination?

Chris's presentation is broad and examination needs to cover multiple systems. These include assessment for signs of infection, assessment of his growth and nutrition, and pubertal development.

Chris's temperature, heart rate, respiratory rate and blood pressure are checked and are all at the lower limit of normal. Chris's height is 127 cm and his weight is 26 kg. He is well hydrated and he looks tired but not unwell. His tonsillar bed is completely healed, with no swelling of cervical lymph nodes. His thyroid is smooth and not enlarged, his chest is clear and his abdomen is soft. Chris's neurological examination is normal. He has no axillary hair, but has thick, dark, adult type pubic hair at the base of his elongated penis (7 cm stretched penile length). His scrotum is pigmented and his testes are enlarged, measuring 3 cm (6 mL, i.e. pubertal) bilaterally.

Are there any other assessments or bedside tests that could be performed today?

Comparing Chris's height and weight today with previous measurements, along with his expected height percentile based on mid-parental height, can give valuable insight into suspected changes in growth pattern. Given his history of polyuria and polydipsia, he should have a finger-prick measurement of his blood glucose level (BGL), along with a urine dipstick test for glucose, ketones and specific gravity.

Chris's height plots between the 75th and 90th percentiles (Figure 2), whereas at his previous measurement one year ago he was tracking along the 50th percentile. His body mass index is 16 kg/m^2. Chris's father is 176 cm and his mother is 165 cm, placing his midparental height on the 50th percentile. This confirms that Chris's growth velocity has increased above the expected level, suggesting a pubertal growth spurt.

Chris's finger-prick BGL measurement is normal at 5.2 mmol/L, and his urine dipstick shows no glucose or ketones, and a specific gravity of 1.000, which is low, and indicates dilute urine.

Chris's GP has not seen a 7-year-old in puberty before and is concerned by Chris's other symptoms. She knows this needs to be investigated, and decides to call her local children's hospital to ask the endocrinology team for advice.

What investigations should be performed for Chris?

Chris has several issues that require investigation.

Chris's pubertal changes should be investigated with measurement of his levels of FSH, LH and testosterone. A full pituitary screen should also be performed, including measurement of his levels of thyroid-stimulating hormone (TSH), thyroxine (free T4), adrenocorticotrophic hormone (ACTH), cortisol, prolactin and insulin-like growth factor-1 (IGF-1; a marker of growth hormone production). A full blood count should be performed, as well as measurement of urea, electrolytes and creatinine and test for osmolality. These blood tests are best performed first thing in the morning, due to increased secretion of gonadotrophins, growth hormone

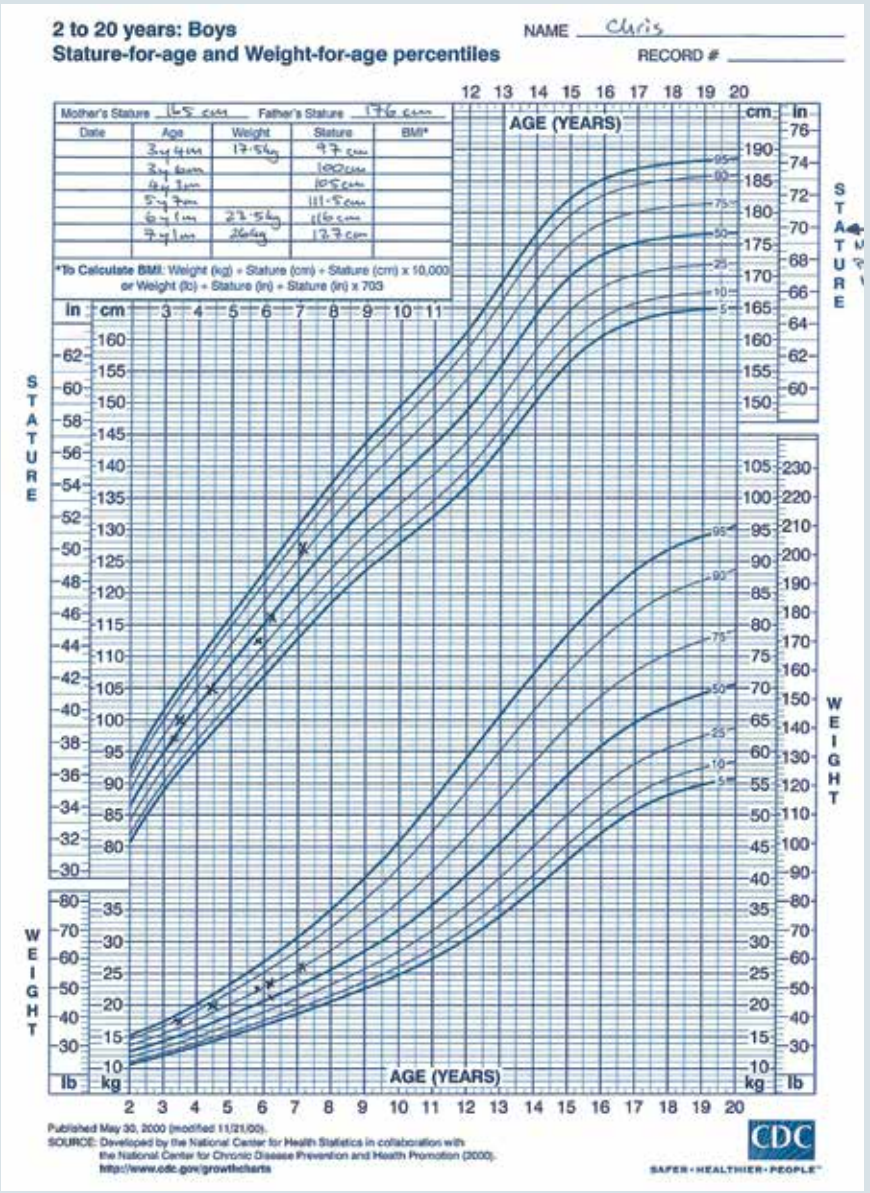

Figure 2. Growth charts for Chris (case 2) showing his height tracking between the 75th and 90th percentile, an acceleration from the 50th percentile a year earlier.

and ACTH overnight and in the early morning.

A paired urine osmolality can be useful in assessing for diabetes insipidus. Asking the family to monitor how much Chris is drinking throughout the day and night, without restricting his access to water, can also be helpful.

A bone age x-ray of the left wrist and hand should also be requested.

Discussion of investigation

A bone age examination gives an estimate of skeletal maturation and is compared against chronological age. An advanced bone age is indicative of exposure to sex steroids. Both boys show signs of advanced bone age (Table 1 and Figure 3); this will be an important marker to track their progress over time.

James

James's presentation without increased testicular size is likely to be due to early production of adrenal androgens (known as premature adrenarche or premature pubarche). The cause of this is unknown. James is also at risk of gonadotrophin-dependent precocious puberty due to his brain injury.

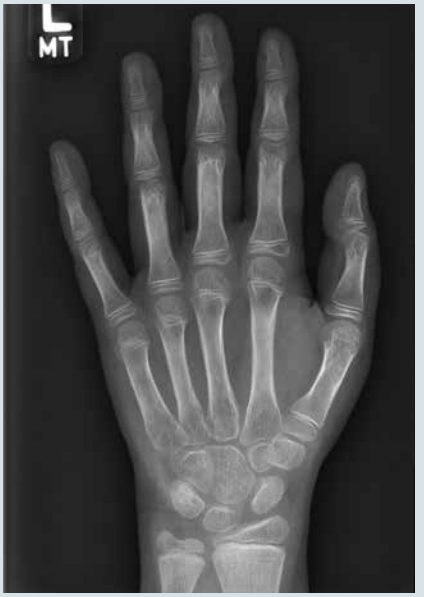

Figure 3. Advanced bone age seen on x-ray of Chris's left hand and wrist.

James is referred to his local paediatric endocrinologist, who performs gonadotrophin-releasing hormone (GnRH) stimulation testing to exclude true precocious puberty. The results of this test are normal, confirming the diagnosis of premature adrenarche, which does not require any treatment. James's GP continues to assess his pubertal status yearly, to monitor for signs of central precocious puberty.

Chris

Chris's blood test results confirm a diagnosis of precocious puberty, and elevated levels of gonadotrophins (LH and FSH) show that his puberty is driven by the pituitary gland. In combination with a low T4 level and an inadequate TSH response, this picture is very concerning for intracranial malignancy affecting pituitary function.

Chris's GP again discusses these results with the local children's hospital, and Chris is referred urgently to the emergency department. An MRI is arranged, and further blood tests are performed to check for tumour markers alpha fetoprotein (αFP) and human chorionic gonadotrophin (hCG).

Chris's MRI shows a large central mass at the optic chiasm (Figure 4), causing pressure on the pituitary gland. Further investigation confirms

Table 1. Results of investigations in James and Chris

Investigation	James	Chris	Normal range in prepubertal boys
FSH	0.9	8*	<6.0 U/L
LH	<0.2	7*	<5.0 U/L
Testosterone	0.5*	12*	<0.5 nmol/L
TSH	1.9	2.2	0.3 to 4.8 mIU/L
T4	12	6.3*	9.0 to 19 pmol/L
ACTH	18	14	10 to 50 ng/L
Cortisol	402	326	60 to 570 ng/L
17-hydroxyprogesterone	2.0	–	0.2 to 3.0 nmol/L
DHEAS	11	–	1 to 11 µmol/L
IGF-1	–	3.5	2.6 to 45 nmol/L
Prolactin	–	224	78 to 428 mU/L
Bone age	7 years (mildly advanced)	10 years (advanced)	

* Abnormal results.
Abbreviations: ACTH = adrenocorticotrophic hormone; DHEAS = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; IGF-1 = insulin-like growth factor 1; LH = luteinising hormone; T4 = thyroxine; TSH = thyroid-stimulating hormone.

this mass to be an optic glioma. Precocious puberty occurs because optic gliomas, which involve the optic chiasm, may disrupt normal hormonal function of the nearby pituitary gland.

Chris is treated with chemotherapy, and his puberty suppressed with intramuscular gonadotrophin analogue until an appropriate age.

Differences between James and Chris

James and Chris have important differences in their presentation (Table 2). These differences suggest different aetiologies, and Chris's presentation contains red flags for more urgent investigation, with testicular enlargement, lethargy, appetite disturbance, polydipsia and polyuria suggesting pituitary gland involvement and intracranial pathology.

Conclusion

Precocious puberty is uncommon in boys, but its presence demands thorough evaluation. Evidence shows that up to two-thirds of cases

Table 2. Comparison of presentations in James and Chris

Presentation	James	Chris
Medical history	Hydrocephalus resulting in cerebral palsy	Tonsillectomy only
Current presentation	Otherwise well	Lethargy, changed behaviour, anorexia
Growth	Tracking along percentile lines	Growth spurt crossing percentile lines
Voice changes	Not present	Present
Scrotal development	Nonpigmented	Pigmented
Testicular volume	2 mL bilaterally (prepubertal)	6 mL bilaterally (pubertal)
Stretched penile length	5 cm, about 25th percentile	7 cm, about 90th percentile

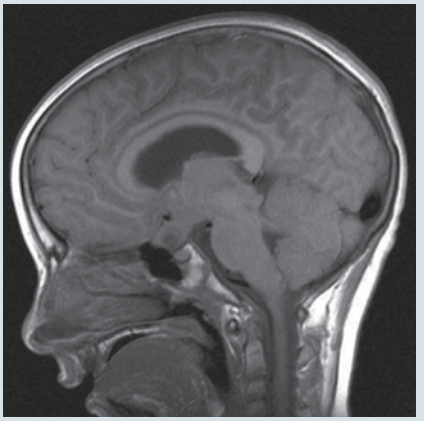

Figure 4. Chris's MRI showing a large central mass at the optic chiasm.

are due to neurological abnormalities, including central nervous system tumours. There are also rare causes of gonadotrophin-independent precocious puberty in boys, including exogenous testosterone administration, unrecognised congenital adrenal hyperplasia and genetic forms such as 3β-hydroxysteroid dehydrogenase 2 deficiency, DAX-1 deficiency and familial male-limited precocious puberty (testotoxicosis).

The GP has an important role in the detection of abnormal pubertal development in children and adolescents. This is particularly important in boys where true precocious puberty may be the manifestation of serious underlying pathology. **ET**

Further reading

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The *Hormones and Me* series of booklets, available through the Australasian Paediatric Endocrine Group (www.apeg.org.au) is a patient resource. *Puberty and its problems* covers indications and treatment options for children with abnormal pubertal development (© 2011, Merck Serono Australia).

COMPETING INTERESTS: None.