Endocrine Therapies

Variations in delayed puberty:

from constitutional delay to Kallmann Syndrome – a European perspective

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Editor:
P. M. Holterhus

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IMPORTANT NOTE:

Editors and authors have bestowed great care of this work, that the information provided in this publication reflect the current state of knowledge. However, the findings in medicine changes constantly through research and clinical experience. Authors, editors and publishers ask for understanding that they cannot assume any liability for the correctness and completeness of the information of any information in this book. Furthermore, the information does not supersede the individual judgment and decision of the doctor.

Foreword CDGP

This is the first volume in our series "Endocrine Therapies" ("Endokrinologische Therapien") to appear in English. The aim of this series of booklets is to provide up-to-date knowledge on clinically relevant topics in Pediatric Endocrinology. This publication concentrates on the constitutional delay of growth and puberty (CDGP) and presents a European perspective. While the prognosis for CDGP is usually very good it can represent a significant diagnostic challenge. Severe CDGP may overlap significantly with permanent forms of hypogonadotropic hypogonadism. Current lab tests and functional lab tests generally lack sufficient sensitivity and specificity; clinical management of severe CDGP therefore belongs in the remit of experienced pediatric endocrinologists.

It was possible to engage two experts from Helsinki University, Finland as authors of this brochure, both with extensive experience in the field of puberty, puberty control, and particularly in CDGP.

Professor Taneli Raivio, MD, PhD is a preeminent clinical and scientific expert in the field of regulation of puberty. He was appointed chief physician of education and research at the Children's Hospital, Helsinki University Central Hospital in 2015 and group leader and professor at the Institute of Biomedicine, University of Helsinki since 2013. He also works as clinical pediatric endocrinologist in the pediatric endocrine outpatient clinic. He has received many honors and awards, including the prestigious Young Investigator Award presented by the European Society for Pediatric Endocrinolo-

gy (ESPE). The second member of the team is Doctor Matti Tapani Hero, who is currently a subspecialist in pediatric endocrinology at the Pediatric Endocrinology Unit, Children's Hospital, Helsinki University Central Hospital, who is concurrently working as a post-doctoral researcher at the Pediatric Endocrinology Unit, Hospital for Children and Adolescents at the same institution. In particular, Matti Hero is principal investigator in several government funded clinical studies on evidence based therapies for CDGP. In 2004, he received the Young Investigator Award at the International Conference on Children's Bone Health in Montreal, Canada.

This brochure offers a brief introduction into the regulation of puberty. It subsequently concentrates on CDGP and the sometimes difficult differential diagnosis. It contains useful tables for clinical practice in every day pediatric endocrinology. As in all previous publications in this series, the authors share their own experience in the field with the readers and round off their work with a rich resource of valuable references.

Paul Martin Holterhus

Foreword

Delayed puberty is a clinical problem commonly encountered by both primary health care physicians and tertiary center pediatric endocrinologists. In most cases the delay is due to extreme late normal variations in the timing of puberty (constitutional delay in growth and puberty, CDGP). The diagnosis of CDGP is based on exclusion of other underlying causes by taking a thorough medical history and performing a physical examination and selected laboratory and imaging investigations. Second-line investigations should be targeted at those where puberty fails to progress during follow-up and at those with specific findings indicative of permanent hypogonadism, or where there are 'red flag' signs or symptoms, such as headache or disturbed vision. Early diagnosis of conditions affecting the timing of puberty appears important for normal psychosocial adaptation. Patients presenting with significant psychosocial problems associated with delayed puberty should be offered psychological counseling and/or pharmacological treatment to induce secondary sexual characteristics and accelerate growth (e.g. low-dose sex steroid therapy). This booklet presents recommendations for the evaluation and treatment of delayed puberty, with the focus on medical treatment.

Matti Hero & Taneli Raivio

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Physiology of puberty

Puberty is the developmental transition period leading to sexual maturation and adult height. Physical changes in puberty are initiated by the gradual reactivation of pulsatile gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. GnRH induces the release of LH and FSH from the pituitary, and these two gonadotropin hormones regulate gonadal gametogenesis and steroidogenesis. Pubertal increase in sex steroids is a prerequisite for several key developmental changes, such as the pubertal growth spurt, sex specific changes in body composition, normal peak bone mass, an adult blood hemoglobin level (boys), and psychosocial adaptation.

Central hypothalamic control of puberty

Although the factors determining the timing of puberty are not completely understood, several environmental, metabolic, genetic and epigenetic factors are known to play a role [1]. Normal activation and progression of puberty require a functional hypothalamic excitatory neuronal network (a.k.a. GnRH pulse generator). GnRH neurons are neuroendocrine cells that originate in the olfactory placode and migrate to the hypothalamus during embryonic development. This developmental background explains the co-occurrence of deficient sense of smell and GnRH secretion in Kallmann Syndrome. A major upstream activator of GnRH neurons is kisspeptin, secreted by specific neurons of the arcuate and anteroventral periventricular nucleus (Fig. 1) [2]. During childhood, the GnRH pulse generator is relatively inactive due to central inhibition (termed 'gonadostat') [3]. Recently, makorin RING-finger protein 3, the product of the imprinted MKRN3 gene, was found to be a significant component of this system [4]. In puberty, the impact of 'gonadostat' on the hypothalamic-pituitary-gonadal (HPG) axis gradually diminishes, allowing the onset and progression of puberty. Thereafter, the negative feedback on gonadotropin secretion is increasingly effected by peripheral signals, particularly gonadal steroids (mainly estrogen) and inhibin B (which inhibits FSH secretion) [5].

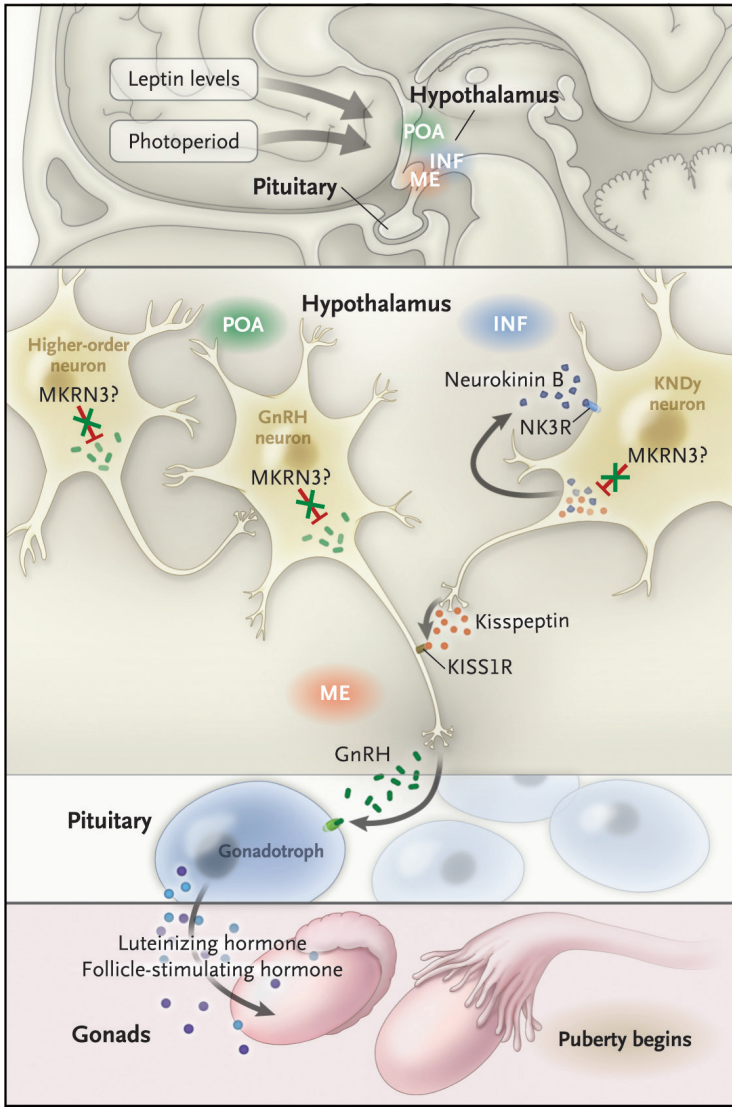

Figure 1. The three levels and main regulatory factors of the hypothalamic-pituitary-gonadal system. The onset of puberty is regulated by peripheral signals such as the photoperiod and leptin, and by the increased expression of neurokinin B, kisspeptin, and their receptors (NK3R and KISS1R, respectively), and MKRN3. MKRN3 inhibits and kisspeptin and neurokinin B stimulate GnRH release. KNDy (kisspeptin–neurokinin B–dynorphin), INF (infundibular nucleus), ME (median eminence), and POA (preoptic area). Reproduced from [59].

Regulation of the HPG axis by peripheral signals

Metabolic and environmental factors significantly influence the timing of puberty. Common causes that delay or prevent pubertal maturation include any severe chronic illness, nutritional deficiency such as anorexia nervosa, endocrinopathies and excessive exercise. The onset of puberty is metabolically gated; adequate energy stores are required for the energy-consuming pubertal development and reproductive maturity, particularly in females. One of the peripheral signals of energy sufficiency that regulates puberty is leptin, secreted from adipose tissue, which appears to have a permissive role in the transition to puberty[6]. Leptin levels are typically low in those suffering from malnutrition and high in obese subjects. In addition, circulating insulin, which is usually elevated in energy-sufficient states, may have a stimulatory role and the gut hormone ghrelin may have an inhibitory role in the control of the HPG axis [7–9]. Exposure to abnormally high levels of sex steroids increases the risk of precocious central puberty. This is borne out by the fact that precocious central puberty is a common clinical problem in children with late diagnosis of congenital adrenal hyperplasia.

Genetics of puberty

It has been estimated that 50 to 80% of the variation in the timing of puberty is explained by genetic factors, and 50 to 75 % of patients with constitutional delay in growth and puberty (CDGP, the most common cause of delayed puberty, represents the late extreme of normal pubertal timing) have a first degree relative with delayed puberty [10–12]. However, very little is known about the genetic factors that regulate the timing of puberty in the general population. For example, in genome-wide association studies, signals from more than 100 loci have been associated with age at menarche, but they appear to explain only a small fraction of the variation in pubertal timing [13]. Genetic studies of patients with congenital hypogonadotropic hypogonadism (CHH) published during the last 20 years have significantly expanded our knowledge of the development of neuronal circuits that govern puberty. To date, defects in more than 15 genes have been found to underlie normosmic CHH and Kallmann Syndrome. However, defects in these

genes have not been found to adequately explain CDGP [14]. Overall, the genetic background of CDGP is currently not well understood.

When is puberty delayed?

According to traditional cutoffs, puberty is delayed in boys who lack testicular enlargement at the age of 14 years and in girls with no breast development at the age of 13 years. These age limits are still recommended [15], although a secular trend towards earlier age of onset of breast and testicular development has been noted [16, 17]. Puberty may also be delayed due to deficient progression once it has started. In fact, it has been estimated that one third of male and half of female patients with CHH may present with halted rather than absent puberty [18, 19].

Diagnostics of delayed puberty

Constitutional delay of growth and puberty (CDGP) is the most common cause of delayed puberty in both sexes, reported to affect approximately 65% of boys and 30% of girls with the condition [20]. The lower percentage of CDGP in females could be partly explained by the fact that medical attention is less actively sought [12]. CDGP is a diagnosis of exclusion and can be made only after sufficient diagnostic work has been done to rule out pathologic reasons for the condition. The diagnoses underlying delayed puberty in a large case series evaluated at a tertiary care center are shown in Table 1 [20].

It is practical to classify the differential diagnostics of CDGP as transient hypogonadotropic hypogonadism (HH; functional HH due to an underlying condition), permanent HH (tumor in the central nervous system, multiple pituitary hormone deficiency or isolated HH), and hypergonadotropic hypogonadism (gonadal failure). In all patients, a thorough history should be obtained and physical examination performed, and basic laboratory and imaging studies should be performed to rule out underlying disorders.

Medical history

The growth patterns and pubertal maturation of the adolescent's 1st degree relatives should be discussed. Delayed growth pattern in the father or mother, menarche at the age of 14 years or more in the mother or delayed puberty in a sibling, with uneventful progression of puberty thereafter, increases the probability of CDGP. Often, an autosomal dominant pattern of inheritance is apparent in familial cases. The patient and the parents should be questioned about any signs indicative of chronic disease or of conditions such as celiac disease, anorexia, inflammatory bowel disease, severe respiratory symptoms, rheumatoid arthritis, excessive exercise, medication use, head trauma and history of radiotherapy or chemotherapy. Headache or disturbed vision should raise the suspicion of a tumor in the central nervous system (CNS). Cues such as (prior) diagnosis of micropenis or cryptorchidism, presence of hyposmia or anosmia, or a history of infertility in the parents indicate

Table 1. Differential diagnosis of delayed puberty. Underlying causes other than CDGP are divided in three main groups, based on serum gonadotropin levels and whether the condition is secondary and transient or permanent.
* Relative frequency of the diagnostic category in a large case series of adolescents with delayed puberty, evaluated at a tertiary care center. Data from [20]. HH (hypogonadotropic hypogonadism), GH (growth hormone), IBD (inflammatory bowel disease), ALL (acute lymphoblastic leukemia), CHH (congenital hypogonadotropic hypogonadism), CNS (central nervous system).

	CDGP	Functional HH	Permanent HH	Hypergonadotropic hypogonadism	Other
Frequency* (%)					
Girls (n=74)	30	19	20	26	5
Boys (n=158)	63	20	9	7	1
Underlying diagnoses		Endocrinopathies (GH deficiency, hypothyroidism, hyperprolactinemia) Bowel disease (IBD, celiac disease) Poor nutrition/ weight gain Anorexia Intense exercise Rheumatoid disease Chronic kidney disease Oncological disease (neuroblastoma, Hodgkin's disease, ALL)	CNS tumor (craniopharyngioma, germinoma, optic glioma) Congenital syndromes (Prader-Willi, CHARGE, panhypopituitarism) Kallmann Syndrome Normosmic CHH Rathke's pouch cyst	<u>Females:</u> Turner Syndrome Radio- or chemotherapy Idiopathic ovarian failure <u>Males:</u> Klinefelter Syndrome Gonadal radiation Gonadal dysgenesia/ anorchia	

the possibility of CHH. Finally, psychosocial adaptation should be discussed both with the patient and the parents. This guides the need for psychological counseling or low-dose sex steroid treatment in order to induce puberty.

Physical examination

It is important to plot previous height and weight measurements on a growth chart to assess longitudinal growth. Although growth rate slowly declines with advancing age in subjects with pubertal delay [21], it is usually more than 3 cm/year. Disturbing growth patterns are those associated with exceptionally slow growth rate (often due to the temporary prepubertal dip in growth rate, but may reflect chronic disease or growth hormone deficiency, hypothyroidism or hypercortisolism), or decreasing BMI or weight-for-height (suggestive of a chronic underlying condition such as chronic bowel disease or anorexia nervosa). Approximately half of the patients with CDGP already have a slow growth rate years before expected puberty, and are at risk of not achieving final height in the mid-parental target height range [22]. Although CDGP is typically associated with slim stature, some of the boys with CDGP are obese [20]. These boys often do not have a significant delay in growth or bone age.

The Tanner stages should be used to assess the current stage of puberty (Table 2). In girls, breast stage (B) 2 is the clinical hallmark for onset of puberty. In boys, the first clinical sign of puberty is growth in testicular size, with a volume of 3 ml or more, or testicular length 25 mm or more, indicating the start of central puberty [15]. Testis size (length and width) is measured using a ruler or the Prader orchidometer. Several equations are available for calculating testicular volume, one of which is the Hansen formula [23]: volume (ml) = length (cm) x width (cm)^2 x 0.52. The stage of pubic hair development should be documented, although this provides less information on HPG axis activity than breast or gonadal stage, since pubic hair may be due to adrenarche.

Table 2. The Tanner stages of puberty [60, 61].

Breast stage	1	Prepubertal
	2	Breast bud stage with elevation of breast and papilla, enlargement of areola
	3	Further enlargement of breast and areola, no separation of their contour
	4	Areola and papilla form a secondary mound above level of breast
	5	Mature stage, projection of papilla only, related to recession of areola
Gonadal stage (boys)	1	Prepubertal
	2	Enlargement of testes and scrotum; scrotum skin reddens and changes in texture
	3	Enlargement of penis (first in length), further growth of testes
	4	Increased size of penis with growth in breadth, development of glans. Testes and scrotum larger, scrotum skin darker
	5	Adult genitalia
Pubic hair stage	1	Prepubertal
	2	Sparse long, slightly pigmented hair, straight or curled, at base of penis or along labia
	3	Darker, coarser and more curled hair, spreading sparsely over junction of pubes
	4	Hair in adult type, but covering smaller area than on adult, no spread to medial surface of thighs
	5	Adult type and quantity, spread to the medial surface of the thighs

A neurological examination should be performed in addition to the regular physical examination, including evaluation of the optic discs for papillary edema and the visual fields, and investigation of mirror movements in the hands and upper extremities. Cleft lip or palate, split hand or foot malformation, renal dysgenesis, coloboma, missing teeth or hearing problems in combination with delayed puberty should increase the suspicion of CHH. The thyroid gland should be palpated and syndromic signs documented. Patients with complex syndromes that include hypogonadism present with additional features, such as extreme obesity and developmental delay (Bardet-Biedl, Prader-Willi), coloboma, heart defect, atresia choanae, retardation of growth and development, genital and ear anomalies (CHARGE), primary hypocortisolism (adrenal hypoplasia congenita with HH), or impaired vision and optic nerve hypoplasia (septo-optic dysplasia).

Laboratory and imaging studies

The reactivation of the HPG axis may already be evident in laboratory tests (obtained early in the morning) before significant clinical signs of puberty can be found. Useful laboratory and imaging studies of delayed puberty are presented in Table 3. The aim of the first-line investigations, performed in all patients, is to diagnose or rule out any underlying condition responsible for the delay with a sufficient level of confidence to justify a period of observation or a short course of low-dose sex steroid treatment if that is desired. Additional investigations should ideally be performed and interpreted by a pediatric endocrinologist. Differentiating between CDGP and isolated CHH may be challenging, especially in the absence of hyposmia/anosmia. Important phenotypic cues that may help distinguish patients with CHH from those with CDGP are the presence of reproductive and non-reproductive features of CHH (see above); in addition, test results of HPG axis function may be helpful (Table 3). In general, basal and stimulated gonadotropin values have limited diagnostic specificity because the values overlap between boys

with CDGP and CHH. Stimulation tests with the potent GnRH agonist buserelin may discriminate better between these two conditions, but published data are limited [24]. Various protocols of the human chorionic gonadotropin (hCG) stimulation test have achieved positive predictive values for distinguishing patients with HH from those with CDGP ranging from 82 to 100% [25], but the protocols are laborious. Single measurement of serum inhibin B is a promising tool for early discrimination of CHH from CDGP, but confirmatory studies are needed. Molecular genetic diagnosis can be made in 30 to 40% of patients with CHH. In two recent Northern European studies, patients with CHH carried mutations mainly in *FGFR1, KAL1, GNRHR* or *CHD7* [26, 27]. However, CHH is genetically very heterogeneous and ethnic background should be taken into account in genetic testing.

Table 3. Imaging and laboratory investigations for delayed puberty. IFMA; immunofluorometric assay, ICMA; immunochemiluminometric assay. Modified from [15].

	Investigations	Comments
All patients	Bone-age radiography	Usually delayed, does not reliably differentiate CDGP from congenital HH or functional HH. Several years of delay in bone age results in overestimation of predicted adult height (Bailey-Pinneau tables).
	Biochemical analyses (before 10 AM)	For diagnosing chronic diseases. Complete blood count, ESR, creatinine, electrolytes, celiac screen, plasma albumin, TSH, free T4. Consider fecal calprotectin if bowel symptoms are present.
	Serum gonadotropins (before 10 AM)	LH > 0.6 (IFMA) or > 0.2 IU/L (ICMA) is a specific (but not sensitive) marker for pubertal activation of the HPG axis [62]. FSH < 1.2 and LH < 0.4 IU/L (IFMA) may suggest hypogonadotropic hypogonadism but is not diagnostic [63]. LH > 0.65 IU/L (IFMA) argues against complete HH [64]. FSH and LH are increased in primary gonadal failure.
	Serum IGF-I	Used to screen for GH deficiency. Should increase during sex steroid treatment/advancing puberty. Use reference values compatible with stage of puberty/bone age.
	Serum testosterone (before 10 AM)	Morning testosterone > 0.7 nmol/L predicts advancement of puberty during the next 12 to 15 months in the majority of boys [65].
Selected patients	GnRH and GnRH agonist (GnRHa) stimulation test	Onset of central puberty: peak LH/FSH > 1 or peak LH > 5 to 8 IU/L in GnRH stimulation test. Peak LH < 5 IU/L after buserelin (GnRHa) stimulation may suggest permanent HH [24].
	Karyotype	Indicated in those with elevated gonadotropin levels; in males with small testes despite progression of other features of puberty; females with signs suggesting Turner's Syndrome.

	Investigations	Comments
Selected patients	HCG-test	HCG 1500 IU i.m. daily for 3 days, serum testosterone on day 4. Cut-off 3.6 nmol/L offered a 92% sensitivity and 92% specificity for the diagnosis of HH (vs. CDGP) in a small retrospective sample [66]. Sensitivity and specificity better in combination with GnRH-stimulation test (peak LH cut-off 2.8 IU/L)
	Serum inhibin B	Based on one study, value of 35 pg/ml or less differentiates (complete) HH from CDGP with 100% sensitivity and specificity in boys with delayed puberty and Tanner G stage 1[67].
	Serum prolactin	Elevated level may indicate hypothalamic-pituitary tumor underlying delayed puberty. Measurement of macroprolactin recommended.
	Brain MRI	Indicated if CNS pathology suspected (headache, disturbed vision) and if there is no progression of puberty after 1 year of treatment. Consider if no signs of puberty at age >15 yrs. In patients with Kallmann Syndrome olfactory bulb and olfactory sulcus aplasia/hypoplasia are common.
	Olfactory function test	As part of evaluation for Kallmann Syndrome
	Genetic testing	In those with specific syndromic features, family history suggesting CHH, or reproductive/non-reproductive phenotypic signs of CHH [68]. Genetic counseling should be included.

Treatment of delayed puberty

General remarks on therapy

CDGP is, by definition, a transient condition with eventual spontaneous progression of puberty. In patients with a (working) diagnosis of CDGP and no signs or symptoms suggesting permanent hypogonadism or chronic disease, the patient should decide whether or not to initiate medical treatment.The delay in physical signs of puberty or relative short stature is not a major concern for many subjects with CDGP, and reassurance and watchful waiting is all that is required. This is also frequently the preferred strategy in those with clinical or biochemical evidence of onset of puberty, in whom spontaneous progression is expected. However, many adolescents presenting with delayed pubertal development and/or relative short stature experience psychosocial stress and negative interaction with their peers, which may lead to problems with self-esteem, anxiety and self-confidence [28]. In these patients, and in those with features of permanent HH, the threshold for initiating low-dose sex steroid treatment and psychological counseling should be low.

Medical therapy in adolescents with CDGP

The goal of the treatment is to alleviate psychosocial stress by inducing secondary sexual characteristics and accelerating the growth rate. In those presenting late, the goal is also to optimize peak bone mass and body composition. At present, the preferred options for treatment are low-dose testosterone in boys and low-dose estrogen in girls. Although low-dose testosterone has been used for decades in boys with delayed puberty, varying indications, doses and schedules have been employed, and only a few well-designed trials have been published [29–33]. Even less published data are available on low-dose estrogen treatment of delayed puberty in girls [34, 35]. However, significant evidence [36, 37] suggests that the bio-identical hormone (17β-estradiol) should be used in preference to ethinyl estradiol (EE) or conjugated equine estrogen (CEE) [38]. In order to avoid the first-pass metabolism, it is probably beneficial to administer 17β-estradiol transdermally rather than orally; this may

have advantages regarding treatment effects on lipids and thrombosis risk [39, 40].

Compounds used for treatment of CDGP and their dosage are presented in Table 4. It is of note that the recommended treatment in boys is low-dose androgen, usually intramuscularly administered testosterone [15]. Aromatase inhibitor treatment has been used in trials on boys with CDGP, but this is experimental, and should ideally be used in clinical trials only until more data on safety and efficacy are available [41]. Aromatase inhibitors decrease estrogen biosynthesis and estrogen-mediated central negative feedback in boys who already show some HPG axis activity.

Medical therapy in adolescents with permanent hypogonadism

The initial goals of treatment in patients with permanent hypogonadism are the same as in CDGP, but concerns of future fertility and sexual function should also be addressed. Puberty in patients with permanent HH is typically induced with sex steroids, and the therapy continues life-long. In patients with CHH, however, the lifetime incidence of reversal (i.e. recovery of gonadotropin secretion) may be as high as 22% [42]. Clinicians treating these patients should be aware of this condition and, if significant testicular enlargement is noted while on sex hormone replacement therapy, they should suspend testosterone treatment and assess whether reversal has occurred [43]. A gradual increase in sex steroid replacement dosage, and the addition of progestin in girls, is required during the course of puberty. Adult doses are usually reached within 3 years of start of treatment, depending on age at initiation and desired tempo of pubertal progression. If puberty induction is started at a relatively young age, low doses such as 50 to 75 mg testosterone i.m. monthly in boys are appropriate for the first 6 months, with gradual increments thereafter. In boys with HH, puberty can also be induced with human chorionic gonadotropin (hCG) alone or in combination with recombinant human FSH (rhFSH) (Table 4). Compared with testosterone, the potential advantages of hCG (with or without FSH) are better testicular growth and induction of spermatogenesis [44]. In terms of inducing spermatogenesis, combined therapy with hCG and rhFSH may be

Table 4. Medical treatments for adolescents with delayed puberty or permanent hypogonadism.

	Drug	Dosing	Comments
Boys	Testosterone enanthate, cypionate, and propionate. Intramuscular injection.	CDGP: 50 (to 100) mg every 4 weeks for (3 to) 6 months. May be repeated with 25 to 50 mg increment in dose (not more than 100 mg). Hypogonadism: 50 mg every 4 weeks. Increase dose every 6 (to 12) months. Adult dose 200 mg every 2 weeks/250 mg every 3 weeks.	CDGP: Usually not recommended below 14 years of age. Hypogonadism: Can be initiated after 12 yrs of age. Gradually increase dose every 6 months, adult dose after (2 to) 3 years; faster if started late. High doses can cause premature epiphyseal closure, erythrocytosis.
	Testosterone undecanoate. Intramuscular injection.	CDGP: no data available. Hypogonadism: Adult dose 1000 mg every 10–14 weeks.	Long-acting testosterone, used successfully in patients with CHH (age >17 yrs) [69].
	Transdermal testosterone.	CDGP: No data available. Hypogonadism: Can be started when approaching testosterone adult dosing (transdermal adult dose 50–80 mg/d).	Close skin contact should be avoided after application.
	Subcutaneous/ intramuscular hCG injections.	Hypogonadotropic hypogonadism: 500 to 1500 IU 2 to 3 times weekly. Adjust dose based on serum testosterone level.	Induces testis growth.
	Subcutaneous rhFSH.	Hypogonadotropic hypogonadism: 75 to 150 IU 2 to 3 times weekly. Adjust based on testicular growth and inhibin B.	In patients with CHH add FSH to induce testicular growth and spermatogenesis.

	Drug	Dosing	Comments
Girls	17β-estradiol. *Transdermal route preferred,* can be administered perorally.	Patch: initial 3.1–6.2 µg/24 h [15] or 0.05–012 µg/kg/24h [34]. Overnight patch initially. Increase by 3.1–6.2 µg/24h every 6 months. Adult dose 50(–100) µg/24h Peroral: initial 5 µg/kg.	Preferred choice. Evaluate response clinically (breast development) and, if available, with serum E2 measurements (mass spectrometry) and adjust dose accordingly.
	Ethinyl estradiol. Peroral.	Initial dose 2 µg/d. Increase every 6 months. Adult dose 20 µg/d.	Possible liver toxicity, increased risk of thromboembolism, increased levels of SHBG.
	Conjugated equine estrogens. Peroral.	Initial dose 0.1625 mg for 6–12 months. Increase dose every 6-12 months. Adult dose 0.625 mg.	Use questioned in CDGP. Increased cardiovascular risk in postmenopausal women.
	Progestogens/ progestins. Peroral.	Usually necessary after prolonged estrogen treatment (>12 months, or break-through bleeding).	To induce endometrial cycling.

better than hCG alone [45, 46]. Further, pretreatment with FSH to increase the Sertoli cell population before exposure to hCG or pulsatile GnRH treatment may be beneficial for future spermatogenesis [46, 47]. Pulsatile GnRH, administered with a pump, is used in specialized centers. These treatment modalities, promoting both the development of secondary sexual characteristics and fertility, may have psychological advantages over sex steroid treatment in males [48].

Practical recommendations for inducing puberty in girls with Turner syndrome and in boys with Klinefelter Syndrome and testosterone deficiency are available [49–51].

Follow-up

In males and females primarily diagnosed with CDGP, a follow-up appointment after 6 (to 9) months of therapy or observation is recommended. The goal of this visit is to document the progression of puberty and the acceleration in growth rate in those receiving sex steroid therapy or to show spontaneous activation of the HPG axis. In males, testicular growth is the clinical sign of puberty progression. In females, breast development reflects estrogen effects, but the assessment of HPG axis activity is more difficult in those receiving estrogen treatment. In these patients serum gonadotropin levels (preferably after GnRH stimulation), estradiol measurements and ultrasound scan of the ovaries and the uterus are helpful. In those who fail to show any activation of the HPG axis, second-line investigations should be performed, including a brain MRI. It is often necessary to discontinue estrogen treatment for a while in order to evaluate the HPG axis reliably. Growth hormone deficiency or underlying chronic disease should be suspected in those patients who fail to show acceleration of growth rate despite sex steroid treatment.

Patients with permanent HH and hormone replacement therapy should be followed up at 6 monthly intervals. During these visits, the sex steroid treatment doses should be adjusted based on clinical and biochemical signs of pubertal progression. Transition from pediatric to adult services requires communication between providers and is preferably done in a structured manner to avoid the risk of discontinuation of treatment.

Long-term consequences of delayed puberty

Bone mineralization

Initially, the findings in some studies of adult males with a history of CDGP suggested impaired peak bone mass [52]. However, bone accrual appeared to be normal when bone mineral density measurements were adjusted for bone age and stage of puberty [53], or volumetric bone mineral density was used [54]. While future studies are needed in order to clarify the impact of CDGP on bone mineralization, major deficits in peak bone mass do not appear to occur. In contrast, lack of sex steroid up to age 18 years [55] or inadequately treated CHH [56] clearly impair bone mineralization.

Psychosocial issues

The impact of delayed puberty and the effect of medical treatment on psychosocial well-being have been poorly characterized despite the importance of this aspect. However, males with CDGP may be at risk of impaired social functioning [57]. Controversial results have been published on the effects of low-dose androgen treatment on psychosocial issues in subjects with CDGP; it may improve specific domains of self-perceived competence [28]. In patients with permanent HH, late diagnosis and delay in starting sex steroid treatment appear to be associated with adverse psychological effects [58].

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