Is there a trigger for puberty in the male? Should early or delayed puberty be treated? If so, how?

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Puberty in boys normally occurs between 10 and 17 years of age, when the individual matures sexually and becomes capable of producing sperm and reproducing. The physical manifestations of puberty in males include growth in the sizes of the testes and the phallus, development of pubic, axillary and facial hair, and adult apocrine odor, accelerated body growth, increased muscle strength, and changes in mood and behavior. Transition from boyhood to adolescence occurs because of two physiological processes, that typically are sequentially and independently activated. The first is adrenarche, which is a maturation of the adrenal cortex associated with increased secretion of dehydroepiandrosterone sulfate and other adrenal androgens. Adrenarche, the cause of which is poorly understood, leads to pubic and axillary hair, apocrine odor, and acne (pubarche). The second is gonadarche, which is comprised of increased secretion of testicular testosterone from the Leydig cells and initiation of spermatogenesis. All phenotypic aspects of pubertal development including spermatogenesis are the result of increased testosterone secretion. The stimulus for testosterone release is increased luteinizing hormone (LH) secretion from the pituitary gland, which in turn is driven by activation of a pulsatile (1 pulse every 2-3 hours) discharge of gonadotropin releasing hormone (GnRH) from axon terminals in the median eminence of the hypothalamus into a portal blood system supplying the pituitary. GnRH is synthesized by approximately a thousand neurons that are diffusely distributed throughout the hypothalamus. Pulsatile GnRH release also increases the secretion of follicle stimulating hormone (FSH), which acts in concert with testosterone at the level of testicular Sertoli cells to amplify the action of the androgen to maintain spermatogenesis at maximal levels. For puberty to be completed and for testosterone and spermatogenesis to be maintained in adulthood a sustained pulsatile GnRH stimulation of the pituitary is required.

The hypothalamic neuronal network responsible for pulsatile GnRH release develops in the fetus where it promotes external genital development, and remains functional during the first 6 months of postnatal life. This is reflected by elevated gonadotropin secretion and testicular testosterone release during infancy. The seminiferous tubule of the infant, however, is unable to respond to the “adult” hormonal milieu because androgen and FSH receptor signal transduction pathways in the Sertoli cell

have yet to mature. Later in infancy, intermittent hypothalamic GnRH release is greatly diminished leading to low gonadotropin levels that guarantee continued quiescence of the prepubertal testis. During childhood, the pituitary and testis are able to respond to stimulation with GnRH and gonadotropin, respectively, and therefore these components of the reproductive axis are not limiting to the onset of puberty.

The up-down-up 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 in the infant, leads to suppression of GnRH release during the greater part of prepubertal development, and the second is responsible for reactivation of intermittent GnRH release at the termination of juvenile development.

The reduction in GnRH release during childhood and juvenile development is viewed to result from imposition of a neurobiological brake on the GnRH pulse generator during these developmental phases. A major component of this brake is accounted for by a reduction in stimulatory kisspeptin input to the GnRH neurons. Kisspeptin is encoded by the gene, *KiSS1*, which is expressed in hypothalamic neurons located in the infundibular nucleus that surrounds the base of the third cerebroventricle. Kisspeptin, a potent stimulator of GnRH release, signals G protein coupled receptor 54 (GPR54 or KISS1R), which is expressed by GnRH neurons. *KISS1* expression is low during childhood and increases at puberty. Inactivating mutations of GPR54 are associated with absent or delayed puberty. Other neuropeptides, in particular neurokinin B, neurotransmitters (GABA and glutamate) and glial derived growth factors have also been implicated in this neurobiological brake.

Two control systems have been proposed to govern the timing of the neurobiological brake dictating the postnatal pattern of GnRH release. The first is a somatometer that posits that GnRH release during postnatal development is governed by a hypothalamic system that tracks circulating signals and reflects somatic growth. Thus, attainment of adult stature is coordinated with the attainment of fertility. The second posits a pubertal “clock” also resident in the hypothalamus and comprised of a hierarchal network of genes encoding for transcriptional factors.

Disorders of puberty may lead to delayed or early (precocious) puberty. Causes of delayed or absent puberty include primary deficiencies in secretion or action of GnRH and/or, gonadotropins, and testicular failure due to Klinefelter syndrome (47,XXY karyotype), single gene disorders, or gonadal dysgenesis (Chapter 17). Chronic illnesses and impaired nutrition may lead to reduced gonadotropin secretion. Laboratory evaluation for delayed puberty includes serum LH, FSH, and testosterone measurements

and a bone age X-ray to assess skeletal maturation. Delayed puberty due to testicular failure can be readily distinguished from hypothalamic and pituitary deficiencies by history, physical examination, and laboratory studies. While testosterone concentrations are subnormal in both cases, 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. Specific treatments and improvement in caloric intake can thus be implemented accordingly to reverse the hypogonadism. Hormonal therapy to elevate testosterone levels using exogenous human chorionic gonadotropin, LH or testosterone may be necessary.

Constitutional delay of growth and development (CD) is a familial variant of normal in which boys develop signs of puberty later than their peers. Often, boys with CD are referred to the pediatric endocrinologist as they become aware of discrepancies between themselves and their peers in height, muscular development, athletic capabilities, and sexual development. For some boys, a delay in pubertal development may be associated with depression, anxiety, and school failure that may lead to major psychosocial dysfunction; short term hormonal therapy can alleviate some of the physical differences and lessen the impact of the psychosocial issues.

Early or precocious puberty occurs less commonly in boys. Potential consequences include tall stature during childhood, advanced skeletal maturation, and premature physical manifestations of puberty. The advanced skeletal maturation often leads to short stature in adulthood due to early epiphyseal fusion in the long bones. Precocious puberty may result from premature reactivation of pulsatile GnRH secretion caused by one of several factors including brain tumors and dysfunction of the hypothalamus. It can also occur as a consequence of central inflammatory disorders, post-radiation therapy, or brain trauma. GnRH receptor “super-agonists” such as leuprolide acetate and histrelin are used to treat these central causes of precocious puberty.

Precocious puberty may also result from excessive and premature GnRH independent androgen secretion caused by either congenital virilizing adrenal hyperplasias, familial autosomal dominant male limited precocious puberty (testotoxicosis), or Leydig cell tumors. Congenital adrenal hyperplasia represents a group of disorders featuring 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 adrenal androgen secretion. Testotoxicosis is due to activating mutations of the LH receptor gene. Tumors located in the liver, mediastinum, or central nervous system may secrete human chorionic gonadotropin that binds to testicular LH receptors resulting in increased testosterone secretion and

precocious puberty. 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.

Suggested reading

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