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section 13 Endocrine disorders 2428 Constitutionally advanced growth and puberty Just as growth delay is a variant of growth at one end of the normal range, so is constitutional tall stature. Assessments such as bone age and dental age are advanced toward the upper end of the predicted range and children usually enter puberty within the early normal range. Consequently, the adolescent growth spurt is accelerated and growth will cease according to the normal pattern of events. This can cause distress for someone who is used to being a tall child but who may end up at an average or below average height as an adult. As better nutrition is leading to obesity, this accelerated growth pattern is becoming more common. Pituitary gigantism Pituitary somatotroph macroadenomas secreting large quantities of GH are extremely rare, but may present insidiously at any age. The classic phenotype of the pituitary giant with acromegaloid features is a late finding, but this diagnosis should be suspected in children of any age who are taller than predicted for their family and who do not show the clinical and radiological features of constitutional advance. As random GH and IGF-1 levels have low specificity, a GH suppression test with glucose loading and a cranial MRI scan may be required. Treatment is with a combination of surgery and somatostatin analogues. Treatment of tall stature Attempts at growth limitation with high-dose sex steroids have not in general been successful and may have short- and long-term complications. An early and rapid induction of puberty with con- ventional hormone doses may offer some help. Absolute cessation of limb growth can only be obtained by epiphysiodesis. High-dose ethinyl oestradiol treatment to limit height in girls may impair long- term fertility, but no long-term adverse effects are seen with high- dose testosterone treatment in boys. FURTHER READING Allen DB, Cuttler L (2013). Short stature in childhood—challenges and choices. N Engl J Med, 368, 1220–8. Butler G, Kirk J (2011). Oxford specialist handbook of paediatric endo- crinology and diabetes. Oxford University Press, Oxford. Corredor B, et al. (2019). Tall stature: a challenge for clinicians. Curr Pediatr Rev, 15, 10–21. Dattani MT, Brook CGD (eds) (2020). Brook’s clinical pediatric endocri- nology, 7th edition. Wiley-Blackwell, Hoboken, NJ, USA. Jee YH, Baron J, Nilsson O (2018). New developments in the genetic diagnosis of short stature. Curr Opin Pediatr, 30, 541–7. Leung AKC, Leung AAC, Hon KL (2019). Tall stature in children. Adv Pediatr, 66, 161–76. Murray PG, Butler GE (2013). How to assess tall stature. Paediatrics and Child Health, 23, 409–13. NICE (2010). Human

Growth Hormone (Somatropin) for the Treatment of Growth Failure in Children (review). https://www.nice.org.uk/ guidance/ta188 Royal College of Paediatrics and Child Health, Department of Health. UK-WHO Growth Charts. http://www.growthcharts. rcpch.ac.uk Vasques GA, Andrade NLM, Jorge AAL (2019). Genetic causes of isolated short stature. Arch Endocrinol Metab, 63, 70–8. World Health Organization. WHO Child Growth Standards. http:// www.who.int/childgrowth/en/index.html 13.7.2 Normal puberty and its disorders Fiona Ryan and Sejal Patel ESSENTIALS Puberty is the physiological sequence of events when secondary sexual characteristics develop, reproductive capacity is achieved, and final adult stature reached. The outward signs usually develop over 3 to 5 years, with significant variation both in the age that puberty starts and the pace at which development proceeds. The events that lead to the triggering of puberty remain uncer- tain, but clinical presentations may arise because the process is abnormally early (precocious puberty) or abnormally late (delayed or absent puberty). Several variants of the normal processes may also present for clinical assessment, for example, premature isolated thelarche (breast development) or adrenarche (pubic and axillary hair development), which do not require treatment. Precocious puberty Aetiology—this is classified into the more common central preco- cious puberty which is gonadotropin dependent, resulting from early activation of the hypothalamic-pituitary-gonadal axis, and the much rarer gonadotropin independent precocious puberty, sometimes known as peripheral or pseudo precocious puberty. The latter is related to sex steroid secretion which may be gonadal or extragonadal or due to the administration of exogenous sex steroids, but is not under gonadotropin control and the sequence of pubertal development is usually nonconsonant. Investigation—this requires measurement of sex steroids, thyroid function, a gonadotropin-releasing hormone provocation test with additional pituitary function testing, usually combined with radio- logical imaging of the pituitary gland. A nondominant wrist radio- graph for determination of bone age (advanced in precocious puberty) helps to estimate the extent of precocity and the possible impact on growth prognosis. In girls, a pelvic ultrasound scan is re- quired to determine ovarian and uterine dimensions and hence estimate the degree of pubertal maturation. Management—the goals are to stop pubertal progression, improve final height prognosis where possible, reduce pubertal mood swings and behavioural changes, and diminish psychological distress. When possible, any underlying cause should be treated. The treatment of choice for central precocious puberty is with a gonadotropin- releasing hormone partial agonist. Delayed or absent puberty Aetiology—this is classified into hypogonadotropic hypogonadism, with constitutional delay much the commonest cause of delayed/ absent puberty, and hypergonadotropic hypogonadism due to go- nadal failure, including chromosomal abnormalities (e.g. Turner’s syndrome, Klinefelter’s syndrome). Investigation and management—investigation is largely as for precocious puberty. Treatment goals are to induce puberty, accel- erate height gain, and improve self-confidence. When possible, any underlying cause should be treated. Hormone replacement therapy is effective when used judiciously.

13.7.2 Normal puberty and its disorders 2429 Introduction Puberty is the physiological sequence of events when secondary sexual characteristics develop, reproductive capacity is achieved, and final adult stature reached. The start of puberty is characterized by the appearance of a palpable breast bud (stage B2) in girls and tes- ticular volumes of more than 3.5 ml in boys. Normal pubertal progression occurs in a specific sequence. Consonance is important as in normal, centrally mediated puberty, there is a temporal relation- ship between the development of the physical features of puberty, the timing of menarche, and the pubertal growth spurt. It is im- portant to understand the normal course of pubertal developmental in order to identify what is a normal variant and what

may indicate underlying pathology. Physiology of puberty Puberty begins with the reactivation of the hypothalamic-pituitary- gonadal (HPG) axis. It is still unclear as to the precise trigger; however, neurotransmitters such as GABA, NMDA (N methyl D as- partate) and KISS1 are involved. In the fetus, 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. The gonadotrophin-releasing hormones (GnRH) neurons are then inhibited by poorly defined pathways. Recent evi- dence suggests reactivation of these pathways is not only centrally controlled but gonadal contribution also plays a part. It is still un- clear why the GnRH neurons are usually inhibited after infancy until the start of puberty. Fat mass (via leptin signalling) and kisspeptin-secreting neurons stimulating the GnRH system certainly play a role. Physical signs of puberty are preceded by an increase in secre- tion 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 oes- trogen production and the development of secondary sexual char- acteristic in girls. Ovulation is triggered by the interaction of LH, FSH, and oestrogen. Timing of puberty This is variable and influenced by a multitude of intrinsic and ex- trinsic factors including nutrition, genetic factors, ethnicity, and environmental exposure. Anorexia nervosa can cause both inhib- ition of pubertal initiation and pubertal arrest. Certain foods, cos- metics, and hair products are potential sources of exogenous sex steroids. Exogenous oestrogens and ‘endocrine disrupters’ have been postulated to be involved in the development of earlier sexual maturation, but this is unproven. A change in environment can also have a significant effect on pubertal timing as seen in children adopted into the United Kingdom from lower-income countries. This is likely multifactorial although nutrition probably plays a key role. There has been a reported increase in earlier breast development in girls over recent decades, although the mean age of menarche has remained fairly stable during the last two decades, implying that the duration of puberty may be increasing in girls. In the United Kingdom, the ranges for normal onset of puberty are shown on the growth charts. Due to the significant variability of normal pubertal development, guidance to consider evaluation of abnormalities in puberty is important. This is usually defined at 2–2.5 SD outside the population’s mean (Fig. 13.7.2.1). Puberty before the age of 8 in girls and 9 in boys is defined as precocious while puberty after the age of 13 in girls and 14 in boys in defined as delayed in the United Kingdom. The definition of the lower age at which puberty is acceptable in girls has been chal- lenged recently. Recent evidence from the United States suggests Breast budding (breast stage 2) Precocious Puberty Precocious puberty Age (years) Delayed puberty Delayed Puberty 16 yrs 14 12 10 8 6 4 2 0 Testicular enlargement (4 ml) BOYS GIRLS Fig. 13.7.2.1 The mean ages +/- 2 standard deviations of the onset of puberty. The definition of delayed and precocious puberty in both sexes currently accepted in the United Kingdom has also been shown. Data from UK-WHO growth charts.

 earlier sexual maturation is occurring in girls especially in the Afro- Caribbean population. The most widely used standard of assessment of pubertal staging was developed by Marshal and Tanner (1969) based on their study of 192 English girls (Fig. 13.7.2.2). A more re- cent study from the United States by Herman-Giddens et al. (1997) analysed data collected from 17 077 US girls between the age of 3 and 12 by the Paediatric Research in Office Settings (PROS) net- work. In 1999, the Lawson Wilkins Paediatric Endocrine Society re-

commended lowering the normal age of the onset of puberty from 8 to 7 years in white girls and to 6 years in African-American girls based largely on this study. However, this has not been formally adopted in the United Kingdom or any other European country. Fig. 13.7.2.2 Diagrammatic representations of Tanner stages 1 to 5, for males and females. Stage 1 is prepubertal; stage 5 adult. Source data from Butler, G., and Kirk, J. (eds) (2011). Paediatric Endocrinology and Diabetes (Oxford Specialist Handbooks in Paediatrics).

13.7.2 Normal puberty and its disorders 2431 Lowering of the age of menarche has been documented in African- American girls between the 1960s and 1990s but longitudinal data has not substantiated this for European girls. Data for a secular trend in the age of onset of puberty in boys is insufficient to suggest a sig- nificant change. Lowering age of pubertal onset has been linked to the emergence of the epidemic of obesity in childhood. It has been postulated that this could be due to greater aromatization of androgens to oes- trogens in subcutaneous fat tissue. Although there is certainly a clear association between childhood obesity and early sexual mat- uration this is not necessarily causal and these may be occurring independently. There is some evidence that the earlier sexual de- velopment is more likely to be innocent thelarche rather than true puberty. The balance of evidence currently suggests there has been no sig- nificant change in the timing of true puberty, but robust longitu- dinal studies are needed to determine this for sure.
Precocious puberty This is classified into the more common central precocious puberty (CPP) which is gonadotropin dependent, resulting from early ac- tivation of the hypothalamic-pituitary-gonadal axis and the much rarer gonadotropin-independent precocious puberty (GIPP) (sometimes known as peripheral or pseudoprecocious puberty). The latter is related to sex steroid secretion which may be gonadal or extragonadal or due to the administration of exogenous sex steroids but is not under gonadotropin control and the sequence of pubertal development is usually non-consonant. Central pre- cocious puberty is more common in Afro-Caribbean or mixed- race children especially if they are overweight. The appearance of signs of puberty before the age of 8 in girls and 9 in boys requires investigation and is defined as precocious. It is important to distinguish normal variants of puberty (adrenarche and thelarche) from central or peripheral precocious puberty. Central precocious puberty has an incidence of about 1 in 5000 children and is 10 times more common in girls. This commences with breast development in girls and is mostly idiopathic. However, the cause is more likely to be pathological in boys. The second most common cause in both boys and girls are tumours around the pi- tuitary stalk and hypothalamus. Clinical evaluation of symptoms related to an intracranial lesion, signs of an associated syndrome and accurate pubertal Tanner staging are of important. This will aid focus on appropriate investigations later on. A list of possible causes is given in Table 13.7.2.1. Normal variants of puberty Premature adrenarche At 5–7 years, the zona reticularis develops in the adrenal cortex and the production of adrenal androgens are increased. This re- sults in increased height velocity (the mid childhood growth spurt). This is a benign condition and typically presents with the following clinical features: 1. Pubic/axillary hair 2. Adult body odour 3. Greasy skin and/or acne There are no other signs of pubertal development. It must be dis- tinguished from virilizing tumours and nonclassical congenital ad- renal hyperplasia, both of which would be expected to give signs of virilization with penile enlargement or clitoromegaly. It requires no treatment but there is an association with later polycystic ovary syn- drome (PCOS) and the family should be advised to avoid excessive weight gain. Final height is not affected. Premature thelarche This is a self-limiting condition characterized by unilateral or bilat- eral breast development in girls. The breast development often fluc- tuates in size. Most often, it occurs before the age of 2 with no other pubertal advancement. This represents partial activation

of the HPG axis, resulting from pulsatile FSH secretion while LH secretion is prepubertal. Investigation is usually unnecessary, but some patients show an intermediate clinical picture between thelarche and central precocious puberty. In this ‘thelarche variant’ breast development occurs but is accompanied by an increased height velocity and often cyclical vaginal bleeding. This can be associated with some bone ad- vancement but low oestradiol secretion. Initial conservative man- agement is reasonable but follow-up is essential. Investigations Several biochemical and radiological investigations are essential for children with precocious puberty. A GnRH (LHRH) test will aid differentiation between CPP and GIPP. An LHRH (luteinizing hormone-releasing hormone) test is mandatory to confirm pubertal response. This test is performed by stimulating the HPG axis with 2.5 μg/kg of LHRH with LH and FSH levels measured at 0, 30, and 60 minutes after stimulation and a baseline oestradiol or testosterone measurement. Table 13.7.2.1 Causes of precocious puberty Idiopathic Includes familial Central: Gonadotropin dependent Central nervous system (CNS) abnormalities • Septo-optic dysplasia • Arachnoid and pineal cysts • Hypothalamic hamartoma • Hydrocephalus • Hypothalamic-pituitary tumours – Optic nerve glioma (+/- NF type 1) • CNS irradiation • Hydrocephalus Prolonged exposure to sex steroids Late onset CAH (21-hydroxylase deficiency) Ectopic source of HCG Hepatoblastoma Choriocarcinoma Mediastinal germ cell tumours Prolonged hypothyroidism Peripheral: Gonadotropin independent Adrenal adenomas/carcinomas Congenital adrenal hyperplasia Ovarian overactivity McCune–Albright syndrome (GS α-activation) Ovarian cysts and tumours Testicular overactivity Testotoxicosis GS α-activation in McCune–Albright syndrome Leydig cell and Sertoli cell tumours Exogenous sex steroids Drugs or diet sources

 A pubertal LHRH test shows LH peak more than 5 units/litre with an LH response usually greater than the FSH response. This confirms CPP. In GIPP the LHRH test shows a prepubertal response with a peak LH less than 5 units/litre, LH response being less marked than the FSH response. Gonadotrophin levels may be completely sup- pressed and sex steroids may be very high. Serum levels of oestradiol in girls are not as helpful as levels of testosterone in boys, as low levels of oestradiol do not exclude precocious puberty in girls. Bone age and thyroid function tests are checked as routine. A radiograph of the nondominant wrist is used to assess for bone age advancement which is associated with precocious puberty. Bone age is advanced usually by more than two standard devi- ations compared to chronological age. Hyperthyroidism advances bone age and may precipitate central precocious puberty. A high thyroid-stimulating hormone (TSH) level in hypothyroidism can stimulate the FSH receptor and induce ovarian and testicular enlargement. A pelvic ultrasound is recommended in girls to confirm any oes- trogen effect on the uterus and any gonadotrophin effect on the ovaries stimulating follicular development. A radiologist experi- enced in taking measurements of ovaries and the uterus is recom- mended and these measurements should be compared to standard centile charts for prepubertal and pubertal uterus and ovaries. MRI brain (if not available then CT) is essential in both boys and girls with a diagnosis of central precocious puberty (Figs. 13.7.2.3 and 13.7.2.4). Tumour markers such as α-fetoprotein and β-HCG should be measured. β-HCG is a tumour marker that is produced by tes- ticular, pineal, and hepatic tumours. Due to molecular similarities, it mainly acts on LH receptors leading to markedly higher androgen levels than expected for the testicular volumes in boys. α-fetoprotein may also help diagnose extragonadal causes of gonadotropin-independent precocious puberty. Treatment The requirement for treatment needs careful discussion with the family as the psychosocial impact of precocious puberty on the child and family is considerable. The aims of treatment are to: 1. Arrest pubertal progression 2. Attenuate skeletal

maturation with the aim of improving final height (only effective in children <6 years) 3. Improve mood swings and behavioural changes to reduce psy- chosocial impact Whether or not treatment is appropriate depends on a multitude of factors, mainly age of onset, pubertal status, and parental pref- erence. For progressive puberty in boys and girls, the mainstay of treatment is GnRH analogues. These are partial agonists of GnRH receptors causing continuous release of LH and FSH briefly. This is followed by a paradoxical downregulation and hence inhibition of gonadotropin secretion. Subcutaneous depot injections have dur- ation of action between 4 to 12 weeks. Clinical response to treat- ment includes stopping further breast development or testicular enlargement, reduced mood swings, and improved behaviour. Close monitoring of response is needed as adjustment of dose or frequency of injections may be necessary if breakthrough occurs. Treatment usually continues until an appropriate time for pu- berty to commence. GnRH analogue treatment is safe and effective. Children with precocious puberty are taller than expected at pres- entation but with the advanced bone age may not achieve an adult height in the predicted range for the family. GnRH analogues slowly reduce epiphyseal fusion rate so will protect future height potential but only in children presenting under 6 years. Growth potential is therefore maximal for children with precocious puberty presenting at a younger age. Sex steroid antagonists like cyproterone acetate can be useful ad- junct therapies especially for the stimulatory effect of GnRH ana- logue treatment. Management of GIPP requires identification and treatment of the cause.
Delayed puberty Delayed puberty is generally regarded as the absence of signs of sec- ondary 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 pri- mary failure of menstruation by 16 years also warrants investigation. Pubertal delay is relatively common, occurring in approxi- mately 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. Delayed puberty is most Pituitary stalk Microadenoma within pituitary gland Fig. 13.7.2.3 MRI brain, T1-weighted sagittal image of an 18-month-old with precocious puberty found to have a pituitary microadenoma. Fig. 13.7.2.4 MRI abdomen. Coronal section showing a large right adrenal tumour in a 2-year-old girl presenting with peripheral precocious puberty.

13.7.2 Normal puberty and its disorders 2433 often due to constitutional delay in growth and puberty. Children present with short stature and no secondary sexual characteristics. However, some features arising from adrenal androgens may be pre- sent (adrenarche). It is important to assess body proportion as well as height as this may indicate a genetic cause for the delayed puberty (e.g. Turners syndrome or Klinefelter syndrome). An associated micropenis may suggest hypopituitarism while an absent/dimin- ished sense of smell warrants investigation for Kallmann syndrome. Causes of pubertal delay The causes of puberty delay can be divided into three main categories (see Table 13.7.2.2): 1. Those with an intact hypothalamic-pituitary-gonadal axis, but a functional problem 2. Hypogonadotropic hypogonadism 3. Hypergonadotropic hypogonadism Functional hypogonadotropic 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 of growth and pu- berty, representing 60% of delayed puberty in boys and 30% in girls. However, this is a diagnosis of exclusion and needs monitoring over time. There is often a history of short stature noted in later child- hood, 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 repro- duction in a less than ideal circumstance. However, simple delay is sometimes difficult to distinguish from idiopathic hypogonadotropic hypogonadism (also known as iso- lated hypogonadotropic hypogonadism). Follow-up and possible testing may determine if puberty is going to spontaneously occur. Hypogonadotropic hypogonadism In this instance there is an inability to produce gonadotrophins from the pituitary (LH & FSH). Congenital, or isolated, hypogonadotropic hypogonadism can be difficult to differentiate from constitutional delay initially. 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 dif- ferentiate between the two conditions; hence follow-up is of utmost importance. The gonads are normal, but as they are not stimulated they remain prepubertal in size. It is 3 to 5 times less common in girls. In boys, there may be a history of micropenis or undescended testes at birth, due to prenatal gonadotrophin and androgen defi- ciency. Associated with lack of smell (anosmia) in approximately 60% of patients, it is defined as Kallmann syndrome. In this condi- tion, 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 as- sociated with cleft lip/palate, sensorineural deafness, and cerebellar ataxia. The KAL1 gene is implicated in the X-linked form, but in 60–70% of cases, the gene is unknown. It is also inherited in auto- somal dominant and recessive forms, giving significant variation in the features present. Prevalence is 1:10, 000 births with a male: fe- male ratio of 5:1. Other causes of congenital hypothalamic–pituitary axis dysfunc- tion include Prader–Willi and Bardet–Biedl syndromes, both of which can present as delayed or absent puberty. Hypogonadotropic hypogonadism may be acquired as part of multiple pituitary hor- mone deficiencies for pituitary adenoma, for example. The causes of hypogonadotropic hypogonadism are listed in Table 13.7.2.2. There may be either a relevant past medical history or the presence of other pituitary deficiencies. Often these children are already being moni- tored for their growth and pubertal delay is diagnosed promptly. Hypergonadotropic 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 hypergonadotropic hypogonadism testos- terone or oestrogen levels are low, indicating testicular or ovarian failure. Klinefelter syndrome (47XXY/mosaicism) is the commonest sex chromosome disorder, but diagnosis is delayed in around 60% of cases, as there is significant phenotypic variation with many individ- uals having only subtle features. Prepuberty, boys have small testes, increased incidence of developmental delay and behavioural prob- lems. The onset of puberty is often not delayed, as there is enough testosterone to initiate puberty; however, the testes remain small and firm. They often present with slow pubertal progression rather than delayed puberty. Testosterone levels rise, but cannot be main- tained, and subsequently oestrogen levels increase. Typically, boys are tall with gynaecomastia and echinoid features. As adults, they Table 13.7.2.2 Causes of delayed or absent puberty Hypogonadotropic hypogonadism Functional Constitutional delay of growth and puberty Chronic disease Anorexia nervosa Hypothyroidism Hyperprolactinaemia Intensive exercise Noonan’s/Down’s syndromes Permanent Kallmann’s syndrome and variants Isolated gonadotropin deficiency Congenital multiple pituitary hormone deficiency: Unknown aetiology Pituitary transcription factor disorders, e.g. PROP1, LHX1, HESX1 CNS tumours: Craniopharyngioma Hypothalamic tumours Pituitary adenoma CNS: Irradiation (high dose) Infiltration Histiocytosis Traumatic brain injury Post CNS infection Syndromes: Prader–Willi Bardet–Biedl CHARGE CHARGE -

Coloboma, Heart disease, choAnal atresia, Retarded Growth and Ear abnormalities (due to mutations in CHD7 gene).

section 13 Endocrine disorders 2434 have reduced facial and body hair and are infertile. In comparison to the general population, the risks of other medical complications are increased including diabetes mellitus, osteoporosis, breast cancer, and thromboembolic events. Turner syndrome (45 XO, mosaicism occurs) is the commonest cause of gonadal dysgenesis in girls. Diagnosis can occur at any age, including with pubertal delay or primary or secondary amenorrhoea. Turner syndrome therefore must be considered in any girl with delayed puberty even if they do not show any phenotyp- ical features of the condition. Up to 20% show spontaneous onset of puberty and spontaneous menstruation may occur, typically in mosaicism. Short stature is present due to insufficiency of the SHOX gene. Streak ovaries may be seen on ultrasound scan. Other causes of hypergonadotropic hypogonadism are listed in Table 13.7.2.3. Many will have a relevant history (e.g. testicular/ab- dominal radiotherapy or total body irradiation).
Arrested puberty If puberty has commenced but then regresses or stops, a dysfunc- tion of the pituitary-gonadal axis is suspected. If a cause is not ob- vious (severe malnutrition, steroid treatment) urgent investigation is needed. Low levels of FSH and LH relative to pubertal status suggests failure in the hypothalamic-pituitary axis and intracranial pathology needs to be excluded. Prolactinomas may primarily pre- sent with pubertal arrest. Autoimmune hypothyroidism should always be excluded. PCOS is increasingly common with associated obesity and meta- bolic syndrome. This mainly presents with amenorrhoea or irregular periods. Due to high insulin levels related to insulin resistance, sex hormone binding globulin levels are low and leads to raised free testosterone. This in turn causes hirsutism and amenorrhoea or oligomenorrhoea. Investigation In cases of delayed puberty, constitutional delay in males is the most common diagnosis. However, as it is a diagnosis of exclusion other causes need to be considered. A comprehensive history and exam- ination are paramount. Most patients may not need a significant number of investigations, and the emphasis must be placed on serial monitoring of growth and pubertal status at 6 monthly intervals. An initial bone age assessment is performed. Baseline bloods are dictated by the clinical assessment. Concerning features would include evi- dence of midline abnormalities, dysmorphic features, learning diffi- culties, tall stature, neonatal history of bilateral crypto-orchidism, or small penis, gynaecomastia if prepubertal, and anosmia. Tests may include a GnRH test, sex steroid levels, other pituitary function tests, and system-related investigations. If appropriate, an MRI brain would exclude a space occupying lesion such as a craniopharyngioma or pituitary adenoma (Fig. 13.7.2.5). All girls with delayed puberty should have karyotype testing and a pelvic ultrasound. It is difficult to differentiate between constitutional delay of pu- berty and idiopathic hypogonadotropic hypogonadism even if a GnRH test is conducted. Prepubertal levels of LH and FSH are seen in both cases, although sometimes much lower levels in idiopathic hypogonadotropic hypogonadism. The psychosocial impact of pu- bertal delay, especially for males can be significant so either way, a trial of sex steroids may be beneficial and could aid diagnosis. Low dose testosterone (50 mg, IM every 4 weeks) in males and oestradiol (2–5 μg, daily) in females can be given for 4–6 months. In constitu- tional delay of growth and puberty, this course is usually sufficient Table 13.7.2.3 Hypergonadotropic hypogonadism Genetic abnormalities Turner’s syndrome and variants Klinefelter’s syndrome Androgen insensitivity syndrome Gonadal dysgenesis Gonadal failure Autoimmune Metabolic (e.g. galactosaemia) Pelvic/spinal irradiation Chemotherapy Anorchia/vanishing testes Cryptorchidism Torsion Post infection (e.g. mumps) Idiopathic Disorders of steroid synthesis
and action Inactivating gonadotropin mutations Adrenal steroid enzyme defects Fig. 13.7.2.5 MRI

brain; left: axial view and right: sagittal view. This is a 15-year-old with pubertal delay, found to have a large craniopharyngioma with mass effect.

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