Abnormalities of growth and development in puberty

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J R Coll Physicians Lond 2000; 34: 141–6

Disorders of growth and pubertal development in the teenage years present as a spectrum of abnormalities embracing common normal variants, less common disease states, and rare disorders increasingly recognised and understood as genetic in origin. This brief review is intended to provide a guide to the diagnosis of problems presenting most commonly in adolescent/teenage children, to help with initial assessment and management and to stress the need for referral to appropriate endocrine or other specialist services. Long-term management of individual diagnoses is beyond the scope of this article (references are provided for further reading). In order to focus on the teenage child, precocious puberty (by definition, before the age of 8 years in girls and 9 years in boys) is not discussed, but readers can seek guidance from a recent review.

Delayed growth and puberty

Pubertal delay is the commonest problem seen. It is usually associated with apparent poor growth – but not necessarily with short stature, as growth rate is intimately related to pubertal development. What may seem to be growth failure is an inevitable consequence if a child is later than average with timing of onset of puberty (as are 50% of children). The clinical problem is to decide whether development is abnormal, in terms of being late with the onset of puberty or of failing to progress to completion of puberty at a normal rate (arrested puberty). Growth delay is common and usually there is no underlying pathology (boys in particular may none the less benefit from treatment), whereas arrested pubertal development is a major cause for concern. By convention, delayed puberty is defined as lack of puberty at an age +2 standard deviations (SD) above the population mean (boys: 14 years; girls: 13 years). The mean time to progress from puberty onset in boys to adult testicular volume is 3.2±1.8 years (mean ±SD), and in girls from onset of breast development to menarche is 2.41±1 (mean ±SD) years. Thus, if 4–5 years have elapsed from puberty onset without completion, investigations should be made.

Delayed puberty may be classified as primary delay (constitutional) or secondary delay (underlying chronic illness). Children with failure to enter puberty because of a disorder of the hypothalamo-pituitary-gonadal axis may also be divided into two groups, having either hypogonadotrophic or hypergonadotrophic hypogonadism depending on whether the defect lies at hypothalamic-pituitary or gonadal level (Table 1). Suggested plans of assessment and investigation are given in Figs 1 and 2.

**Table 1. Summary of main causes of delayed/arrested puberty.**

**Hypogonadotrophic (low LH/FSH) disorders**

| No underlying disease | Constitutional delay of growth and puberty |
|-----------------------|--------------------------------------------|
| Hypothalamic-pituitary disorder | Congenital or acquired multiple pituitary hormone deficiencies |
| Dystrophic syndromes | Isolated gonadotrophin deficiency (eg Kallmann syndrome) |
| Chronic illness | eg Noonan syndrome, Prader-Willi syndrome |

**Hypergonadotrophic (high LH/FSH) disorders**

| Sex chromosome anomalies | Turner syndrome, Klinefelter syndrome |
| Other causes of gonadal failure | Gonadal dysgenesis/agenesis |
| | Surgery, radiotherapy, chemotherapy |
| | Galactosaemia (girls) |
| | Autoimmune gonadal failure |
| | Primary ovarian failure |

LH = luteinising hormone; FSH = follicle-stimulating hormone.

**Pubertal delay**

Constitutional (primary) delay of growth and puberty

A normal variant of growth, more frequently seen in clinical practice in boys than girls, is constitutional primary delay of growth and puberty. This preponderance of males vs females partly reflects social values in respect of the significance and disadvantages of both short stature and delayed puberty. There is often a family history of delayed puberty. Children will have sustained a normal growth rate through the prepubertal years, but the delayed onset of puberty (usually by an age of 13–15 years at presentation) and lack of attendant growth spurt lead to a progressive fall in height centile. Physical examination should be normal, but it is important to note whether signs of pubertal development are present and delayed, rather than absent. All endocrine investigations (Table 2)
should be normal for a pre- or early pubertal child, with some delay in bone age of perhaps 2–3 years.

Dysmorphic features may suggest Noonan syndrome (perhaps as common as 1 in 2,000, with autosomal dominant inheritance\(^2\)), in which severe pubertal delay is common. Girls may share many similar physical features with Turner syndrome, with short stature from infancy but, unlike Turner syndrome, impaired intellectual development is often a major feature. Boys have a high incidence of cryptorchidism. The diagnosis is made on clinical grounds, although the gene defect may soon be determined. Other syndromes with pubertal delay (such as Prader-Willi syndrome) are nowadays likely to have been recognised before the adolescent years.

Unfortunately, there is no endocrine test which will reliably distinguish constitutionally delayed puberty from isolated hypogonadotropic hypogonadism (see below): time, observation and spontaneous pubertal development are the critical factors. Management is therefore focused on exclusion of those disorders which may be associated with pubertal delay through chronic illness or with multiple pituitary hormone deficiencies. By the age of 13–14 years raised serum gonadotrophin levels are likely to identify patients with hypergonadotropic hypogonadism.
Secondary pubertal delay

Most chronic illnesses will affect growth and/or pubertal development, with increasing effect in relation to their severity and duration, through undernutrition, chronic inflammation and certain drug treatments (eg glucocorticoids for asthma or renal disease). Mechanisms underlying these effects on growth are becoming better understood. For many children, the management of a long-standing illness will include anticipation of the need for help or adjustment of treatment throughout puberty (eg cystic fibrosis, asthma, renal failure, diabetes mellitus), whereas other children may first present only with impaired growth and/or impaired pubertal development (eg anorexia nervosa), possibly even with minimal other signs or symptoms of chronic disease (especially inflammatory bowel disease). Thus, from a diagnostic approach, all patients with delayed growth and puberty should be assessed clinically and investigated to exclude such chronic diseases (Table 2). Specific endocrine causes of delayed puberty in this category include primary hypothyroidism, hypercortisolism, hyperprolactinaemia (prolactinoma), thalassaemia major and sickle cell disease (in which pituitary or gonadal damage may also occur). As with constitutional delay, the bone age is likely to
be delayed in keeping with the physical maturity of the child.

**Pubertal failure**

*Hypogonadotropic hypogonadism*

Patients with hypogonadotropic hypogonadism may have congenital or acquired disorders. It is important to distinguish isolated gonadotrophin deficiency disorders from those with multiple pituitary hormone deficiencies.

**Multiple pituitary hormone deficiencies.** These are more readily diagnosed by history or demonstration of coexisting abnormalities of growth hormone, thyroid or adrenal function on pituitary hormone tests, and abnormal magnetic resonance imaging (MRI). The most common acquired causes include tumours in the hypothalamo-pituitary region and the sequelae of surgery and radiotherapy. The possibility of a previously unrecognised craniopharyngioma or, for example, suprasellar germinoma, focuses the need for adequate investigation without delay before impaired vision or devastating tumour progression occurs. The serum prolactin level may be modestly elevated (2–3 fold) in the presence of a mass lesion compressing the pituitary stalk and reducing the dopaminergic constraint on prolactin release. A prolactinoma may be the commonest pituitary tumour in adults, but is very rare under 18 years. It may present with delayed puberty (more often in girls) but is more likely to present with headache or secondary amenorrhoea.

**Kallmann syndrome.** Isolated gonadotrophin deficiency (Kallmann syndrome) is uncommon, but four times more prevalent in boys than girls, with X-linked abnormalities of the KAL gene (at Xp22.3) commoner than other autosomal defects yet to be characterised. These patients are of normal stature until they fail to undergo a normal pubertal growth spurt. Anosmia/ impaired olfaction and mirror movement of upper limbs are important diagnostic features, while family history, ichthyosis, *cafe au lait* pigmentation and structural renal abnormalities may support the diagnosis until definitive confirmation of a gene defect can be obtained through a supportive laboratory. MRI imaging of the olfactory bulbs may be helpful.

**Hypergonadotropic hypogonadism**

Gonadotrophin levels are raised in response to primary gonadal failure, which results most frequently from sex chromosome anomalies causing gonadal dysfunction.

**Turner syndrome.** This syndrome is caused by the absence or structural abnormality of one X chromosome (45XO or variant), and occurs in approximately one in 3,000 women. Most are diagnosed in early childhood on account of dysmorphic features, associated medical problems (eg congenital cardiac or renal abnormalities) or short stature. However, a proportion of girls, in particular those with a mosaic sex chromosome constitution, have few or only subtle features. They may present with short stature only at about the age of 12–13 years old when their progressive early childhood decline in height centile, together with lack of a normal pubertal growth spurt, leads to a height deficit of about 15 cm from their expected genetic potential – sufficient to arouse concern.

It is estimated that perhaps only 20% of Turner girls will have spontaneous onset of puberty, while nearer to 90–95% will require sex hormone treatment to allow them to complete puberty and establish menses. Thus, most will present with failure to enter puberty. Almost all (except for the few with tall parents) will by then be below the 2% height centile, and a proportion will present with arrested puberty/ primary amenorrhoea. The diagnosis is confirmed in most cases by lymphocyte karyotype analysis, but in girls with low grade mosaicism the diagnosis may occasionally prove difficult without analysis of a different cell source (eg fibroblasts from skin biopsy). Psychological support may be more crucial for these girls with 'late' diagnosed Turner syndrome to come to terms with the rather sudden recognition of implications for their future fertility rather than short stature, as most will achieve a final height close to or in the low but 'normal' centile channels.

**Klinefelter syndrome (47XXY).** This syndrome occurs in approximately one in 600 men, but few are diagnosed before puberty and many not even in adult life. Pubertal onset is not necessarily delayed, but inadequate virilisation results from impaired Leydig cell synthesis of testosterone; seminiferous tubule dysgenesis results in infertility and the characteristic inappropriate smallness of the testes (<6 ml) in relation to the degree of virilisation in later puberty. The association of features such as eunuchoid body proportions, gynaecomastia, a smallish penis in some, relatively tall stature for parental heights, and behavioural problems in earlier childhood should suggest the diagnosis in a boy in early puberty before the diagnosis is more readily apparent from the small testes. Treatment requires careful counselling, with long-term testosterone replacement treatment to support completion of pubertal development and epiphyseal fusion, and through adulthood to meet the physical and psychological needs of the individual.
Noonan syndrome and Prader-Willi syndrome. These two syndromes are commonly associated with delayed puberty in both sexes (see above). The men may have undescended testes which may be hypoplastic/dysgenetic and manifest as a hypergonadotrophic hypogonadism requiring long-term testosterone replacement. This needs to be distinguished from the relatively hypogonadotrophic state if puberty is simply delayed.

Primary gonadal failure. Primary gonadal failure may uncommonly arise in the teenage years through autoimmune disease, or there may be recognised antecedent factors such as orchidopexy for undescended testes, orchitis, or exposure of the gonads to irradiation or gonadotoxic chemotherapy for childhood malignancy. Ovarian failure is common in women with galactosaemia now surviving to adulthood, although the mechanism for this is unclear; men seem to have normal testicular function.

Resistance to luteinising hormone and follicle-stimulating hormone are autosomal recessive genetic disorders caused by mutations in their respective receptors. Together with other single gene disorders, they may prove to be commoner than previously suspected cases of delayed puberty or gonadal failure16-15.

Gynaecomastia

Another problem is gynaecomastia, which is extremely common during male puberty (30–50% of all healthy boys) and may persist for a few months or 1–2 years before resolution. It is thought to result from oestrogen (derived in men by aromatisation of a small proportion of testosterone) being able to exert more biological effect in early puberty before higher sustained testosterone levels are achieved. In obese boys it may be particularly marked, and in slimmer boys more obvious. Provided that growth and pubertal development are otherwise progressing appropriately, it does not normally require investigation unless there are particular features of concern.

Increased incidence, severity and likelihood of persistence are associated with Klinefelter syndrome (see above), but testes greater than 6 ml volume would generally exclude Klinefelter syndrome and the need to check a karyotype.

Gynaecomastia with gynaecomastia should raise suspicion of a prolatinoma. There are extremely rare cases of severe, progressive gynaecomastia associated with an oestrogen secreting gonadal tumour, with accelerated growth and bone age, and lack of normal pubertal virilisation.

Management of gynaecomastia requires reassurance that it is a common, normal occurrence and should regress with time, with advice that no effective medical treatment exists but weight reduction is helpful in the obese boys. Surgical removal of the breast tissue through a circumareolar incision, if indicated for psychological reasons, can have excellent results, particularly in non-obese individuals.

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Key Points

- Short stature presenting in the early teenage years most commonly results from pubertal delay
- Pubertal delay is usually 'constitutional' but systemic disorders, and Turner syndrome in girls, should be excluded
- Gonadotrophin deficiency cannot be easily distinguished from constitutional delay unless associated features (eg anosmia) make the diagnosis likely
- Elevated basal gonadotrophin (LH/FSH) levels are helpful to identify patients with primary hypogonadism
- After identifiable causes of delayed puberty have been excluded, treatment with sex steroids may proceed, and observation over time will distinguish delay from gonadotrophin deficiency
- Gynaecomastia is very common in boys: clinical assessment and reassurance are usually sufficient
Musculoskeletal diseases
in adolescence

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This review discusses the problems facing adolescents with juvenile idiopathic arthritis (JIA) and how they are managed. Similar problems face adolescents with juvenile dermatomyositis, systemic lupus erythematosus, rarer connective tissue diseases and other musculoskeletal conditions, but a detailed discussion concerning these diseases is beyond the scope of this article.

The size and scope of the problem

JIA has a prevalence of approximately 130 per 100,000 children. The classification has recently been changed (Table 1). Although principally a disease of younger children, JIA presents between the ages of 10 and 16 years in 25% of patients. Those who develop systemic or polyarticular disease at a younger age have a higher incidence of destructive joint disease. The common belief is that JIA 'burns out' before or during adolescence, so the ensuing problems improve or remain static, but in fact one-third of these children inflammatory activity continues into adult life.

Approximately 20% of children with JIA will be unable to perform some aspect of self-care: the longer the follow-up, the greater both the disability and the deterioration in psychosocial function. Unemployment is common and, significantly, does not correlate with educational achievement. While many people with major disabilities enjoy happy, fulfilled lives, others with much milder functional impairment lead seriously restricted lives limited by factors, often simple, that may be avoided.

Now that 90% of children with chronic disabilities reach their 20th year, attention has been focused on their successful transition to adulthood. The key elements have been identified for an effective transition programme for adolescents with various chronic illnesses leaving the paediatric service. While the key elements also apply to adolescents with JIA, the details of the ideal transition programme for this group are far from established. Only 20% of the paediatric rheumatology departments in the UK provide a transition service and their standards are variable. To appreciate the late

Key Points

- 25% of children with juvenile arthritis present between 10 and 16 years of age
- A significant number of children with juvenile idiopathic arthritis (JIA) develop progressive, destructive joint disease
- New treatments, such as methotrexate, have revolutionised outcome measures in JIA
- An ongoing, multidisciplinary transition programme is important both to allow the adolescent independence and to ensure a smooth transfer to the adult service