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Constitutional delay of puberty versus congenital hypogonadotropic hypogonadism: Genetics, management and updates

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Delayed puberty (DP) affects approximately 2% of adolescents. In the vast majority of patients in both sexes, it is due to constitutional delay of growth and puberty (CDGP), a self-limited condition in which puberty starts later than usual but progresses normally. However, some CDGP patients may benefit from medical intervention with low-dose sex steroids or peroral aromatase inhibitor letrozole (only for boys). Other causes of DP include permanent hypogonadotropic hypogonadism, functional hypogonadotropic hypogonadism (due to chronic diseases and conditions), and gonadal failure. In this review we discuss these themes along with the latest achievements in the field of puberty research, and include a brief synopsis on the differential diagnosis and management of patients with CDGP and congenital hypogonadotropic hypogonadism.

Physiology of puberty: a brief overview

Puberty is one of the most astonishing periods of human life, when significant physical alterations occur along with psychosocial maturation. The mechanisms governing the timing of puberty are not

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completely understood, although factors such as general health, nutrition, genetic factors, endocrine-disrupting environmental chemicals and environmental cues including societal changes all play a role [1]. The apparent plasticity of puberty timing and the importance of environmental factors in this process is exemplified by the shift of the age at menarche in Europe during the last two centuries from approximately 17.5 years to 12.5–13 years [2]. A shift towards an earlier age of breast development in Copenhagen area during the last few decades has been reported, which is a phenomenon speculated to reflect the impact of endocrine-disrupting chemicals [3]. In Copenhagen area, boys entered puberty 3 months earlier in 2006 compared to the findings 15 years earlier, a finding which, unlike in girls, disappeared after adjustment for BMI [4].

The most important physiological changes of puberty include the attainment of adult height, the initiation of spermatogenesis and menstrual cycles, and the development of secondary sex characteristics. These changes are accompanied by peak bone mass accrual, and are all brought about by the reactivation of the hypothalamic-pituitary-gonadal (HPG) axis, a functional unit that is comprised of gonadotropin-releasing hormone (GnRH) pulse generator, gonadotrope cells in the pituitary and the gonads. The current view is that KNDy neurons (which co-express kisspeptin, neurokinin Bm and dynorphin) in the arcuate nucleus form the GnRH pulse generator in males and females [5]. The HPG axis is active already *in utero*, and it re-activates during the minipuberty of infancy (see below), and, thereafter, remains largely quiescent due to central inhibitory signals until gradual loosening of the inhibitory signals on GnRH secretion and reawakening of the HPG axis in puberty [6].

Delayed puberty

The delay in the onset of puberty has been traditionally defined as the absence of testis enlargement or breast development at an age that is 2–2.5 SDS later than the population mean. In practice, Tanner stage G2 in boys should be achieved by the age of 14 years and B2 stage in girls by the age of 13 years [7]. It is important to note that these definitions, while useful and highly recommended for clinical practice, do not take into account the rate of puberty progression. Puberty nomograms (Fig. 1), available for girls and boys, have attempted to overcome this, and may be of additional help in defining normal and abnormal puberty timing [8,9]. It is also of particular note that the nomograms presented in Fig. 1 are based on Danish adolescents, and do not account for ethnicity and the family background in puberty timing. According to two large patient series, the most frequent cause for delayed puberty (DP) in both sexes is self-limited constitutional delay of growth and puberty (CDGP), which accounts for the vast majority of cases (Table 1) [10,11]. The remaining three main etiological categories are functional hypogonadotropic hypogonadism (FHH; largely attributed to chronic diseases and conditions), hypergonadotropic hypogonadism (Hyper H) (i.e. gonadal failure) and permanent hypogonadotropic hypogonadism (PHH). The comparison of the distribution of these entities in the two above-mentioned large studies is shown in Table 1.

Constitutional delay of growth and puberty (CDGP)

As already mentioned, self-limited CDGP is by far the most frequent cause of DP in both sexes, and for an unknown reason, is more commonly encountered in boys than in girls (Table 1). By definition, CDGP is a diagnosis of exclusion, and once puberty in these patients has started, it will progress normally and should be completed by the age of 18 years. However, DP in an otherwise healthy child may cause significant psychosocial burden, and some patients may benefit from medical intervention that will promote sexual maturation (see below).

Functional hypogonadotropic hypogonadism (FHH)

This is a broad category of diseases and (often chronic) conditions, and explains 16–20% of cases in boys and girls (Table 1); Table 1 also summarizes the most common causes of FHH in both sexes [10,11]. It is remarkable that conditions related to negative energy balance (*i.e.* poor nutrition and anorexia nervosa) constituted approximately one third of the FHH patients in girls, whereas CNS disorders were

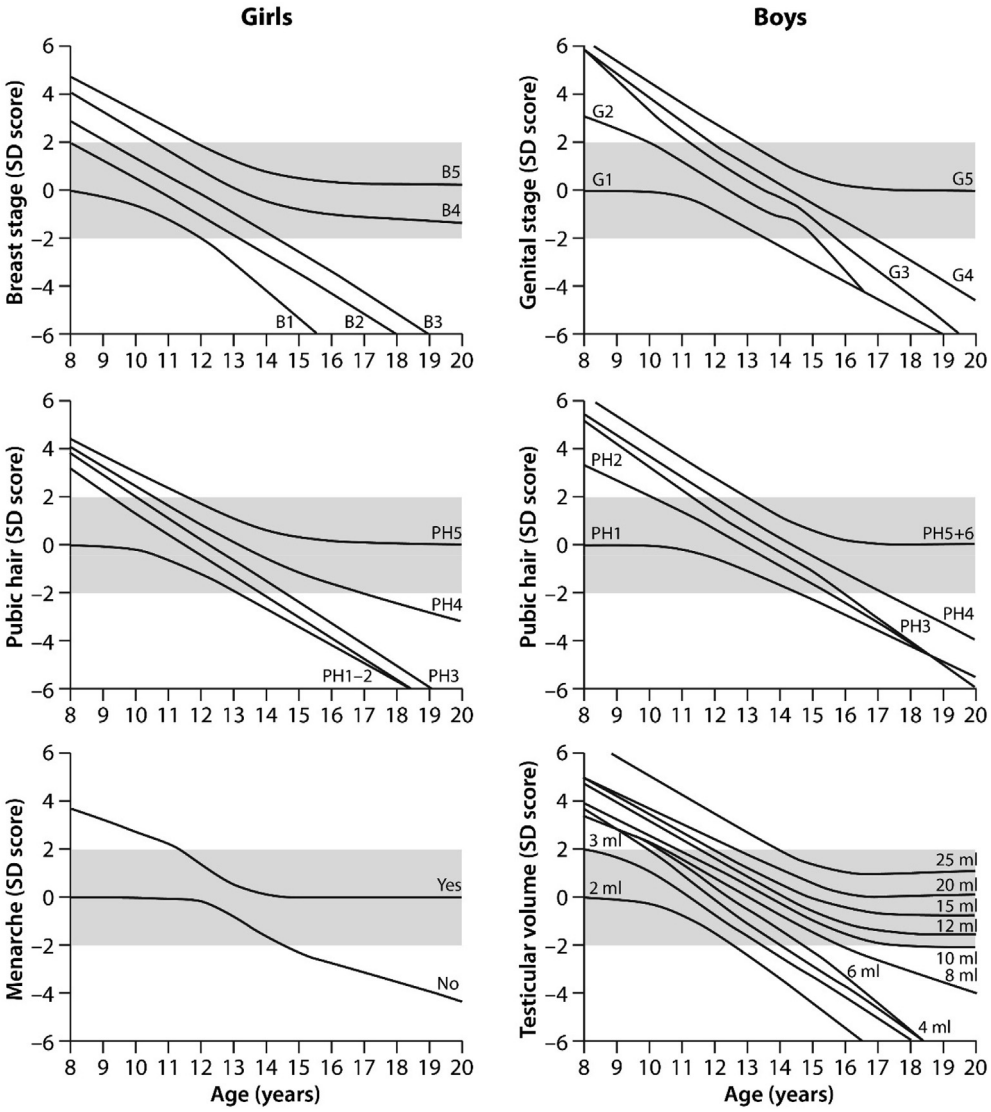

Fig. 1. Puberty nomograms for girls and boys. Age-specific SD scores for Tanner breast and pubic hair stages, and menarche (*left panel*) in girls, and puberty nomogram for Tanner stages and testicular volume in boys (*right panel*). Re-drawn from references [8,9]. The shaded area represents the mean ± 2 SD.

the most common cause in boys (Table 1). Examples of other causes of DP in boys include growth hormone deficiency and Crohn's disease (both 11%), and intense exercise in girls (6%) [10,11].

Hypergonadotropic hypogonadism (Hyper H)

Gonadal failure as a cause of DP is a relatively frequent cause of DP in girls (21%), but clearly more seldom encountered in boys (4%) (Table 1). In girls, approximately one quarter of patients in this category is attributable to Turner syndrome (Table 1).

Permanent hypogonadotropic hypogonadism (PHH)

This entity contains organic causes, syndromic causes, hypopituitarism of any cause, iatrogenic forms, hypophysitis and isolated forms of hypogonadotropic hypogonadism [10,11]. For the interested readers, the terminology related to isolated congenital hypogonadotropic hypogonadism is reviewed elsewhere in detail [6]. In this review, the term congenital hypogonadotropic hypogonadism (CHH) refers to gonadotropin deficiency which can be of hypothalamic or pituitary origin, but for the sake of brevity, gonadotropin deficiency as a part of combined pituitary hormone deficiency is not covered. PHH explained 8% of DP patients in boys and 15% in girls (Table 1), CHH being the most frequent cause in both sexes (Table 1). When CHH is accompanied by anosmia (absence of the sense of smell) or hyposmia, it is called Kallmann syndrome (KS) (see below). In the presence of intact sense of smell and CHH, the condition is referred to as normosmic CHH (nCHH). The frequency of CHH (nCHH and KS) among patients with PHH, ranged from 24% to 85% [10,11]. The estimates for CHH frequency at population level are relatively scarce, and, in males, range for KS is from 1:10,000 to 1:86,000 [12–14]; the prevalence of KS in females in Finland was shown to be 1:125,000 [14]. The prevalence estimates of nCHH are scarce.

It is noteworthy that the clinical spectrum of CHH is highly variable ranging from complete gonadotropin deficiency (cryptorchidism and microphallus as surrogate markers of profound gonadotropin deficiency) to partial puberty variants, fertile eunuch variants, and reversal of CHH [6,15–17], a phenomenon attributed to kisspeptin responsiveness [18]. Similarly to males, the phenotypic spectrum of CHH in females is wide, as 10% have menarche, half exhibit thelarche, and 88% pubarche [19]. Differentiating CHH, especially its partial form, from CDGP is very challenging and sometimes even impossible [6,20].

Genetics of normal and delayed puberty

The timing of puberty is a highly polygenic trait. Based on a relatively large epidemiological study, 57% of the variation in the age at menarche was attributed to additive genetic factors [21]. By using twin modeling and the timing of pubertal growth spurt as a marker of puberty timing, Wehkalampi et al. reported that >80% of pubertal timing was attributed to additive genetic factors in both sexes [22]. In the largest genome-wide association study (GWAS) (~370,000 women) to date, Day et al. reported 389 independent genome-wide signals that were associated with the timing of menarche, and which explained ~7.4% of the variation in the age at menarche in an independent replication study of 39,543 females [23]. The proportion of the genome-wide heritability (estimated by dividing the variance explained by the index SNPs by the total variance explained by all genotyped SNPs across the genome) for the age at menarche was ~25% [23]. Imprinted genes were enriched among the age at menarche-associated variants [23], and as such, paternally-inherited mutations in two such genes (*MKRN3* and *DLK1*) have been described in patients with precocious puberty giving further credence on the importance of this theme in the regulation of puberty timing [24–26]. Interestingly, circulating levels of MKRN3 may also have some implications in the assessment of the HPG axis activity, since the levels decrease in girls and boys prior to the onset of puberty [27–29]. However, the clinical usefulness of this marker is questionable, since the circulating levels are highly variable and some children have undetectably low levels, and, besides, the source of circulating MKRN3 is unknown [28]. Moreover, serum MKRN3 levels in adult men with HH did not differ from those of healthy controls [30].

In men, reliable retrospective timing of puberty is challenging due to the lack of a single memorable milestone which could be recalled with an acceptable accuracy, although voice break has been such a marker [31]. Therefore, longitudinal studies based on serial assessment of male puberty (Tanner stages and testicular volume) are of particular interest. Busch et al. reported that the SNP rs10835638 upstream of the *FSHB* gene was associated with the onset of puberty (testis volume 4 ml) in boys following statistical adjustment of BMI; in the GWAS study by Day et al. this SNP just slightly exceeded the adjusted significance limit for genome-wide signals implicated in puberty-timing (age at menarche) [23,32]. A genetic model of reduced FSH action, resulting from variation in the SNP

Table 1
Combined distributions of patients referred to two centers [10,11] for evaluation of delayed puberty (DP). There were data on 156 boys and 70 girls from the study by Sedlmeyer et al. [10] after exclusion of two boys and four girls due to unclassified etiology of DP, and 174 boys and 70 girls from the Finnish study by Varimo et al. [11]. Number of patients (%) in each group is shown along with the most common causes for functional hypogonadotropic hypogonadism (FHH), permanent hypogonadotropic hypogonadism (PHH), and hypergonadotropic hypogonadism (Hyper H). CDGP, constitutional delay of growth and puberty.

	Boys	Girls
CDGP	242/330 (73%)	61/140 (43%)
FHH	47/330 (16%)	28/140 (20%)
	- CNS disorder: 6/47 (13%)	- poor nutrition: 6/28 (21%)
	- growth hormone deficiency: 5/47 (11%)	- anorexia nervosa: 4/28 (14%)
Hyper H	14/330 (4%)	30/140 (21%)
	- syndromes: 10/14 (71%)	- Turner syndrome: 8/30 (27%)
		- idiopathic ovarian failure: 7/30 (23%)
PHH	27/330 (8%)	21/140 (15%)
	- CHH: 14/27 (56%)	- CHH: 8/21 (38%)
	- syndromes: 6/27 (22%)	- CNS tumors: 6/21 (29%)
	- CNS tumors: 5/27 (19%)	

CDGP, constitutional delay of growth and puberty.
FHH, functional hypogonadotropic hypogonadism.
PHH, permanent hypogonadotropic hypogonadism.
HyperH, hypergonadotropic hypogonadism.

genotypes in the *FSHB* and *FSHR* promoter regions, has been suggested to explain 1.5–1.7% of the variance in the age at puberty onset in boys [32].

Clinical entities such as CDGP, CHH (with or without a defect in the sense of smell), patients with hypothalamic amenorrhea, adult-onset of HH and reversal of CHH are often considered to belong to the same entity of patients with variable manifestation of gonadotropin deficiency. For example, rare sequence variants implicated in CHH are present in women with hypothalamic amenorrhea, and in adolescents and young adults with signs of partial gonadotropin deficiency, and biallelic partial loss-of-function *GNRHR* mutations have been found in patients with delayed or stalled puberty [33–35]. There is a clear genetic component in CDGP, however, as up to 80% of patients with CDGP have a first degree relative with DP [36]. On the other hand, although one of the strongest GWAS signals for the timing of puberty arises from near and within *LIN28B*, mutations in this gene have not been encountered in CDGP patients [37]. Howard et al. identified recently with exome sequencing in Finnish CDGP index patients likely pathogenic variants underlying CDGP phenotype in (i) fat mass and obesity-associated (*FTO*) gene (in three of 67 families) [38]; (ii) Heparan Sulfate 6-O-Sulfotransferase 1 (*HS6ST1)* gene (in one in 67 families) [39]; and (iii) enhanced at puberty 1 (*EAP1*) gene (in two in 67 families) [40]. The fourth relevant genetic finding related to CDGP was published in 2016, when Howard et al. described that rare sequence variants in *IGSF10,* a gene which encodes a protein that belongs to the immunoglobulin superfamily, underlay CDGP in six Finnish families [41]. In rats, *Igsf10* (a.k.a. calvaria mechanical force protein 608, encoded by *Cmf608*) is a marker of early osteochondroprogenitor cells, and has been proposed to regulate the differentiation of these cells into more mature cell types [42]. The role of *IGFS10* in DP remains open, as in a follow-up study, *IGSF10* mutations were not reported to be enriched in CHH or CDGP patients when compared to controls [43].

The past, current and future strategies to identify genes implicated in CHH have been recently reviewed in depth [44]. The latest estimate of the number of main genes implicated in CHH is 35–40 [45–47]; it is noteworthy, however, that the degree of evidence of these genes being causative for CHH is variable (Stamou et al., 2016) [44]. Recently, Francou et al. reported a comprehensive molecular genetic analysis of a large cohort (n = 603) of homogenous nCHH patients in a French center [48]. The analyzed patients harbored biallelic mutations (the combined prevalence of mono- and biallelic mutations is given in parentheses) in the following order: *GNRHR*, 3% (4.7%); TACR3 1.5% (3.6%), *KISS1R*, 1.3% (2.0%), *TAC3*, 0.5% (1.0%), *GNRH1*, 0.2% (1.5%), and KISS1 0% [48]. Interestingly, four of the five males with biallelic loss-of-function mutations in *KISS1R* had a high frequency of micropenis, which suggests that kisspeptin signaling is important for gonadotropin secretion early in development [48]. These

relatively low numbers of "known" genetic etiology for nCHH suggests a significant role of other genes underlying this entity.

The connection between the sense of smell and the reproductive function is related to the complex ontogeny of GnRH neurons. These cells are originally formed outside the CNS, in paired structures called olfactory placodes, which provide the putative neurogenic niche and appropriate signals for the development of these cells (young et al., 2019 endo rev) [6]. Taking advantage of this information, Lund et al. were the first to model GnRH decapeptide-secreting neurons from human pluripotent stem cells [49]. *In vivo*, GnRH neurons migrate from the olfactory placode (OP) area to the hypothalamus by using the vomeronasal nerve and olfactory nerve as guides [50]. In Kallmann syndrome, a clinically and genetically heterogeneous disease, this process is disrupted, which explains the unexpected relationship between olfaction and reproduction [6]. The first gene implicated in the etiology of KS was X-chromosomal *KAL1* (now *ANOS1*) [51], a gene that encodes FN3 domain-containing protein, anosmin-1, a branching factor and chemoattractant for lateral olfactory tract axons in the rat [52]. Subsequently, loss-of-function mutations in *FGFR1* were demonstrated to underlie autosomal dominant KS [53]. The evolving story of the identification of other KS-causing genes has been recently reviewed [44,45]. Although animal studies suggest that lack of certain miRNAs lead to HH, the first study on this topic did not report mutations in *MIR7-3*, *MIR141*, *MIR429* and *MIR200A* in 24 CHH patients [54].

Recently, Cassatella et al. reported the genetic landscapes of CHH and CDGP patients by reporting exome sequencing results [43]. Overall, they demonstrated that 51% of the CHH patients carried a mutation in at least one CHH gene, which was clearly a higher proportion than was observed in patients with CDGP (7%) [43]. Indeed, the next generation sequencing methods have not only revolutionized novel disease gene identification, but also posed clinical geneticists into a challenging position since even up to 15% of CHH cases may be explained by oligogenic inheritance [43], and thus the traditional forms of Mendelian inheritance are not always easy to apply [45].

Diagnostic pathway

The diagnostic pathway of a patient with DP starts from thorough medical history. A useful concept of using "red flags", *i.e.* cues pointing towards a certain diagnosis or diagnostic subgroup (CDGP, FHH, PHH or HyperH) has been recently introduced (Tables 2A and 2B) [55]. It should be noted that this approach is based on extensive clinical experience and has not yet been prospectively validated. Recent advancements in this field include the finding that history of cryptorchidism was associated with an increased risk for permanent hypogonadism (*i.e.* Hyper H or PHH), and was thus more frequent in these

Table 2A
Red flags on history and associated etiologies in patients presenting with delayed puberty. Adapted from Abitbol et al. [55], and Varimo et al. [11].

History	Possible underlying aetiology
Abdominal pain, constipation, diarrhoea, haematochezia	Inflammatory bowel disease, diarrhoea, coeliac disease
Weight gain, cold intolerance, fatigue	Hypothyroidism
Weight loss, heat intolerance, insomnia	Hyperthyroidism
Excessive exercise, food restriction	Anorexia nervosa
History of chemotherapy, radiation or testicular trauma	Acquired hypergonadotropic hypogonadism
Cryptorchidism, micropenis	Permanent hypogonadism
Visual disturbance, intellectual disability, seizures, congenital midline defects	Congenital syndrome (e.g. septo-optic dysplasia)
Headaches, visual changes, seizures	Acquired central nervous system disease such as a brain tumor
Abnormal sense of smell	Kallmann syndrome
Dysmorphic features	Syndromic form of congenital hypogonadotropic hypogonadism (CHARGE)
Family history of delayed puberty	Constitutional delay of growth and puberty, congenital hypogonadotropic hypogonadism
Family history of chronic diseases	Evaluate individually

Table 2B
Examples of the findings in physical examination and associated etiologies in patients presenting with DP. Adapted from Young et al. [6], Varimo et al. [11], and Abitbol et al. [20].

Physical examination	Possible underlying aetiology
Low height growth velocity	Growth hormone deficiency, multiple pituitary hormone deficiency
Low weight for height, dental changes	Anorexia, ortorexia, excessive exercise
Low weight for height with exophthalmos, sweaty skin, tremor, hypertension, goitre	Hyperthyroidism
Increased weight for height with dry skin, dry hair, bradycardia, goitre	Hypothyroidism
Low weight for height, pallor, abdominal distention or tenderness	Coeliac disease, inflammatory bowel disease
Visual field abnormalities, abnormal neurological exam	Congenital or acquired central nervous system disease
Midline defects (e.g. cleft lip and/or palate, congenital heart disease), dysmorphic features (e.g. hypertelorism, webbed neck)	Congenital syndrome (e.g. septo-optic dysplasia, Turner's syndrome)
Small testis size	Hypogonadotropic hypogonadism
Abnormal sense of smell	Congenital hypogonadotropic hypogonadism
Missing teeth	
Pigmentation defects	
Hearing loss	
Split hand/foot malformation	
Cleft lip/palate	
Findings suggesting CHARGE syndrome (Coloboma, Heart defect, Atresia Choanae, Retardation of growth and development, Genital anomalies, Ear anomalies)	
Bimanual synkinesis (involuntary movement of upper limbs)	

patient groups than in those with FHH or CDGP [11]. Similarly, a history of cryptorchidism was more frequent in CHH patients than in those with CDGP (36% vs 2%, respectively). In contrast, a boy with normally descended testes and a positive family history of DP had very low probability of HyperH of PHH [11]. Additional set of red flags comes from the clinical features of patients with CHH (Table 2B) [6,20,56]. It has been suggested that growth velocity would be helpful in the differential diagnosis of DP [7]. Indeed, annual growth velocity (GV) in boys with FHH (3.2 ± 1.3 cm/yr) was smaller than in boys with CHH or CDGP (4.1 ± 1.7 cm/yr) ($P < 0.05$); the best cut-off growth velocity was 3.6 cm/yr with a sensitivity of 71% and specificity of 64% in differentiating boys with CHH or CDGP from those with FHH; in girls, the value of GV was inferior to boys [11].

The initial diagnostic approach towards a patient with DP has been described recently in detail [6,55], and presented in Fig. 2. The process starts with verifying the presence or absence of DP (lack of testicular enlargement by the age of 14 yrs, absent breast development by the age of 13 yrs in girls), preferably by using the puberty nomogram (Fig. 1). Thorough clinical history should cover the red flag questions presented in Table 2A, and similar red flag physical findings should be sought after in the clinical examination Table 2B. Full clinical examination should include also assessment of the sense of smell, preferably with a validated method, and a verification of the presence or absence of split hand-foot deformity (suggestive of an *FGFR1* mutation) [57], and assessment of bone age [6,55]. In the absence of red flag findings, and especially in the presence of a positive family history for DP, the diagnosis of CDGP is probable and broad untargeted biochemical testing is usually unnecessary [55]. In the presence of early stigmata of complete CHH (such as bilateral cryptorchidism and/or micropenis), especially if the patient has anosmia or a syndromic form of CHH (such as CHARGE syndrome *etc.*) or phenotypic cues listed in Table 2B, the differentiation of CDGP from CHH can be relatively straightforward. It is of particular note that the minipuberty of infancy, *i.e.* transient activation of the HPG axis during the first months of life [58], offers a window of opportunity for establishing an early diagnosis of CHH [59,60]. This holds true especially in boys, whereas for infant girls such early markers of gonadotropin deficiency have not been identified.

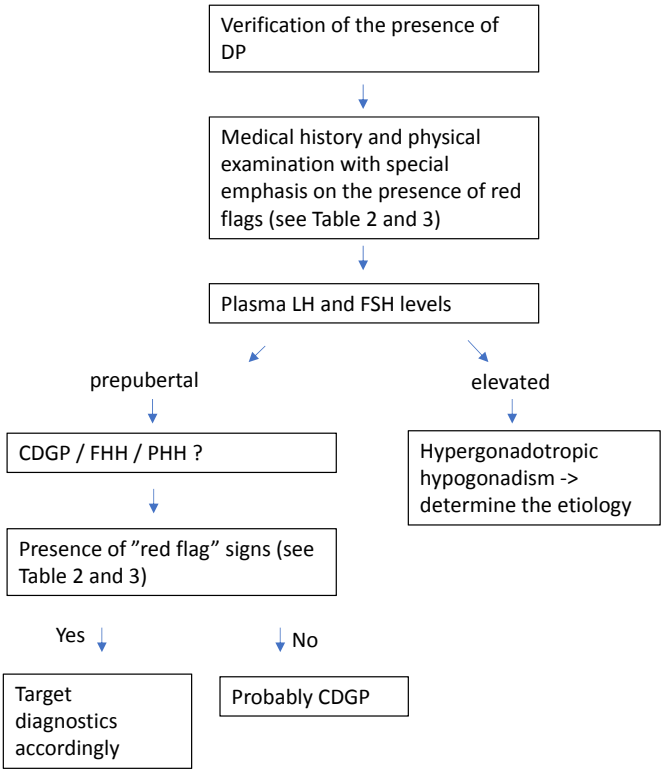

Fig. 2. Approach to a patient with delayed puberty (DP). Adapted from Young et al. [6], and Abitbol et al. [55].

Review of the endocrine tests and their performance has been described in detail by Harrington & Palmert in 2012 [61]. In brief, suggested endocrine tests include measurement of circulating Sertoli cell markers inhibin B and AMH, hCG stimulation test (with different doses and administration and sampling times), GnRH stimulation test (with GnRH or more powerful GnRH analogs), LH sampling and urine gonadotropin excretion [61]. Many of these tests are costly and none of them allows differentiation of CHH from CDGP with 100% sensitivity and specificity, especially in the case of partial CHH [6,20,61]. Since the evaluation of each test separately is beyond the scope of this review, we only discuss the latest development in the field of differential diagnostics between CHH and CDGP. Coutant et al. proposed that a single measurement of inhibin B less than 35 ng/l would differentiate prepubertal CDGP boys from those with CHH with 100% sensitivity and specificity [62]. In the Finnish series of prepubertal boys with DP, the odds ratio of this cut off value to detect CHH in the prepubertal boys with DP was 10.0 (95% CI: 2.16–46.3, $P < 0.01$), but 40% of CHH boys had higher inhibin B levels and 7% of CDGP boys had inhibin B below this value [11]. Another concern of single point measurements is the variable performance of the inhibin B assay at low analyte concentrations. One approach to circumvent this was introduced by Varimo et al. [11], who modelled the risk of CHH by taking into account the testis size (a surrogate of prepubertal Sertoli cell number) [63], and the performance of the inhibin B assay. The results showed that very small testis size (<1 ml) in combination with inhibin B of 10–49 ng/l conveyed the highest mean risk for CHH (90%; range 50–100%), whereas the risk appeared tremendously smaller in those with larger testes (1.1–2 ml) accompanied by inhibin B levels between 111 and 212 ng (risk estimate for CHH, 0–10%) [11]. Very recently Chan et al. reported that single intravenous bolus of kisspeptin to 14.1–17.8 yr-old patients (11 boys and four girls) with delayed/stalled puberty elicited heterogenous LH responses (surrogate of GnRH secretion) [64]. Given that kisspeptin does not induce LH secretion in adult patients with CHH, it will be of high interest to learn

whether kisspeptin administration to pediatric patients will help in differentiating CDGP patients from those with partial forms of CHH [64]. In conclusion, even in 2019 the differential diagnosis of CHH from CDGP is not always possible, and thus, in some patients, only the completion of puberty by the age of 18 years will solve this important differential diagnostic question.

Management of delayed puberty

Treatment of constitutional delay of growth and puberty

For many subjects with CDGP, reassurance and watchful waiting are the only required undertakings. However, when the adolescent feels psychosocial stress, negative interactions with peers, anxiety or depression, medical intervention and psychological counseling should be considered. Interestingly, only few well-designed trials have been published on the topic on boys and even less on girls. Recently, Varimo et al. published a controlled prospective multicenter trial comparing aromatase inhibitor letrozole (Lz) and low-dose intramuscular testosterone (T) in the treatment of boys with CDGP and the very first signs of puberty [65]. The results showed that 2.5 mg of Lz perorally for six months induced HPG axis and faster testicular growth than low-dose T; both treatments accelerated height growth (testosterone slightly more than Lz), and were well-tolerated [65]. These results suggest that peroral aromatase inhibitor Lz activates the HPG axis, and can be used as a novel treatment modality for boys with CDGP. Treatment options for boys with CDGP are shown in Table 3. Gonadotropins or GnRH are not recommended for the treatment of CDGP (Dunkel & Palmert NEJM 2012) [7]. For girls presenting with CDGP, there are four options for the induction of puberty *i.e.* oral ethinylestradiol, and oral and transdermal/gel form of 17β-oestradiol (Table 3). Only sparse clinical studies exist on the topic and the drug of choice varies between pediatric units. According to Matthews et al. (ADC 2017), however, "transdermal 17β-oestradiol has the most favourable efficacy, safety and cost profile." [66].

In boys and girls with CDGP, a follow-up appointment is recommended after 6 months of therapy or watchful waiting to ensure that puberty has progressed (testicular growth in boys, breast development in girls). In equivocal situations, it is possible to monitor biochemical progression of puberty by measuring serum gonadotropin, inhibin B and sex steroid levels from a morning blood sample. In those who fail to show any activation of the HPG axis and progression of the puberty, second-line investigations for the etiology of delayed puberty should be started [7]. Cessation of sex steroid treatment is often needed for a reliable evaluation of the HPG axis.

Treatment of hypogonadotropic hypogonadism

Management of CHH in males and females has been recently thoroughly reviewed [6]. In principle, the initial goals of treatment in patients with CHH are the same as in CDGP, but, in addition, concerns of future fertility and sexual function need to be addressed. Therefore gonadotropins and GnRH treatments are additional realistic options for patients with CHH. In boys, prepubertally administered recombinant FSH Rx, which aims at increasing the number of Sertoli cells and thereby improve future sperm-producing capacity, has been discussed in detail [6,63,67,68]. Also other gonadotropin protocols for the induction of puberty have been employed [69–71], and in specialized centers puberty in CHH boys may even be induced with pulsatile GnRH [72]. There is also great interest towards the treatment of CHH in boys during infancy [73]. The expected long-term benefits of this treatment require further studies, and very recently Kohva et al. reported the long-term data on five gonadotropin-deficient boys treated with recombinant FSH and testosterone in infancy [74]. The results showed that recFSH treatment given in infancy was not associated with a permanent increase in inhibin B.

When puberty is induced with sex steroids, gradual increase in sex steroid replacement dosing and addition of progestin in girls are required during the course of puberty [66]. Adult doses are

Table 3
Treatment of constitutional delay of growth and puberty and congenital hypogonadotropic hypogonadism. Adapted from Young et al. [6], Dunkel & Palmert [7], Varimo et al. [65], and Matthews et al. [66].

Treatment	Dosing & administration	Comments
Short-term treatment of CDGP in boys		
Testosterone enanthate (TE)	1 mg/kg, usually 50 mg i.m. monthly for 6 months (different protocols exist)	Promotes androgenic signs of puberty. Misdosing may lead to premature epiphyseal closure. Not to be used before bone age 10 years.
Letrozole (LZ)	2.5 mg p.o., daily for 6 months	Activates HPG axis and testis growth. No risk for premature epiphyseal closure. Effective in boys with first signs of puberty. Limited long-term experience.
Short-term treatment of CDGP in girls		
17-β-oestradiol (oestradiol hemihydrate) gel (0.6 mg/g)	(0.5-) 1 cm gel on skin daily (equivalent to 10 ug 17-β-oestradiol patch/24hr; or 0.2 mg 17-β-oestradiol p.o; or 2 ug ethinyl estradiol p.o)	Promotes estrogenic pubertal signs (e.g. breast development, and growth acceleration) and may induce bone maturation. No large studies.Bypasses first-pass hepatic metabolism
17-β-oestradiol (oestradiol valerate) patch (25 ug)	¼ patch once/twice weekly	Promotes estrogenic pubertal signs (e.g. breast development, and growth acceleration) and may induce bone maturation. Bypasses first-pass hepatic metabolism
17-β-oestradiol (oestradiol valerate) p.o	0.25–0.5 mg daily	Promotes estrogenic pubertal signs (e.g. breast development, and growth acceleration) and may induce bone maturation. Submitted to first-pass hepatic metabolism May increase lipid levels and blood pressure
Ethinyl estradiol (EE2) p.o	1-2 ug once daily for 6 months	See above
Induction of puberty in CHH boys		
Testosterone enanthate	Initial dose: 1 mg/kg; often 50 mg i.m. monthly Increase (25)-50 mg every 6–12 months, up to 250 mg per 3–4 weeks (or testosterone undecanoate 1000 mg i.m. every 10–14 weeks in adult males)	Standard care with long clinical experience Possible premature epiphyseal closure (with high doses)
Gonadotropins	hCG: initial dose 250–500 IU once/ twice weekly, s.c. Increase 250–500 IU every 6 months Up to 1500 IU 3 times weekly rFSH: initial dose 50 IU three times weekly then 75–150 IU three times weekly, s.c.	Stimulates testis growth & spermatogenesis Pre-rFSH treatment can be beneficial in patients with TV < 4 ml or history cryptorchidism Needs good compliance in adolescent patients and studies in larger cohorts
Induction of puberty in CHH girls		
17-β-oestradiol (oestradiol hemihydrate) gel (0.6 mg/g)	Initiation as in CDGP. Increase gel up to 5 cm (equivalent to 50 ug patch or 10 ug EE2 p.o) during 24 months, then adult combined oral contraceptive pill or hormone replacement therapy	See above
17-β-oestradiol (oestradiol valerate) patch (25 ug) or tablet p.o.	Initiation as in CDGP. Increase up to 25–50 ug transdermal patch twice weekly or 0.25 mg tablet up to 1 mg p.o. daily during 24 months, then adult combined oral contraceptive pill or hormone replacement therapy	See above

Table 3 (*continued*)

Treatment	Dosing & administration	Comments
Ethinyl estradiol (EE2) p.o.	Increase from 1 to 2 ug to 10 ug during 24 months, then adult combined oral contraceptive pill or hormone replacement therapy	See above
Progesterone p.o.	Various forms; usually added after 2–3 of estrogen treatment years or when breakthrough bleeding occurs	Used in 10–14 day blocks in 1–3 months intervals.Can be replaced by adult combined oral contraceptive pill or hormone replacement therapy.

usually reached within 3 years of treatment, depending on the age at initiation and desired tempo of pubertal progression [6]. Those with permanent HH and hormone replacement therapy should be followed up at least 6 month intervals. During these visits, their sex steroid treatment doses should be adjusted based on clinical and biochemical signs of pubertal progression. Uterine ultrasound scan is useful for optimizing the timing of progesterone to girls. Transition from pediatric to adult services requires communication between providers and preferably is done in a structured manner, otherwise there may be a risk of discontinuation of treatment. Finally, it should be noted that the reversal of CHH (i.e. recovery of gonadotropin secretion often following exposure to sex steroids) occurs in 10–15% of CHH men [17], and the estimated lifetime-incide may be as high as 22% [15]. A useful clinical sign suggesting reversal of CHH is an increase in testicular size while on testosterone Rx.

Delayed puberty: what do we know about long-term consequences?

Timing of puberty and long-term associations have intrigued researchers for decades. In 2015, Day and coauthors published a large UK biobank study that reported associations of puberty timing with health outcomes in 197,714 males and in 250,037 women (age range 40–69 years) [75]. In linear models, age at menarche was associated with 26 adverse health outcomes such as type 2 DM, obesity, and breast cancer. In categorical late menarche models, following adjustment for potential confounding by available 'SEP'-related variables (alcohol intake; education – eight dummy variables for different levels of qualification, maternal smoking, reported income level, smoking, Townsend index of deprivation) and adiposity/body composition, eight associations remained significant: increased risk for early natural menopause, malabsorption/coeliac disease, low intelligence, asthma, poor overall health, poor sleep, and reduced risk for obesity and short stature [75]. In males, the corresponding associations with delayed puberty were anxiety/panic attacks, depression, asthma, eczema, poor

Practise points

- Constitutional delay of growth and puberty (CDGP) is the most common cause of delayed puberty in both sexes. Other causes (FHH, PHH, and HyperH) each explain ~4–20% of cases each.
- Timing of puberty is a highly inherited trait. The significant signals identified in the largest GWAS study to date were able to explain <10% of the variance in the age at menarche.
- Differential diagnosis between CDGP and CHH can be notoriously difficult, and there is not a single test that could differentiate between all forms of CHH from CDGP.
- Peroral letrozole offers a new modality for the treatment of CDGP in boys with the first signs of puberty.

Research agenda

- High-quality research is required to address long-term consequences of treatments used for the induction of puberty in CDGP patients.
- The efficacy of the recombinant FSH pre-treatment in the induction of puberty and spermatogenesis in boys with CHH should be assessed in a large prospective randomized, controlled study.

overall health and a reduced risk for obesity [75]. Finally, in a recent review on self-limited delayed puberty, Zhu and Chan summarize that (i) in some patients, adult height may be reduced; (ii) late menarche is associated to decreased BMD in early adulthood and in both sexes late puberty is associated with increased fracture risk; (iii) late puberty was protective for breast cancer and possible also for testicular cancer; and (iv) both early and late puberty timing are associated with an increased cardiovascular risk [76].

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