Precocious Puberty

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Normal Puberty and its control

Puberty is an important process in the development of all children during which a series of hormonal changes take place resulting in the appearance of secondary sexual characteristics and an immature child changes into a fertile adult. In addition to these changes, they undergo various other physical and emotional changes also.

The normal age of onset of puberty is between 8 and 13 years in girls and 9 and 14 years in boys. There is a common misconception amongst people, that menarche in girls and voice change or appearance of facial hair in boys equates to the onset of puberty. However this is not correct. In girls, the most common first physical sign of puberty is breast development and in boys, the first physical sign is an increase in testicular volume above 3 ml (using Prader orchidometer). The classic pattern of progression of pubertal development in girls is thelarche (breast development)' adrenarche/pubarche (axillary hair and pubic hair) ' menarche (2.5- 3 years after onset of thelarche). In boys the pattern of progression is as follows: testicular enlargement ' adrenarche/pubarche 'penile growth. The above can be documented with the help of sexual maturity rating (SMR) also known as Tanner's Stages (Fig. 1). Voice changes occur in boys at around 10-12 ml testicular volume.

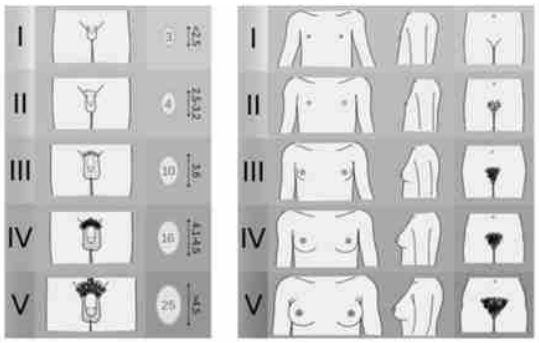

Fig. 1: Tanners stages of sexual maturity rating in boys and girls

Within physiological limits, the timing of onset of puberty does not influence the final height, however precocious puberty leads to reduced adult height. Up to 25% of total adult height is achieved from growth during puberty. In girls, peak height velocity (PHV) occurs at stage 2-3 of breast development, with PHV of 8.3 cms/year and in boys PHV coincides with stage 3-4 of testicular development with PHV of 9.5 cms/year. This leads to mean difference in adult height between men and women, as boys are taller at onset of pubertal growth spurt and also gain more height during the growth spurt. In girls, following menarche only 2-3% of growth is remaining i.e. they gain only 5-7.5 cms more height following menarche.

The control of puberty is based on the balance between activation and feedback inhibition of various components of the hypothalamic-pituitary-gonadal (HPG) axis and to a small extent on the adrenal axis. In the foetus, the HPG axis is active

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by 12 weeks. By term, increased placental production of oestradiol leads to suppression of GnRH neurons. After birth, withdrawal from maternal oestrogens leads to activation of HPG axis which is termed as minpuberty. The GnRH and gonadotropin levels increase and reach a peak between 2 weeks and 3 months. This minipuberty lasts till 6 months in boys and upto12-24 months in girls. In late infancy and childhood, the HPG axis enters a phase of quiescence brought about by direct inhibitory signals from central nervous system and feedback inhibition from gonadal steroids. This decade long dormant period is then followed by increase in GnRH pulse amplitude which then results in the onset of puberty. Towards the end of puberty, oestrogen induced LH surge starts in females.

Definition and Types of Precocious Puberty

Precocious puberty is defined as the onset of physical signs of puberty before the age of 8 years in girls and 9 years in boys.

Precocious puberty is categorised into 2 main types: Central (gonadotropin dependent precocious puberty, GDPP) which involves activation of hypothalamic GnRH pulsatility or peripheral (gonadotropin independent precocious puberty, GIPP) which involves autonomous activation of gonadal steroid production.

However there can be some physiologic variants of puberty which include

- Premature thelarche: It is transient isolated breast development in girls mostly noted at 2-4 years of age, not associated with any other sexual development, no acceleration of height velocity or significant advancement in skeletal maturation. Usually regresses after 2 years but can persist in some girls for 3-5 years.
- Premature pubarche: The appearance of pubic or axillary hair before the age of 8 years in girls and 9 years in boys. It corresponds to adrenal maturation (production of adrenal androgens including dehydroepiandrosterone, DHEAS and androstenedione). It is commonly seen in small for gestational age born children and can sometimes lead to polycystic ovarian syndrome later on in life.

Causes of Precocious Puberty

The causes of precocious puberty are enlisted in Table 1. Central precocious puberty (CPP) is more common than peripheral precocious puberty. In CPP there is activation of the hypothalmic pituitary gonadal (HPG) axis while in peripheral precocity there is suppression

Table 1: Normative data of size of pubertal organs in Indian children

CENTRAL PRECOCIOUS PUBERTY	PERIPHERAL PRECOCIOUS PUBERTY
• Idiopathic • Hypothalamic hamartoma • CNS tumours ✓ Glioma ✓ Astrocytoma ✓ Ependymoma ✓ Pinealoma ✓ Germ cell tumour ✓ Craniopharyngioma • Cerebral malformations ✓ Suprasellar arachnoid cyst ✓ Hydrocephalus ✓ Myelomeningocele ✓ Septo-optoc dysplasia • Acquried ✓ Post irradiation ✓ Infection ✓ Perinatal insults ✓ Head trauma • Genetic mutations (familial) ✓ MKRN3 ✓ KISS1R ✓ DLK1	• Autonomous gonadal activation ✓ McCune Albright Syndrome ✓ Familial male limited precocious puberty/ testotoxicosis ✓ Autonomous ovarian cysts • Tumours ✓ Granulosa cell tumour of ovary ✓ Androgen producing ovarian tumours ✓ Testicular Leydig cell tumours ✓ HCG producing tumour • Adrenal tumours ✓ Congenital adrenal hyperplasia ✓ Adrenal tumours ✓ Generalized glucocorticoid resistance • Severe untreated hypothyroidism • Exposure to estrogenic endocrine disrupting chemicals (postulated to have a role in adopted children, but not proven)
COMBINED PERIPHERAL AND CENTRAL PRECOCIOUS PUBERTY • Treated congenital adrenal hyperplasia • Late McCune Albright Syndrome • Late familial male precocious puberty	

of the HPG axis at least in the initial phase. CPP is always isosexual (sexual consonance is present). The most frequent cause of CPP in girls is idiopathic which is seen in 90% of cases. In boys, 75% of cases of CPP are due to structural abnormalities or tumours of central nervous system. Peripheral precocious puberty (PPP) could be either isosexual due to McCune Albright syndrome (fibrous dysplasia, café-au-lait spots) and testotoxicosis or heterosexual (sexual discordance) due to congenital adrenal hyperplasia, virilising adrenal or ovarian tumours.

Clinical Approach

Whenever we suspect a case of precocious puberty, certain questions need to be addressed

1. Is the puberty really precocious and is this a normal variation? - is it occurring before the age of 8 years in girls or before the age of 9 years in boys, premature thelarche at the age of 2-4 years for girls can be normal
2. Is the pubertal development isosexual or heterosexual? - Is the pubertal development concordant or discordant i.e. whether the pubertal signs are following the natural progression as described above or is it discordant (for example: appearance of pubic hair and phallic enlargement in boys with CAH without testicular enlargement)?
3. Is the precocious puberty central or peripheral?
4. Is the rate of progression of puberty rapid or slow? - this is important as not all forms of CPP progress rapidly and hence do not always require treatment and just need to be closely monitored for the rate of progression.

History of gelastic seizures and developmental delay (hypothalamic hamartoma), weight gain, constipation, goitre (hypothyroidism), drug intake (topical androgens), family history (testotoxicosis, CAH), fractures and birthmarks (McCune Albright syndrome) head trauma, CNS infections, increasing head size, radiotherapy, liver disease, SGA or adoption greatly helps in coming to the aetiology of precocious puberty. However in majority of the cases, such history is not available. Sometimes the only history is that the child is the tallest in the class or has become more aggressive than before.

The most important examination to be performed is the SMR to determine the stage of puberty. Also never forget to look for acne, voice change, gynaecomastia in boys and behavioural changes. These children are tall or normal for their age but always tall for their mid parental height. Other important findings include bony deformities, café au lait spots (McCune Albright syndrome), goitre, dry skin, puffiness (hypothyroidism), abnormal fundus, focal neurological deficit (central cause), hyperpigmentation, acne or hirsutism.

Evaluation of child with Precocious Puberty

Once history and examination reveal that the child is having precocious or early puberty we need to perform a few tests to confirm our findings and to find the aetiology. These include the following

- *Bone age:* Using Tanner Whitehouse 3 or Greulich and Pyle atlas. If bone age is > 2 years of chronological age it

indicates true precocious puberty, if bone age is 1-2 years advanced it could be an incomplete form of precocious puberty or early true precocious puberty and if bone age is delayed than the chronological age it indicates hypothyroidism. The bone age is also used to monitor rate of progression of puberty as well as response to therapy. In well treated children rate of increment of bone age is less than rate of progression of chronological age.

- *Ultrasound of pelvic organs:* It helps to assess the oestrogenic exposure of the internal genitalia in girls. The normative data of pelvic organ dimensions for Indian children is given in Table 2. Prepubertal uterus is usually < 3 CM and tubular shaped whereas pubertal uterus is > 3.5 CM and pear shaped with bulging fundus. Endometrial thickness provides secondary evidence of oestrogenisation. Menarche occurs at endometrium thickness of 8 mm. Ovarian size and follicles are not criteria for assessment of pubertal development but increase in size and number of course of maturation. Leydig cell tumours in boys which are not usually palpated can be picked up with the help of ultrasound.

Table 2: Aetiology of precocious puberty in children

Age	Uterine Size (cm)	Ovarian volume (cm3)
1-2 years	2.5	0.24
2-3 years	2.5	0.28
3-4 years	2.4	0.36
4-5 years	2.8	0.5
5-6 years	2.8	0.51
6-7 years	3.0	0.51
7-8 years	3.0	0.62
8-9 years	3.2	1.2

- *Biochemical evaluation*: All children suspected to have precocious puberty should undergo thyroid function tests, LH, FSH and oestradiol/testosterone. Basal LH > 0.3 mIU/mL or testosterone > 25 ng/dL or oestradiol > 10 pg/mL indicates pubertal onset. However in most cases GnRH stimulation test is required to test the diagnosis. On GnRH stimulation, FSH predominant response is seen in premature thelarche, elevated gonadotropins (LH mediated response i.e. LH > 4-5 mIU/mL) is seen in central precocious puberty and elevated sex hormones but suppressed gonadotropins is seen in peripheral precocious puberty.
- *MRI brain*: should be undertaken in all boys with central precocious puberty and in girls < 6 years with central precocious puberty or those with neurological signs.
- *Others:* In boys and girls with peripheral precocious puberty, evaluation of tumour markers (alpha foetoprotein, beta hCG, LDH) and 17-OHP for CAH should be done. Once tumours are ruled out, they should be evaluated for McCune Albright syndrome (bone scan, genetic tests and screening for other endocrinopathies) or testotoxicosis (genetic tests). Each case should be investigated on its merit.

Management of child with Precocious Puberty

Central precocious puberty

GnRH analogues are the mainstay of treatment of central precocious puberty.

The most commonly available preparation is depot leuprolide which is given intramuscular (3.75 mg every monthly or 11.25 mg every 3 monthly). The other preparations available are Triptorelin, Buserelin and Goserelin depot. Medroxyprogesterone (2.5-5 mg) daily should be added initially for 30-45 days to prevent flare up while starting GnRH therapy. The adequacy of response to treatment is judged based on resumption of normal growth, regression of SMR stage, slow increment of bone age as compared to increment of chronological age. It is not necessary to check hormonal status if the above parameters are being attained. The GnRH analogues are continued till 11 years in girls and 12 years in boys. After stoppage, there is gradual reappearance of secondary sexual characteristics in boys and in girls menarche is usually attained 6-18 months after discontinuation of treatment. If there are brain lesions, they need to be treated either by surgery or chemo-radiotherapy depending on type, size and location of tumour. Non progressive lesions like hypothalamic hamartoma should be treated with GnRH analogues and require regular MRI monitoring.

Peripheral precocious puberty

- Treatment of the underlying cause- thyroxine replacement (hypothyroidism), hydrocortisone supplementation (CAH), orchidectomy or testis sparing surgery (testicular tumours) or surgical removal of ovarian tumours
- *Ovarian cysts*- Need to be followed up conservatively in most cases and surgery is rarely indicated. Only in cases of very large cyst where there is risk of ovarian torsion, surgical excision is indicated.
- McCune Albright Syndrome- aromatase inhibitors like letrozole and anti-oestrogens like tamoxifen form the mainstay of the treatment.
- Testotoxicosis- Aromatase inhibitors and anti-androgens have been used in its treatment

References

1. Prasad H. Precocious Puberty. In:Khadilkar V. IAP Textbook of Pediatric Endocrinology, 1st ed. New Delhi: Jaypee Medical Publishers; 2019. P. 119?29
2. Howard S, Roux N, Leger J, Carel J, Dunkel L. In: Brook C, Dattani M. Brook's Clinical Pediatric Endocrinology, 7th ed. Oxford UK: John Wiley & Sons Ltd; 2019. P.235-87
3. Khadilkar V, Khadilkar A, Kinare A et al (2006) Ovarian and uterine ultrasonography in healthy girls between birth to 18 years. *Indian Pediatr* 43:625-630
4. Fuqua, J.S. (2013) Treatment and outcomes of precocious puberty: an update. *Journal of Clinical Endocrinology and Metabolism,* 98, 2198-2207.
5. Bangalore K, John K, Alan SF, et al. Use of Gonadotropin-Releasing Hormone Analogs in Children?: Update by an International Consortium. Horm Res Paediatr. 2019;Jul(18):1-16.