Sexual precocity and its treatment

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Background: **Puberty is a complex and dynamic period in development during which individuals transition from the juvenile to adult state. Regulated by multiple genetic and endocrine controls, it is characterized by somatic growth and sexual maturation. Sexual precocity is defined as the appearance of secondary sexual characteristics before the lower limit of the normal age for pubertal onset.**

Data sources: **Based on recent publications and the experience with the disease of our group, we reviewed the normal timing and order of puberty, the definition of sexual precocity, the classification of sexual precocity, the differential diagnosis of sexual precocity, variations in pubertal development, the diagnosis of sexual precocity, and the treatment of sexual precocity.**

Results: **Sexual precocity can be classified as either gonadotropin-releasing hormone (GnRH)-dependent or GnRH-independent. Regardless of the etiology, sexual precocity causes increased height velocity, somatic development, and skeletal maturation, which may have profound physical and psychological implications.**

Conclusions: **The treatment of sexual precocity is focused on its cause and must address both its psychosocial and clinical implications. For GnRH-dependent precocious puberty, GnRH agonists are the main pharmacological agents used. Alternatively, the treatment of disorders causing GnRH-independent sexual precocity is directed toward the underlying abnormality.**

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Review article

Introduction

Puberty is a complex process of developmental change regulated by multiple genetic and endocrine factors. It is characterized by increased statural growth, somatic development, skeletal maturation, the appearance of secondary sex characteristics, and, ultimately, the onset of reproductive capability. Pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH) due to the pubertal "reawakening" of the GnRH pulse generator from its relative quiescent state during childhood regulates the release of the pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The pulsatile and rising FSH and LH levels then lead to the increases in serum gonadal sex steroids (estrogen in females and testosterone in males), which yield the physical changes of puberty.

Normal timing and order of puberty

Descriptive standards for assessing pubertal development are in wide use (sexual maturation stages or Tanner stages),[1,2] and make it possible to objectively record the progression of secondary sexual development.

In girls, the first sign of puberty is typically an increase in linear growth, though breast development is often the first sign noted by parents and physicians.[3] Both are due to the actions of estrogen;[4] the rapid growth is secondary to estrogen-mediated increases in growth hormone (GH) secretion and insulin like growth factor-1 levels,[5,6] whereas breast development is secondary to estrogen-mediated effects on the glandular and connective tissues of the mammary glands.[7,8] Areolar changes in size, erectility, and color also occur in a predictable sequence. Other features reflecting estrogen action include enlargement of the labia minora and majora, dulling of the vaginal mucosa, and the production of a clear or slightly whitish vaginal secretion. Alternatively, pubic hair development is due to the secretion of adrenal and gonadal androgens. Moreover, although breast development and pubic hair growth often occur at similar rates, they are best staged separately as discrepancies may exist. In boys, the first sign of puberty is usually an increase in the size of the testes to more than 2.5 cm in longest diameter (excluding the epididymis), equivalent to a testicular volume of 4 mL or greater.[9] As in females, pubic

hair development is secondary to adrenal and gonadal androgen production. Furthermore, as in females, pubic hair growth is best classified separately from genital development.

The normal age of onset of puberty, particularly in girls, is controversial. Secondary sexual development starting after the age of 6 years in African American girls and 7 years in Caucasian girls in the United States have been reported by some to be "normal"; however, these age cut-offs must be used with caution and only in the absence of findings suggesting a condition that might predispose the girl to precocious puberty.[10,11] A more traditional cut-off for the age of normal pubertal onset in girls is 8 years. Moreover, while the mean age at menarche in the US was previously stable at about 12.8 years, there appears to be a recent decrease in the age of menarche by several months.[12,13] This decrease is partially explained by the obesity epidemic. Studies[14-16] have shown that pubertal development is inversely related to body mass index (BMI) in girls; the age of onset of puberty may also be inversely related to BMI in boys.[17] Twin studies, as well as the concordance of age at menarche between mother-daughter pairs and females within ethnic populations, also demonstrate genetic effects on the age of menarche. African-American girls typically have menarche 6 months earlier than Caucasian girls, but this difference is less than the 1-year difference in the age at onset of puberty between the two groups.[18,19] However, 9 years is taken as the lower limit of "normal" pubertal development in all boys.

The timing and duration of puberty may also be influenced by body composition, social milieu, and environmental exposures.[20] As alluded to above, the presence of obesity is an important factor in determining the age of puberty,[21] and leptin (an adipose-derived hormone) has been shown to play a significant role in mediating gonadotropin secretion.[22] Insulin levels, which are often elevated in obese non-diabetic states, may also be a codeterminant of pubertal tempo due to insulin-induced reductions in sex hormone-binding globulin, resulting in an increased bioavailability of gonadal sex hormones.[23] Moreover, exposure to endocrine disruptors, such as phthalates, bisphenol A, and plant-derived phytoestrogens has been implicated in precocious sexual development.[24]

Importantly, pubarche (i.e., the onset of pubic hair development), which results from increases in gonadal or adrenal androgen production, is different than puberty. The adrenal cortex normally begins to secrete dehydroepiandrosterone (DHEA), its sulfate, DHEA sulfate (DHEA-S), and androstenedione in increasing amounts at about 6-7 years of age in girls and 7-8 years of age in boys. A continued rise in these hormones (which act as weak androgens) persists until late puberty. Adrenarche (the secretion of adrenal androgens) thus occurs before gonadarche (the secretion of gonadal sex steroids). Moreover, the age at adrenarche does not significantly influence the age at gonadarche, and suppressed gonadarche does not alter the progression of adrenarche.

Definition of sexual precocity

Sexual precocity is defined as the appearance of any sign of secondary sexual maturation before the normal lower age limit for pubertal maturation for race and sex. For practical purposes, we use the age limits of 8 years for girls and 9 years for boys to determine when children with secondary sexual characteristics should be medically evaluated. However, some[12,25-28] but not all[29] studies suggest a secular trend toward a younger age of pubertal onset; thus, the acceptable lower age limit for normal pubertal development, especially in girls, remains a matter of debate.[30]

Classification of sexual precocity

Sexual precocity can be classified as (i) true or central precocious puberty (CPP), in which increased gonadal sex steroid production is dependent on the pulsatile hypothalamic GnRH stimulation of pituitary gonadotropes; or (ii) incomplete sexual precocity, in which increased gondal sex steroid production occurs independent of GnRH release or the subject is exposed to exogenous sex steroids. CPP is always isosexual, whereas incomplete sexual precocity can either be iso- or contrasexual. Regardless of the etiology, the increased sex steroid exposure increases height velocity, somatic development, and the rate of skeletal maturation. Affected individuals may therefore be tall during childhood but short as adults secondary to premature closure of the growth plates.[31,32]

Differential diagnosis of sexual precocity

Causes of sexual precocity are listed in Table 1. A comprehensive discussion of all the etiologies of sexual precocity is beyond the scope of this article, but has recently been reviewed.[3,33,34]

True or central precocious puberty (GnRH-dependent sexual precocity)

Causes of true or central precocious puberty are listed in Table 1. In this group of disorders, increased sex steroid production is dependent on the pulsatile release

Table 1. Classification of sexual precocity

True or central precocious puberty (GnRH-dependent sexual precocity)
Idiopathic central precocious puberty
CNS tumors
Optic glioma (associated with neurofibromatosis type 1)
Hypothalamic astrocytoma
Other CNS disorders
Developmental abnormalities (including hypothalamic hamartoma of the tuber cinereum)
Head trauma
Cranial irradiation
Central precocious puberty after late treatment of virilizing CAH
Incomplete sexual precocity (GnRH-independent sexual precocity)
Isosexual incomplete sexual precocity in boys
Gonadotropin-secreting tumors
hCG-secreting CNS tumors
hCG-secreting tumors located outside the CNS
Increased androgen secretion by adrenal or testis
Virilizing CAH (e.g., CYP21, CYP11B1, or 3-HSD type 2 deficiency)
Virilizing adrenal neoplasm
Leydig cell adenoma
Familial testotoxicosis
Isosexual incomplete sexual precocity in girls
Ovarian cyst
Estrogen-secreting ovarian or adrenal neoplasm
Iatrogenic or exogenous (including exposure to estrogens in foods, drugs, or cosmetics)
Isosexual incomplete sexual precocity in boys and girls
McCune-Albright syndrome
Hypothyroidism
Contrasexual incomplete sexual precocity in boys
Adrenal neoplasm
Testicular neoplasm
Aromatase excess syndrome
Iatrogenic (i.e., exposure to estrogens)
Contrasexual incomplete sexual precocity in girls
Virilizing CAH (e.g., CYP21, CYP11B1, or 3-HSD type 2 deficiency)
Virilizing adrenal neoplasm (e.g., Cushing's syndrome)
Virilizing ovarian neoplasm (e.g., arrhenoblastoma)
Aromatase deficiency
Iatrogenic (i.e., exposure to androgens)

CAH: congenital adrenal hyperplasia; GnRH: gonadotropin releasing hormone; CNS: central nervous system; hCG: human chorionic gonadotropin; CYP21: 21-hydroxylase; CYP11B1: 11-hydroxylase; 3-HSD type 2: 3-hydroxysteroid dehydrogenase type 2. (Modified from Styne, et al[35])

of GnRH from the hypothalamus.

For reasons that remain unclear, true precocious puberty (i.e., GnRH-dependent CPP) is much more common in girls than boys,[36] with female/male ratios ranging from 3/1 to 23/1.[37] Furthermore, although central nervous system (CNS) lesions seem to predispose males and females equally to CPP, there is a striking sex difference (females > males) among children with CPP in whom no underlying pathology is found (i.e., idiopathic CPP). Specifically, whereas CPP caused by CNS abnormalities appears to occur as least as often as idiopathic CPP in boys, CPP caused by neurological lesions is estimated to be only one-fifth as common as idiopathic CPP in girls. Thus, evaluation for a neurogenic cause of CPP in both sexes-but especially males-is essential, particularly since sexual precocity may be the only manifestation of an underlying CNS tumor.[38] Furthermore, organic forms of CPP usually occur at an earlier age than the idiopathic form, and the progression of secondary sexual maturation is often more rapid.[39]

CNS tumors

The most common organic cause of CPP in an individual with sexual precocity is a hamartoma of the tuber cinereum.[40] These hypothalamic lesions are congenital, static, and composed of heterotopic neural tissue that often secrete GnRH. It is postulated that these neurons are not controlled by the intrinsic CNS mechanisms that normally inhibit GnRH, thereby releasing the CNS restraint of gonadotropin secretion. Hamartomas frequently cause the development of CPP before 3 years of age, and can be associated with seizures [particularly laughing (gelastic) seizures], mental retardation, behavioral disturbances, and dysmorphic syndromes.[39,41-43] Neurosurgical resection of CNS tumors causing CPP is difficult because of their location. Thus, after biopsy, these lesions are usually treated with radiation therapy and/or chemotherapy, depending on the pathological findings. Hamartomas of the tuber cinereum in particular are preferentially treated medically, barring evidence of associated complications such as intractable seizures or hydrocephalus.

Non-CNS tumors

In addition to CNS tumors, infectious, post-infectious, or granulomatous conditions such as a brain abscess or sarcoidosis of the hypothalamus can cause CPP. CPP may also follow brain trauma or cranial irradiation for other types of CNS lesions or leukemia. Other CNS abnormalities associated with CPP are listed in Table 1. Interestingly, septo-optic dysplasia, although most often associated with anterior pituitary hormone deficiency and pubertal delay, has also been associated with CPP,[44] possibly due to hypersecretion of some anterior pituitary hormones (i.e., the gonadotropins) with concomitant hyposecretion of others.[45]

Incomplete precocious puberty (GnRH-independent sexual precocity)

Causes of incomplete sexual precocity are listed in Table 1. In this group of disorders, increased sex steroid production is independent of the hypothalamic GnRH pulse generator. Etiologies include exogenous sex hormone exposure or excess secretion of endogenous

sex hormones from the adrenal glands or gonads.

Incomplete sexual precocity in boys

Causes of isosexual incomplete sexual precocity in boys are listed in Table 1. Human chorionic gonadotropin (hCG)-secreting tumors, either located in the CNS (e.g., chorioepitheliomas, germinomas, or teratomas) or outside the CNS (e.g., hepatomas, teratomas, or choriocarcinomas) can cause isosexual incomplete sexual precocity in males, as can increase androgen secretion by either the adrenal [e.g., congenital adrenal hyperplasia (CAH) or virilizing adrenal neoplasm] or testis (e.g., Leydig cell adenoma or familial testotoxicosis). Causes of contrasexual incomplete sexual precocity in boys are also listed in Table 1. One cause is the aromatase excess syndrome, which causes increased aromatization of adrenal steroids (such as androstenedione) to estrogens.[46] Feminizing testicular tumors (often associated with the Peutz-Jeghers syndrome) are another cause of contrasexual incomplete sexual precocity in boys.[47]

Incomplete sexual precocity in girls

Causes of isosexual incomplete sexual precocity in girls are listed in Table 1. In this condition, females have excessive estrogen exposure from either exogenous or endogenous sources, whereas serum LH and FSH levels remain low. The most common ovarian cause of sexual precocity in females is an autonomous follicular cyst;[48] granulosa cell tumors of the ovary occur less frequently. Other causes of isosexual incomplete sexual precocity in girls include the Peutz-Jeghers syndrome and estrogen-secreting adrenal tumors. Causes of contrasexual incomplete sexual precocity in girls are listed in Table 1. Hyperandrogenism, secondary to CAH or androgen-producing tumors of the adrenal gland, can also cause virilization and contrasexual incomplete sexual precocity in girls. Furthermore, aromatase deficiency due to inactivating mutations in the aromatase gene (*CYP19*) is associated with progressive virilization, lack of female secondary sex characteristics, multicystic ovaries, tall statue, and osteopenia.

Isosexual incomplete sexual precocity in boys and girls

Among the causes of isosexual incomplete sexual precocity in boys and girls (Table 1), McCune-Albright syndrome and hypothyroidism are particularly important.

McCune-Albright syndrome is an uncommon cause of precocious puberty in both sexes due to mutations in the *GNAS1* gene, which result in constitutional activation of adenylyl cyclase in a sporatic pattern of tissues and cells. It is clinically characterized by irregularly shaped café-au-lait spots, polyostotic fibrous dysplasia of long bones, and GnRH-independent sexual precocity.[49]

In contrast to other forms of sexual precocity, primary hypothyroidism-related sexual precocity is associated with growth impairment and delayed skeletal maturation.[50] Although the precise mechanism underlying hypothyroidism-associated sexual precocity is unknown, studies suggest that it may be two fold. An increase in hypothalamic thyrotropin-releasing hormone enhances FSH release from the pituitary.[51] Also, thyroid-stimulating hormone (TSH), which is elevated in primary hypothyroidism, may act on the FSH receptor.[52] Thus, stimulation of the FSH receptor by either its natural ligand or TSH may account for the increased ovarian estrogen secretion or testicular enlargement noted in affected girls or boys, respectively.[53]

Moreover, the chronology of secondary sexual characteristics development is also important. For example, the onset of menses before later Tanner stages of breast development in girls or the presence of secondary sexual characteristics in boys with no testicular enlargement would suggest incomplete sexual precocity rather than true precocious puberty.

Variations in pubertal development

Premature thelarche

Premature thelarche is characterized by unilateral or bilateral breast development without other signs of secondary sexual development. Patients are usually younger than 2 years of age, and breast enlargement regresses within months, but may remain until actual pubertal development at a normal age.[54] Generally, premature thelarche is self-limiting and does not lead to central precocious puberty, though it may require provider reassurance with follow up at regular intervals to assess for further secondary sexual development or accelerated skeletal maturation.

Premature adrenarche

Premature adrenarche is characterized by the early appearance of pubic or axillary hair without other signs of virilization or pubertal development.[55] It is more common in girls and is typically found in children older than 6 years of age. Plasma DHEA-S levels may be elevated, and bone and height ages may be slightly advanced. Although this condition is considered a variant of normal development and for most individuals benign, it is associated with an increased risk for polycystic ovary syndrome in girls.[56] The presenting signs and symptoms of premature adrenarche may overlap with non-classical CAH, and the differentiation between the two may require adrenocorticotropic hormone stimulation testing.

Diagnosis of sexual precocity

In general, the evaluation of children with sexual precocity focuses on identifying the source of the increased sex steroids. The source can be either exogenous or endogenous; if endogenous, it can be either from the gonad or adrenal, and the underlying process either primary (from the gland) or secondary (from the hypothalamic-pituitary unit).

The detailed history and physical examination guide further workup. The history should focus on the age of onset of sexual precocity, a family history of premature pubertal development, and possible head trauma. It should also include a careful review of systems for headaches, changes in vision, seizures, and abdominal complaints. On physical examination, it is important to assess breast development by inspection and palpation in order to differentiate breast tissue from adipose tissue. A visual examination to evaluate papilledema or restricted visual fields, and a full dermatologic examination to evaluate for café-au-lait spots should also be performed. In addition, a linear growth chart and height velocity should be assessed.

Given the effects of sex steroids on skeletal maturation, patients who have early secondary sexual development should be initially evaluated with a radiographic assessment of bone age by the Greulich & Pyle or Tanner methods. The subsequent diagnostic evaluation of sexual precocity in girls before age of 8 years is outlined in Fig. 1, whereas the subsequent diagnostic evaluation of sexual precocity in boys before age of 9 years is outlined in Fig. 2.

Hormonal testing usually consists of measuring baseline concentrations of gonadotropins and gonadal sex steroids (estradiol in girls, testosterone in boys). There are many assays that are currently used; however, we recommend the use of highly sensitive and specific immunochemiluminometeric assays (ICMA) for the evaluation of gonadotropin concentrations and high-performance liquid chromatography tandem mass spectrometry for the measurement of gonadal sex steroids.[57] Importantly, these measurements should also be made in a laboratory with established pediatric pubertal and pre-pubertal reference ranges. In the event of equivocal basal gonadotropin levels, a GnRH-stimulation test with a GnRH analogue (leuprolide acetate, 20 mcg/kg) can be performed.[58] Whereas a peak LH concentration >5 mIU/mL (measured by ICMA) is indicative of maturing gonadotropin secretion, a diagnostic cut-off of 8 mIU/mL (measured by ICMA) is a more stringent threshold for CPP and

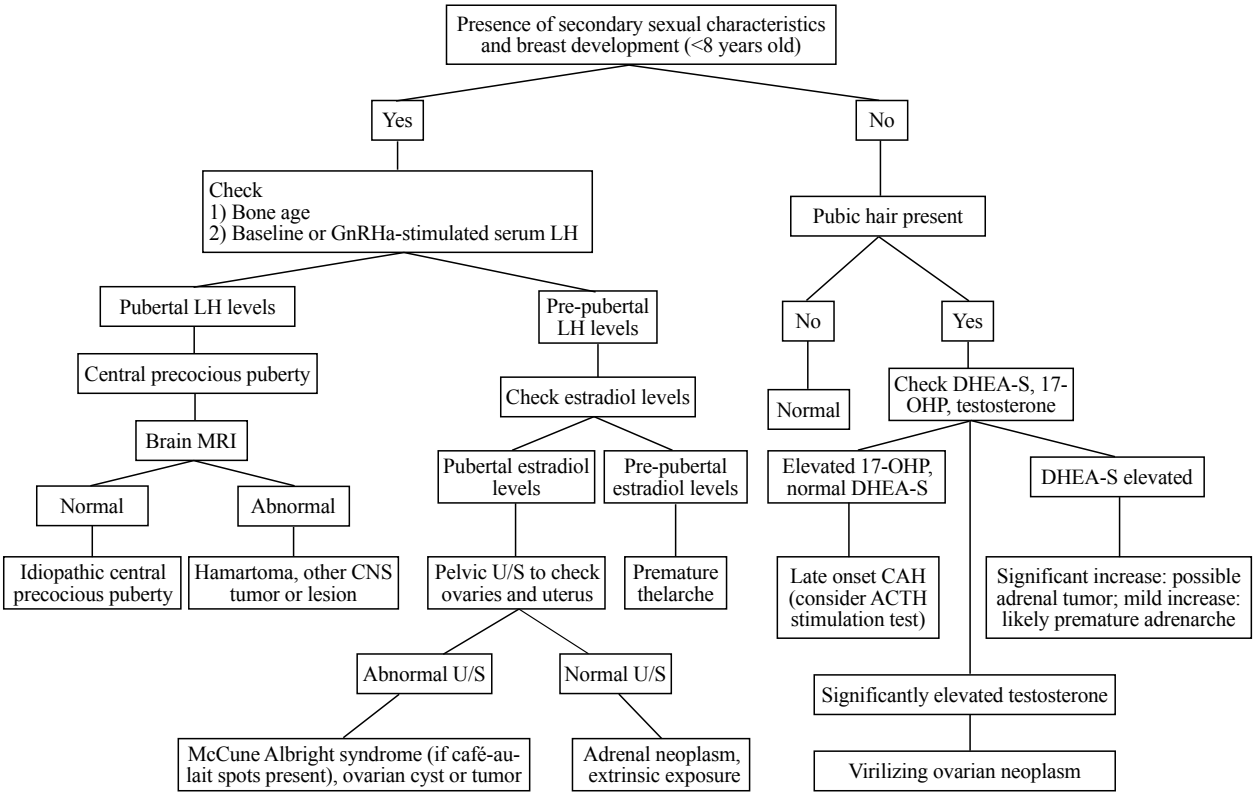

Fig. 1. Algorithm for the evaluation of girls with sexual precocity prior to age 8. ACTH: adrenocorticotropic hormone; GnRHa: gonadotropin-releasing hormone agonist; CAH: congenital adrenal hyperplasia; CNS: central nervous system; DHEA-S: dehydroepiandrosterone-sulfate; LH: luteinizing hormone; MRI: magnetic resonance imaging; 17-OHP: 17-hydroxyprogesterone; U/S: ultrasound.

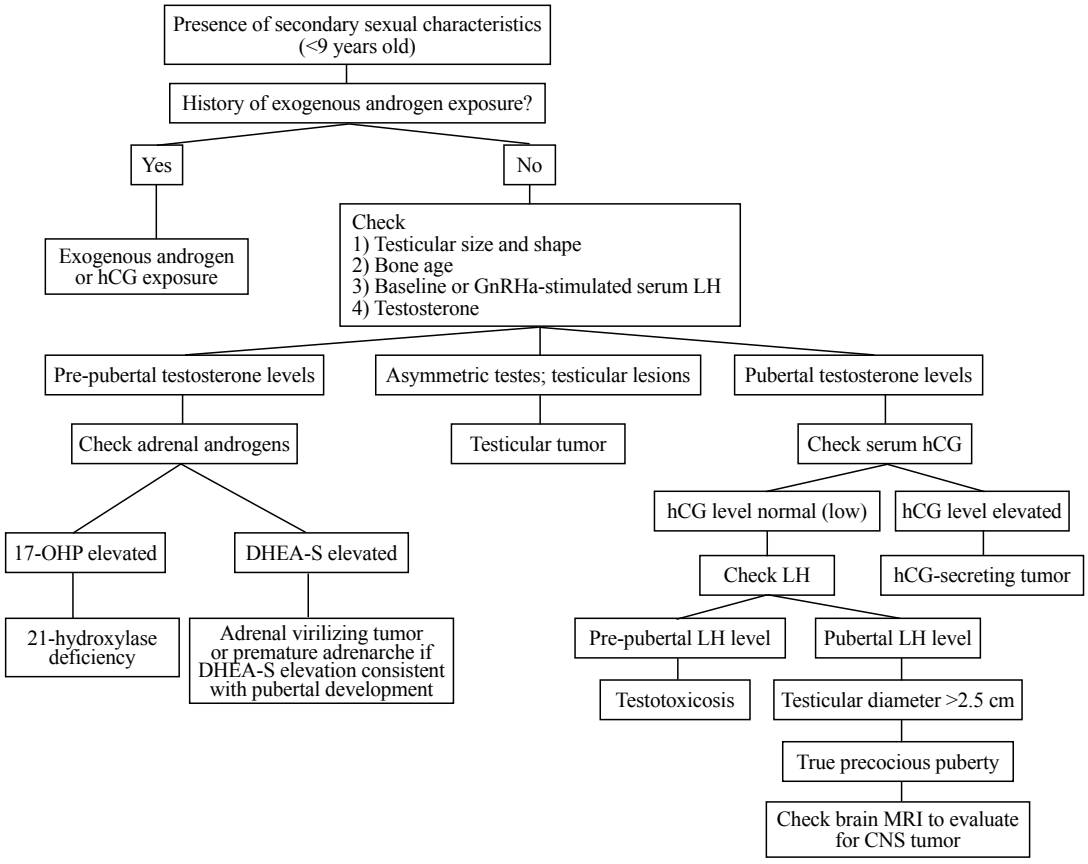

Fig. 2. Algorithm for the evaluation of boys with sexual precocity prior to age 9. CNS: central nervous system; DHEA-S: dehydroepiandrosterone-sulfate; GnRHa: gonadotropin-releasing hormone agonist; hCG: human chorionic gonadotropin; HSD: hydroxysteroid dehydrogenase; LH: luteinizing hormone; MRI: magnetic resonance imaging; 17-OHP: 17-hydroxyprogesterone.

is suggestive of gonadotropin-dependent precocious puberty;[59] conversely, gonadotropin levels do not rise following GnRH analogue stimulation in gonadotropin-independent precocious puberty.

Ultrasonography is also indicated to evaluate abdominal or pelvic masses when feminizing or virilizing disorders are suspected. In cases of CPP, the anatomical evaluation of the CNS is preferentially done by magnetic resonance imaging using a hypothalamus/pituitary imaging protocol, since computed tomography is not sufficient to diagnose hypothalamic and other intracranial lesions.

Psychosocial implications of sexual precocity

Whereas sexually precocious males are often perceived as more mature, attractive, and smart, and are often given more leadership roles than later developing boys, sexually precocious females often tend to experience more difficulty in academic and social environments due to their physical development, especially in the middle school and junior high school settings where they may attract the attention of older, more mature boys[60]-putting them at risk for possible sexual exploitation and/or abuse.[61] Moreover, sexual precocity in females may lead to a negative self-body image[62] and is a risk factor for aggression and delinquency.[63] The age of onset of many psychological conditions, including depression, panic attacks, and schizophrenia, also tend to mirror the onset of puberty,[64-69] and boys and girls who mature earlier are at increased risk of risk taking behavior as well as substance use and abuse.[70]

Treatment of sexual precocity

Treatment of sexual precocity is directed toward the underlying cause and is summarized in Table 2. For GnRH-dependent precocious puberty, the primary treatment is with a long-acting GnRH agonist (GnRHa). Chronic administration of long-acting analogs of GnRH (via monthly depot injection or subcutaneous implant) desensitizes the pituitary gonadotropes to GnRH, thereby inhibiting pulsatile LH and FSH release and gonadal sex steroid synthesis. Importantly, individuals affected by precocious puberty may be tall during childhood (due to early secretion of sex steroids) but

Table 2. Pharmacological therapy for sexual precocity

Disorders	Treatment	Action
GnRH-dependent		
True or central precocious puberty	Long-acting GnRH agonist*	Desensitizes the gonadotropes to GnRH, thereby inhibiting pulsatile LH and FSH release and gonadal sex steroid synthesis
GnRH-independent		
Incomplete sexual precocity		
Girls		
Autonomous ovarian cyst	Medroxyprogesterone acetate	Inhibits gonadal steroidogenesis
McCune-Albright syndrome	Medroxyprogesterone acetate†	Inhibits gonadal steroidogenesis
	Aromatase inhibitor (e.g., letrozole)	Inhibits aromatase; blocks estrogen synthesis
	Selective estrogen receptor modulator (e.g., tamoxifen)	Selective inhibition of estrogen action
	Estrogen receptor antagonist (e.g., fulvestrant)	Inhibition of estrogen action
Boys		
Familial testotoxicosis	Ketoconazole†	Inhibits CYP17
	Spironolactone or flutamide+letrozole	Antiandrogen+aromatase inhibitor
	Medroxyprogesterone acetate†	Inhibits gonadal steroidogenesis

*: In a case with combined central precocious puberty and GH deficiency, recombinant human GH therapy can be added; †: If central precocious puberty develops, a long-acting GnRH agonist can be added. CYP17: P450c17; GH: growth hormone; FSH: follicle stimulating hormone; GnRH: gonadotropin releasing hormone; LH: luteinizing hormone. (Modified from Styne, et al[35])

short as adults (secondary to premature closure of the growth plates); thus, one of the main goals of therapy of CPP is to modulate sex steroid production to maximize final adult height.

GnRHa therapy usually results in the reduction of gonadal sex steroid production to prepubertal levels within 2-4 weeks in girls and 6 weeks in boys. Changes in secondary sex characteristics, such as reduction in breast size, thinning of pubic hair, and cessation of menses (if present before treatment) in girls, and reduction in testicular size, thinning of pubic hair, and regression of acne in boys, usually occur within the first 6 months of therapy.

Height velocity decreases approximately 60% during the first year of therapy, and skeletal maturation slows during the first 3 years of therapy, often to a rate less than expected for chronological age. However, after the first year of therapy, height velocity is usually appropriate for bone age. The optimal age for therapy discontinuation is variable, since the post-treatment growth spurt is important in determining final height.[71] In general, stopping GnRHa therapy at an age close to the median physiological age of puberty is likely adequate;[72] however, the longer the treatment is continued, the greater the final height outcome. After cessation of therapy, the hypothalamic-pituitary-gonadal axis usually returns to normal within 1 year.[73,74]

Treatment of the disorders leading to incomplete precocious puberty is directed toward the underlying abnormality. If the primary pathology is controlled, sexual development will be halted, and possibly regress. Furthermore, premature thelarche and adrenarche require no treatment, as both are self-limited benign conditions. Other pharmacological agents used in the management of particular causes of incomplete sexual precocity such as azoles, antiandrogens, and aromatase inhibitors are listed in Table 2.

Conclusions

Sexual precocity can be classified as (i) true or central precocious puberty, in which increased sex steroid production is GnRH-dependent, or (ii) incomplete sexual precocity, in which increased sex steroid production is GnRH-independent or exogenous. Regardless of the etiology, sexual precocity causes increased height velocity, somatic development, and skeletal maturation in affected children; it also can have profound psychological consequences. The treatment of sexual precocity addresses both its psychosocial and clinical implications, and for CPP, GnRH agonists are the main pharmacological agents used.

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