Investigating precocious puberty in girls

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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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General practice is a common site for the first presentation of many important endocrine disorders, including precocious puberty. This relatively common condition in girls may be associated with serious underlying pathology, and has the potential to cause significant psychosocial distress to the child and family. The cases presented in this article help demonstrate how to select and correctly interpret investigations for girls in early puberty, ensuring the best long-term clinical and psychosocial outcomes.

Pathophysiology

Normal physiology of puberty

Puberty is the appearance of secondary sexual characteristics combined with increased growth velocity and the maturation of primary sexual organs.[1] It is triggered by pulsatile secretion of hypothalamic gonadotrophin-releasing hormone (GnRH), which in turn results in secretion of the gonadotrophins follicle-stimulating hormone (FSH) and luteinising hormone (LH) from the anterior pituitary (Figure 1). The resulting oestradiol surge results in breast development, as well as growth of the uterus and its endometrial lining, and ultimately in menstrual bleeding (menarche).

Genetic and environmental factors control the onset of puberty through their effects on this hypothalamic–pituitary–ovarian axis.[2] Axillary and pubic hair growth, acne and the development of body odour (known as adrenarche) occur as a result of increased androgen secretion. The androgens may come from either the maturing ovary or from the adrenal glands. In girls, these excess androgens may cause virilisation.

Distinguishing central from peripheral precocious puberty

Precocious puberty in girls is defined as the onset of breast development (thelarche) and/or pubic hair (adrenarche) before the age of 8 years, or menarche before the age of 9.5 years.[2] It is important to distinguish central from peripheral precocious puberty because the investigations and management for each differ considerably.

In central precocious puberty, maturation of secondary sexual characteristics comes from central nervous system (CNS) activation of the pituitary–gonadal axis. In patients with central precocious puberty, it is imperative to exclude a CNS lesion, such as a brain tumour, by performing an MRI of the brain and pituitary gland. The younger the patient presenting with central precocious puberty, the more likely there will be a CNS lesion (20% in patients younger than 6 years of age *vs* 2% in those aged 6 to 8 years).[3] Peripheral precocious puberty occurs through autonomous activation of target organs without activation of the hypothalamus and pituitary. Some causes of precocious puberty are listed in the Box.

Incidence

The true incidence of precocious puberty is estimated to be one in five to 10,000.[1] However, some recent US studies have found higher rates of early pubertal changes (possibly due to increasing obesity). A 2010 study of 1239 girls from urban centres in the USA found early (Tanner stage 2) breast development in 10.4% of white girls, 23.4% of black girls and 14.9% of Hispanic girls.[4] Thus accurately distinguishing benign from pathological

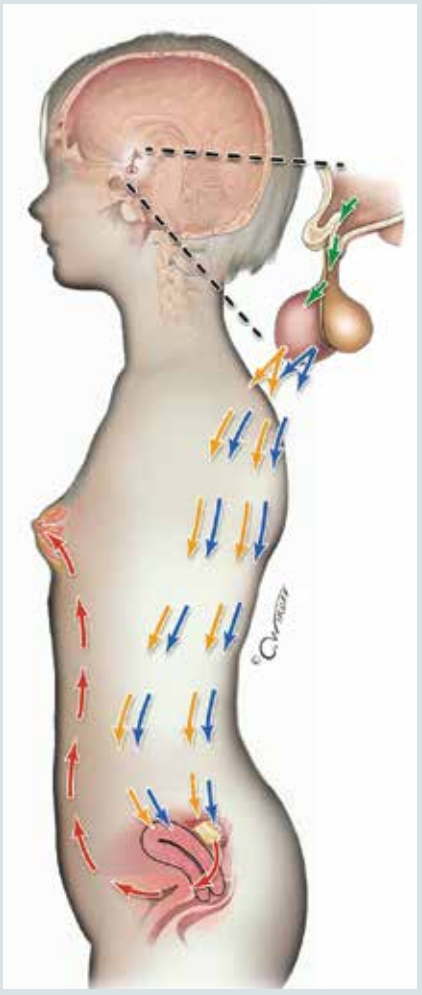


Figure 1. Puberty in girls. Pulses of gonadotrophin-releasing hormone (green arrows) are released from the hypothalamus, and follicle-stimulating hormone and luteinising hormone (blue and yellow arrows) from the anterior pituitary. The resulting oestradiol surge (orange arrows) results in ovarian follicle development, uterine enlargement, endometrial growth and breast budding.

causes is an important task for GPs. The correct diagnosis and prompt treatment of precocious puberty reduces mortality and also significantly reduces morbidity through improved adult height and reduced psychological distress that is associated with early puberty. Initial investigations are carried out through history taking, physical examination and review of growth rates. Following this, the GP's choice of appropriate screening investigations will direct the patient to the most appropriate referral centre for treatment.

Case 1. Congenital adrenal hyperplasia

A girl presented at age 14 months with pubic hair and clitoromegaly. Pubic hair was first noticed by the parents at 4 months of age. The pregnancy was uncomplicated and there was no relevant positive family history. On examination, Tanner stage 2 pubic hair was present (over the mons pubis) and she had a mildly enlarged clitoris. Initial investigations and results are outlined below (with the reference ranges shown in brackets).

- FSH, 1.1 IU/L (0.1–8.7 IU/L)
- LH, 0.2 IU/L (0–3.5 IU/L)
- Oestradiol, 39 pmol/L (<80 pmol/L)
- Total testosterone, 1.6 nmol/L (0–1.0 nmol/L)
- 17-Hydroxyprogesterone, more than 75 nmol/L (0–5.0 nmol/L)
- Beta human chorionic gonadotrophin test, negative
- Sodium, 137 mmol/L (135–145 mmol/L)
- Potassium, 4.7 mmol/L (3.8–5.5 mmol/L)
- Fasting blood glucose, 4.2 mmol/L (3.0–5.5 mmol/L)
- Thyroid-stimulating hormone, 1.3 mIU/L (0.8–6.3 mIU/L).

What did the patient's growth chart show?

The growth chart showed accelerated growth from 3 months of age (Figure 2). At the time of presentation, she was on the 90th percentile for height, out of keeping with her mid-parental height (25th percentile). The mid-parental height for female children is calculated as the average parental height minus 6.5 cm.

What other investigations were ordered?

A bone age study was performed with an x-ray of the patient's left wrist and hand. The growth plate development was then compared with age typical standards. This revealed a bone age of 3 years at a chronological age of 14 months. An advanced bone age indicates reduced growth potential. In older children, the bone age and current height can be used to estimate final height.

A urine steroid profile was also ordered, which uses liquid chromatography mass spectrometry to determine the relative concentrations of steroid metabolites. It is a more specific test than immunoassay of serum adrenal androgens, which is prone to interference from cross reactivity.[5] This test confirmed a diagnosis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

How was this patient treated?

This girl was started on hydrocortisone replacement (12 mg/m^2/day) in divided doses, with subsequent normalisation of her 17-hydroxyprogesterone and testosterone levels. Her growth velocity, bone age and pubertal status will be monitored closely.

Case 2. Idiopathic central precocious puberty

A girl presented at 7 years and 4 months of age with a one-month history of breast tenderness, pubic hair growth, axillary moistness and body odour. She was tall for her age (90th percentile) and above her mid-parental height of 10th to the 25th percentile. Her past medical history was unremarkable with the exception of

Classification and causes of precocious puberty

Central precocious puberty (gonadotrophin-dependent puberty)

- Hypothalamic hamartoma
- Pituitary tumour
- Cranial radiation
- Idiopathic

Peripheral precocious puberty (gonadotrophin-independent puberty)

- Nonpathological
  - benign infantile thelarche
- Ovarian hypersecretion
  - tumour/cyst
  - McCune Albright syndrome
  - dysgerminoma (note: may secrete human chorionic gonadotrophin)
- Adrenal hypersecretion
  - congenital adrenal hyperplasia
  - adrenal tumour
  - following intrauterine growth restriction
- Exogenous source
  - sex steroid exposure (e.g. exposure to oral or topical testosterone or oestrogen)

intermittent headaches. Her mother had early menarche at 9 years of age.

What did the investigations reveal?

Investigations revealed raised gonadotrophin levels, with an FSH level of 10.2 mIU/L (reference range 0–5 mIU/L) and LH level of 13.6 mIU/L (reference range 0–5 mIU/L), along with a detectable oestradiol level of 96 pmol/L (reference range <73 pmol/L). Her dehydroepiandrosterone sulfate level was mildly elevated at 1 µmol/L (reference range 0.5–0.9 µmol/L) and a human chorionic gonadotrophin test was negative. Her bone age was advanced at 10 years for a chronological age of 7 years and 6 months and her pelvic ultrasound revealed an adult appearance with increased uterus to cervix ratio (>1), enlarged size and the presence of an endometrial stripe, indicating a thickened endometrium.

What other test was necessary?

An MRI of the hypothalamus, pituitary and brain was requested and no CNS lesion was found. It is important to specify these areas when requesting the scan so that a detailed examination of this area is undertaken. Some radiology centres offer play therapy in young children so that general anaesthetics are not required.

How was this patient treated?

The mainstay of treatment for central precocious puberty is the GnRH agonist leuprorelin. Leuprorelin removes the pulsatile nature of central gonadotrophin release and suppresses pubertal progression. Within two months of commencing leuprorelin, this girl's breast tissue regressed and growth velocity normalised.

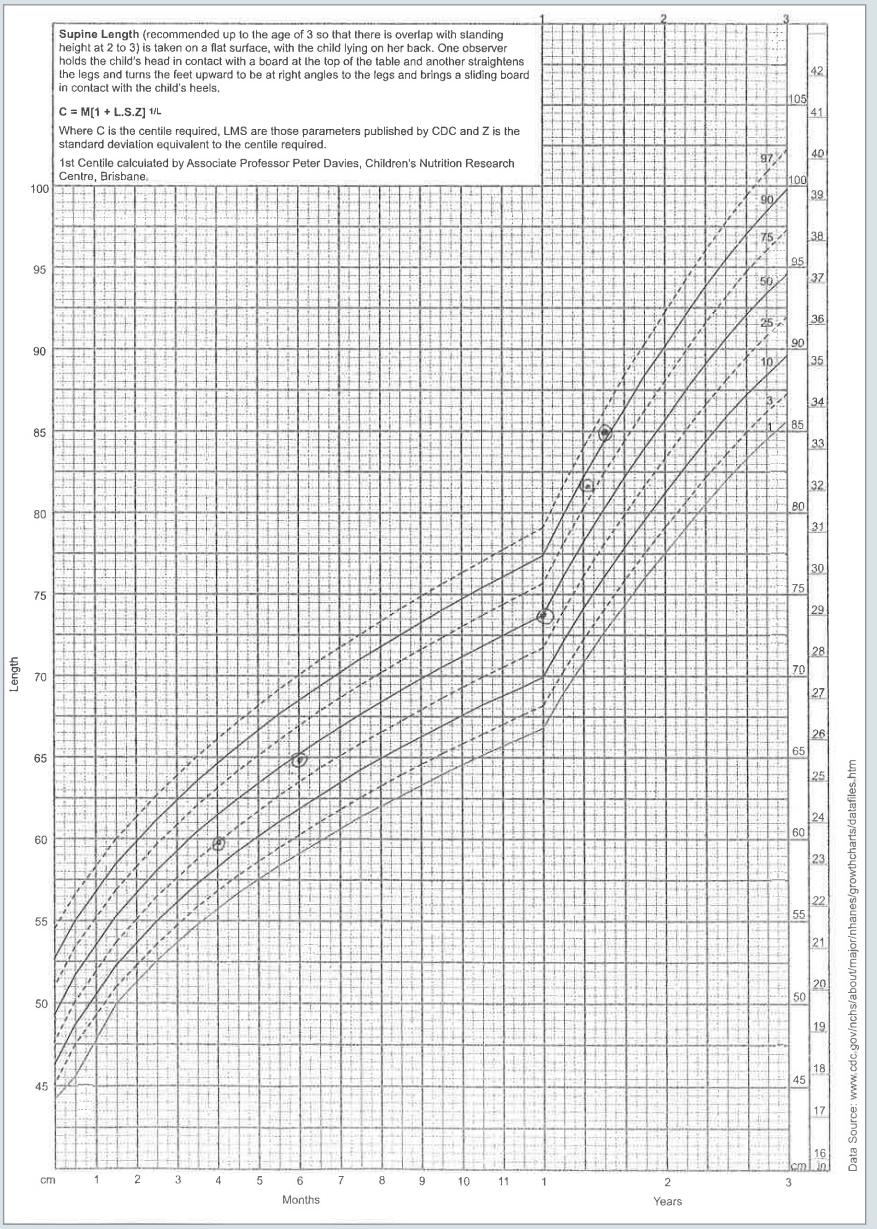


Figure 2. Growth chart of the girl in case 1 showing acceleration from the 25th to the 90th percentile. The mid-parental height was 156.6 cm (25th percentile), which is calculated as average height of parents (163.1 cm) minus 6.5 cm.

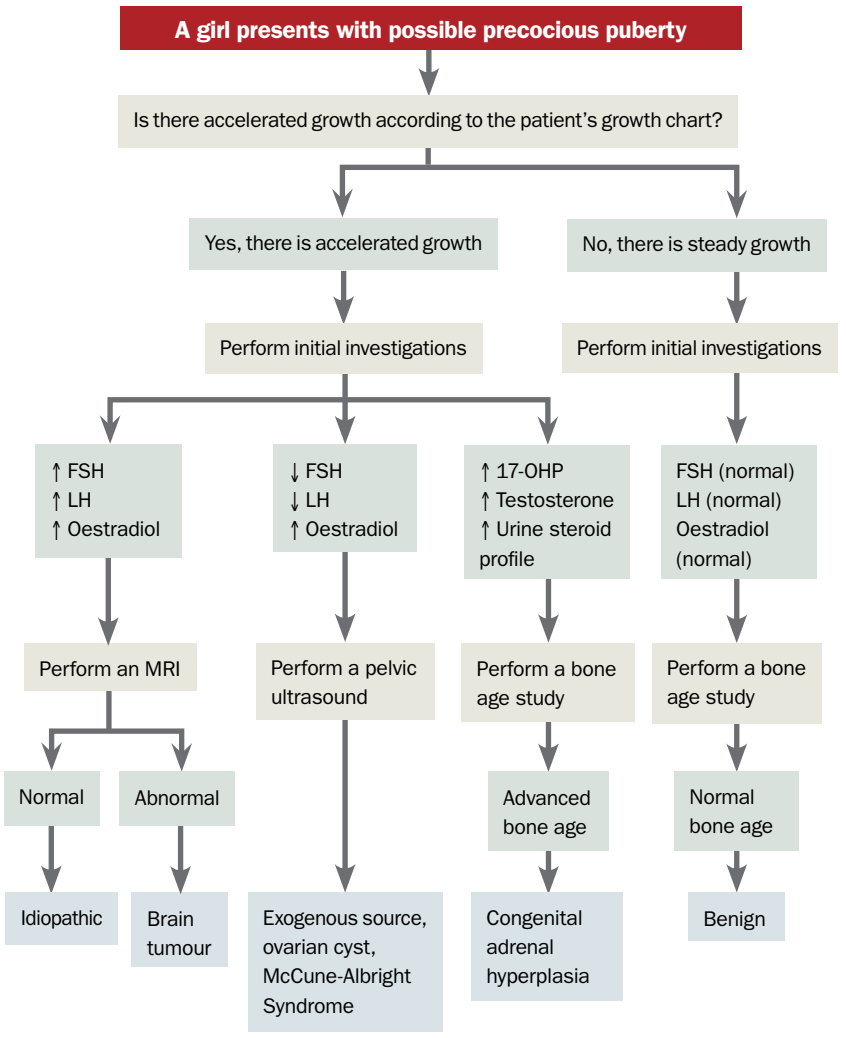
Case 3. Peripheral precocious puberty associated with a recurrent ovarian cyst

A 20-month-old girl presented with a few days of vaginal bleeding and linear growth acceleration from the 50th to 75th percentile over a three-month period. The pregnancy was unremarkable and there was no relevant family history. On examination two large coast of Maine café-au-lait spots on her sacrum and upper back were identified,which did not cross the midline.[6] She had Tanner stage 2 breast development and a slightly oestrogenised perineum (thickened epithelium with shallow transverse rugae).

What did the investigations reveal?

Investigations revealed suppressed gonadotrophins, raised oestradiol levels (266 pmol/L; reference range 0–55 pmol/L), negative tumour markers and normal thyroid function. A pelvic ultrasound showed a 3.9 cm follicular cyst in the right ovary. Given the size of the cyst, there was concern that it could cause ovarian torsion. Therefore, the patient underwent a laparoscopy six weeks after the ultrasound, at which time the cyst could not be identified. In keeping with this, her oestradiol levels and clinical signs of early puberty remitted. She continued in this fashion until the age of 2 years and 8 months, when the vaginal bleeding returned and further blood

A systematic approach to the investigation of early puberty in girls



Abbreviations: FSH = follicle-stimulating hormone; LH = luteinising hormone; 17-OHP = 17-hydroxyprogesterone.

tests and pelvic ultrasound showed a return of an oestrogen-producing ovarian cyst. She also displayed an advanced bone age of 4 years for her chronological age of 2 years and 8 months. This same clinical course of relapsing/remitting ovarian cyst and vaginal bleeding has recurred a total of three times. The patient is currently in remission with no further surgery planned.

What could be a possible underlying diagnosis, and what further investigations were performed?

McCune-Albright Syndrome is a rare cause of peripheral precocious puberty associated with polyostotic fibrous dysplasia and the characteristic coast of Maine café-au-lait lesions. It is caused by continuous activation of G protein intracellular second messengers. This patient displayed no other features of McCune-Albright Syndrome, including a negative bone scan and no other autonomous hormonal secretion. No treatment has been required.

Summary

Early puberty is a relatively common reason for girls to present in general practice, with GPs often being the first point of contact and the main source of referrals of these patients to paediatricians and paediatric endocrinologists. As leuprorelin was recently added to the Pharmaceutical Benefits Schedule for the treatment of central precocious puberty, many patients receiving this therapy will now start to present to their GP for ongoing administration of these intramuscular injections. The three cases described in this article provide examples of how to investigate early puberty in girls, and the flowchart provides a systematic approach for the investigation. **ET**

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COMPETING INTERESTS: None.

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Investigating early puberty in boys, coming up later this year in *Endocrinology Today*.