

.....

Precocious Puberty (Complete, Partial)

R. Stanhope, C. Traggiai

Department of Endocrinology, Great Ormond Street Hospital for Children and The Middlesex Hospital (UCLH), London, UK

Two decades ago, the diagnosis of premature sexual development was considered to be simple; the conditions that were recognised were either central precocious puberty, isolated premature thelarche or an adrenal aetiology. The use of pelvic ultrasound and gonadotrophin-releasing hormone (GnRH) analogue treatment was to completely alter our understanding of these disorders. Pelvic ultrasound led to differentiating ovarian appearances in conditions such as McCune-Albright syndrome and the variation in ovarian maturation in premature thelarche and central precocious puberty. Failure to respond to GnRH analogue therapy in children with precocious puberty led to the concept of gonadotrophin-independent precocious puberty (GIPP). During the 1980s, several variants of premature sexual maturation were described and this was important, both for the natural history of these conditions and the requirement for therapy. Adrenal lesions causing sexual maturation are included in this chapter for completeness. Their diagnosis and management is considerably simpler than premature sexual maturation of a gonadal aetiology.

Investigations

In the diagnosis of disorders of premature sexual maturation, there are two investigative procedures of significance, which are simple and relatively easy to interpret: the GnRH test and pelvic ultrasound assessment.

Pelvic ultrasound is a non-invasive technique which gives two important pieces of information. The uterine volume (and the endometrial thickness) is a measure of oestrogen secretion. The ovarian morphology can be used as an index of gonadotrophin secretion. The initial hormonal events of normal puberty are predominantly LH, rather than FSH, dependent.

There is a nocturnal rise in LH pulsatility and the amplitude gradually increases. When the corresponding increase in oestrogen becomes sufficient to induce breast development, then phenotypic puberty has commenced. However, the endocrine events that culminated in the onset of phenotypic puberty have been occurring for several years. Ovarian morphology changes from about 8 years of age and, in response to pulsatile nocturnal gonadotrophin pulsatility, the ovary develops into a multicystic morphology [1]. The multicystic morphology contains more than six follicles of 4 mm in diameter, or greater. This morphology is different from a polycystic ovarian appearance [2]. The multicystic ovarian appearance is a marker for the presence of pulsatile nocturnal gonadotrophin secretion. Thus, this ovarian morphological appearance is always present in girls with central precocious puberty, as it is in girls with normal puberty. Other disorders of premature sexual maturation have other characteristic morphological appearances, but not multicystic, and these are described in the sections below. With a progressive increase in amplitude of gonadotrophin pulsatility, the next stage of ovarian development, after multicystic, is the appearance of a dominant follicle, >10 mm in diameter.

The GnRH stimulation test has relatively little use in delayed puberty [3] but is of enormous significance in investigating children with premature sexual maturation. Girls with central precocious puberty have a dominant LH response to a bolus of intravenous GnRH, whereas girls with premature thelarche have a predominant FSH response. There is a broad spectrum between these two extremes and this will be discussed under the various specific diseases below. Certainly, without a dominant LH response, it is almost certain that there will be no response to GnRH analogue therapy [4]. Of course, children without a gonadotrophin response to a bolus injection of GnRH are likely to have GIPP, which will require an alternative treatment regimen.

In the investigation of adrenal disorders, an ACTH stimulation test is often helpful and, by measuring intermediate steroid metabolites, such as serum 17-hydroxyprogesterone, as well as urinary steroid metabolites of both cortisol and androgen metabolism, it is possible to distinguish the specific lesion in adrenal steroid biosynthesis.

Precocious Puberty

There are many causes of precocious sexual development and these are probably best categorised into those that are gonadotrophin dependent and independent (table 1). Such a classification helps both in understanding the aetiology the condition, and also in deciding the treatment options. In central precocious puberty, the most characteristic feature is maintenance of the

Table 1. Classification of disorders of premature sexual maturation of a gonadal aetiology

Gonadotrophin dependent

Central precocious puberty

Idiopathic

Hypothalamic tumours/cysts

Low dose cranial irradiation

Primary hypothyroidism with elevated FSH secretion

Tumours producing β -hCG secretion (e.g. hepatic tumours) in boys

Gonadotrophin independent

Testotoxicosis in boys

McCune-Albright syndrome in girls

Hypomelanosis of Ito in girls

Premature thelarche

Premature thelarche variant (also called slowly progressive precocious puberty or exaggerated thelarche)

Isolated menarche

harmony (consonance) of normal puberty. Thus, there is breast and pubic hair development, and a growth acceleration, which all occur in exactly the same sequence of events as in normal puberty, with the exception that this occurs at an earlier age. In all the other variants of premature sexual maturation, this harmony of normal puberty is lost, namely early vaginal bleeding with minimal breast development in McCune-Albright syndrome or breast development in the absence of a growth spurt in premature thelarche.

In the older nomenclature, children with central precocious puberty were described as having ‘complete’ precocious puberty, whereas those with other variants of sexual maturation were called ‘partial’ or ‘incomplete’ precocious puberty. Central precocious puberty is also known as ‘idiopathic’ precocious puberty or gonadotrophin-dependent precocious puberty. The cut-off age for the definition of precocious puberty is 8 years; precocious sexual maturation in a girl under 8 years of age is called precocious.

Adrenal Dysfunction

Various adrenal disorders may cause premature sexual maturation. However, this does not involve ‘gonadarche’ and so there is no breast development. There is usually pubic and axillary hair development with associated cutaneous manifestations of acne, behavioural difficulties and an increase in growth rate with advance in skeletal maturation. Adrenal tumours may present

with such symptoms, but they are usually of a rapid nature and more severe. The clitoris is always enlarged. The serum testosterone is usually >5 nmol/l and it is not difficult to make the diagnosis of the presence of an adrenal tumour clinically. Imaging of the adrenal glands, initially using ultrasound but also CT, will usually reveal the lesion.

Congenital adrenal hyperplasia, of which the commonest form is 21-hydroxylase deficiency, usually presents in the neonatal period with ambiguous genitalia and a salt-losing crisis. However, milder forms of congenital adrenal hyperplasia may present in later childhood with virilisation. The clitoris is almost always enlarged. The diagnosis is made using a standard ACTH test and measuring adrenal metabolites in the blood, as well as the urine.

Simple adrenarche is a diagnosis of exclusion. This is a benign condition where there is pubic hair development, which usually commences between the ages of 5 and 7 years. It is self-limiting and the hair development is usually along the line of the labia majora and not on the mons pubis (as in normal puberty). The clitoris is normal. The growth rate may be mildly accelerated, but this condition is not usually difficult to differentiate from an adrenal tumour or a biosynthetic adrenal steroid disorder. Simple adrenarche is a condition and not a disease, and requires reassurance and not treatment. The serum adrenal androgens are only mildly elevated, either towards the top, or just above, the normal range. However, recent data has suggested that there may be more sinister long-term sequelae for girls with simple adrenarche and this may be associated with the development of hyperinsulinism, obesity and polycystic ovarian disease in later life.

Central Precocious Puberty

This is known as central, idiopathic or gonadotrophin-dependent precocious puberty. The pattern of sexual development is indistinguishable from normal puberty and investigations reveal LH predominance to a GnRH stimulation test and a multicystic ovarian morphology on pelvic ultrasonography. This may be associated with low-dose cranial irradiation [5], especially in girls and when irradiation is given at a young age. Once the initial investigations have indicated that the sexual maturation is gonadotrophin dependent, then imaging of the hypothalamic pituitary region is essential. It used to be considered that most girls with central precocious puberty had 'idiopathic' precocious puberty, whereas with the availability of high-resolution CT scanning, it was appreciated that many such girls had hypothalamic lesions which were most commonly hamartoma [6]. Recent studies in much larger numbers from both Italy [7] and France [8] have shown that there is a significant risk of any girl with central

precocious puberty having a hypothalamic/pituitary tumour with sexual precocity being the only abnormal sign. Although reinforcing the original findings of Cacciari et al. [6] that young girls with central precocious puberty usually have a hypothalamic hamartoma, tumours such as astrocytoma may present with central precocious puberty in girls between the ages of 5 and 7 years, and it is extremely important not to miss such an underlying aetiology at an early stage of the tumour's growth. These findings reinforce the clinical guideline that all girls with central precocious puberty should have neuroradiological imaging of the hypothalamic pituitary region. It is interesting that some tumours of the hypothalamic region, such as hamartoma, optic nerve glioma and astrocytoma, commonly produce precocious puberty, whereas others, such as craniopharyngioma, Langerhans' cell histiocytosis and germinoma, only rarely cause precocious puberty [9] despite involving the same anatomical site. Hamartomata are the commonest hypothalamic tumours found in girls with central precocious puberty. Any surgical excision which may be indicated for intractable fits, would not cause a resolution of the precocious puberty. Interestingly, relatively high LH concentrations, not related to an LH surge, are often an indication of the presence of a tumour in the hypothalamic pituitary region [6].

Since 1980, older treatments with cyproterone acetate or medroxyprogesterone have been superseded by the use of GnRH analogues. These suppress gonadotrophin pulsatility and gonadotrophin secretion, and initially suppress and, hopefully, regress sexual maturation. They are relatively free of side effects and are effective. They can be given either as daily subcutaneous injections, intranasal sprays 2–3 times a day, or by depot injections lasting between 1 and 3 months. If puberty is well advanced and there is an endometrial echo of more than 4 mm in thickness, then it is usually appropriate to use cyproterone acetate in conjunction with a GnRH analogue for the first 3 weeks in order to prevent a uterine withdrawal bleed associated with the initial stimulatory phase of the GnRH analogue's action.

The indications for treating girls with central precocious puberty are to suppress sexual maturation and to help with psychological difficulties. Certainly, GnRH analogue treatment is effective for both of these sequelae, but it is also important to have an expert psychologist available to give appropriate support. When GnRH analogues were initially introduced, there was a promise of increasing final height prognosis. However, there is no convincing evidence that there is an improvement in final height with the exception of 1 or 2 cm. It is probable that the reasons why it was initially considered that height prognosis was improved was the inclusion of patients with thelarche variant (see below) into the cohort of patients considered to have central precocious puberty. There has been some evidence that adding biosynthetic human growth hormone to gonadotrophin-releasing analogue therapy may improve final stature [10].

Isolated Premature Thelarche

Premature thelarche is a benign, self-limiting condition which is characterised by breast development with no other signs of sexual maturation. There is no pubic or axillary hair development, behaviour is normal, growth is normal and the skeletal age is appropriate. The breast development has atypical appearance with relatively immature nipple development and is never more than Tanner Breast Stage III. Breast development is usually asymmetrical and the breasts increase and decrease in size at about 6-weekly intervals. The condition tends to resolve after about 1–2 years and then the onset of normal puberty occurs at the appropriate age and in the normal way. Very occasionally, vaginal bleeding can occur. There have been some reports of women who have had premature thelarche as a child developing large follicular cysts during their menstrual cycles and, thereby, having reduced fertility [11]. However, this has not been substantiated and what limited follow-up has been achieved in further series suggests that there are no long-term sequelae [12]. Isolated premature thelarche is a relatively common condition. It is characterised by FSH dominance and overnight gonadotrophin secretion, which is characterised by single FSH pulses [13]. On ultrasound the ovaries are small, but often contain large follicular cysts, which increase and decrease in synchrony with the breast development [14].

There may well be two types of premature thelarche. The classical type commences during the first year of life and tends to resolve by the age of 2. There is a second form of premature thelarche, of which the age of onset is over 2 years of age and this tends to be more persistent and with a higher incidence of uterine bleeding. In this ‘non-classical’ form of premature thelarche, it may well be associated with progression to gonadotrophin-dependent precocious puberty [15]. Isolated premature thelarche is a condition which is easy to diagnose clinically and requires no treatment.

Thelarche Variant

This encompasses a spectrum of conditions, which lie between premature thelarche and central precocious puberty. It may be difficult to distinguish from central precocious puberty. Indeed, there is a complete spectrum of gonadotrophin secretion in these conditions [16] between LH and FSH dominance. This condition has been described under different names, which has led to confusion. It has been known as unsustained precocious puberty [17], slowly progressive precocious puberty [18], thelarche variant [4] and exaggerated thelarche [19]. In all these conditions, there is a similar clinical description

of breast development, which is similar to that seen in premature thelarche, although the breast cycling is less common. There is usually pubic hair development, so that the condition cannot be classified as ‘isolated’ premature thelarche. However, the rate of growth is usually faster than normal, but without an advanced epiphyseal maturation. Growth prognosis appears to be normal, or near normal. The breast development frequently arrests and, certainly, does not advance to full sexual maturation. Behavioural problems are unusual. The condition only requires reassurance, but if treatment with a GnRH analogue is attempted, it may well result in a change of sexual maturation to central precocious puberty [4].

Patients with this condition of thelarche variant have often been included in patients with central precocious puberty and analysed contemporaneously in their response to GnRH analogue. As the growth prognosis is normal in the thelarche variant, it may well have compromised the analysis of patients with central precocious puberty and produced results which have suggested that GnRH analogue therapy produces an artificially improved benefit in terms of final height attainment. As this condition was only described a decade ago, there are no studies about the effect into adult life and longer-term studies will need to be undertaken.

Isolated Menarche

This is a condition where young girls have cyclical uterine bleeding without any other signs of sexual maturation, and they have normal growth. The natural history during childhood has been described [20] and the pattern of gonadotrophin secretion has also been documented [21], which is predominantly FSH. A clue to the diagnosis is often obtained because of the frequency of uterine bleeding, which is more often 6-weekly than monthly. It is important to exclude a local labial or vaginal cause for the bleeding, and there is often confusion about whether this is related to sexual abuse. No treatment is available and there tends to be a resolution of the condition after 1 or 2 years. No long-term sequelae have been described.

Gonadotrophin-Independent Precocious Puberty

GIPP occurs more commonly in boys (described as testotoxicosis) than in girls. However, when it does occur in girls, it is due to either McCune-Albright syndrome or hypomelanosis of Ito [22]. McCune-Albright syndrome consists of pigmented skin lesions (often referred to as a ‘Coast of Maine’ appearance)

and fibrous dysplasia of the bones. However, the most common presentation is with GIPP and the characteristic skin lesions. The bony lesions often present at a later date and the usual distribution is sphenoid and femur, but any bone can be involved. There may be hypersecretion of numerous endocrine glands, including the ovaries, adrenal glands, thyroid gland, parathyroids and pituitary. Severe McCune-Albright syndrome presenting in the neonatal period almost always presents with Cushing's syndrome from adrenal disease [23] even before the appearance of the classical skin lesions at approximately 6 weeks of age. The ovarian ultrasound appearances have been characterised [24] and the ovaries are large, cystic and usually asymmetric. Because of the gonadotrophin independence, GnRH analogues are unhelpful and treatment should be with a combination of drugs, including cyproterone acetate, medroxyprogesterone, spironolactone, ketoconazole and testolactone. In severe cases, it is usually the bone disease that predominates with both early fracturing and arteriovenous fistulae, causing heart failure.

To summarise: Girls with adrenal causes of premature sexual maturation are usually easy to distinguish. Premature adrenarche is common and is a diagnosis of exclusion. Of disorders of premature sexual maturation of a gonadal aetiology, the commonest is isolated premature thelarche, which is usually a clinical diagnosis. Retention of the normal harmony of puberty suggests central precocious puberty, and this can be confirmed by an intravenous GnRH test and pelvic ultrasound assessment. Once it has been demonstrated that a girl has central precocious puberty, then neuroradiological imaging will be mandatory. Treatment with a GnRH analogue both suppresses sexual maturation and improves psychological problems. Other variants of premature sexual maturation of a gonadal cause only require reassurance.

Acknowledgement

We are grateful to the Child Growth Foundation for their support of CT, as well as to Novo Nordisk Pharmaceuticals Ltd, UK.

References

- 1 Stanhope R, Adams J, Jacobs HS, Brook CG: Ovarian ultrasound assessment in normal children, idiopathic precocious puberty, and during low-dose pulsatile gonadotrophin-releasing hormone treatment of hypogonadotrophic hypogonadism. *Arch Dis Child* 1985;60:116–119.
- 2 Adams J, Franks S, Polson DW, Mason HD, Abdulwahid NA, Tucker M, Morris DV, Price J, Jacobs HS: Multifollicular ovaries: Clinical and endocrine features and response to pulsatile gonadotropin-releasing hormone. *Lancet* 1985;ii:1375–1379.
- 3 Abdulwahid NA, Armar NA, Morris DV, Adams J, Jacobs HS: Diagnostic tests with luteinising hormone-releasing hormone should be abandoned. *Br Med J* 1985;291:1471–1472.

- 4 Stanhope R, Brook CGD: Thelarche variant: A new syndrome of precocious sexual maturation? *Acta Endocrinol (Copenh)* 1990;123:481–486.
- 5 Leiper AD, Stanhope R, Kitching P, Chessells JM: Precocious and premature puberty associated with treatment of acute lymphoblastic leukaemia. *Arch Dis Child* 1987;62:1107–1112.
- 6 Cacciari E, Frejaviile E, Cicognani A, et al: How many cases of true precocious puberty in girls are idiopathic? *J Pediatr* 1983;102:357–360.
- 7 Cisternino M, Arrigo T, Pasquino AM, et al: Etiology and age incidence of precocious puberty in girls: A multicentric study. *J Pediatr Endocrinol Metab* 2000;13:695–701.
- 8 Chemaitilly W, Trivin C, Adan L, et al: Central precocious puberty: Clinical and laboratory features. *Clin Endocrinol (Oxf)* 2001;54:289–294.
- 9 Stanhope R: Central precocious puberty and occult intracranial tumours. *Clin Endocrinol (Oxf)* 2001;54:287–288.
- 10 Pucarelli I, Segni M, Ortore M, Moretti A, Iannaccone R, Pasquino AM: Combined therapy with GnRH analog plus growth hormone in central precocious puberty. *J Pediatr Endocrinol Metab* 2000;13(suppl):811–820.
- 11 Cohen A, Zecca S, Gaggero M, Dassori A, Parodi L, Martella M, Romano C: Premature thelarche: The long-term follow-up. *Horm Res* 1996;46(suppl):104.
- 12 Van Winter JT, Noller KL, Zimmerman D, Melton LJ 3rd: Natural history of premature thelarche in Olmsted County, Minnesota, 1940–1984. *J Pediatr* 1990;116:278–280.
- 13 Stanhope R, Abdulwahid NA, Adams J, Brook CG: Studies of gonadotrophin pulsatility and pelvic ultrasound examinations distinguish between isolated premature thelarche and central precocious puberty. *Eur J Pediatr* 1986;145:190–194.
- 14 Stanhope R, Adams J, Brook CG: Fluctuation of breast size in isolated premature thelarche. *Acta Paediatr Scand* 1985;74:454–455.
- 15 Pasquino AM, Pucarelli I, Passeri F, Segni M, Mancini MA, Municchi G: Progression of premature thelarche to central precocious puberty. *J Pediatr* 1995;126:11–14.
- 16 Pescovitz OH, Hench KD, Barnes KM, Loriaux DL, Cutler GB Jr: Premature thelarche and central precocious puberty: The relationship between clinical presentation and the gonadotropin response to luteinizing hormone-releasing hormone. *J Clin Endocrinol Metab* 1988;67:474–479.
- 17 Schwarz HP, Zuppinger K: Unsustained central sexual precocity in girls. *Pediatr Res* 1986;20:1198.
- 18 Fontoura M, Brauner R, Prevot C, Rappaport R: Precocious puberty in girls: Early diagnosis of a slowly progressing variant. *Arch Dis Child* 1989;64:1170–1176.
- 19 Garibaldi LR, Aceto T Jr, Weber C: The pattern of gonadotropin and estradiol secretion in exaggerated thelarche. *Acta Endocrinol (Copenh)* 1993;128:345–350.
- 20 Heller ME, Dewhurst J, Grant DB: Premature menarche without the evidence of precocious puberty. *Arch Dis Child* 1979;54:472–475.
- 21 Saggese G, Ghirri P, Del Vecchio A, Papini A, Pardi D: Gonadotropin pulsatile secretion in girls with premature menarche. *Horm Res* 1990;33:5–10.
- 22 Daubeney PEF, Pal K, Stanhope R: Hypomelanosis of Ito and precocious puberty. *Eur J Pediatr* 1993;152:715–716.
- 23 Bareille P, Azcona C, Stanhope R: Multiple neonatal endocrinopathies in McCune-Albright syndrome. *J Paediatr Child Health* 1999;35:315–318.
- 24 Foster CM, Feuillan P, Padmanabhan V, Pescovitz OH, Beitins IZ, Comite F, Shawker TH, Loriaux DL, Cutler GB Jr: Ovarian function in girls with McCune-Albright syndrome. *Pediatr Res* 1986;20:859–863.

Dr. R. Stanhope

Department of Endocrinology, Great Ormond Street Hospital for Children

Great Ormond Street, London WC1N 3JH (UK)

Tel. +44 207 905 2139, Fax +44 207 404 6191

E-Mail r.stanhope@ich.ucl.ac.uk