Delayed Puberty

Normal puberty occurs across an age range, and diagnosis of pathology requires familiarity with the normal range. See the separate article Normal and Abnormal Puberty for more details. Delayed puberty is defined by:

- In boys: the absence of testicular development (or a testicular volume lower than 4 ml) by age 14 years.\[1\]
- In girls: the absence of breast development by the age of 13 years, or primary amenorrhoea with normal breast development by the age of 15.\[2\]

Most boys and most girls with delayed puberty have simple constitutional delay in growth and puberty (CDGP) and do not need detailed investigation.

Epidemiology

- Exact prevalence of delayed puberty is not known. Variations in normal puberty occur in approximately 3% of children.\[3\]
- CDGP, also called simple delay, is more common in boys than in girls.\[4\]
- There is a strong correlation within families and ethnic communities for age at puberty. 50-75% of those with CDGP have a family history of delayed puberty.\[5\]
- Idiopathic hypogonadotropic hypogonadism (IHH) has an incidence of 1-10 cases per 100,000 births.\[6\] It accounts for around 10% of cases of delayed puberty in boys.\[1\]
- Delayed puberty in around 5-10% of boys is caused by hypergonadotropic hypogonadism, most often due to Klinefelter's syndrome.\[1\]

Causes of delayed or abnormal puberty

Central (both sexes)

- Intact hypothalamo-pituitary axis:
  - CDGP - sporadic or familial; see also separate Short Stature article. Constitutional delay is by far the most common cause in both boys and girls but can only be diagnosed once other causes have been eliminated.\[5\]
  - Chronic illness - eg, kidney disease, Crohn's disease.
  - Malnutrition - eg, anorexia nervosa, cystic fibrosis, coeliac disease.
  - Excessive physical exercise, particularly athletes or gymnasts.
  - Psychosocial deprivation.
  - Steroid therapy.
  - Hypothyroidism.

- Impaired hypothalamo-pituitary axis:
  - Tumours adjacent to the hypothalamo-pituitary axis - eg, craniopharyngioma, optic glioma, germinomas, astrocytomas, pituitary tumours (including hyperprolactinaemia).
  - Congenital anomalies - eg, septo-optic dysplasia, congenital panhypopituitarism.
  - Irradiation treatment.
  - Trauma: surgery, head injury.
  - IHH. This describes low gonadotrophin and sex steroid levels in the absence of abnormalities in the hypothalamic-pituitary-gonadal system. As well as cryptorchidism, associated features include micropenis, synkinesia (mirror movements), cleft lip and palate, dental agenesis, skeletal anomalies and hearing loss. Many have associated loss of smell - Kallmann's syndrome.\[1\]
Peripheral

- Boys:
  - Bilateral testicular damage: cryptorchidism, failed orchidopexy, atresia, testicular torsion, infection (mumps rarely causes prepubertal damage).
  - Syndromes associated with cryptorchidism or gonadal dysgenesis: Noonan's syndrome, Prader-Willi syndrome, Bardet-Biedl syndrome, Klinefelter's syndrome, other XY aneuploidy syndromes, XO/XY.
  - Irradiation, total or testicular.
  - Drugs - eg, cyclophosphamide.

- Girls:
  - Gonadal dysgenesis: Turner syndrome, Prader-Willi syndrome, Bardet-Biedl syndrome, Swyer syndrome (45,XY).
  - Irradiation, total or abdominal.
  - Drugs - eg, cyclophosphamide, busulfan.
  - Intersex disorders - eg, complete androgen insensitivity syndrome (primary amenorrhoea may be the presenting symptom), congenital adrenal hyperplasia.
  - Polycystic ovary syndrome.
  - Toxic damage: galactosaemia, iron overload (thalassaemia).

Assessment

A diagnosis can almost always be made by taking a thorough history, a proper assessment of growth, pubertal status and skeletal maturity (bone age) and a thorough physical examination. The cause of pubertal delay may be obvious (eg, ovarian failure following total body irradiation prior to bone marrow transplantation, bilateral testicular torsion).

History

- Growth pattern: adolescents with CDGP have a long-standing history of short stature. Use any available growth charts.
- General health: any symptoms of chronic ill health.
- Gonadal impairment: history of cryptorchidism, orchidopexy and gonadal irradiation.
- Sense of smell (for Kallmann's syndrome).
- Family patterns: age at menarche in female members of family, delayed growth spurt.
- Social and educational aspects: any indication of psychosocial problems.

Examination

- Height, weight; any suspicion of malnutrition.
- Measured parental and sibling heights (reported heights are much less reliable). See separate Short Stature article.
- Pubertal staging.
- Dysmorphic features.
- Full general examination, including fundoscopy and visual fields (pituitary tumour) and any indication of chronic disease - eg, finger clubbing.

Investigations

Most boys and girls with delayed puberty have CDGP and do not need detailed investigation. In selected cases:

- Investigations for chronic disease: FBC, ferritin, renal function tests and electrolytes, coeliac screening, urinalysis for blood and protein, etc.
- Investigations related to disorders of gonadal axis:
  - Chromosomes (eg, for Turner syndrome and Klinefelter's syndrome).
  - Basal FSH and LH and serum estradiol/testosterone. Basal levels of LH and FSH are low in CDGP or hypogonadotropic hypogonadism and usually elevated in those with gonadal failure.
  - Prolactin, insulin-like growth factor I (as a screen for growth hormone deficiency), TTFs.
  - GnRH test and growth hormone (see separate Pituitary Function Tests article). Some cases of central delay are difficult to assess and the GnRH stimulation test cannot distinguish between physiological delay and gonadotrophin deficiency.
  - Pelvic ultrasound in girls.
  - Bone age: a delayed bone age may occur in CDGP, growth hormone deficiency and hypothyroidism. Bone age is established by a wrist X-ray.
  - MRI or CT scan of the pituitary and surrounding structures may be indicated.

Management[1, 2, 4]

CDGP

- Medical treatment is often not necessary and reassurance and monitoring may be sufficient. However, short courses of sex hormones may be used to allow individuals to catch up with their peers and prevent psychological and emotional sequelae.
- CDGP in boys: induction of puberty may be achieved with short courses of low-dose testosterone therapy for appropriately selected boys with delayed puberty[7]. Testosterone is given by mouth as capsules or by depot injection. Treatment is given for 3-6 months and then the situation reassessed. Response is usually rapid and effective. There is not yet sufficient evidence for the routine use of other therapies (eg, growth hormone, aromatase inhibitors or anabolic steroids) for CDGP.[8]
- CDGP in girls: gradually increasing doses of oestrogen treatment, with cyclical progestogen therapy once adequate oestrogen levels have been achieved.
**Chronic disease**
- Treat the underlying cause if possible; induction of puberty and hormone treatment may be required.

**Primary testicular and ovarian failure**
- Pubertal induction followed by ongoing hormone replacement. Testosterone/oestrogen production may be adequate and ongoing hormone treatment unnecessary.
- In those with severe congenital hypogonadism, early gonadotrophins in the neonatal period or infancy may be indicated.
- Boys:
  - Regular testosterone injections are preferred but oral testosterone or testosterone patches, gel and buccal pellets are alternatives.
- Girls:
  - Oestrogen replacement should be gradual to avoid premature fusion of the epiphyses and prevent overdevelopment of the areolae of the breasts.
  - Induction of puberty usually starts around age 10. Gradually increased doses of oral ethinylestradiol or transdermal estradiol are used, with cyclical progesterone therapy once adequate oestrogen levels have been achieved or if breakthrough bleeding occurs. If growth hormone is also needed, oestrogen therapy is usually delayed until age 12.
  - Transdermal estradiol is thought to be more effective and have a better safety profile. [9, 10]
  - A low-dose combined oral contraceptive pill can then be used.

**Central delay**
- Treatment of any underlying cause - eg, craniopharyngioma.
- Pubertal induction and hormone replacement.
- Counselling with respect to sexual function and fertility as appropriate.
Further reading & references

- Pitteloud N; Managing delayed or altered puberty in boys. BMJ. 2012 Dec 3;345:e7913. doi: 10.1136/bmj.e7913.
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