TRANSITION IN ENDOCRINOLOGY

Hypogonadism in adolescence

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Abstract

Puberty is a remarkable developmental process with the activation of the hypothalamic–pituitary–gonadal axis culminating in reproductive capacity. It is accompanied by cognitive, psychological, emotional, and sociocultural changes. There is wide variation in the timing of pubertal onset, and this process is affected by genetic and environmental influences. Disrupted puberty (delayed or absent) leading to hypogonadism may be caused by congenital or acquired etiologies and can have significant impact on both physical and psychosocial well-being. While adolescence is a time of growing autonomy and independence, it is also a time of vulnerability and thus, the impact of hypogonadism can have lasting effects. This review highlights the various forms of hypogonadism in adolescence and the clinical challenges in differentiating normal variants of puberty from pathological states. In addition, hormonal treatment, concerns regarding fertility, emotional support, and effective transition to adult care are discussed.

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Introduction

Adolescence is generally defined as the transitional phase between childhood and adult life, encompassing a broad range of cognitive, psychological and sociocultural adaptations in parallel with the biological changes in puberty. Puberty begins in boys as in girls with pulsatile secretion of gonadotropin-releasing hormone (GnRH) that stimulates pituitary release of gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone

(FSH)) (1, 2). This hormonal cascade results in gonadal maturation with subsequent production of sex steroids, non-steroidal factors, and gametes. The physical changes in puberty and the corresponding neurocognitive development culminate in sexual maturity and reproductive capacity. This transformation is recognized via pubertal rites of passage in many cultures (3, 4) culminating in the individual being socially accepted as an ‘adult’.

Invited author's profile

Prof. Nelly Pitteloud is the chief of the Endocrine, Diabetes, and Metabolism service at the University Hospital (CHUV) in Lausanne Switzerland. As the head of the Pediatric Endocrine Service she has helped develop a structured transition clinic (CEMjA) for adolescents with chronic endocrine disorders. Prof. Pitteloud's translational research focuses on the neuroendocrine control of human reproduction and she is the chair of the EU-funded COST European Network investigating GnRH deficiency (www.gnrhnetwork.eu).

Therefore, absent or disrupted puberty can result in significant emotional and psychosocial morbidity for adolescents (5, 6, 7, 8, 9).

Endogenous GNRH secretion first occurs in the fetus around the second trimester of pregnancy. During the first months of life the hypothalamic–pituitary–gonadal (HPG) axis is active (termed ‘mini-puberty’) and results in sex hormone levels near adult concentrations (2, 10, 11, 12, 13). Notably, there are sex differences *in utero* as testes are very active in testosterone secretion during fetal development, whereas ovaries do not secrete much steroid. Moreover, the postnatal activation in females during the first 24 months of life is less striking than that in boys. In males, robust HPG-axis activity in the first 6 months of life is crucial for final testicular descent and penile growth as well as proliferation of immature Sertoli cells and spermatogonia (13). Importantly, despite high serum levels of LH, FSH, and testosterone, spermatogenesis is not initiated at this time as the androgen receptor is not expressed in Sertoli cells before age 5 (14, 15, 16). The hormonal dynamics of the neonatal mini-puberty represent the first opportunity to observe the activity of the HPG axis before adolescence, as childhood is a period of quiescence with low GNRH secretion (Fig. 1). Episodic GNRH secretion resumes in early puberty with nocturnal, pulsatile GNRH secretion that extends progressively through the day and is sustained throughout adult life (1). However, the genetic, molecular and environmental influences upon these complex processes have not been fully unraveled.

Pubertal timing varies across ethnicities and is strongly influenced by both genetic and environmental

factors (17, 18, 19). A number of studies have demonstrated an earlier age of pubertal onset possibly influenced by nutrition and the growing rates of obesity (20, 21, 22). Clinically, pubertal onset is defined by Tanner II breast development in girls and testicular growth (volume >3 ml) in boys. Timing of puberty is physiologic if the appearance of these characteristics occurs within two s.d.s from the mean, which translates to 8–13 years in females, and 9–14 years in males for European populations (23). Normally, puberty is completed within 2.5–3 years. Delayed puberty therefore is statistically determined and defined either by absent pubertal onset at 13 (girls) or 14 (boys) years of age. Alternatively, it can be diagnosed with absent menarche by age 15 in adolescent girls or absent growth spurt in boys by age 16 years (23, 24). This review concentrates on various forms of disrupted puberty that presents as hypogonadism in adolescents.

Constitutional delay of growth and puberty

Constitutional delay of growth and puberty (CDGP) can be considered as the extreme end of the spectrum of normal pubertal timing and is marked by a very delayed spontaneous onset of puberty (24). It is the most common cause of delayed puberty in boys (~65% of cases) and girls (~30% of cases) (25). As detailed in a recent master review (24), CDGP is a diagnosis of exclusion to be made after ruling out pathological causes of delayed puberty. Differential diagnoses include functional (i.e., systemic illness), as well as permanent causes (i.e., congenital GNRH deficiency or ovarian/testicular insufficiency). In addition to clinical and biochemical assessment, initial evaluation should also include detailed family history because 50–75% of cases have a family history of delayed puberty (25). Clinically, CDGP is often associated with low BMI, slow growth velocity for chronological age, delayed bone maturation, and a biochemical profile of low serum gonadotropins sex steroids and growth factors (i.e., insulin-like growth factor 1 (IGF1)) in an otherwise healthy individual. Importantly, CDGP often appears to be familial with an autosomal-dominant trait (26, 27). Thus, family history is a critical part of the evaluation, because it can provide clues for identifying this diagnosis and guiding the diagnostic and treatment process.

The management of CDGP often entails a watchful waiting approach. Indeed, the eventual onset and progression of puberty confirms the diagnosis of CDGP. Alternatively, short-term, low-dose sex steroid treatment (testosterone in boys or estrogen in girls) can be used to try

Figure 1

Gonadal activation throughout development. Schematics depicting gonadal activation from fetal life through adulthood. Gonadal dysfunction (i.e., disorders of sexual development) in fetal life is depicted by blue, while incomplete activation of the hypothalamic–pituitary–gonadal axis is shown in red (i.e., congenital hypogonadotropic hypogonadism). The spectrum of pubertal development includes normal (gray), delayed (green), and partial/stalled and absent (purple).

to 'jump-start' spontaneous puberty. Such treatment increases growth velocity and pubertal development, results that may also positively affect psychosocial quality of life without significant side effects (28, 29). Yet to date, only limited, small randomized controlled trial have been conducted (30, 31, 32). Importantly, neither growth hormone nor the use of aromatase inhibitors (33) is recommended for CDGP.

Forms of hypogonadism in adolescence

Hypogonadotrophic hypogonadism

Absent or partial puberty in association with low serum sex steroids in the setting of low or inappropriately normal serum gonadotropin levels defines hypogonadotrophic hypogonadism in adolescence. There are a number of different etiologies that will be reviewed (Table 1).

Congenital hypogonadotrophic hypogonadism

Congenital hypogonadotrophic hypogonadism (CHH) is clinically characterized by absent or partial puberty and infertility. Biologically, CHH is defined by low or normal serum levels of LH and FSH in the setting of low sex steroids. Pituitary function is otherwise normal as is the imaging of the hypothalamo–pituitary region. Patients with CHH typically present in adolescence or early adulthood with delayed onset of puberty, primary amenorrhea, poorly developed sexual characteristics, and/or infertility. When CHH is associated with anosmia or hyposmia it is termed Kallmann syndrome (34, 35, 36). In some cases, signs of insufficient genital development (i.e., micropenis and cryptorchidism) may raise early suspicion of CHH (Fig. 1) (37). In such cases, a neonatal CHH diagnosis can be made via measurement of serum hormone levels around 2–3 months of life (peak levels

during mini-puberty) (12). Additional developmental anomalies can occur with CHH including unilateral renal agenesis, synkinesia (mirror movements), cleft lip and/or palate, sensorineural hearing loss, dental agenesis, and skeletal malformations (38). Notably, hypogonadotrophic hypogonadism and a constellation of specific phenotypes define syndromes such as coloboma, heart defect, atresia of nasal choanae, retarded growth/development, genital abnormalities, and ear abnormalities/deafness (CHARGE) syndrome or Bardet Biedl syndrome (Table 1). Furthermore, some of these developmental disorders have a genetic overlap with CHH (39, 40) (Table 2).

An important differential diagnosis of CHH is CDGP. However, associated clinical features such as cryptorchidism, microphallus, anosmia/hyposmia, or other congenital anomalies may raise suspicion of congenital GNRH deficiency (37). A battery of tests are available to assess CHH. Unfortunately, most have limited specificity in differentiating CHH from CDGP (24). Serum inhibin B has received recent attention as a simple discriminatory test as reports indicate cutoffs of 100 and 35 pg/ml have 73 and 93% positive predictive value for identifying CHH (41, 42). Yet, there is a large overlap between combined pituitary hormone deficiency (CPHD) and partial CHH. Therefore, there is yet to be a clear, reliable diagnostic test to differentiate these two entities (43) and thus, the diagnostic decision-making process is challenging (Fig. 2).

In contrast to CDGP, CHH is typically permanent as it is caused by a congenital defect in GNRH secretion or action (44). To date, more than 25 loci have been shown to underlie hypogonadotrophic hypogonadism (Table 2) and listings of European centers offering genetic screening is available via www.gnrhnetwork.eu and www.orpha.net. Spontaneous reversal has been documented in 10–20% of CHH patients following treatment (45, 46). A clinical cue suggesting recovered HPG axis function is testicular growth on testosterone treatment (45). Thus, serial

Table 1 Causes of hypogonadotrophic hypogonadism.

Acquired forms

Tumors (pituitary adenoma including prolactinoma, craniopharyngioma, germinomas, meningiomas, gliomas, and astrocytomas)
Infiltrative disease (hemochromatosis, granulomatous disease, histiocytosis, and sarcoidosis)
Iatrogenic (irradiation, high dose corticosteroids, and anabolic steroids)
Functional (stress, depression, eating disorders, excessive exercise, weight loss, obesity, and metabolic syndrome)

Congenital forms

Isolated GNRH deficiency (congenital hypogonadotropic hypogonadism, and Kallmann syndrome)
Combined pituitary hormone deficiency
CHARGE syndrome (coloboma, heart defect, atresia of nasal choanae, retarded growth/development, genital abnormalities, and ear abnormalities/deafness)
Lawrence–Moon–Bardet–Biedl syndrome

Table 2 Genes underlying congenital forms of hypogonadotrophic hypogonadism. Genes noted in bold have been identified in genetically overlapping syndromes. Mutations in *CHD7* have been identified as underlying CHH/KS and CHARGE syndrome (40). *FGF8*, *HESX1*, and *PROKR2* mutations underlie normosmic CHH and KS as well as CPHD (39). Mutations in *FGFR1* (denoted by *) have also been identified in cases of septo-optic dysplasia with multiple pituitary hormone deficiencies (39).

Condition	Genes	
Congenital hypogonadotrophic hypogonadism (CHH)	<i>GNRH1</i>	<i>LEP</i>
	<i>GNRHR</i>	<i>LEPR</i>
	<i>KISS1</i>	<i>TAC3</i>
	<i>KISS1R</i>	<i>TAC3R</i>
Kallmann syndrome (KS)	<i>FEZF1</i>	<i>KAL1</i>
	<i>HESX1</i>	<i>SEMA3A</i>
	<i>IL17RD</i>	<i>SOX10</i>
	<i>AXL</i>	<i>HS6ST1</i>
Both CHH and KS	<i>CHD7</i>	<i>NSMF (NELF)</i>
	<i>FGF8</i>	<i>PROK2</i>
	<i>FGF17</i>	<i>PROKR2</i>
	<i>FGFR1*</i>	<i>WDR11</i>
Combined pituitary hormone deficiency (CPHD)	<i>FGF8</i>	<i>POU1F1 (PIT1)</i>
	<i>GLI2</i>	<i>PROKR2</i>
	<i>HESX1</i>	<i>PROP1</i>
	<i>LHX3</i>	<i>SOX2</i>
CHARGE syndrome Lawrence–Moon–Bardet–Biedl syndrome	<i>LHX4</i>	<i>SOX3</i>
	<i>OTX2</i>	
	<i>CHD7</i>	<i>SEMA3E</i>
	<i>ARL6</i>	<i>BBS5</i>
	<i>BBS1</i>	<i>BBS7</i>
	<i>BBS10</i>	<i>BBS9</i>
	<i>BBS12</i>	<i>CEP290</i>
	<i>BBS2</i>	<i>MKKS</i>
	<i>BBS4</i>	<i>MKS1</i>
	<i>BBS5</i>	<i>TRIM32</i>
	<i>BBS7</i>	<i>TTC8</i>
	<i>BBS9</i>	

monitoring (with periodic discontinuation of treatment) is needed to assess for possible recovery of HPG axis function. The goals for treatment in CHH adolescents include induction of secondary sexual characteristics and growth, maximizing possible future fertility, decreasing long-term morbidity, and improving psychological well-being (see companion article on induction of puberty).

Combined pituitary hormone deficiency

Hypogonadotrophic hypogonadism can present as part of a broader pituitary deficiency disorder – CPHD. CPHD is defined by the presence of two or more pituitary hormonal deficiencies. In some cases, neonatal signs such as hypoglycemia can point to a CPHD diagnosis early in

life yet typically, adolescents present for evaluation with absent/partial puberty and short stature. Most often, multiple pituitary deficiencies are caused by lesions (e.g., tumoural, infiltrative, inflammation, autoimmune-process, iatrogenic, and traumatic). More rarely, CPHD is caused by a pituitary developmental disorder resulting in pituitary hormone deficiency and/or defects in pituitary gland anatomy (47). Interestingly, there is some genetic overlap between CHH and CPHD (Table 2) (39). Treatment relies on thorough identification of specific deficiencies based on clinical and biochemical investigation as well as results of dynamic testing and neuroimaging (48). With appropriate gonadotropin therapy inducing ovarian activity, CPHD patients can have very good chances for developing fertility (49).

Intra-cranial tumor is a common cause of acquired hypogonadism in adolescence (e.g., craniopharyngiomas and pituitary adenomas including prolactinoma) (50). Hypogonadotrophic hypogonadism can result from the compression of pituitary tissue/stalk or secondary to inhibition of GNRH secretion in the case of prolactinoma or Cushing's disease. Clinically, visual disturbance or headaches may accompany pubertal arrest in these cases. Importantly, all patients with pituitary tumors should have a complete evaluation of anterior and posterior pituitary function. Hypogonadotrophic hypogonadism resulting from prolactinoma can be treated medically (51) while surgical intervention is the usual first-line treatment for other tumours (52, 53, 54). In some cases, surgical resection may be complemented with radiotherapy and/or chemotherapy. These treatments *per se* may lead to permanent hypogonadism (55, 56).

Functional causes

Functional hypogonadotrophic hypogonadism (FHH) denotes a wide range of etiologies that can inhibit the gonadotrophic axis, by various mechanisms (Table 1). Eating disorders (i.e. anorexia nervosa and bulimia) are a well-known etiology of FHH among young women (57, 58). Hypothalamic amenorrhea, defined as HH in the setting of excessive exercise, psychological stress or weight loss, is a common cause of FHH in females and is usually reversible with correction of predisposing factors (59). Conversely, energy excess such as obesity or the metabolic syndrome are associated with FHH (60, 61). Among obese adolescent males, serum testosterone concentrations are 40–50% lower than normal BMI peers (62). In addition, chronic, systemic illnesses can cause FHH via deficits in nutritional intake creating a negative energy

balance or chronic inflammatory states resulting from immunologic disorders (i.e., inflammatory bowel disease and celiac disease) or psychological stress. Drugs such as opiates and steroids can also suppress the HPG axis (63, 64) yet this is rarely seen in adolescents.

Hypergonadotrophic hypogonadism

Delayed onset of puberty or stalled pubertal development can also be caused by gonadal defects that may first become evident in adolescence. In such cases,

Figure 2

The schematic depicts the process for assessing adolescent patients presenting with lack of spontaneous pubertal development. Shaded boxes show the major differential diagnoses of constitutional delay of growth and puberty

(CDGP), hypogonadotrophic hypogonadism, and hypergonadotrophic hypogonadism. No clinical algorithm can identify all cases with absolute certainty, thus clinical decision-making is important at each stage.

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Table 3 Causes of hypergonadotropic hypogonadism.

Acquired forms
Chemotherapy/radiotherapy
Ovarian/testicular torsion
Gonadectomy
Autoimmune disease
Congenital forms
Turner syndrome
Klinefelter syndrome
Galactosemia
Testicular regression syndrome
Disorders of sexual development (gonadal dysgenesis and androgen resistance)
Mutations in LH or FSH receptor

unresponsive defective gonads lead to increased serum gonadotropin levels that characterize hypergonadotrophic hypogonadism. Congenital forms as well as acquired forms should be considered (Table 3). Among males, the most common cause is Klinefelter syndrome (KS), resulting from one (or more) additional X chromosomes (i.e., 47,XXY karyotype or mosaic forms). In these patients, onset of puberty is typically normal but may progress slowly and testicular volume remains small. It affects ~1–2 per 1000 males and often remains undiagnosed (65) (see accompanying article in this issue). Turner syndrome (TS) is among the most frequent forms of hypergonadotrophic hypogonadism in females (66). TS affects 1/2500 females and is caused by the loss of an X chromosome (all or partial deletion as well as mosaic forms) (67).

A 30-year review of a Danish registry found that ~15% of TS cases were diagnosed at birth, 21% in childhood, 26% during puberty, and the remaining 38% in adulthood (68). In adolescence, key diagnostic features include short, disproportionate stature, and ovarian insufficiency resulting in absent or incomplete puberty. In some instances, primary amenorrhea is the only presenting symptom. Clinical stigmata (i.e., webbed neck, shield chest, and widely-spaced nipples) may point to TS. Associated congenital heart and/or kidney malformation, lymphoedema, liver disease, eye, orthodontic and orthopedic problems can also occur at variable degrees and warrant investigation (69). Auto-immune diseases and metabolic defects occur at increased rates among women with TS necessitating monitoring and long-term follow-up (70). While most patients with TS will require pubertal induction, about one-third of girls present with spontaneous initiation of puberty and 5% exhibit menarche and 2% spontaneous pregnancy (71). Thus, the timing of gonadal failure is variable and can occur anytime between

childhood and young adulthood (69). Hypogonadism in these patients not only affects puberty and reproductive capacity but also has consequences on metabolic, hepatic, cardiovascular, and bone health (density) (72).

Advances in the treatment of childhood cancer (surgery, chemotherapy/radiotherapy) have improved survival rates and growing numbers of adolescents are presenting with acquired forms of hypogonadism secondary to treatment of pediatric cancers (73, 74). For young cancer survivors, infertility is often a major concern (75). In general, ovaries are more resistant to insult from adjuvant treatment compared with the testes (76). The type of treatment, dosage/exposure, and age at treatment are important determinants of gonadotoxicity and patients treated at a younger age typically have lower risk for long-term, deleterious reproductive effects (73, 74, 77). In cases of intracranial tumors, treatment (surgery, chemotherapy/radiotherapy) can also result in permanent hypogonadism.

Management of hypogonadism

In general, there are several goals for treating hypogonadism in adolescents: developing secondary sexual characteristics and growth as well as inducing gonadal maturation for future fertility (see accompanying article on pubertal induction). Furthermore, psychological well-being and limiting comorbidities are also important considerations.

Psychological well-being

The physical development of puberty is accompanied by psychosocial and emotional changes, and disrupted puberty can carry a psychological burden as well as victimization and bullying that are associated with increased anxiety and depression (5, 6, 7, 8, 9). Indeed, young men with CHH (78, 79) and KS (80, 81) have increased levels of anxiety and depressive symptoms compared with peers and this psychosocial impact can persist as lingering feelings of shame and isolation (82). As such, treatment inducing growth and development of secondary sexual characteristics may be helpful in alleviating some of the distress hypogonadal adolescents experience related to their lack of development (80). Furthermore, studies in patients with TS and KS suggest that initiating treatment at a physiologically appropriate age (and continuing treatment through transition to adulthood) can have beneficial effects on self esteem and social outcomes (81, 83). These patients also have needs

relating to their psychosexual development and identity. Frank discussion of patients' concerns, anticipatory guidance, and emotional support should be an integral part of their care. For those survivors of childhood cancer, abnormal development and concerns regarding sexuality and fertility can have significant lasting effects on quality of life (73, 74, 84). Therefore, a holistic, collaborative approach including psychological counseling is a key component of managing hypogonadism in adolescence.

Transition of adolescents to adult care

The transition from pediatric to adult care is a challenge for patients with chronic endocrine conditions with different disorders having condition-specific needs (85). Too often the transition process is characterized by cracks and gaps in care as reported for patients with TS (86) and CHH (82). Such disjointed care can negatively impact health and quality of life for adolescents with hypogonadism as periods without treatment result in decreased sexual function, diminished energy, poor bone density (87, 88), and impaired glucose tolerance (86, 89). Special transition clinics where pediatric and adult endocrinologists work together are increasingly being created to bridge care and promote continuity and adherence to treatment to limit potential negative skeletal, cardiovascular, and metabolic sequelae of discontinuity of care among young adults with hypogonadism. Indeed, systematic reviews support the notion that structured transition programs can be effective in bridging gaps in care (90). However, it is important to underscore that transition is a process rather than a singular event that involves needs and expectations of patients, parents, and providers alike (91, 92, 93). Effective transitions should include collaboration between pediatric and adult providers as well as open communication with adolescents and families. The teen's emotional development and readiness for transition must be taken into account encompassing both physical health needs and psychological and emotional aspects (i.e., coping).

Conclusions and future directions

Hypogonadism in adolescence results from a variety of causes including congenital and acquired forms. Discerning CHH from CDGP remains challenging as there is yet no gold-standard test to differentiate the two. Early diagnosis is important for initiating treatment to develop secondary sexual characteristics and growth as well as for inducing gonadal maturation for future fertility. Furthermore, early treatment may help to minimize some of the

psychosocial impact of hypogonadism on adolescents. This is a vulnerable time for teens with chronic health conditions as they must simultaneously develop autonomy and self care skills to manage their health into adulthood. This demands an integrated approach including coordinated transitional care into adulthood. Possible future directions include novel biomarker discovery (and potentially genetic testing) that could enhance timely and accurate diagnosis. Moreover, for progressive forms of gonadal failure such as TS and KS, earlier detection may be increasingly important for fertility preservation given rapidly evolving assisted fertility technologies. The growing effectiveness of pediatric cancer treatments has resulted in increasing numbers of survivors with ramifications on fertility as well as metabolic and bone health demanding long-term monitoring. Regardless of the etiology of hypogonadism, transition and continuity of care are important components for promoting health and well-being of adolescent patients. Further studies are needed to further understand the long-term health consequences of hypogonadism in adolescence.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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