

Precocious Puberty in Children; An overview

Nasir AM, Al-Jurayyan^{1*}, Huda A. Osman², Abdulrahman NA Al-Jurayyan³,
Amal A Al-Hakami⁴, Sharifah DA Alissa⁵

¹MD, Professor and Senior Pediatric Endocrinologist,

²MRCPCH(UK), Senior Registrar in Pediatric Endocrinology,

⁴MD, Senior fellow in pediatric Endocrinology,

⁵MD, Consultant Pediatric Endocrinologist,

Division of endocrinology. Department of pediatric.

College of medicine and King Khalid University Hospital (KKUH), Riyadh Saudi Arabia.

³Medical student, College of medicine, King Saud University, Riyadh Saudi Arabia.

ABSTRACT

Puberty is the process of physical maturation manifested by an increase in growth rate, and the appearance of secondary sexual characteristics.

The diagnosis is made with the help of a careful history and physical examination in conjunction with the use of appropriate radiologic and laboratory evaluation. GnRH stimulation is the gold standard for diagnosis.

In this review, we highlight the definition of precocious puberty, pathophysiology, aetiology and management of the disorder.

Keywords: Precocious, Puberty, Girl, Boy, Central, Peripheral, Pathophysiology, Saudi Arabia.

INTRODUCTION

Puberty is a process leading to physical and sexual maturation that involve the development of secondary sexual characteristics as well as growth changes in body composition and psychosocial maturation which usually begins between eight and 14 years of age in girls, and between nine and 14 years of age in the boys. Therefore the appearance of signs of sexual development before eight years in girls or 9 years in boys is defined as precocious puberty. Recent studies showed that signs or symptoms of early puberty are often present in girls of American African as early as 6 years.

Detailed longitudinal studies of British children by Tanner and Marshall provide information about the sequence and timing of the physical and sexual changes that occur throughout the puberty. For convenience, breast and pubic hair development in girls, and genital and pubic hair development in boys. These were arbitrarily divided into five stages (Table 1 and 2)^{1,2} referenced as Tanner breast, pubic hair, and genital stages.¹⁻⁵

EPIDEMIOLOGY

A review of trends in timing of puberty around the world showed no clear trend towards earlier puberty. Central precocious puberty being the commonest and had an incidence of 1 in 5- 10000

*Correspondence to:

Nasir AM Al-Jurayyan

Department of Pediatric (39)

College of medicine and KKUH

PO Box 2925 Riyadh 11461

Saudi Arabia.

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children with a female to male ratio of greater than 20:1 with predominance of idiopathic form. The younger the age of girls with proven CPP, the higher the likelihood of serious underlying disorder.

The study by Herman- Giddens et al and the data from the National Health and Nutrition Examination Survey [NHANES] 111 study conclusively showed that black girls in the united states have onset of breast development and pubic hair about one year earlier than white girls. The incidence of precocious puberty among boys is similar in both races.⁶⁻¹⁰

PATHOPHYSIOLOGY

The onset of puberty is caused by the secretion of high-amplitude pulses of gonadotrophin-releasing hormone (GnRH) by the hypothalamus. The hypothesized mechanisms that suppress onset of puberty include the hypothalamus-pituitary gonadal (HPG) axis, which is highly sensitive to feedback inhibition by small amounts of sex steroids, and central neural pathways that suppress the release of GnRH pulses.

High amplitude pulses of GnRH cause pulsatile increases in the pituitary gonadotrophin-luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Increased LH levels stimulate

production of sex steroids by testicular Leydig cells or ovarian granulosa cells. Pubertal levels of androgens and estrogens cause the physical changes of puberty, including penile enlargement and sexual hair in boys and breast development in

girls. These levels also mediate the pubertal growth spurt. Increased FSH levels cause enlargement of the gonads in both sexes and eventually promote follicular maturation in girls and spermatogenesis in boys.^{3,10-12}

TABLE 1. Tanner Staging of Female Puberty

Stage	Breasts	Pubic Hair
1—Prepubertal	Elevation of papilla only	Any vellus over pubes no different from abdominal hair
2	Breast bud with elevation of breast and papilla and enlargement of areola	Slightly pigmented, downy hair along the labia
3	Further enlargement of breast and papilla with no separation of their contours	Darker, coarser, more curled hair over pubes
4	Projection of areola and papilla to form a secondary mound	Adult pubic hair that does not reach thighs (axillary hair)
5—Adult	Mature breast, projection of papilla only as areola conforms to breast contour	Adult hair now on thighs

TABLE 2. Tanner Staging of Male Puberty

Stage	Genitalia	Pubic Hair
1—Prepubertal	Testes, penis, and scrotum same size and proportion as early childhood	Any vellus over pubes no different from abdominal hair
2	Early enlargement of testes >2 cm ³ ; scrotal skin reddens and changes in texture	Slightly pigmented, downy hair at base of penis
3	Penis lengthens; testes enlarge 3–6 cm ³ ; growth of scrotum	Darker, coarser, more curled, over pubes
4	Further penile and scrotal growth; testes 8–12 cm ³	Adult pubic hair that does not reach thighs (axillary hair)
5—Adult	Genitalia adult in size and shape, testes 15–25 cm ³	Adult hair now on thighs

GnRH-Dependent Females and Males	GnRH-Independent Females	GnRH-Independent Males
Idiopathic	MAS	FMPP
International adoption	Estrogen-secreting ovarian tumor	Leydig cell tumor
Acquired CNS insults	Ovarian cyst	Human chorionic gonadotropin-secreting tumor
Brain tumor [astrocytoma, pineal tumor, optic pathway glioma (NF1), craniopharyngioma (rare)]	Estrogen-secreting adrenal tumor	Androgen-secreting adrenal tumor
Cerebral palsy	Exogenous estrogen exposure	Exogenous T exposure
Hydrocephalus	Peutz-Jegher syndrome	Congenital adrenal hyperplasia
CNS irradiation	Primary hypothyroidism	Primary hypothyroidism (testicular enlargement only)
CNS trauma	hypothyroidism	Familial glucocorticoid resistance
CNS infection	Aromatase excess	MAS (rare)
CNS granulomatous disease		
Subarachnoid cyst		
Hypothalamic hamartoma		
Neurofibromatosis, type 1		
Tuberous sclerosis		
Sturge-Weber syndrome		
Withdrawal of chronic sex hormone exposure		
Septo-optic dysplasia (rare)		
Gain of function mutation of kisspeptin/kisspeptin receptor		

Table 3: Etiologies of Precocious Puberty²⁹

THE AETIOLOGY

Two types of precocious puberty (PP) are recognized; central (true) precocious puberty, (CPP), and peripheral (pseudo-) precocious puberty (PPP). CPP is caused by early activation of the hypothalamic-pituitary axis, with gonadotrophin-releasing hormone (GnRH), therefore it is known as gonadotropin-dependent PP. In PPP, serum sex steroid levels are elevated independent of gonadotrophin secretion, and therefore, gonadotrophin levels are low, and the gonads do not undergo maturation. Precocious puberty may be isosexual involving secondary sex characteristics that are gender matched or heterosexual involving sex characteristics of the opposite gender. CPP is always isosexual, whereas PPP may be isosexual or heterosexual. CPP may be idiopathic or related to central nervous system (CNS) lesions such as neoplasia, cyst, or hydrocephallus. CPP in girls is usually idiopathic, whereas the vast majority in boys are due to an intracranial lesion. (Table 3) Isosexual PPP in girls, is most commonly caused by an autonomously functioning

ovarian cyst (Fig 1 A,B) , but also be caused by a juvenile granulosa cell tumor (GCT) of the ovary or rarely, a feminizing adrenal cortical neoplasia (ACN). Heterosexual PPP in girls (virilization) is most often related to androgen production by the adrenal gland due to a functioning ACN or congenital adrenal hyperplasia (CAH). In boys, PPP is usually due congenital adrenal hyperplasia (Fig 2), sex steroid hormone secreting cord-stromal tumor of the testis. Human chorionic gonadotrophin-secreting tumors such as hepatoblastoma, mediastinal teratoma, some testicular germ cell tumor, and suprasellar germinoma can stimulate testosterone production by leydig cell of the testes because human chorionic gonadotrophin is biologically similar to luteinizing hormone. Other causes of precocious puberty includes inherited conditions, such as neurofibromatosis type 1 (NF-1), systemic disease, such as untreated hypothyroidism, and McCune-Albright syndrome, consisting of precocious puberty, coast of Marine Café-au-lait spots, and polyostotic fibrous dysplasia.^{3,13-16}

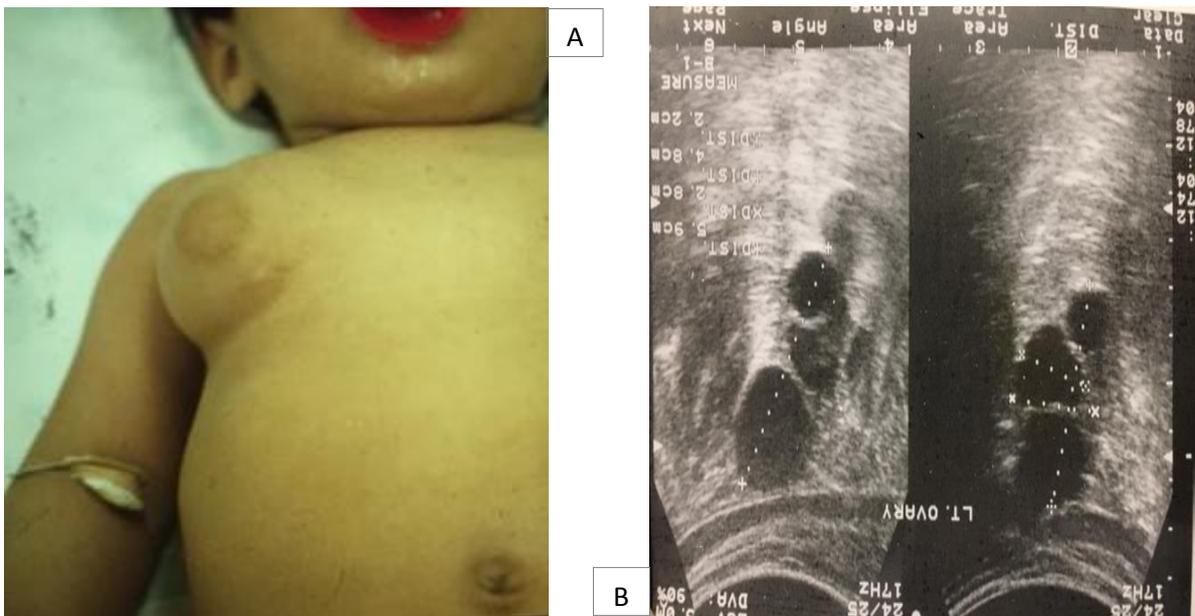


Fig 1: (A) a 3-year-old girl with precocious puberty. She proved to have (B) Ovarian cyst.



Fig 2: A 5 year old boy with precocious puberty. He proved to have 11-B hydroxylase deficiency, congenital adrenal hyperplasia (testes were prepubertal)



Fig 3: Sagittal T1 weighted Magnetic Resonance Image (MRI) showing a small homogenous, well delineated round mass (arrow) indicating hypothalamic hamartoma



Fig 4: Computed Tomography (CT) scan of abdomen reveal right adrenal mass (oestrogen-secreting-tumor).

EVALUATION OF A CHILD WITH SUSPECTED PRECOCIOUS PUBERTY

The initial evaluation begins with detailed history and physical examination. Findings of interest such as, café-au-lait spots (NF-1 or McCune Albright syndrome), evidence of neurological deficit and presence of a testicular or adrenal masses. The finding of bilateral gonadal enlargement indicates the presence of CPP. Laboratory evaluation of hormone levels include LH, FSH, testosterone and estradiol Thyroid function and adrenal studies may be helpful.

Radiological imaging should be directed by history, physical examination and laboratory data. For example CNS imaging, should be performed if CPP. (Fig 3), while in PPP with suspected adrenal or ovarian pathology abdominal CT or MRI should be performed (Fig 4). Furthermore radiological studies may be directed by history and physical examination. Finding skeletal changes and skin lesions will lead to the work up for McCune-Albright syndrome.

There are no universally accepted criteria for making the diagnosis of precocious puberty. Measurement of basal or random levels of FSH and LH or one may measure GnRH stimulated levels of gonadotrophins. Spontaneous LH levels correlate strongly with peak stimulated LH levels in subjects with precocious puberty. LH values over 0.1 IU/L using a third-generation assay detected true PP with 94% sensitivity and 88% specificity, whereas LH values more than 0.3 IU/L had 100% specificity. Some children with early puberty, however, can have spontaneous LH values less than 0.3 IU/L. LH to FSH ratio of less than one are also suggestive of prepubertal gonadotrophin secretion. In fact, it has been stated that if the LH is elevated above the prepubertal range and the LH to FSH ratio is more than one, the diagnosis of CPP can be made without GnRH stimulation test. FSH value alone are not generally helpful in evaluation of PP. Since stimulation values of pubertal children overlap significantly with those of prepubertal children. The gold standard for determination of pubertal gonadotrophin secretion is the GnRH stimulation test. A single time point at 40 minutes following subcutaneous (sub Q) administration of 100 mcg GnRH, which has been reported to correlate reliably with multiple samples following IV or

subcutaneous GnRH administration in its ability to rule in or out the clinical diagnosis of CPP. Peak LH and E₂ response to GnRH analogue has also been proposed as a more sensitive method for identifying a pubertal response. In boys serum testosterone level are useful for the diagnosis of PP. With the advent of newer more sensitive estradiol assays. Estradiol level in girls will likely be as useful as testosterone level are presently for boys for assessing the degree of puberty progress. Endocrine tests include an assessment of the gonadotrophin (LH and FH) response to stimulation by GnRH and measurement of plasma concentration of HCG exclude a rare gonadotrophin producing tumors such as hepatoblastoma or teratoma.¹⁷⁻²¹

Acceleration of growth is almost invariably seen in PP. Skeletal age is generally advanced but to varying degree. Pelvic Ultrasound can be useful in assessment and diagnosis of girls with PP. the ovaries may be significantly enlarged. Small ovarian cysts may be seen in both pubertal and prepubertal girls. The size of the uterus and the thickness of the endometrium can be measured and used as an additional information. In pubertal girls, the uterus is more bulbous and longer than cervix.

Computed tomography (CT) and Magnetic Resonance Imaging (MRI) scans are useful diagnostic tool for evaluation. The use of contrast does not reveal new abnormalities, but is useful primarily for improving diagnostic certainty.²²⁻²⁶

MANAGEMENT

Management is directed at treating the under-lying cause, if that is appropriate blocking the actions of gonadotrophin and sex steroids, and, above all providing suitable counselling for emotional and behavioral problems. Neurosurgical treatment of a lesion in the central nervous system is not warranted solely on the basis of isolated signs of early puberty. A slow growing benign hamartoma may be observed closely with serial radiological investigation. Medical treatment with potent long activity GnRH analogues have resulted in significant improvement in outcome.^{13,27-30}

CONCLUSION

Although, the debate still continues on defining precocious puberty in girls, it is most commonly considered precocious if breast or pubic hair development occurs before 8 years of age, for girls and nine for boys. Careful history and physical examination coupled with basal and stimulated levels of gonadotrophins have been used in clinical diagnosis. GnRH therapy seems to be a safe and effective way to suppressing early pubertal development and improving height in many, if not most with CPP.

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