

Evaluation and management of precocious puberty

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Abstract

Puberty is an important event in adolescence. Altered timing of puberty brings about anxiety and fears in both the child and parents. Precocious puberty is usually idiopathic in a girl whereas a secondary cause needs to be excluded in a boy. Diagnosis and management require a careful evaluation in a logical sequence. The normal variants of puberty may not need extensive investigations but child will have to be followed up. The diagnostic and therapeutic approaches to a child with precocious puberty are discussed in this article.

Introduction

Puberty is the process of physical, hormonal and psychological changes in a child's body facilitating the reproductive capabilities. Pubertal changes are triggered by sex hormones following activation of the hypothalamo pituitary gonadal axis.

Genetic and environmental factors are implicated in the timing of puberty (1). Human studies have shown a relationship between body mass index or body fat, dietary and physical activity with the timing of puberty (2, 3, 4). More recently a G-protein coupled receptor, GPR54 and its ligand Kisspeptin have been identified as important signals in pubertal induction (5). The role of leptin in the pubertal induction is permissive rather than definitive and there are many unanswered questions in relation to role of leptin (6).

Precocious puberty

Precocious puberty has been traditionally defined as development of secondary sexual characteristics before 9 years in a boy and before 8 years or menstruation before 9.5 years in a girl. However there has been a secular trend towards early pubertal development (7).

Based on 1997 Pediatric Research in Office Settings (PROS) network study Kaplowitz and Oberfield (8) recommended to reset the age limit for precocious puberty to breast development at 7 years in Caucasian girls and 6 in African-Americans. However, due to the dissociation of age of breast development and age at menarche, this opinion was not accepted by many. A recent review by

Midyett et al (9) reported 12 % of black girls to have non idiopathic sexual precocity between 6 and 8 years.

There are two types of precocious puberty.

1. Gonadotrophin dependent precocious puberty (CPP) or central/ true precocious puberty.

This is when pubertal signs are consonant but may be more rapid in progression than in normal puberty.

2. Gonadotrophin independent precocious puberty or sexual precocity.

This is diagnosed when there is no activation of the hypothalamo pituitary gonadal axis and signs of puberty are not consonant.

Diagnosis

A detailed history is a prerequisite in the diagnosis and management of a child with precocious puberty. If more than one pubertal signs are present and growth is accelerated with advanced bone age, investigations are needed to confirm the diagnosis. In isolated vaginal bleeding the possibility of sexual abuse, foreign body or nonspecific vaginitis should be considered. Exposure to exogenous oestrogen in the form of creams, pills should also be excluded.

Pubertal staging, anthropometry, presence of café au lait patches and examination of the systems including testes are important aspects in the examination.

The height should be compared with the mid parental height and heights of siblings.

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The following investigations are indicated to confirm the clinical diagnosis of precocious puberty

1. Bone age

Bone age is advanced in precocious puberty but may be delayed in gonadotrophin independent precocious puberty due to untreated hypothyroidism (Van Wyk-Grumbach syndrome) (10).

On average, bone age is 10.75 years at the onset of puberty and 13 years at menarche. Testicular volume of 4 ml is seen at the bone age of 11.5 years (11).

2. Sex hormone levels

Testosterone >25ng/dl or oestradiol >10pg/ml are suggestive of precocious puberty.

If the oestradiol levels are in the upper end of normal range (75pg/ml), it is necessary to exclude an ovarian or adrenal tumour (12).

3. Gonadotrophin releasing hormone (GnRH) stimulation test.

The response after 20 and 60 minutes of intravenous 100ug of GnRH can be used to differentiate the two types of precocious puberty. Luteinising hormone (LH) predominant response will be seen in gonadotrophin dependent precocious puberty (CPP). There will be no response or a FSH predominant response in gonadotrophin independent precocious puberty.

In the absence of this investigation a FSH/LH assay done at midnight will show the sleep associated rise in LH in CPP.

The following published data are useful in the interpretation of the gonadotrophin levels using the chemiluminescent assay:

In gonadotrophin dependent precocious puberty;
LH/FSH- >1 (13)
Peak LH response > 5U/L from baseline (14)
FSH has a poor diagnostic utility (15)
Basal LH >0.1 IU/L was diagnostic for CPP with 94% sensitivity and 88% specificity (16).

4. Ultrasound scan of the abdomen (USS)

This is a useful investigation to differentiate CPP from gonadotrophin independent puberty.

- In CPP uterine length ranges from 3.4-4cm and the range of ovarian volume is between 1-3ml in (18).
- Endometrial echo is 100% specific but less sensitive (42-87%) in differentiating CPP (18).
- Adrenal hypertrophy will be seen in precocious puberty due to CAH.
- Multicystic ovaries will be seen in hypothyroidism.

5. When clinically indicated adrenal androgens or thyroid function tests are useful to identify the cause of gonadotrophin independent precocious puberty.

6. Magnetic resonance image (MRI)

Hypothalamic hamartoma is the commonest central nervous system pathology associated with CPP.

All boys with CPP and girls < 6 years should have an MRI of the brain. It is questionable whether it is useful in girls between 6-8 years.

It is useful to know that the size of the pituitary is large for the chronological age in CPP; correlates with LH/FSH ratio as this knowledge will avoid misdiagnosis of pituitary adenoma (19).

7. Insulin like growth factor (IGF1)

This is not a routine investigation. But it has been found to be raised in CPP (20).

Management

Treatment with a gonadotrophin releasing hormone (GnRH) analogue is only effective in gonadotrophin dependent precocious puberty. Initially the progression of puberty can wax and wane. Therefore in the absence of an identifiable central nervous system pathology and a rapid progression of symptoms and signs, treatment can be withheld with close monitoring of the patient.

Local sterile abscess, hot flushes with headache, weight gain and mild hypersensitivity reactions are the reported side effects which occur rarely.

Pubertal staging and growth velocity need monitoring every 3-6 months. Reduction of breast or testicular size may be noted on follow up.

The decision to stop treatment is based on the age of puberty of peers, siblings and parents and wishes of the patient and family. Discontinuation of treatment at chronological age 11 years (bone age 12) has been associated with maximal adult height (21). It is not recommended to continue treatment beyond 12-12.5 years of chronological age.

Once treatment is stopped menstruation will commence 2-61 months later (22).

The decision to commence treatment therefore would depend on the rapidity of the progression of puberty, the presence of CNS pathology and the age of the child. The short and long term implications of treatment should be discussed with the parents prior to treatment.

The treatment is with a long acting GnRH analogue. There are several subcutaneous and intramuscular preparations and in addition an intranasal preparation.

In a girl the treatment is combined with norethisterone for initial 1-2 weeks to prevent withdrawal bleeding.

A height loss of 20 cm in boys and 12 cm in girls has been documented in untreated patients (23). Girls <6 years gain a greater benefit from treatment (24). Girls between 6-8 years may have a modest benefit. It is necessary to discuss with the family in borderline cases before commencing treatment. All boys <9 years with compromised adult height warrant treatment. Treatment solely for psychological reasons or cessation of menses should be individually assessed.

Long term effects

BMD reduces during therapy but once the treatment is discontinued normal peak bone mass is gained provided they have an adequate calcium and vitamin D intake. GnRH therapy is associated with an increased risk of PCOS (25). Long term studies have revealed that GnRH therapy has no adverse effect on fertility (26).

Psychological support should be offered to the parents and child if needed.

Gonadotrophin independent precocious puberty

McCune-Albright syndrome (MAS)

MAS is defined as a triad of precocious puberty, fibrous dysplasia of bones, and café-au-lait macules caused by an activating mutation of the GNAS1 gene. Precocious puberty is the most common endocrine abnormality though rare in males. GnRH analogues are ineffective as a treatment. Aromatase inhibitor, anastrozole has been used with success and tamoxifen, an antiestrogen has been found to be beneficial in girls. The use of testolactone in combination with spironolactone or flutamide appears to be effective in boys (27). Third generation aromatase inhibitor letrozole has been shown to be effective in treating girls with MAS even though ovarian enlargement or cyst formation may be seen in patients on higher doses (28).

Testotoxicosis (Familial male precocious puberty)

Testotoxicosis occurs due to a heterozygous mutation of the luteinizing hormone receptor gene resulting in constitutive activation of the LH receptor giving rise to autonomous Leydig cell hyper function. Affected boys generally present before 4 years of age. Testolactone and spironolactone have been shown to be effective in the long term treatment (29). Combined therapy with a third generation aromatase inhibitor (anastrozole) and the selective anti-androgen bicalutamide (non-steroidal anti-androgen) was used with promising results in the recent past (30).

Variants of puberty

a. Premature thelarche

Premature breast development before 3 years of age is defined as premature thelarche which may be unilateral or bilateral. Puberty occurs at the normal age and there is no advance in the bone age. The condition spontaneously resolves by 4 years of age.

The larche variant

The Majority of these patients present between 7-8 years of age. They have an advanced bone age and an increase in the height velocity. They do not need treatment and the final adult height is not affected.

b. Premature adrenarche

Premature adrenarche is defined as the presence of secondary sexual hair in girls <8 years and boys <9 years. This is more frequently seen in girls and in children from African or Indian origin. CAH and adrenal tumour need exclusion before the diagnosis of premature adrenarche is made. This may be associated with low birth weight, insulin resistance and PCOS. No specific treatment is needed and their final height is normal.

c. Isolated menarche

Isolated menarche is a benign self-limiting condition. They present with recurrent vaginal bleeding without secondary sexual characteristics. A localised lesion of the genital tract, McCune-Albright syndrome, exogenous administration of oestrogens and child abuse need exclusion. There are no long term sequelae associated with this condition.

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