

An Update on Aetiopathology, Various Genetic Causes and Management of Delayed Puberty-A Minireview

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Abstract

Delayed Puberty (DP), especially in boys, is a common presentation in paediatrics. By definition DP is defined as the presentation of clinical signs of puberty 2-2.5SD later than in the normal population. With the recent advances in understanding of the neuroendocrine, genetic and environmental factors controlling pubertal development it has become easier to understand the pathophysiology of DP. The discovery of kisspeptin signaling through its receptor identified neuroendocrine mechanisms controlling the gonadotropin releasing hormone (GnRH) pulse generator at the onset of puberty. Genetic mechanisms from single gene mutations to single nucleotide polymorphisms associated with DP are being identified. Environmental factors, including nutritional factors, besides endocrine disruptors, have been associated with the secular trends and abnormal timing of puberty. In spite of these advances, the main question remains how to differentiate DP associated with underlying pathology of hypogonadism from constitutional delay in growth and puberty (CDP) that remains challenging as biochemical tests do not always discriminate the 2. The diagnostic accuracies of newer investigations which include the 36-hour luteinizing hormone releasing hormone (LHRH) tests, GnRH agonist tests, antimüllerian hormone and inhibin B, need further evaluation. Sex hormone replacement remains the main therapy that is available for DP, whose choice is based on clinical practice and the availability of the various sex steroid preparations. Spontaneous reversal of hypogonadism has been reported in boys having idiopathic hypogonadotropic hypogonadism following sex steroid treatment, which highlights the importance of reassessment at the end of pubertal induction. Novel therapies having a more physiological bases like gonadotropins or kisspeptin agonists are getting investigated for the management of hypogonadotropic hypogonadism. A careful assessment and knowledge of the normal physiology remains the mainstay of managing patients with DP.

Keywords: Delayed Puberty; hypogonadotropic hypogonadism; kisspeptin; CDP; sex steroid treatment; gonadotropins.

Introduction

Puberty involves a complicated physical along with psychological process which ends in development of reproductive capacity. For puberty to occur there is need for hypothalamic neurons to get activated required for increasing pulsatile GnRH secretion, along with activation of the gene networks which bring about this activation, that have been defined clearly now. That there is an increase in excitatory and reduction of inhibitory inputs along with glial secretory factors like TGF- α and prostaglandin, which leads to the activation of the gonadotropic axis at the onset of puberty [1-3]. GnRH synthesis begins very early in fetal life in case of boys while 2 years in girls. This early neonatal period is also labeled as minipuberty, while gonadotropic axis quietens down after this.

At what time the puberty actually gets initiated varies with some heritable factors along with racial and ethnic factors and occurs with the reactivation of GnRH Secretion from the hypothalamus, determined by genetic, nutritional, ethnic along with environmental factors [2]. Delayed puberty is defined as the absence of physical signs of puberty by the age ≥ 2 SD beyond the population mean, a statistical definition which is necessary in view of the incomplete understanding by us regarding how the timing of puberty is defined [4]. One can classify the late onset of puberty into 3 subgroups i) Hypogonadotropic hypogonadism (HH) ii) hypergonadotropic hypogonadism and iii) constitutional delay of puberty (CDP) [5]. The causes of delayed puberty (DP) may be congenital or acquired, of which CDP constitutes the commonest cause of DP among boys, though the final diagnosis can only be made by elimination of other causes (Figure 1).

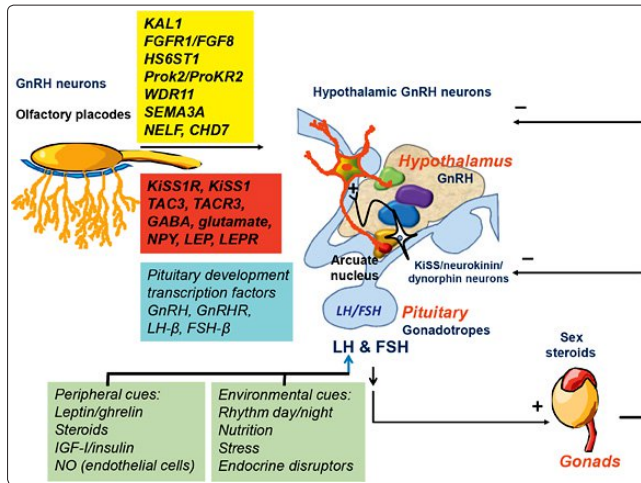


Figure 1: Gene network implicated in gonadotropic axis activation. Kisspeptin neurons located in the arcuate nucleus of the hypothalamus stimulate GnRH neurons. In yellow, the factors involved in GnRH neuron migration from the olfactory placodes; in red, hypothalamic excitatory and inhibitory neurotransmitters and neuropeptides; in blue, hormones and other factors from the gonadotropic axis at the pituitary level, and in green, peripheral and environmental cues influencing GnRH secretion.

How to diagnose DP

As discussed earlier DP by definition is the absence of enlargement of testis in boys /breast development in girls at an age which is 2-2.5 SD later than their population mean. Although in Europe it is the age 13 years in girls and 14 yrs in boys decided to be the guideline for the need for further examination. But these don't consider the differences racial and ethnic groups or a recent trend of earlier pubertal onset seen in United States along with other developed countries [6-16]. One needs to examine for pubertal development both clinically and biochemically.

Medical History

A detailed medical, family history along with lifestyle factors history (like exercise, nutritional level, developmental along with any psychological problems) needs to be accounted. Details of birth and pregnancy like (icterus, neonatal hypoglycaemia), childhood growth patterns, along with any surgical or medical treatments are needed. An account of any family history of pubertal delay, parental size along with age at which onset of puberty occurred, any infertility or anosmia [4] along with history of any chronic autoimmune or endocrine diseases need to be taken. If there is any possible acquired hypogonadism, signs of intracranial hypertension might be present and need to be looked for.

Physical Examination

One needs to measure weight and height. Breast examination and tanner staging needs to be done Tanner stage 2 indicates onset of pubertal development with breast development in girls and in boys a testicular volume >4ml in boys. Further an analyses of dimorphic features like those present in turners syndrome or klinefelters syndrome, presence of any operative scars if any, cryptorchidism / undescended testis, micropenis, gynaecomastia, sense of smell status and signs of any acquired disease.

Investigations

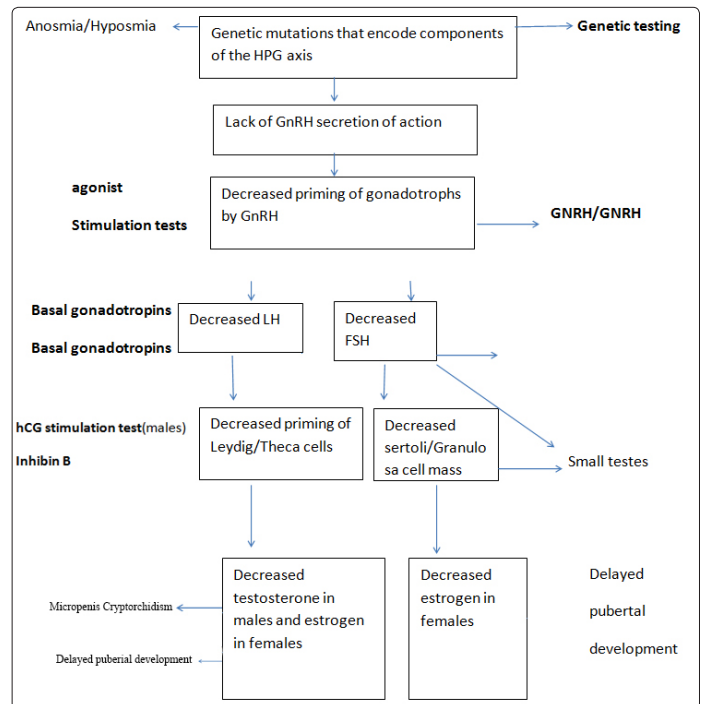
One has to make the diagnosis of hypogonadism and further how it is caused –whether there is a primary cause or some central pathology is involved needs to be ascertained. Despite various tests involved still it has been very difficult to differentiate patients having CDP from those having idiopathic hypogonadotropic hypogonadism [17 reviewed in kkk]. Till date the achievement of pubertal development by the age of 16-18yrs remains the golden standard for making a DD of CDP against HH [5]. Though having a family history of delayed puberty gives a strong suggestion of CDP, the problem lies in that patients having CDP may be found in pedigrees of those having isolated HH [18].

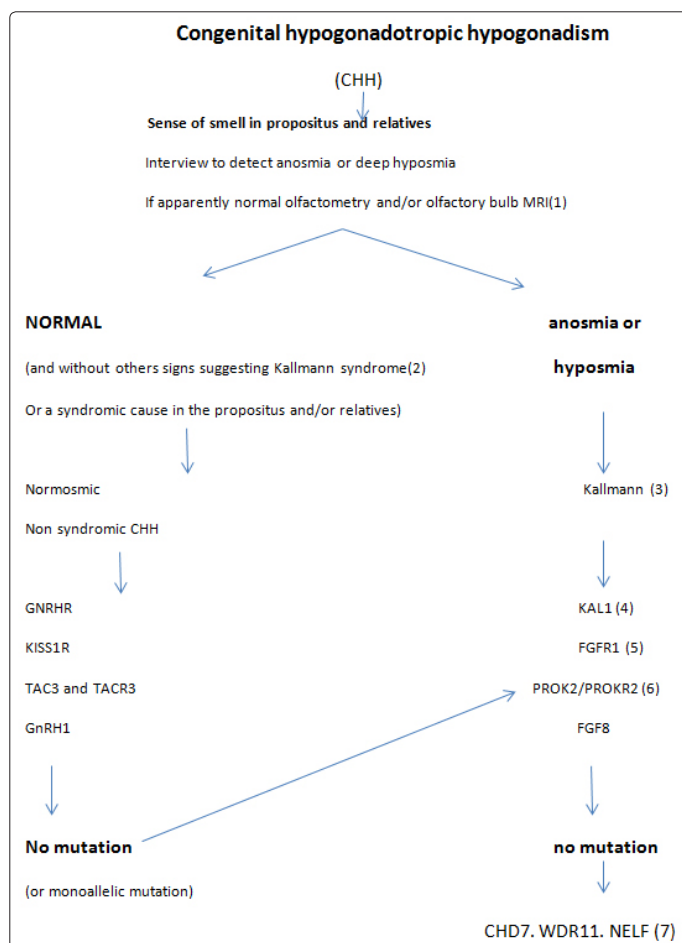
Hormonal levels

The basal FSH along with LH levels are low as is following GnRH injections in patients with HH or CDP but increased in those having hypergonadotropic hypogonadism. On an injection of 0.1mg GnRH, pubertal onset gets characterized by LH/FSH Rtio >1. Testosterone (T) levels in boys are >0.5ng/ml at pubertal onset and estradiol in girls being <10ng/ml before puberty increase to >40ng/ml. Both levels of inhibin and antimullerian hormone (AMH) might be of use in separating CDP from HH, as in prepubertal boys inhibin B>35pg/ml and AMH>110pmol/l are more commonly seen in CDP than in hypogonadism [19, 20]. Other pituitary deficiencies can be ruled out by measuring IGF-1, T4, TSH and cortisol, and GH. [21] (Figure2,3)

Bone Age-One encounters a bone age of <11yrs in girls or <13yrs in boys with growth failure in CDP. If bone age is >11yrs in girls or >13yrs in boys it needs further tests to rule out hypogonadism.

Pelvic Ultrasound-In case of ovarian volume >2ml and uterus >35mm implies that puberty is imminent [22]. In hypergonadotropic hypogonadism, one might find small or absent gonads, and testis in males probably located intra abdominally.





puberty. Different neurotransmitters along with neuropeptides in the hypothalamic arcuate nucleus have been found to be of importance to reactivate the gonadotropic axis. Of these if there are loss of function mutations in genes that encode for neuropeptides like kisspeptin (Kp) or neurokinin B (TAC3) or their receptors (KISS1 or TAC3R respectively) =>hypogonadism [26, 27]. In case of sheep, neurokinin B is expressed by the same neurons which manufacture Kp [28]. In man these neurons are present in the arcuate nucleus (in infundibular nucleus), that has an important role in the pulsatile GnRH release [29]. In case of mice an increased activity of a tumor related gene network in the hypothalamus has been observed at the pubertal onset of female mice and its suggested that it participates in the reactivation of the gonadotropic axis [30]. Also pubertal onset might depend on epigenetic factors and complex regulation by LIN 28 protein has been seen [31].

Two neurotransmitters like GABA and glutamate control the excitability of GnRH neurons, directly with GABA causing inhibition and glutamate stimulation [32]. This balance between GABAergic inhibitory and glutamatergic excitatory inputs of Gn RH neurons gets modified at puberty, shifting towards activation. There is different involvement of the opioid peptides along with action of different peptides at various receptor subtypes making it complex which act to inhibit GnRH secretion either directly or indirectly [23,33]. Neuropeptides RFamides, both RFRP1 and RFRP3 act on GnRH neurons through the GPR 47 receptor [34]. Peripheral hormones like leptin are also implicated in the regulation of GnRH network.

Another causative factor has been found in heterozygous activating germline mutations seen in rat sarcoma-mitogen-activated protein kinase (RAS-MAPK) pathway genes, which lead to developmental disorders like RAS opathes like Noonan Syndrome, Costello and cranio facio-cutaneous syndromes. The RAS-MAPK pathway plays a central role in signal transduction from extracellular stimuli to the intracellular environment. These RASopathies are usually associated with delayed puberty although occasional cases of precocious puberty has been defined making it difficult to ascertain role of RAS-MAPK genes in the development of puberty [35van]. Thus if any of the above factors get disrupted it modifies the onset of puberty.

Etiopathology Hypergonadotropic Hypogonadism

Increased FSH/LH suggest a primary gonadal deficit with Hypergonadotropic Hypogonadism being either congenital or acquired. Any history of previous surgery or disease affecting the gonads helps in focusing on the diagnosis that is generally easy in cases of delayed puberty where gonadal pathology is present. Klinefelters syndrome (46XXY) is the commonest cause of Hypergonadotropic Hypogonadism which is very often related to Turners Syndrome in girls .This diagnosis gets confirmed by karyotyping.

Hypogonadotropic Hypogonadism

The diagnosis of HH in boys is done based on the low plasma testosterone concentrations that are associated with low LH and FSH (both basal along with following Gn RH injection) as well as at age 14 years when a testicular volume is found to be <4ml. As far as girls are concerned one proposes HH when plasma gonadotropins are normal or low, with any lack of pubertal sign as by the age of 13yrs. Certain infiltrative or infectious lesions of the pituitary (like histiocytosis or tumors), any medications (like GnRH analogs), brain

Karyotype

This is needed in case of hypergonadotropic hypogonadism, if patients history doesn't explain the gonadal pathology and if any dysmorphic feature which suggest Turners or Kinefelters are seen. Brain Magnetic Resonance Imaging (MRI)-If any gonadotropin deficiency is met with MRI stands as the best tests to rule out organic pituitary or hypothalamic disease. Very important is measuring the pituitary and pituitary stalk. One encounters agenesis of olfactory bulbs in case of Kallmann Syndrome (KS).

Molecular Studies

A genetic analysis is warranted in patients having hypogonadism, with a normal karyotype and if possibly other clinical features of syndromic hypogonadism are present. On testing if genes that are involved in pubertal diseases are normal one can do other genetic analyses which are being used in research presently. Exomic sequencing may find mutations in genes which are representative of new cases of hypogonadism [23]. In case siblings are also affected with similar hypogonadism phenotypes, genetic variants having a single nucleotide polymorphism is found more commonly in patients having hypogonadism and is said to be associated with the disease [24], and one needs to mark the region of the genome which influences the risk of disease.

Puberty Timing

Variations are seen in initiation and end of puberty in boys and girls, girls show signs of puberty before boys [25]. Recent advances in onset of puberty obtained through study of genetic determinants of normal

trauma or radiation may=>acquired HH. If the HH gets corrected following the reversal of pathology it implies that pathology is the causative factor. This is mainly important in patients having hypercortisolism, renal failure, celiac disease and malnutrition, with especial emphasis on anorexia nervosa that is the major cause of HH among girls.

In case of isolated gonadotropin deficiency, congenital hypogonadism may or may not be associated with anosmia.

On detailed analysis of families having knowledge ,it was demonstrated that in cases of normosmic HH, which is a monogenic mendelian disease there is an involvement of 6 genes namely GnRH1[36,37], Gn RH R[26,38-,39], KISS1R [40-41], KISS1 [42,43] reviewed in kkk] TAC3 and its receptor TAC3R [44,]. Animal model studies have given a better understanding regarding the role of these factors in the gonadotropic axis [33, 44]. [17 reviewed in kkk].

Kalman's syndrome (KS) has variable clinical presentations, having an X linked along with autosomal dominant and recessive causes which have different penetrance. There may be coexisting renal anomalies along with synkinesia. Its prevalence is 1/8000 men, and that in women is five times lower. On MRI, aplasia or hypoplasia of the olfactory bulbs, which are associated with defective migration of GnRH neurons through the cribriform plate [45].

Genes implicated in causation of KS are the 8 genes that are involved in the olfactory bulb development. Initially inactivating mutations were described in the KAL1 gene (that encodes anosmin1) that is located on X chromosome [46,47], subsequently on autosomal genes which included Fibroblast growth factor receptor FGFR1/KAL, fibroblast growth factor8 (FGF8), [48-50, prokineticin2 (PROK2/Kal4), PROKR2/Kal 3[51-56], reviewed in ref 57, nasal embryonic LHRH factor (NELF) [58], WD repeat containing protein 11(WDR11) [59] and Semaphorin 3 A(SEMA3A) and SEMA7 [60-62], CHD7, [63-65], TSHZ1, AXL, HESX1[66-69].

Further 5 new genes of the FGF8/FGFR1 network in which mutations were present in patients suffering from HH was reported by Miraoui etal [70 already reviewed in17]. Roughly FGFR1 mutations are present in 10% of patients having idiopathic HH. The same FGFR1 mutations might present with severe hypogonadism -kuldinder or reversible phenotypes [71, 72].

HH might be syndromic and also part of the HH developmental anomalies of GnRH neurons. Also there might be an association with other pituitary deficiencies and hence one needs to rule out tumoral pathology along with infiltrative diseases which need to be ruled out. If there are various deficits present during the neonatal period or infancy a classification of congenital panhypopituitarism is made. Both combined or multiple pituitary hormone deficiencies might get acquired during childhood. One performs the genetic testing for known monogenic or digenic causes of HH in the 2nd phase of testing. Yet, that an overlap is present between KS, combined pituitary deficiency and septo-optic dysplasia has been reported, hence pituitary function needs to be reexamined if any doubt is present [73].

Constitutional Delay of Puberty (CDP)

Important fact to note is that the initial cause of pubertal delay in boys is represented by CDP (idiopathic) that might be difficult to separate

from other congenital or acquired types of HH. This is a diagnosis confirmed by exclusion if puberty onset occurs spontaneously. These are healthy girls and boys reaching puberty spontaneously by the age of 13yrs and 14 yrs respectively. There is delay in puberty, growth along with bone maturation. Thus to diagnose this, slow growth for age, but within the prepubertal range, with other siblings with constitutional delay of growth and puberty and a normal physical examination with normal olfaction are required [4,74,75]. A family history of delayed puberty is seen in half of the CDP cases, that strongly suggests CDP [74, 75]. But patients having CDP may be also seen in pedigrees of families of isolated HH. In most cases the first signs of sexual maturation occur within 1 year after gonadotropin and testosterone or E2 concentrations begin to increase spontaneously [76]. Mostly the 1st signs of sexual maturation occur within 1 year after LH rises >2u/l in 3rd generation assays after administration of LHRH or within 1 year of gonadotropin and testosterone or E2 concentrations begin to rise spontaneously [76]. Mostly patients with CDP consult initially for short stature instead of delayed puberty. It is much more common in boys comparable to girls since pubertal growth does not occur and they remain small compared to other children of the same age. They have delayed epiphysis maturation. A 2nd important point is that the physical sign is a relatively short upper body segment which is seen after 9 years of age with growth delay [77]. Important is to rule out any chronic illness or intense exercise that can =>growth and pubertal delay.

If no criteria for any suspected disease, careful monitoring and a brain MRI is required in teenagers having gonadotropin deficiency. Since there is a dilemma whether self limited delayed puberty (DP) is benign or is associated with long term effects and on role of giving sex steroids in these pts Zhu et al reviewed the literature and found that CDP may be both harmful and have protective effects on different adult health outcomes. Especially, height and bone mineral density have been observed to be compromised in some studies of adults having a history of DP. DP might also negatively affect adult psychosocial functioning and educational achievement, besides which individuals having history of DP carry a risk of metabolic and cardiovascular disorders. While in contrast, history of DP seems to be protective for breast and endometrial cancer in women and for testicular cancer in men. Although most studies of adult outcomes of self limited DP have been in small series with significant variability in outcome measures and study criteria. Thus more future research is needed to fill the gaps in our knowledge [78].

Environmental factors

Recent trends of early puberty reflects how modern environment has changed. One of the reasons is global warming. Besides that endocrine disruptors play a part, but besides that the family context and psychological development during pre adult life are important influences in transition between childhood and puberty, possibly via epigenetic changes [79].

Treatment principles

2 important aims are to make sure full pubertal development occurs and that reproductive capacity is achieved.

Treatment for Pubertal Development

Cause of hypogonadism found have to be treated if possible following which pubertal development will take a normal course following treatment of underlying disease. Pituitary tumors need treatment before initiating hormonal replacement for correcting

delayed puberty. For other causes aim is to make sure full pubertal development, associated with growth acceleration, development of sexual features, optimal bone mass is achieved along with normal sexual activity.

Before starting replacement therapy, it is important to differentiate hypogonadism from CDP, for which a short term test with low dose sex steroids will induce the growth spurt, that will be sustained in CDP. Low doses do not influence the final height. In boys use of low doses of T (50mg i/m every 4weeks) for 6 months or classic protocols with low doses of anabolic steroids like oxandrolone (1.5-2.5mg/day for 6 mths) have been used. In girls low doses of estrogen (2-5µg/day of ethinyl estradiol or equivalent transcutaneous estrogen doses-5µg/kg body weight of 17β estradiol for 6 months [4, 77]. T in males and estrogens and estrogen-progestogen in girls are given in gradually increasing doses. In girls E2, is the commonest replacement via oral or cutaneous administration. Patches have fewer secondary effects, as the estrogen do not pass into the liver. In CDP no treatment should start before 13 years or a bone age of 12yrs. No international consensus, but usually E2 is given at the dose of 2-6µg/kg(1/12th to 1/4th of patch of 25µg/day (6 months to 1year) [1]. When hypogonadism is present, low doses are given initially-0.3mg of estrogen or 5µg/kg body weight daily of E2 or one eighth of transdermal patch of 25µg, which is increased progressively between 0.3and 0.6mg or 1/8th-1/4th patch every 6 mths or 2-3yr still dose of 2mg E2/day or 10µg/kg/day is reached [4]. Following 2yrs of treatment, progesterone is given to induce cycles-2mg/day of E2 from day 1 to 21and P from day 10 to day 21. Estrogen progestin pills can also be used. Bone age, ultrasonography and monitoring of the evolution of pubertal clinical features, growth and estrogen tolerance should be done every 6 mths. Lipid levels, glycaemia and liver enzyme levels are assessed before starting treatment. In boys CDP is treated when the delay has psychological consequences. This replacement therapy needs to start when bone age is 12-13years. Treatment entails an i/m injection of the ester of T (enanthate, cypionate or propionate) every 4 weeks beginning at 50mg and increasing to 100mg during 6mths-1year. T patches prevent abrupt increase of T at treatment onset. One needs clinical monitoring every 6mths. In both cases, if no responses is observed after 1year hypogonadism should be taken into account.

Treatment with gonadotropins (subcutaneous weekly multi-LH or HCG and FSH or recombinant GnRH or pump) is used in adulthood for specific treatment of infertility In HH [80], but it can be used to induce puberty [81]. Here an increase in testicular volume is observed. Reviewing the possible benefits of neonatal gonadotropin treatments in males with congenital HH, Bouvattier [82] found that pulstile GnRH could be effective to help in orchidopexy a surgery on a small testis would be more difficult. But these treatments are more complex and expensive with compliance problems.

Fertility Treatment

On diagnosis of hypogonadism during adulthood, the aim of treatment for most young men and women is there desire for fertility, which needs hormonal therapy. Men having hypergonadotropin hypogonadism don't respond to this hormonal therapy since primarily the disease is caused by testicular dysfunction. T enanthate is given to reverse signs and symptoms of hypogonadism. In HH, GnRH and gonadotropin therapies remain the best way of treating men who have a desire for fertility. Therapy with HCG alone 1000-2500IU twice a week for 8-12weeks, increases testosterone and

sometimes induces spermatogenesis, or combined with recombinant FSH (75-150IU thrice a week) to stimulate sperm production along with T levels. Subcutaneous GnRH administration with a pump (100-400ng/kg every 2h in the abdominal subcutaneous tissue if available) during 4mths can also restore fertility in HH. Although semen sperm concentration usually remains below the normal range. Hence treatment is required for 6-12 mths, that is essential to restore spermatogenesis. Since this is costly all patients might not afford it [83, 84]. Recently Kp agonists have been tried in some cases having KISS1/KISS1R mutations [43, 85] although not available in every country. Although NKB is not effective it being downstream of KISS, KP agonists are also effective in TAC3/TAC3R mutations [86-88].

Conclusions

Diagnosis of hypogonadism is based on when clinical features appear, that depends on when hypogonadism starts. In case of congenital delayed puberty, degree to which the child gets affected is related to when during fetal life the gonadotropic axis gets affected [5]. If there is influence early in utero, it results in more severe defects, which possibly explains why there are severe, moderate and even reversible forms of DP [5]. GnRH deficiency occurring during fetal life is accompanied by cryptorchidism and micropenis. In Case of GnRH deficiency starting in infancy, before puberty or after, infertility, lack of libido, gynaecomastia and low bone density are the common presenting features, but in these testis and penile size may be normal and them having secondary sex characters.

Thus it may be difficult to diagnose in children if no features are seen in the newborn. In adults., hypogonadism, might be post pubertal or partial with hormone levels during GnRH test, AMH and inhibin confirming the diagnosis. MRI has importance in the diagnosis of secondary hypogonadism and in KS. One needs specific therapy in hypogonadism, which depends on when to treat. In CDP, if treatment is to be done needs consideration.

With the advances in puberty research one has received a greater insight into initiation of puberty through studying different genetic diseases, along with populations having normal puberty, besides animal studies. This initiation of puberty occurs because of post natal hypothalamic maturation=>increased secretion of hypothalamic Gn RH neurons. This involves a complex gene network. With the identification of new monogenic diseases, new members of the network are getting identified. Genotyping and epigenetic study might further help for finding the status of the complex neuronal hypothalamic network. With these methods one might be able to understand the potential problems in the gonadotropic axis even before puberty gets initiated. Further research is needed to get answers for these queries.

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