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Puberty (Delay/Precocious)

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Puberty (Delay/Precocious)

82

Introduction

- ☑ Puberty is the hallmark of normal adolescent development. Onset of puberty is associated with marked apprehensions both for the parents and the child.
- ☑ At times, puberty may be ushered in early and sometimes is delayed which is a cause for the concern and needs to be addressed.
- ☑ As a primary attending physician one must be able to identify and address and manage the concerns.
- ☑ This write up provides an insight as to how to address and mange those children presenting with the disorders related with pubertal timings.

Delayed Puberty

Definition

Delayed puberty is when:

- ☑ Boys have no signs of testicular development by 14 years of age.
- ☑ Girls have not started to develop breasts by 13 years of age, or there is no onset of menarche by the age of 15 years.

Delayed Puberty

Causes of Delayed Puberty

- ☑ Constitutional delay in pubertal growth and development
- ☑ Familial
- ☑ Chronic illness—thalassemia, chronic renal diseases, chronic hepatic diseases, and celiac disease
- ☑ Endocrine—hypothalamus, hypopituitarism, suprasellar space occupying lesions, and hypothyroidism
- ☑ Abnormal development of the reproductive system—congenital anomalies
- ☑ Inability of the body to use androgen hormones (androgen insensitivity syndrome)
- ☑ Too much exercise—athletes and ballerinas
- ☑ Eating disorders.

Symptoms of Delayed Puberty

The symptoms are a lack of secondary sexual characteristics.

Common symptoms in girls can include:

- ☑ No breast growth by age 13
- ☑ More than 5 years between first breast growth and first menstrual period
- ☑ No menstrual period by age 15

Common symptoms in boys can include:

- ☑ No testicular enlargement by age 14
- ☑ No pubic hair by age 15
- ☑ More than 5 years to complete adult genital growth.

Investigations

Initial Workup for Delayed Puberty not due to a Chronic Condition

- ☑ History taking including developmental history and history of operations for testicular anomalies, oncology history, and history of radiotherapy
- ☑ Clinical examination including a Tanner staging
- ☑ Plotting growth chart including estimation of mid parental height
- ☑ Bone age radiography—X-ray of the left wrist and hand would evaluate for bone age
- ☑ Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol/testosterone
- ☑ *Imaging:*
  - Ultrasonography (USG) of the uterus and ovaries—looking for streak gonads (Turners)
  - USG of the testicles for cryptorchidism/masses.
  - MRI brain to look for craniopharyngioma

Investigations

Further Workup of Delayed Puberty: According to Clinical Findings

- ☑ A complete blood count including looking for hemoglobinopathies.
- ☑ Complete metabolic panel including tissue transglutaminase (TTG).
- ☑ Free T4 and thyroid-stimulating hormone for thyroid function.
- ☑ Galactorrhea with delayed puberty, an evaluation for a prolactinoma with a prolactin level is necessary.
- ☑ Some clinicians may add tests to access for adrenarche and may include DHEA-S.
- ☑ If panhypopituitarism or growth hormone deficiency is a concern, insulin-like growth factor 1 (IGF-1) require testing.
- ☑ A pediatric endocrinologist may choose to perform a gonadotropin-releasing hormone (GnRH) stimulation test in the future, but this is usually not included in the initial evaluation for delayed puberty.
- ☑ Lastly, if there is any suspicion for a syndrome, testing for karyotyping should be done.

Treatment

Delayed puberty can be treated by:

Basic treatment	☑ Using medication for a few months to increase hormone levels and trigger the start of puberty
Specific treatment	☑ Treat an underlying cause

Guidelines to Basic Treatment

- ☑ Constitutional delay in puberty and growth is the most common cause.
- ☑ Treatment is usually guided by patient and parental goals:

Males:
- ☑ Oral and intramuscular (IM) forms of testosterone are available.
- ☑ IM form is usually more appropriate due to the serious side effect of liver toxicity caused by oral testosterone.

Females:
- ☑ Oral and IM forms of estrogen are available.
- ☑ Oral estrogen is more often the therapeutic choice.

Close monitoring is essential after starting therapy.

Delayed Puberty

Treatment

Permanent hypogonadism:

Males:
A low dose of IM testosterone is started and increased gradually over time until achieving adult levels of testosterone.

Females:
"Initial treatment of choice"

- ☑ Low dose estrogen is also increased incrementally over time until breakthrough vaginal bleeding occurs.
  Or
- ☑ 12–24 months of treatment have passed

"Subsequent treatment"

- ☑ Combination estrogen and progesterone therapy for normal monthly withdrawal of bleeding.
- ☑ The transition helps the body to experience more normal physiological menstrual cycles.
- ☑ Commonly used hormone replacement therapies include oral contraceptives or transdermal estrogen patches with oral progesterone.

Precocious Puberty

- ☑ *Precocious puberty* is defined as onset of puberty occurring earlier than the norms for gender and race or ethnic background (2.5 standard deviation below the population mean).
- ☑ Puberty is precocious if *onset of breast development occurs before the age of 8 years and menarche before the age of 10 years in girls and testicular enlargement before the age of 9 years in boys.*

Classification of Sexual Precocity

Early pubertal development is classified as central or peripheral depending on the trigger for puberty:

- ☑ *Central precocious puberty (CPP) or true or gonadotropin-dependent precocious puberty*: It results from premature activation of hypothalamus–pituitary–gonadal (HPG) axis.
- ☑ *Peripheral precocious puberty (PPP)* or pseudo- or gonadotropin-independent precocious puberty with incomplete or partial pubertal development results from the production of sex steroids and not influenced by HPG axis.
- ☑ *Mixed type*: CPP may be triggered in children with PPP when the advanced state of somatic and skeletal maturation due to premature release of adrenal or gonadal steroids, e.g., congenital adrenal hyperplasia (CAH), McCune–Albright syndrome (MAS), and familial male-limited precocious puberty.
- ☑ *Incomplete form of pubertal variants*: Premature thelarche, premature menarche, premature pubarche, adolescent gynecomastia in boys, and macroorchidism.

Causes of Early Puberty and Normal Variant

- ☑ Familial
- ☑ Obesity
- ☑ Intrauterine growth restriction (IUGR)
- ☑ Environmental conditions
- ☑ Endocrine-disrupting chemicals.

Differences between Central Precocious Puberty and Peripheral Precocious Puberty

CPP = 1 in 5,000–10,000	***PPP = one-fifth common as CPP***
Isosexual	Isosexual/heterosexual
Premature HPG axis activation	HPG axis not activated
Progressive sexual maturation in sequence observed in normal puberty	Sequence of pubertal changes is discordant
Female:Male::5:1 to 20:1, more common in females	More common in males
The causes are similar in both the genders	Etiology differ in the two genders and may result in heterosexual development

Precocious Puberty

Causes of Central Precocious Puberty

Idiopathic
Acquired central nervous system (CNS) insults ☑ Trauma and perinatal insult, postinfectious meningitis, or encephalitis ☑ CNS granulomatous disease, low dose cranial irradiation, chemotherapy, and surgery
Tumors ☑ Hypothalamic hamartoma, astrocytoma, and pineal tumor ☑ Ependymoma, optic pathway glioma, and craniopharyngioma
Structural defects ☑ Hydrocephalous, subarachnoid cyst, and septo-optic dysplasia
Phakomatoses ☑ Tuberous sclerosis, Sturge–Weber syndrome, and neurofibromatosis
Other pathology ☑ Cerebral palsy, IUGR, and prolonged untreated PPP ☑ Adopted children from developing countries
Withdrawal of chronic sex hormone exposure
Genetic: Mutations in the MREKN-3, DLK-1, kisspeptin/kisspeptin receptor gene *Syndromes*: Temple, Silver–Russell, and Williams–Beuren

Causes of Peripheral Precocious Puberty

GnRH-independent in girls	***GnRH-independent in boys***
Isosexual ☑ Ovarian disorders ☑ Ovarian cyst ☑ McCune–Albright syndrome ☑ Ovarian tumors ☑ Granulosa theca cell tumor ☑ Gonadoblastoma ☑ Teratoma ☑ Choriocarcinoma ☑ Adrenal tumor ☑ Exogenous estrogen exposure ☑ Peutz–Jeghers syndrome ☑ Primary hypothyroidism ☑ Aromatase excess	*Isosexual* ☑ Adrenal disorders ☑ Congenital adrenal hyperplasia ☑ Tumors ☑ Familial male-limited precocious puberty (FMPP), testotoxicosis, autosomal dominant ☑ Testosterone-secreting tumors ☑ Leydig cells ☑ Adrenal rests ☑ Human chorionic gonadotropin (hCG) secreting tumors ☑ Hepatoblastoma ☑ Pineal gland tumors ☑ Cerebral tumors (germinoma) ☑ Mediastinal tumors ☑ Gonadal tumors ☑ Exogenous androgen (testosterone exposure) ☑ Primary hypothyroidism ☑ Familial glucocorticoid resistance ☑ McCune–Albright syndrome
Heterosexual ☑ Congenital adrenal hyperplasia ☑ Masculinizing adrenal or ovarian tumors ☑ Familial glucocorticoid resistance ☑ Exogenous androgens	*Heterosexual* ☑ Feminizing adrenal or testicular tumors ☑ Aromatase excess ☑ Exogenous estrogens

Differential Diagnosis

	Sequence of pubertal changes	*Growth*	*BA*	*Gonadal hormones*	*Gonadotropins*	*GnRH stimulation*
CPP	Concordant	+	+	↑	LH↑	LH predominant
PPP	Discordant	+	+	↑	Suppressed	No rise
PT	No progression	N	N	Prepubertal	Prepubertal	FSH predominant
PA	No progression	N	N	Prepubertal	Prepubertal	Prepubertal

(BA: bone age; CPP: central precocious puberty; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PA: premature adrenarche; PPP: peripheral precocious puberty; PT: premature thelarche)

Investigations

Hormonal Evaluation

S. No.	*Investigation*	*Inference*
1.	Gonadotropin stimulation test with GnRH or GnRHa	LH predominant response is seen in CPP after GnRH stimulation CPP—LH levels >5–8 IU/L are diagnostic for CPP in children between 2 and 8 years of the age PPP—gonadotropin levels are suppressed by gonadal hormones and do not rise in response to GnRH/GnRHa stimulation and in premature adrenarche response is prepubertal FSH is raised in premature thelarche and intermediate between premature thelarche
2.	Serum estradiol	>20 pg/mL suggest that puberty has started >100 pg/mL are seen in estrogen secreting ovarian tumors and follicular cysts
3.	Serum testosterone	Basal levels are higher in both CPP and PPP, but are much higher in PPP <30 ng is prepubertal, 10–30 ng may indicate early puberty, 30–100 ng early pubertal, 100–300 ng mid puberty
4.	Adrenal androgens Dehydroepiandrosterone (DHEA) Dehydroepiandrosterone sulfate (DHEAS)	Usually elevated in second stage of puberty Serum androgen is useful in girls to differentiate between premature adrenarche and virilization Pubertal levels of DHEAS characterize premature adrenarche Greatly elevated levels go in favor of adrenal tumors
5.	Thyroid hormone test (TSH, T4)	Hypothyroidism is very relevant, especially PPP
6.	Serum prolactin	In galactorrhea
7.	hCG and alpha-fetoprotein	Raised in PPP

Investigations

Image Studies

S. No.	*Image studies*	
1.	Radiological examination of bones for the bone age and bone dysplasia	Acceleration of growth and skeletal maturation results in early closure of epiphysis as occurs in PPP, CPP, and leads to compromised adult height but not seen in pubertal variants
2.	CT and MRI of brain	To determine etiology of CPP in all the boys
3.	CT and MRI of adrenal	Is suspicion of an adrenal tumor
4.	Pelvis and abdominal ultrasonography	Is advised to evaluate the size and morphology of the uterus and ovaries. Adrenals in PPP Uterus is considered to be pubertal when it is pear shaped The uterus remains prepubertal in premature thelarche and thelarche variant
5.	Testicular sonography	Can detect nonpalpable Leydig cell tumors in cases of asymmetric testicular volume or PPP
6.	Bone scan and skeletal survey are indicated in suspected cases of McCune–Albright syndrome (MAS) Extensive investigations are required in a child with initial signs of puberty only if more than one sign of puberty is present, the growth is accelerated, bone age is advanced, or a new sign of puberty appears during the period of observation.	

Genetic Studies

In family with history of CPP and genetic syndromes such as Temple syndrome and Williams Beuren syndrome.

Treatment

S. No.	*Type*	*Mode of management*
1.	*The normal variants:* Premature pubarche, thelarche, and thelarche variants	Do not need treatment. Reassurance and regular follow-up
2.	*CPP:* Directed to the treatment of any identified underlying pathology CNS tumors Idiopathic	Surgical resection or radiotherapy Gonadotropin-releasing hormone analog therapy The aim of the management is to reverse the premature sexual maturation and decreasing the acceleration of the bone age and premature closure of epiphysis Treatment outcomes are affected by initial patient characteristics such as age of the child, tempo of sexual maturation, bone age and target height, and treatment duration

Contd...

Treatment

Contd...

S. No.	Type	Mode of management
	Treatment modalities depend: On clinical parameters such as pubertal signs at 3–6 monthly intervals, growth velocity, and skeletal maturation Considering the high cost of GnRH analog therapy and should be used judiciously Decision of stopping treatment is individualized Pubertal maturation will resume in few months and menstrual cycles will start after few months to 2 years of stopping treatment Concomitant GH and/or thyroid hormone deficiency should be diagnosed and treated promptly for better adult height prognosis Hypothalamic hamartoma may be associated with intractable gelastic or psychomotor seizures and need to be treated	
3.	PPP	Treatment is indicated in children with rapidly progressive puberty with significantly advanced bone age. This should be done by monitoring for 3–6 months Exogenous sex steroids to be stopped Classic CAH to be treated with glucocorticoids Tumors of the ovary, testis, and adrenals to be removed surgically Autonomous ovarian cysts may usually recur to be treated with medroxyprogesterone or cyproterone to accelerate involution of cysts
4.	Familial male-limited precocious puberty (FMPP)	Treated with drugs that suppress gonadal steroidogenesis such as ketoconazole, spironolactone, cyproterone acetate, and medroxyprogesterone
5.	McCune–Albright syndrome	Treatment indicated only when there is rapidly progressive puberty and adult height is severely compromised. Cyproterone acetate and medroxyprogesterone should be used to control breast development and vaginal bleeding but do not influence final adult height

Earlier puberty has higher risk of psychological problems, higher body mass index (BMI), and development of metabolic syndrome.

Psychological support for the child and parents is very important in precocious puberty.

Mental development is usually compatible with chronological age. Emotional behavior and mood swings are common.

Further Reading

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