Chapter 28
What activates puberty in the male? What causes early or delayed puberty?

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Puberty is the developmental stage denoted by the maturational transition from a juvenile prepubertal state to attainment of sexual and reproductive maturity. In boys, activation of the hypothalamic-pituitary-gonadal axis initiates puberty and first manifests as testicular enlargement. During male puberty, secondary sexual maturation is characterized by growth and virilization of the external genitalia (increase in testicular size, phallic and scrotal enlargement), and the development of pubic, axillary and facial hair and adult apocrine odor. Somatic changes include the pubertal growth spurt, changes in body composition and proportions, increased muscle development and strength, deepening of the voice, and neuroendocrine maturation associated with changes in behavior, mood, and cognition.

Pubertal development: adrenarche and gonadarche

Two physiologic processes underlie the hormonal and physical changes associated with puberty. The first is adrenarche or maturation of the adrenal cortex marked by a shift in the pattern of adrenal steroidogenesis. The maturation of the zona reticularis is ACTH independent and results in increased secretion of dehydroepiandrosterone sulfate and other adrenal androgens. The adrenal androgens stimulate growth of pubic and axillary hair, apocrine odor, and acne (termed adrenarche or pubarche). The timing of adrenarche is influenced by familial and ethnic factors as well as adiposity and prematurity. The genetic regulation of adrenarche is not fully delineated but it typically precedes activation of the hypothalamic-pituitary gonadal (HPG) axis and gonadarche, the second pubertal process.

An increase in the amplitude and frequency of secretion of GnRH pulses is necessary to stimulate pulsatile release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the

pituitary gland. The secretion of LH and FSH drives maturation of the testes and increases secretion of sex steroids (Chapter 2). Pituitary FSH stimulates proliferation and differentiation of the Sertoli cells to form the seminiferous tubules to support spermatogenesis, while LH is the main stimulus for increased secretion of the virilizing hormones, testosterone and its more active metabolite, dihydrotestosterone. FSH acts in concert with androgens to stimulate germ cell proliferation and maintain spermatogenesis.

A shift in the balance of the network of central neuro-inhibitory modulators and stimulatory neuromodulators occurs at the onset of puberty. This transition from the juvenile to the pubertal state is marked by a decrease in the tonic inhibition of the GnRH neurons by a group of genes identified to inhibit the HPG axis, such as neuropeptide Y, GABA, Dyn, MKRN3, and ghrelin as well as by increased secretion of kisspeptin and other HPG excitatory genes. Several genes have been identified to be critical to the initiation of puberty, such as glutamine, KISS1 (kisspeptin) and TAC3 (neurokinin B, NKB) and their respective receptors. Kisspeptin, a potent stimulator of GnRH release, signals through a G protein coupled receptor 54 (GPR54 or KISS1R), expressed by GnRH neurons. KISS1 expression is low during childhood and increases at puberty. In addition to genetic influences on pubertal timing, pubertal onset is also modified by other factors such as nutritional status, chronic illness, strenuous physical activity, environmental stress, and mental health. These factors may affect the onset and tempo of puberty via epigenetic mechanisms and impede the attainment of full reproductive capacity. Mutations in many of these inhibitory and stimulatory genes have been linked to disorders of pubertal development.

During embryonic development, the initial activation of the hypothalamic neuronal network results in pulsatile GnRH secretion and stimulates fetal testicular Leydig cell production of testosterone to promote internal and external genital masculinization. The fetal Leydig cells continue to secrete testosterone after birth for a few months to stimulate ongoing differentiation of the external genitalia. During this “mini-puberty” of infancy, despite the high levels of gonadotropins and androgens, the seminiferous tubule of the infant does not undergo further maturation because androgen and FSH receptor signal transduction pathways in the infant Sertoli cells remain immature. In later infancy, the GnRH-gonadal axis becomes inhibited and remains quiescent during childhood.

The pattern of GnRH release during the infant-childhood/juvenile-adolescent transitions indicates that there are two critical postnatal "switches" or "triggers" related to the onset of puberty: the first, operational by late infancy, leads to inhibition of GnRH release during prepubertal development, and the second transition occurs when there is reactivation of intermittent GnRH release at the onset of puberty. The term GnRH pulse generator was coined to describe the main "trigger" for the onset of puberty and has been used to describe the role of kisspeptin in regulating pubertal onset, although it is now appreciated that there is a complex interplay of inhibitory and stimulatory genes responsible for activation of the HPG axis at puberty.

Assessing pubertal development

Pubertal development is assessed using a genital staging scale first developed by Dr. James Tanner that evaluates adrenarche and gonadarche independently based upon visual inspection. The scale is scored from 1 (prepubertal) to 5 (sexual maturity) for genital development (G1-5) and pubic hair growth (P1-5). Measurement of testicular volume yields a more accurate assessment of male pubertal development. An orchidometer or Prader beads are a string of elliptical beads ranging in size from 1 cc to 25 or 30 cc. Prepubertal testes are 1-2 cc in size; a 3 cc testis is indicative of pubertal onset, and full maturity is seen with testes of 20-30 cc in volume. Typically, development of adrenarche and gonarche are synchronized and seldom discordant by more than two stages. The average onset of puberty in boys is now 10-11 years with a normal range from 9-13 years. Progression through puberty from stage 2 to 5 occurs over approximately 3.5 to 5 years. In boys the pubertal growth spurt occurs during mid-to late puberty, and sexual maturity is attained by age 15-16 years on average. Over the past 50 years, secular shifts in the age of onset of puberty have been reported world-wide. This has been attributed to factors such as improved nutrition as well as exposures to environmental endocrine disrupting chemicals.

Precocious puberty: causes and treatments

Any deviation from the average (+/- 2 SD) age of puberty that is inconsistent with familial patterns might be considered a disorder of pubertal development. Early puberty is less common in boys than in

girls and warrants close examination to determine if puberty is isolated to adrenarche (only pubic hair with or without other findings of virilization) in conjunction with prepubertal testes or if the gonads are also enlarging and if there are other somatic signs of excess androgen exposure. Potential consequences include tall stature during childhood, sexual maturity and appearance discordant with chronologic age and with emotional/social maturity, and advanced skeletal maturation leading to early epiphyseal fusion and cessation of linear growth resulting in adult short stature. Adrenarche and virilization without growth in testicular size suggests either exposure to exogenous androgens or secretion of androgens from congenital adrenal hyperplasia or a virilizing tumor. Congenital adrenal hyperplasia represents a group of disorders with inactivating mutations in steroidogenic enzyme genes that result in low levels of cortisol that in turn lead to increased pituitary secretion of adrenocorticotrophic hormone (ACTH) and shunting to the pathway of adrenal androgen secretion. True precocious puberty may be idiopathic but organic causes must be excluded. The first step is to differentiate between a central versus peripheral process. Central precocious puberty with premature activation of pulsatile GnRH secretion can be caused by a CNS process--brain tumor or hypothalamic activation due to a central inflammatory disorder, brain trauma, infection, or radiation. A condition mimicking central precocious puberty can be caused by tumors located in the liver, mediastinum, or central nervous system that secrete human chorionic gonadotropin which binds to testicular LH receptors and stimulates testosterone secretion. Central precocious puberty can be suppressed using long-acting GnRH receptor analogues such as leuprolide acetate and histrelin. These GnRH receptor agonists lack the pulsatile pattern that is needed to stimulate pituitary gonadotropin secretion and instead the high levels lead to a negative feedback mechanism to inhibit FSH and LH secretion.

Precocious puberty may also result from GnRH independent androgen secretion caused by familial autosomal dominant male limited precocious puberty (LH receptor activating mutations/ testotoxicosis), McCune-Albright syndrome (GNAS somatic mutation), or Leydig cell tumors. Therapy is directed at the underlying disorder. In some instances, these peripheral causes of precocious puberty are complicated by secondary development of increased pulsatile GnRH secretion as central puberty can ensue.

Delayed puberty: causes and treatments

Delayed puberty is more common than precocious puberty in boys. The most common cause is a familial variant of normal, termed constitutional delay of growth and development (CDGD), i.e., "late bloomers". Often, boys with CDGD are referred to the pediatric endocrinologist because they appear noticeably younger and shorter than their peers and are less muscular with no signs of puberty. For some boys, reassurance is sufficient, particularly if there is a strong family history; for others, the delayed puberty and growth may be associated with depression, anxiety, and school failure that may lead to major psychosocial dysfunction. As genes are identified that mediate the tempo of puberty, mutations have been identified that are responsible for familial delayed puberty. A short course of androgen therapy can be beneficial in accelerating linear growth and pubertal development and alleviating the psychosocial concerns.

Organic etiologies of delayed or absent puberty should be differentiated as centrally or peripherally mediated. Primary gonadal failure is typically accompanied by elevated gonadotropins and can be due to testicular trauma, gonadotoxic drugs, radiation, intrauterine torsion, or genetic causes. The most common genetic condition is Klinefelter syndrome (Chapter 37) (47,XXY) which can cause a late onset of puberty or incomplete progression through puberty. Single gene disorders, gonadal dysgenesis, and XX sex reversals are other rarer causes. Central causes of delayed puberty may include a mutation in one of the myriad of genes involved in the control of GnRH or gonadotropin secretion or action, chronic illnesses, psychosocial factors such as depression or stress, and impaired nutrition.

Conclusion

The detailed physical examination, growth pattern, and family history can provide valuable diagnostic clues for syndromic or associated findings. Skeletal bone age film is useful for assessment of both early and late puberty. A bone age that is discordant with chronological age reflects the key contribution of sex steroids to skeletal maturation and linear growth. Laboratory evaluation for delayed puberty includes serum LH, FSH, and testosterone measurement. While testosterone concentrations are subnormal in both central and primary causes of delayed puberty, gonadotropin levels are elevated only in testicular failure. Chronic illnesses and impaired nutrition (including restricting calories to limit weight gain) can generally be diagnosed based on history, physical examination, and

laboratory data. Treatment of the primary illness and improvement in mental health or nutritional status can often help in hypothalamic hypogonadism.

Suggested reading

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