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.

World J Pediatr 2013;9(2):103-111

Key words: puberty; sex precocity

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, erection, 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

World J Pediatr, Vol 9 No 2 · May 15, 2013 · www.wjpch.com
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. 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. This decrease is partially explained by the obesity epidemic. Studies 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. 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. 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. As alluded to above, the presence of obesity is an important factor in determining the age of puberty, and leptin (an adipose-derived hormone) has been shown to play a significant role in mediating gonadotropin secretion. 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. Moreover, exposure to endocrine disruptors, such as phthalates, bisphenol A, and plant-derived phytoestrogens has been implicated in precocious sexual development.

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 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.

**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 gonadal 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.

**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.

**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...