Delayed puberty

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Abstract

Delayed puberty is common, occurring in 3% of the population. It is seen much more frequently in boys than girls and in the majority of cases is due to constitutional delay in growth and puberty. These individuals do not need significant numbers of investigations and treatment is usually unnecessary. Regular monitoring is indicated to ensure puberty does progress in due course, with reassurance for the child and family that this is a common occurrence. A short course of low dose testosterone or oestrogen may be beneficial in inducing puberty if this is significantly delayed as this can be psychologically difficult. Puberty will usually then proceed spontaneously to completion.

All girls with pubertal delay require karyotyping to exclude Turner syndrome. More detailed investigation would be indicated in individuals with any additional features such as: a history of pituitary hormone deficiencies, previous radiotherapy or chemotherapy, evidence of chronic disease, midline or dysmorphic features, learning difficulties, tall stature, gynaecomastia or anosmia, neonatal history of bilateral cryptorchidism or small penis.

For those patients requiring treatment, this involves commencement of low dose testosterone in boys or oestrogen in girls, with slowly increasing doses as puberty progresses.

Keywords constitutional delay in growth and puberty (CDGP); delayed puberty; hypergonadotrophic hypogonadism; hypogonadotrophic hypogonadism; puberty

Introduction

There is wide variability in the timing of the onset of puberty, which is influenced by a variety of factors including sex, genetics and environment. In girls, puberty starts with breast bud development (Tanner breast stage 2). The pubertal growth spurt occurs from breast stage 2, peaking in velocity mid puberty. Menstruation is regarded as completion of puberty, following which only 5–10 cm of height gain remains.

The onset of puberty is less obvious in boys. Testicular enlargement occurs first (>4 ml), followed by development of pubic hair. The peak growth spurt in boys, in contrast to girls, occurs 2–3 years later once testicular volume is >10 ml. During this phase, the voice deepens and facial hair growth starts.

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The duration of puberty usually lasts between 3 and 5 years.

Refer to Figure 1 for the diagrammatic representations of Tanner stages.

Delayed puberty is generally regarded as the absence of signs of secondary sexual development in a girl by the age of 13 years and a boy by 14 years. Of note, failure of progression through puberty or primary failure of menstruation by 15 years also warrants investigation.

Pubertal delay is relatively common, occurring in approximately 3% of the population and is much more frequent in boys (male: female ratio 7:1). It is relatively rare in girls and is more likely to be secondary to underlying pathology.

Puberty is a time of immense change in adolescents, and is accompanied by psychological/psychosocial changes. A delay in onset therefore can cause significant stress to the child and the family.

Physiology of normal puberty

It is important to understand the normal course of pubertal developmental in order to identify what is a normal variant and what may indicate underlying pathology.

Puberty begins with the activation of the hypothalamic–pituitary–gonadal axis. It is still unclear as to the precise trigger; however neurotransmitters such as GABA, NMDA (N methyl D aspartate) and KISS1 are involved. In the foetus, the pituitary–gonadal axis is active and levels of gonadotrophins and sex steroids are high in the first few months of life, before dropping to very low levels during childhood.

Physical sings of puberty are preceded by an increase in secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Gonadotrophin releasing hormone (GnRH) is released in a pulsatile fashion from the hypothalamus and stimulates the pulsatile release of LH and FSH from the anterior pituitary. LH stimulates the Leydig cells in the testes to produce testosterone which induces secondary sexual development in boys. FSH stimulates germ cell maturation leading to spermatogenesis. LH and FSH work together to stimulate follicular development in the ovaries resulting in oestrogen production and the development of secondary sexual characteristic in girls. Ovulation is triggered by the interaction of LH, FSH and oestrogen.

Refer to Figure 2 for the illustrative pathway in both males and females, including the negative feedback mechanism in place.

The hypothalamus in females has both positive feedback from oestrogen prior to ovulation, as well as negative feedback post ovulation from oestrogen and progesterone.

Androgens are produced both by the gonads (corpus luteum in girls) and the adrenal glands. The predominant androgen is testosterone, and is responsible for development of pubic and axillary hair, body odour and skin changes.

Causes of pubertal delay

The causes of puberty delay can be divided in to three main categories (Table 1):

- Those with an intact hypothalamic–pituitary–gonadal axis, but a functional problem;
- Hypogonadotrophic hypogonadism;
- Hypergonadotrophic hypogonadism.

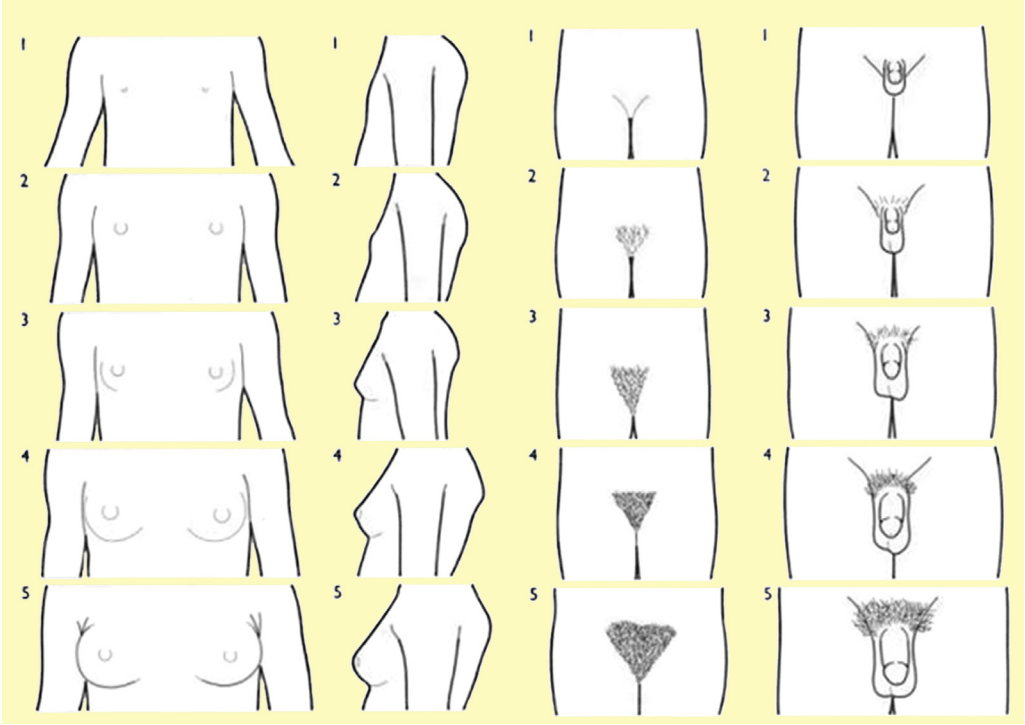

Figure 1 Diagrammatic representations of Tanner stages 1—5, for males and females. Stage 1 is pre-pubertal; Stage 5 adult.

Functional hypogonadotrophic hypogonadism

In this instance the hypothalamic—pituitary—gonadal axis is intact but remains inactive past the usual time for the initiation of puberty.

The most frequent cause is constitutional delay in growth and puberty (CDGP), representing 60% of delayed puberty in boys and 30% in girls. However, this is a diagnosis that can be only be made by exclusion of other causes, along with monitoring over time. There is often a history of short stature noted in later childhood, associated with a bone age delay of around 2 years. A positive family history of pubertal delay, which is not sex specific, is found in 50—75%. FSH, LH and sex steroid levels are low. Progression through puberty is slowed. Not all patients reach a final height within parental range but the majority do.

Any underlying chronic disease can lead to delay in activation of the hypothalamic—pituitary—gonadal axis and so lead to delayed puberty as can psychosocial deprivation and intensive exercise. Anorexia and malnutrition also commonly lead to pubertal delay and this is thought to be a secondary adaptation to prevent reproduction in a less than ideal circumstance.

Hypogonadotrophic hypogonadism

In this instance there is an inability to produce gonadotrophic hormones from the pituitary (LH & FSH).

Congenital, or isolated, hypogonadotrophic hypogonadism can be difficult to differentiate from CDGP initially, as both have low levels of sex steroids and gonadotrophins, and often a positive family history of pubertal delay. There is no reliable single test to differentiate between the two conditions; hence follow-up is of upmost importance. The gonads are normal, but as they are not stimulated they remain pre-pubertal in size. It is 3—5 times less common in girls. There may be a history of micropenis or undescended testes at birth, due to prenatal gonadotrophin and androgen deficiency. Associated with lack of smell (anosmia) in approximately 60% of patients, it is defined as Kallmann syndrome. In this condition, during embryonic development, there is a failure of migration of GnRH neurones from the olfactory placode to the brain and the olfactory bulbs, hence the association with anosmia. It is also associated with cleft lip/palate, sensorineural deafness and cerebellar ataxia. The KAL1 gene is implicated in X-linked form, but in 60—70% of cases, the gene is unknown. It is also inherited in autosomal dominant and recessive forms, giving significant variation in the features present. Prevalence is 1:10, 000 births with a male: female ratio of 5:1.

Other causes of hypogonadotrophic hypogonadism are listed in Table 1, and there will either be relevant past medical history or the presence of other pituitary deficiencies. Often these children are already being monitored for their growth and pubertal delay is diagnosed promptly.

Hypergonadotrophic hypogonadism

In this case the hypothalamic—pituitary part of the axis is intact but levels of LH and FSH are high indicating a lack of negative feedback to the hypothalamus. In hypergonadotrophic hypogonadism testosterone or oestrogen levels are low indicating testicular or ovarian failure.

Klinefelter syndrome (47XXY, mosaicism also occurs) is the commonest sex chromosome disorder, but diagnosis is delayed in around 60% of cases, as there is significant phenotypic variation with many individuals having only subtle features. Pre-puberty, boys have small testes, increased incidence of developmental delay and behavioural problems. The onset of puberty