Minerva Pediatrica
EDIZIONI MINERVA MEDICA

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Journal: Minerva Pediatrica
Paper code: Minerva Pediatr-5860
Submission date: April 2, 2020
Article type: Review Article

Files:

1. Manuscript
   Version: 1
   Description: Manuscript
   File format: application/vnd.openxmlformats-officedocument.wordprocessingml.document

2. Figures 1
   Version: 1
   Description: Figure 1
   File format: application/pdf

Pubertal Delay. The challenge of a timely differential diagnosis between Congenital Hypogonadotropic Hypogonadism (CHH) and Constitutional Delay of Growth and Puberty (CDGP): a narrative review.

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Keywords: idiopathic hypogonadotropic hypogonadism, GnRH deficiency, inhibin B, genetic, dynamic test

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ABSTRACT

Distinguishing between Constitutional Delay of Growth and Puberty (CDGP) and Congenital Hypogonadotropic Hypogonadism (CHH) may be challenging. CDGP and CHH appear to belong to the same clinical spectrum (with low sex hormones and low LH and FSH), although one is classically transient and known as a self-limited form of delayed puberty (CDGP) while the other is permanent (CHH). Thus, the clinical history and the outcomes of these two conditions require different approaches, and an adequate and timely management for the patients is mandatory. Since the initial presentation of CDGP and CHH is almost identical and given the similarities of CDGP and partial forms of CHH (i.e. patients with partial and early interrupted pubertal development) the scientific community has been struggling to find some diagnostic tests able to allow an accurate differential diagnosis between these two conditions in delayed puberty. In this review we provide an up to date insight on the tests available, their meanings and accuracy, as well as some clues to effectively differentiate between constitutional pubertal delay and pathologic CHH.

Delay of puberty

The process of puberty and its delay

Puberty is the transition period between childhood and adulthood in which each different stage is the result of the action of neuroendocrine factors that regulate the journey to sexual maturity through physical and hormonal changes. Pubertal development begins due to the spontaneous activation of the hypothalamus-pituitary-gonadal axis (HPG axis), which stimulates the gonads to produce sex steroids (testosterone in males, estrogen in females): this results in growth spurt and the appearance of secondary sexual characteristics, and the process culminates in the achieving of a complete sexual maturity. Physiological pubertal development encompasses a predictable and sequential series of stages, as illustrated by Tanner and Marshall[1]. Usually between the age of 8 and 13 years old in females, and the age of 9 and 14 years old in males, an increase of hypothalamic GnRH secretory pulses (quiescent during childhood) starts the process of puberty, stimulating the pituitary to secrete FSH and LH which, in turn, stimulate directly the gonads. First signs of the pubertal development are represented by the testicular enlargement (testicular volume >4mL) in male and the breast budding (thelarche) in female. The mechanisms involved in the timing of puberty are complex and currently not fully understood: what is known is that the onset of puberty is a multifactorial process in which diet, environment, genetic factors and even ethnicity play an important role [2].

Normally the HPG axis is active during fetal life, and for a short period of time after birth called "minipuberty". This is the only period of childhood in which FSH and LH levels are measurable. After this brief window of activation, the axis remains quiescent until the beginning of puberty [3,4].

The physical changes that characterize puberty include the development of secondary sex characteristics along with the achievement of adult height, the initiation of spermatogenesis in males and menstrual cycles in females; the testis enlargement in males (volume >4ml) and the appearance of breast buds in females, are the clinical signs marking the onset of puberty. On the contrary, the appearance of pubic and axillary hair, though usually simultaneous to these early events, is regulated

by the adrenal androgens, and, thus, its isolated advent should not be interpreted as the beginning of puberty [5,6].

Pubertal delay refers to the absence of the first signs of pubertal development beyond the normal expected age for the population (more than 2-2.5 standard deviation values above the mean of the reference population) or , when puberty has previously started, failure of proper progression. [7]. Since puberty is a delicate phase from the psychological point of view, it is understandable that a delay may have an important impact on the child. In fact, subjects with delayed puberty find themselves at great discomfort with their peers regarding both height and secondary sexual characteristics [4,8]

Causes of Delayed Puberty

Delay of puberty is a very common condition, and it includes a vast variety of causes. We can distinguish between the more frequent and transient form, represented by the constitutional delay of growth and puberty (CDGP) and the other rarer and usually permanent pathologic conditions, such as the primary and secondary hypogonadisms (Table 1).

Primary hypogonadism, also known as hypergonadotropic hypogonadism, refers to a gonadal disfunction, where the central compartment of the HPG axis activates normally but the gonads do not respond as expected. This condition can be diagnosed and differentiated from the other forms of pubertal delays through the medical history, the physical examination and particularly through both the hormone levels, characterized by low sex steroids and high gonadotropin levels and diagnostic imaging.

Secondary/central or hypogonadotropic hypogonadism includes hormonal disorders that may be due to either an organic (both structural and congenital defects) or functional (such as chronic illnesses or anorexia requiring nutritional rehabilitation) disease affecting either the pituitary and/or the hypothalamus. The most important organic form of secondary hypogonadism is represented by the Congenital Hypogonadotropic Hypogonadism (CHH), which can be either normosmic (nCHH) or associated with an olfactory defects in the so called Kallmann's Syndrome (KS) [9]. Etiopathogenesis of both forms is so far largely unknown, although a genetic background is strongly suggested. [10]

The CDGP refers to a benign, self-limited form of delayed puberty that usually represents an extreme of the normal spectrum of pubertal timing. It is the most common cause of pubertal delay, affecting 2-2.5% of the population and it is much more common in boys than girls [7]. The precise cause of CDGP is so far unknown. Nevertheless, the significant familial recurrence of this defect, which spans from 50 to 75%, is indicative of a strong genetic component. Although the inheritance of the CDGP is variable, an autosomal dominant pattern, in association with environmental modifiers, has been frequently observed, either with a complete or incomplete penetrance. So far, no specific causal gene has been identified to account for the majority of cases of CDGP.[11]Patients with CDGP may experience slower growth rate, which results in a lower final adult height [5,12], delayed sexual maturation and delayed skeletal age compared to peers. Usually, it is a condition associated with good prognosis and normal achievement of full puberty, with no effect on pubertal maturity.

Up to date, CDGP is a diagnosis of exclusion: pathologic causes of delay of puberty such as hypergonadotropic hypogonadism and either functional or organic hypogonadotropic hypogonadism must be excluded before considering a diagnosis of CDGP. However, the differential diagnosis between CDGP and CHH can be extremely challenging since related to distinguish at an early age which children need to be treated from those who will undergo through normal puberty spontaneously. Leaving the diagnosis for later in life, though easier, may have negative consequences on the final height, self-esteem and reproductive system of the subjects [13–17].

CHH vs CDGP

It is very hard to diagnose CDGP during initial evaluations. Both boys with CHH and boys with CDGP have the same clinical features, and most importantly they both have similar hormone level such as low levels of gonadotropins (FSH, LH) and sex steroids (testosterone in male and estradiol in female). Once ruled out systemic pathologies determining functional HH, the differential diagnosis between these two conditions is not straightforward.

There have been studies on the effectiveness of Sertoli cell markers or GnRH and hCG stimulation tests, but none of them has proven to be truly reliable [18–20]. If clinical features are a fundamental tool to identify subjects with high risk of CHH, a correct knowledge of the meaning and accuracy of the diagnostic tests available could improve the clinician effectiveness in an early diagnosis (or at least a suspicion) and a timely intervention.

Clinical features

Primarily, in order to diagnose a pubertal delay, an accurate medical history collection and a thorough physical examination are necessary. In males the testicular volume (which should be higher than 4 mL by the age of 14) should be measured using Prader's orchidometer [9,21,22].

Recently, some "cues" have been labeled as "red flags", indicating that the finding of these features might suggest a specific diagnosis or a diagnostic subgroup (CDGP, Functional Hypogonadotropic Hypogonadism -FHH-, CHH, Hypergonadotropic Hypogonadism) [7]. The abnormal sense of smell, for example, is knowingly linked to CHH in the abovementioned KS. Other hallmarks and symptoms of CHH that should be looked for include clefting of the palate and lips, hearing loss, alteration of digital bones, daltonism, nystagmus and bi-manual synkinesia [23–26]. Renal malformations are often seen in KS, so a renal ultrasound should be included to rule out renal disgenesis or agenesis.

Family history appears to be positive in both CDGP and CHH even with an overlap between the two conditions within the same family, so it cannot be considered a red flag (on the contrary, it makes the differential diagnosis even harder) [27,28]. Nevertheless, it is surely important to investigate concerning a familial recurrence for self-limited pubertal delays or CHH/KS, as well as other possible familial reports of either singular CHH-KS-related feature (i.e. anosmia, renal malformations, hearing loss, daltonism, etc..).

The presence of neonatal cryptorchidism (particularly the bilateral forms) and micropenis in male is an important finding to report in these patients. In fact, it can be explained by pre- and post-natal gonadotropin deficiency, and it is independent of olfactory disorders. Micropenis and cryptorchidism

might lead to an early diagnosis of CHH because they are neonatal features strongly suggesting a lack of minipuberty [6,29]. Evaluation of the specific hormonal tests (LH, FSH and sex steroids) performed in the first three-six months of life might eventually confirm the lack of minipuberty. On the other hand, after this specific neonatal temporal window, there are no more indication in performing any hormonal tests, due to the physiological reductions of gonadotropins: therefore, after the first 6 months CHH can only be suspected on the basis of micropenis and cryptorchidism, but it still needs to be confirmed [4,29,30]. Unfortunately, in the neonatal period, no specific signs might be searched for in CHH female patients, since they do not differentiate from the healthy subjects. Patients with CHH have normal stature growth during childhood, and the absence of long-bone epiphyseal closure explains these patients' frequent eunuchoid aspect and relative tallness; also, retarded bone maturation, osteopenia and osteoporosis are often found in these patients when the diagnosis is made later in life [31–34].

Other important findings in physical examination include low height, low BMI and low growth velocity which could point out functional forms of HH [22].

In the absence of these findings, and especially if there is a family history of constitutional delay of puberty, the most probable diagnosis is CDGP which would not necessitate further analyses [7].

However, the abovementioned congenital abnormalities are often not evident during childhood and the clinical features of GnRH deficiency become evident only at the time of puberty. Therefore it is much more common to reach a diagnosis during adolescence because of the signs and symptoms connected to the lack of puberty, such as eunuchoid body proportions (upper/lower body ratio less than 1 with an arm span 6 cm greater than standing height, reflecting the delayed closure of the epiphysis of long bones in the absence of gonadal steroids), high-pitched voice and prepubertal testes in the male: all these features are the consequences of the failure to establish a timely diagnosis of hypogonadism [35] . During adolescence, patients with complete or partial CHH forms seek medical help for absent or minimal virilization, whereas in the adult onset forms patients usually complain

about low libido and erectile disfunction. In most of CHH patients, puberty never actually occurs, which is the reason for the lack of secondary sexual characteristics that we listed here above, but the same clinical features are initially found in CDGP patients. Nonetheless, in patients with isolated GnRH deficiency the finding of a partial progression through puberty followed by a permanent arrest of sexual maturation is not uncommon, which makes the differentiation between the two conditions even harder [36] . The association between CHH and a decreased or absent sense of smell (hyposmia and anosmia respectively) typical of the KS is the consequence of the common origin of olfactory and GnRH neurons [37]. This condition should be evaluated with a quantitative olfactory test; however, it should be noted that defects of smell only affect less than a half of subjects with CHH. Still, whenever present, olfactory defects should be considered a reliable clue towards the diagnosis of KS [38].

Hormones and stimulation tests

An important feature in CHH patients is the very low circulating gonadotropin levels, but this feature alone cannot be used to differentiate between CDGP and CHH in early adolescence, when gonadotropin levels are normally low even in healthy subjects.

Nocturnal sampling

The study of LH nocturnal pulses has been proposed in this setting: in fact, the lack of nocturnal LH pulses in adolescence was described to be specific for hypogonadotropic hypogonadism. In one study published in 2002, the 91% of the prepubertal children examined (age 4-8 years old) showed a distinct pulsatile LH and/or FSH secretion: this pulsatile secretion is similarly observed in older prepubertal patients and suggests the existence of a sleep-entrained rhythm of gonadotropin secretion during prepuberty as well as during established puberty: so it seemed plausible to suppose that an absence of this pulsatile secretion with undetectable levels of LH and FSH could lead the diagnosis towards an hypogonadotropic hypogonadism; but surprisingly, when using ultrasensitive assays with lower limits of detection, a similar pulsatile fluctuation was found in patients with Kallmann's syndrome as well[39]. The only difference between prepubertal children and hypogonadotropic patients seems to be

the absence of entrainment to nocturnal sleep and the low incidence of synchronization between LH and FSH pulses, resulting in the possibility of distinguishing patients with Kallmann's syndrome from patients with constitutional delay of growth basing on the nocturnal pattern of gonadotropin secretion [39,40]. However, the analysis of the nocturnal patterns of gonadotropins is a kind of evaluation which is definitely too much invasive and could hardly be used as a practical routine diagnostic test. This resulted in a shift of attention towards less invasive and less laborious tests.

In order to avoid the nocturnal sampling, the diagnostic utility of a single basal gonadotropin level has been looked at: some studies, in fact, showed that there are significantly lower basal gonadotropins in CHH patients than age- and Tanner stage-matched patients with CDGP (especially in females) [41–43]. It has indeed been demonstrated that LH and FSH levels over 0.2 U/L indicate successful onset of puberty. However, if the finding of gonadotropins levels above 0.2 U/L points out patients with no sign of puberty that are about to start physical development (thus not requiring further investigation but a simple "wait and see" strategy), it cannot be used to distinguish between partial CHH and CDGP in patients already having signs of puberty, that could have had a pubertal arrest. Similarly, if gonadotropins levels are below 0.2 U/L it is not possible to distinguish between an early stage CDGP and complete CHH [7,44].

GnRH and GnRHa tests

Several studies have been reported with the aim to demonstrate whether the LH or FSH levels response to provocative tests could accurately discriminate between the two conditions. Some of them, initially stated that it would be possible to diagnose CHH with 100% sensitivity and 96% specificity by assessing LH response to GnRH. However, these studies were conducted on small sized pools of very selected patients not reflecting the complexity and heterogeneity of the possible presentations of the disease [45]. The real effectiveness of GnRH-stimulated LH and FSH pulses in distinguishing CDGP from CHH, in fact, is far less accurate. Indeed, it was shown that even if adolescents with CHH have overall lower stimulated LH levels compared with subjects with CDGP, up to 30% of these latter have LH responses indistinguishable from those with CDGP. So, once again,

the main problem remains the overlap between the two conditions [46]. The use of GnRH agonists seemed to have a higher discriminatory potential compared to GnRH for dynamic testing in distinguishing CDGP from CHH [47]. The GnRH agonists studied include Nafarelin, Triptorelin, Buserelin and Leuprolide: they all have shown increased potency and half-life due to a greater affinity for the GnRH receptor, resulting in a much more effective stimulus for the activation of the gonadotropic cells in patients with CDGP. In a pilot study the authors found that the response to a single test dose of Nafarelin distinguished CHH from CDGP in a way similar to the sampling of nocturnal LH level [48]. However, all the studies had the same abovementioned limitations, with a retrospective design and a low number of selected CHH patients. On the contrary, GnRH test is widely used to identify an initial onset of puberty, in order to choose a wait and see strategy in patients without signs of puberty but a positive response to the test. In fact, both GnRH test and GnRHa test point out if there is an activation of gonadotropic cells (which occurs whenever puberty is started). However, since this activation has occurred also in partial forms of CHH (forms in which puberty may not progress, but starts anyway), it is impossible to perform an accurate differential diagnosis. Thus, GnRH and GnRHa tests can both be used to identify puberty onset rather than a true differential diagnosis between CDGP and CHH.

Inhibin B, AMH, INSL3, hCG and Kisspeptin dynamic testing

Other endocrine tests that have been used to guide the differential diagnosis, including the measurement of the circulating markers of Sertoli cells (such as inhibin B), of immature Sertoli cells (such as AMH), and of Leydig cells (such as INSL3 and testosterone after hCG stimulation test).

INSL3 is a marker of Leydig cell function [49] which has a low secretion during childhood while increasing during puberty and peaking in the adulthood [50]. It was reported that CHH male individuals have typically low INSL3 levels (either at diagnosis or during testosterone replacement therapy) that are prone to increase whether LH and/or hCG stimulated[51]. However, data so far available are insufficient to clearly identify the potential clinical utility of INSL3 measurements in differentiating CHH from CDGP.

Inhibin B and AMH are both glycoproteins produced by Sertoli cells: their levels reach a peak after birth and then they decrease, but while inhibin B rises again with the onset of puberty as a result of the FSH stimulus, AMH keeps decreasing due to the down-regulation induced by the increasing Testosterone levels. Two recent studies evaluated Inhibin B measurement: one of them, including 82 subjects with delayed puberty, showed that circulating Inhibin B had a 93% positive predictive value to identify patients with CHH from those with CDGP, while the measurement of AMH, T, FSH, LH were not as reliable markers for such differential diagnosis, even though their levels appeared to be lower in most of CHH patients compared to the CDGP patients [41]. The lower reliability of AMH seemed to be linked to the fact that AMH responds to FSH through a non-classical pathway and it also normally decreases during puberty under the effect of Testosterone. In contrast, the second study found a lower positive predictive value of Inhibin B at distinguishing CHH from CDGP, but the authors still concluded that, although it requires further verification, a single inhibin B level might be used as a first-line test in the diagnosis of CHH [52]. In fact, it was shown that the combined basal test (inhibin B plus LH) could be a valid alternative to GnRHa test, which is time consuming and more expensive, and some authors endorsed this strategy as a first line test of the patients with delayed puberty [47].

The testing of AMH serum levels combined with inhibin B levels has proved to give comforting results in cases of clinical suspicion of puberty disorders, since these levels reflect Sertoli's cells health and number: while these tests can't discriminate with guaranteed accuracy between CHH and CDGP, however, they can be helpful in the early detection of testicular tubular damage [41].

The use of HCG test in association with GnRH test and has also been suggested, combining short-term HCG stimulation and long-term HCG stimulation followed by the classic GnRH stimulation test. Indeed, the peak testosterone response to the short-term and long-term HCG stimulation was found in one study to be significantly lower in CHH patients, as were the peak serum FSH responses to the GnRH stimulation [53]. Still also these data were never reproduced, and thus found no application in clinical practice.

Finally, among the new frontiers of hormonal evaluation, also the responsiveness to the neuropeptide kisspeptin has been investigated in boys with delayed puberty: Chan YM et al. hypothesized in 2018 that kisspeptin would stimulate LH secretions in healthy subjects but not in CHH patients. Thus, a kisspeptin stimulation could stimulate overnight LH pulses in boys with emerging reproductive endocrine function, while the absence of response may be due to a true hypogonadotropic hypogonadism. The results showed different profiles of patients: the responders, the ones who were thought to have normal reproductive endocrine function, the non-responders (who were believed to have an underlying pathology concerning the pituitary), and ultimately a group of intermediate responders, that could be the cases diagnosed with partial HH. At this point, further studies are needed to see if the kisspeptin stimulation test in prepubertal children can accurately predict outcomes for boys presenting delayed puberty, since the study included 17 years old patients, and our main priority is to diagnose correctly the condition in pediatric patients, before delayed puberty shows itself [54].

Priming

Another mean to investigate pubertal delay, which is also the treatment of choice in CDGP, is the so-called "priming" using low doses of sex hormones. In fact, recent studies have been focusing on the diagnostic utility of performing testosterone priming not only to treat CDGP, but to perform a differential diagnosis with CHH, relying on the idea that after a three-months period of testosterone injections in boys with CDGP, the withdrawal of testosterone should awaken the hypothalamus-pituitary axis, with an enlargement of the testis and an endogenous production of testosterone [55]. One of the advantages of this interventive approach is a shorter delay in the diagnosis, since the "diagnostic test" is also a treatment, with both psychological and physical benefits on height and virilization. Moreover more expensive test could be reserved to those who do not reach puberty even after testosterone priming [55]. On the other hand, it has to be considered that nowadays it is not known if, in CHH patients, a pretreatment with testosterone before a gonadotropin therapy could affect the future fertility potential of the subjects [56–58]. Concerning the side effects of testosterone priming

(including acne and in a minority of cases also aggressive behavior and painful erections), it has to be said that they only occurred in boys who were treated with excessive doses of testosterone [59]. Anyway, although testosterone priming cannot be considered an "unsafe" treatment, patients and their family need to be informed of the connected risks, and most importantly, in case of priapism a urologist has to be consulted timely [59].

The same approach has been attempted in female with a priming therapy using low doses of estradiol. The evidence that we have at the moment on females, however, is based mostly on β-Thalassemic patients, who are affected in 60-80% of the cases by hypogonadotropic hypogonadism: In a 6-year prospective study concerning children (boys and girls) with absent or arrested puberty and β-Thalassemia, sex hormones priming proved to be successful in inducing puberty in 80% of the subjects, suggesting that the estradiol priming could be as useful as the testosterone priming in the awakening of the hypothalamus-pituitary axis in the CDGP female patients [60].

The data we analyzed also suggests that the priming technique could increase the discriminatory power of dynamic tests (such as GnRH stimulation) if performed before such tests, indicating an interesting application of the technique in terms of the differential diagnosis between CHH and CDGP[55].

Genetics

The genetics underlying the two conditions is another aspect that needs to be carefully considered. Up to date, 60 genes are known to be associated with the multiple forms of hypogonadotropic hypogonadism[10], all of them being genes that regulate development, migration and secretory function of GnRH neurons, but there is less knowledge regarding the genetic background of congenital delay of puberty. The family history that is found in the majority of the CDGP patients suggests that the genetic aspect of the condition is not to be underestimated. In fact, as already above mentioned, it seems that CDGP clusters in families [61]. In 2015 a study aimed in determining whether the genetic

mutations linked to CHH could also be found in the boys with CDGP, showed that there is actually an overlap between the genetics of these two conditions, which could even share the same underlying pathophysiology [62]. These findings were confirmed in a further study that, despite being designed to find difference in the genetic architecture of the two conditions, found a similar genetic basis, even if a greater prevalence of CHH variants and oligogenicity were more typical of hypogonadal patients [63]. So, the main utility of genetic studies, nowadays, remains the family counselling once the diagnosis is completed, rather than as a routine first-line test.

Conclusions: what to do?

Every careful reader should have understood by now that there are no strong and univocal evidences to guide us in the differential diagnosis and management of CDGP and CHH. However, according to the pathophysiology of these two conditions, we can draw some considerations which could lead us through this tangle of tests and approaches.

First of all, any treatment should be considered only when actually needed. Thus, before 14 years old [9,64,65] it is important to simply reassure patients and their parents since the most likely condition is normality. After 14 years old, if no sign at all of puberty has intervened, the evaluation of gonadotropins could be highly useful to point out subjects that are about to start their (delayed) puberty, non-requiring other action than watchful follow up [44]. On the contrary, if gonadotropins are below 0.2 U/L, a GnRH test could be performed with the same purpose [66].

Finally, in those not showing any of these signs of initial puberty, new markers such as inhibin B could be evaluated [41], and, after a thorough discussion with the patient and their parents, a priming with low doses of sex hormones could be proposed, especially in patients suffering for their physical immaturity. Obviously no patient should ever be left untreated after 18 years old (this being by definition a CHH [32,67]), and after 16 years old a psychologic discomfort is very likely on the contrary of a CDGP thus demanding particular attention to a more interventional approach.

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Declaration of interest

Authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the data reported.

Funding: The study was supported by funds from Italian Ministry of Health (Young Investigators funds: GR-2016-02362389) and IRCCS Istituto Auxologico Italiano (Ricerca Corrente funds: O5C202_2012).

Author contributions statements:

A.B. and B.C. conducted the literature review, A.B., B.C. and G.G. prepared the manuscript.

S.F., V.V., P.D., L.G., E.G., M.B. and L.P. performed the critical revision of the manuscript. All authors read and approved the submitted version.

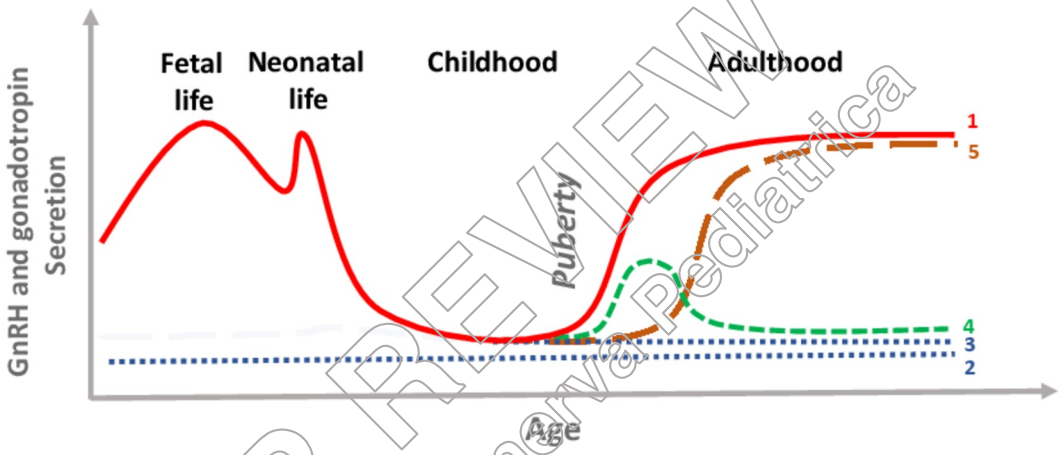
Figures

Figure 1. GnRH secretion profile in normal subjects, patients with constitutional delay of growth and puberty (CDGP), and with partial and complete forms of congenital hypogonadotropic hypogonadism (CHH). Adapted from Cangiano et al. 2020

Tables

Table 1. pubertal delay classification

	Classification		Etiology							Frequency (%)	
										Male	Female
Pathologic forms	Central Hypogonadism	Organic	- CHH (normosmic CHH; Kallmann's syndrome)	- CHARGE syndrome	- CHH with CAH	- MPHD	- Hypothalamic-Pituitary region lesions (eg. craniopharyngiomas)	- Metabolic diseases (eg. hemochromatosis)	- Pituitary inflammation	10	20
			- Infiltrative diseases	- thalassaemia	- Infection	- Inflammatory eg Langerhans Cell Histiocytosis	- Granulomatous disease (eg. sarcoidosis)	- Iatrogenic causes (eg. radiotherapy)	- Other genetic syndromes (eg. Prader-Willi, Laurence Moon-Biedl etc)		
		FHH	- Chronic illness	- Malnutrition	- Strenuous exercise	- Stress	- Drugs	- Other endocrine disorders (eg. hyperPRL, hypothyroidism)	-	20	20
	Primary Hypogonadism		- Klinefelter syndrome	- Tuner syndrome	- Anorchia	- Enzymatic defects	- DSD eg gonadal dysgenesis	- LH/FSH resistance	- Secondary forms (eg. chemo- and/or radio-therapies; autoimmune diseases, trauma, gonadal torsion)	5-10	25
Non-pathologic form	CDGP	Unknown (genetic backgroud?)								60-65	35



1: normal GnRH secretion profile
2 and 3: complete forms of CHH
4: partial forms of CHH
5: CDGP