Male Hypogonadism-Areview of Secondary Hypogonadism with Special Emphasis on Hypogonadotropic Hypogonadism

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Abstract

Male hypogonadism refers to low serum testosterone (T) (<200-250ng/dl) checked at 8am in fasting subjects. Secondary hypogonadism with low normal gonadotropins can be due to congenital or acquired causes. Congenital hypogonadotropic hypogonadism (CHH) is considered when low serum inhibin B levels are found to accompany low S. FSH/LH and T. The differential diagnosis of CHH includes pituitary tumours /pituitary infiltration, juvenile hemochromatosis and other anterior pituitary functional disorders ruled out by neuroimaging and detailed hormone testing respectively. The abuse of anabolic steroids/opioids/corticosteroids which may result in hormonal changes similar to those seen in CHH need to be excluded. However confusion may result in case of constitutionally delayed pubertal growth in adolescents. Following detailed family history a genetic study performed helps to segregate the two commonest forms namely anosmic/hyposmic Kallmann Syndrome (KS) or normosmic IHH. Till date 9 genes(KAL1 (Kallmann syndrome 1)/FGF8(fibroblast growth factor 8)/ FGFR1(fibroblastgrowthfactor receptor 1)/HS6ST1(Heparan -6-O -transferase 1)/PROK2(prokineticin 2)/ PROKR2 (prokineticinreceptor2)/CHD7(chromodomain 7)/WDR11/SEMA3A(semanaphorin 3A)) have been found to be associated with KS and further for nIHH the “ones associated with GnRH function” (KISS1(Tumor metastasis suppressor)/KISSR1(KISS1 receptor)/GNRHR(gonadotropin releasing hormone)/GNRH(gonadotropin releasing hormone receptor)/TAC3(tachykinin 3)/TAC3R (tachykinin receptor3) only 30%-32%of these genes account for KS and isolated GnRH deficiency respectively. Treatment protocol is individualized according to patients requirements; ranging from Tenanthate /pulsatile GnRH therapy/rFSH-hCG or in some specific cases kisspeptin 10 agonists are prospectively being tried as future therapeutic options. Still a lot of work needs to be done on transcription factors considering genetic overlap between midline disorders like septooptic dysplasia, holopresencephaly in KS” given the developmental role of transcription factors in forebrain development as causative genes for KS.

INTRODUCTION

Male hypogonadism usually refers to a low testosterone level. Since the definition of low testosterone (T) varies from various laboratories, in general values <200-250ng/dl are considered low and values between 250-350ng/dl considered borderline low. Considering that normally testosterone levels follow a diurnal rhythm and at about 8am are about 30%higher than the serum levels later in the day, especially in younger men, one should repeat or confirm low testosterone values at 8am [1-3]. Also glucose ingestion induces a significant reduction in total and free T levels in men which is similar across spectrum of glucose tolerance. This decrease in T appears to be because of a direct testicular defect, but the absence of compensatory changes in LH suggest an additional central component, hence men found to have low nonfasting T levels should be reevaluated in the fasting state [4]. Besides that it should be confirmed that sample is obtained
during normal health and not during any acute illness or state of decompensation. Once one encounters low testosterone levels then one should check serum FSH and LH levels.

I) if raised LH and FSH (hypergonadotropic) found, namely- 
Primary hypogonadism -then cause lies in testis and one has to evaluate for any testicular disorder like.

i) Karyotypic abnormalities like Klinefelters syndrome XXY-most common

ii) Toxin exposure, chemotherapy

iii) Congenital defect in testosterone biosynthesis (in cryptorchidism) [5]

iv) Orchitis (mumps, autoimmune)

v) Testiculat trauma/infarction

vi) Haemochromatosis

vii) Mediations that inhibit androgen biosynthesis eg ketoconazole

ix) Increase in temperature of testicular environment

II) Low or normal range LH/FSH (hypogonadotropic)-namely 
Secondary hypogonadism—one has to evaluate for gonadotroph suppression/Hypothalamo-Pituitary process which may be A) Congenital-a) anosmic-Kallmanns Syndrome

b) normosmic-IdiopathicHypogonadotropic Hypogonadism (nIHH)

B) Acquired-Causing gonadotroph suppression

i) Medicationsv (opioids, corticosteroids) [6-8]

ii) Obesity/insulin resistance [9, 10]

iii) Type 2 diabetes mellitus [11]

iv) Obstructive sleep apnea [12-14]

v) Ageing [15]

vi) Hemochromatosis [16, 17]

vii) Hyperprolactinaemia [18]

viii) Anabolic steroid abuse

ix) Alcohol abuse [19]

x) Human immune deficiency virus infection [20]

xi) Chronic medical conditions (cirrhosis, rheumatoid arthritis, renal failure [21-26]

xii) Severe primary hypothyroidism [27]

xiii) Anorexia nervosa [28]

xiv) ConstitutionalDelay of Growth of Puberty [29]

xv) Acute illness

xvi) Estrogen excess [30-32]

B) Secondary hypogonadism-b) Acquired causing damage

i) Sellar or infiltrative lesion

ii) Metastatic lesion
underlie either X-linked recessive or autosomal dominant form of the disease [37-42]. The discovery of Kallmann syndrome1 (KAL1) gene has led to a pathophysiological model co-relating GnRH deficiency with abnormal olfactory bulb development in X linked KS. This gene comprises 14 exons spanning across 210kb on Xp22.3, escapes inactivation, and encodes a protein anosmin sharing homology with molecules involved in neuronal migration and axonal path finding [43]. In fact in humans since Kallman phenotype can be associated with other syndromic diseases like CHARGE syndrome [44, 45] and can display neural crest(NC) associated defects involving craniofacial dysmorphisms, cleft palate, dental agenesis, synkinesis, lack of mirror movements, deafness, ocular albinism, cerebellar defects and dementia [46, 47] besides the presence of KS and lack of pubertal onset, Forni demonstrated that these genes rise to the olfactory ensheathing cells (OEC) [48], that provide essential growth and guidance to olfactory sensory neurons axons [49], as well as subpopulation of GnRH 1 neurons, olfactory and vomeronasal cells .This data demonstrates that both Schwann cells and OEC’s share a common developmental origin and conditions like KS which impact olfaction as well as sexual development are actually neurocristopathies [48]. Developmental abnormalities in this migratory journey like those demonstrated with the deletion of the KAL 1 gene results in KS [43,50]. Recently the fibroblast growth factor (FGF)signaling pathway genes (FGF8 and FGF11) [40,41,51], PROK2 signaling pathway genes (PROK2 and PROKR2) [52-57], reviewed in [58], and CHD7 [42], WDR11 [59] and SEMA 3A [60,61] have joined the KAL1 gene as genetic pathways that have an identical neurodevelopment function and cause KS in humans .In contrast IHH also occurs in subjects with a normal sense of smell (nIHH) wherein their GnRH deficiency is secondary to impaired function of genes, that govern the neuroendocrine function of GnRH neurons, including KISS1(tumor metastasis receptor) (MIM603286) and KISS1R (KISS1 receptor) [MIM604161], TAC3 [tachykinin 3] [MIM162330] TACR3 [tachykinin receptor 3][MIM162332] [62-65] reviewed in [66]), GNRH 1 (gonadotrophin releasing hormone 1; MIM 152760), GNHR (gonadotrophin releasing hormone receptor; MIM 139850) [67-72]. However, mutations in some genes (e.g. FGF8/FGFR1/PROK2/PROKR2/CHD7) have an overlapping function and can be seen in both KS and nIHH. Lewkowitch-Shpuntoff et al studied the olfactory phenotype in 286 IHH of which 201 were male subjects and found of the IHH cohort 31.5% were anosmic, 33.6%hyposmic and 34.9% normosmic. Within the hyposmic cohort 7/11 subjects exhibited olfactory structure abnormalities on MRI, and 39.5%harboured normosmic. Within the hyposmic cohort 31.5% were anosmic, 33.6%hyposmic and 34.9%

The discovery of mutations in FGF8-FGFR1 in CHH has demonstrated a previously unappreciated role of FGF8-FGFR1 signaling in GnRH ontogeny. Subsequently Chung et al have established FGF8 as critical for both GnRH as well as olfactory system development [75]. Besides those ears, eyes, kidneys and limbs are also influenced by FGF8 [76-79] all of which can be affected in CHH [80]. Among the >15 genes implicated in CHH, mutations in FGF8-FGFR1 account for 12% of cases and importantly KAL1 and HS6ST1 (Heparan sulfate-6-O-sulfotransferase 1[MIM 604846]-twogenes known to be mutated in CHH, also encode important components of FGF8-FGFR1 signaling, KAL1 encodes anosmin 1, which enhances FGF1 signaling by direct physical interactions with the FGF-FGF heparansulfate proteoglycan (HSPG) complex on the cell surface. HS6ST1, which encodes a heparansulfotransferase enzyme, was found mutated in CHH and that heparan6-O-sulfation was required for anosmin function in vivo [81]. Based on the fact that multiple genes from FGF family are mutated in CHH, Miraouli studied 386 individuals from CHH group with 155 controls to study role of “FGF syn expression group” and found except for FGF18 [MIM 6063726] and SPRY2 (Sprouty homolog2 [MIM602466]), all other genes were found to be mutated in CHH individuals[FGF17(n=3indivinduals), IL17RD(Interleukin 17 receptor D)[MIM6068007](n=8)DUSP6(Dual Specificity phosphatase 6)[MIM602740] (n=5), SPRY4(Sprouty homolog 4)[Drosophila][MIM607994](n=4), FLRT3(Fibronectin leucine rich transmembrane protein 3) [MIM604808] (n=3)while FLRT3 is an enhancer, as compared to others which are inhibitors. They further concluded mutations in IL17RD were found only in KS individuals and were strongly linked to hearing loss individuals (6/8). Further mutations in genes encoding components of FGF pathway are associated with complex modes of CHH inheritance, and act primarily as contributors to an oligogenic genetic architecture underlying CHH [82].

Since genetic testing is becoming complex and costly Costa-Barbosa et al suggested prioritizing genetic testing in patients with KS using clinical phenotypes. For example certain clinical features commonly associated with genetic causes are synkinesis (KAL1), dental agenesis(FGF8/FGFR1), digital bony abnormalities(FGF8/FGFR1) and hearing loss (CHD7) and these can be useful to prioritize genetic screening, although renal agenesis and cleft lip and palate did not emerge as statistically significant predictors [83].This is in slight contrast with the report of Dode et al where they report associations of renal agenesis with KAL1 and cleft lip/palate with FGF8/FGFR1 mutations which was not found in this study [40,84].

However Moya-Plana found disolated congenital anosmia (ICA) and olfactory bulb agenesis without gonadotropin deficiency and found three PROK2 mutations previously described for KS and one new PROK2 mutation, and incomplete penetrance on investigation of families, on screening for KAL1/FGF8/FGFR1/ PROK2/PROKR2 which suggests the considerable complexity of GnRH neuron development in humans [74].

However before coming to a diagnosis of CHH one must rule out the differential diagnosis of pituitary tumours, or pituitary infiltration by neuroimaging studies like MRI [85,86], juvenile hemochromatosis by serum iron and serum ferritin levels [87], and a systemic disorder that by undermining nutritional status could affect gonadotropin secretion and pubertal development like anorexia nervosa, celiac disease [88]. Anterior pituitary function must be thoroughly evaluated to
rule out hyperprolactinemia [18,85], primary hypothryoidism, GH, ACTH and investigate adrenal axis or somatotrope specifically when pubertal delay is accompanied by statural retardation and rule out multiple hormone deficiencies. Indeed diagnosis of any associated endocrinopathy of this type will reorient the etiologic diagnosis towards a specific lesional genetic disorder [89-94] which will thus conclude that the HH is isolated. The most likely differential diagnosis before 18 year is constitutional delay of puberty. Since HH may present as delayed puberty it becomes essential to know how to distinguish constitutional delay of growth of puberty (CDGP) from isolated HH with definitive diagnosis of HH awaiting lack of spontaneous puberty by 18years. Although basal gonadotropins and GnRH Stimulation tests have limited diagnostic specificity, with overlap in gonadotropin levels between adolescents with CDGP and HH, Stimulation tests using more potent GnRH agonists (especially leuprolide acetate) and/or human chorionic gonadotropin (hCG) may have better discriminatory value, but small study size, lack of replication of diagnostic thresholds, and prolonged protocols limit clinical application. Basal inhibin B may offer a simple discriminatory test, however in a recent metaanalysis Harrington J2012 didn’t find any reliable diagnostic test and recommend this an important area for future investigation ([29] for review and figure 1).

In paediatric endocrinology this differential diagnosis is far more difficult as CHH is rare whereas CDGP is infrequent [95]. Serum inhibin B levels in CHH males correlate with testicular volume and thus with clinical severity of gonadotropin deficiency [39,96,97] and with very broad and overlapping values this single marker is not dependable. In view of all difficulties classical clinical features distinguishing CHH from CDGP are still of practical value, especially observing testicular volume over time, in patients receiving exogenous testosterone. In male patient with pubertal delay and low gonadotropins presence of micropenis and/or cryptorchidism practically rules it out since they are rarely seen in CDGP and favours CHH [95,98]. Signs of a particular etiology are also useful like anosmia etc figure 2(see [99] for review).

Recently a novel syndrome has been defined known as TUBB3E410 K Syndrome where one of the eight missense mutations in TUBB3 gene, that encodes the neuronal specific protein β tubulin isotype 3, have congenital fibrosis of the extraocular muscles, facial weakness developmental delay, and possible peripheral neuropathy. This occurs due to c.1228G >A resulting in a TUBB3E410K amino acid substitution which directly alters a kinesin moto4r protein binding site. In detailed phenotype of eight unrelated individuals Chew confirmed electrophysiology that a progressive sensorimotor polyneuropathy does indeed segregate with the mutation and expand the TUBB3E410K phenotype to include KS, stereotyped midface hypoplasia, facial weakness, and HPE may display a genetic overlap and in view of this the involvement of genes implicated in the etiology of midline defects of the anterior midline in the human forebrain. It has been recently shown that deficient migration of GnRH neurons is also a feature in forebrain formation defects [101]. Hence Raivio studied 103 patients with either CPHD (n=35), or SOD (n=68) and investigated them for mutations in genes implicated in the etiology of KS (FGFR1, FGFR8, PROKR2, PROK2 and KAL1). Mutations in FGFR1/FGFR8/PROKR2 contributed to 7.8%of their patients with CPHD/SOD which suggests a significant genetic overlap between conditions affecting the development of anterior midline in the human forebrain. Of the SOD 3 patients had heterozygous mutations in FGFR1, with these either shown to alter receptor signaling (Ps450F, Pp483S) or predicted to affect splicing (c.216G >A, p.T72T) that was shown to affect splicing and ligand signaling activity. Four patients with CPHD/SOD were found to harbor heterozygous rare loss of function variants in PROKR2 (p.R85H, p.R85H, p.R266C) [102]. To further study the role of PROKR2/PROK2, McCabe further studied 422 patients of congenital hypopituitarism (CH) and detected that variations in PROKR2 but not PROK2 are associated with CH and SOD. They detected 5PROMR2 variants in 11 patients with SOD/CH: novel p.G371R and previously reported p. A51T, p.R85L, p.L173R and p.R266C-the latter three being known as functionally deleterious variants. Surprisingly, although 1patient with SOD was heterozygous for the p.L173 Rvariant, his phenotypically unaffected mother was homozygous for the variant [103]. Midline defects are encountered in all three disorders, namely KS [MIM; 147950], SOD[MIM;182230] and holoprosencephaly [HPE; MIM 236100], a complex brain malformation that affects both the forebrain and face. In SOD mutations have been identified in number of transcription factor genes such as SOX2, HESX1, SOX3, and OTX2, which are essential for normal forebrain development [104], and also in HPE genes like SHH, SIX3, TGF1, TDF1, FOXH1and GLI2 have been found to be mutated [105,106]. Hence Vaaralahti 2012 studied 19 subjects (18 males) with KS without known KS genes and screened them for mutations in SOX2, SHH, SIX3, TGF1, TDF1, FOXH1, GLI2 and GLI13. One male carried 2heterozygous missense changes, one in SIX3 (c.428G>A, p.G143D) and the other in GLI2 (c.2509G>A, p.E837K).Both of these genes have been implicated in etiology of HPE and none was present in 200 control subjects. Thus they concluded thatKS and HPE may display a genetic overlap and in view of this the involvement of genes implicated in the etiology of midline defects in patients with KS warrants further studies [107].

**MANAGEMENT**

The initial goal of treatment for adolescents and young men who present with CHH is to induce physical and behavioral development matching that of normal healthy subjects of same age. This includes development of secondary sex characters like pubic and axillary hair, increase in penis size, voice masculinization and development of muscle mass. Further one aims at correcting the delay in bone maturation and deficient bone mineralization, enhance libido and modify sex behavior. Mostly effective testosterone replacement therapy can lead to a spectacular improvement in quality of life, which demonstrates a causal relationship between testosterone deficiency and these patients’ symptoms.

Although it is more physiological to achieve such benefits with
pulsatile GnRH administration or with combined gonadotropin therapy (human chorionic gonadotropin and FSH) [108,109] with both therapies effectively inducing testicular growth and secretion of testosterone and estradiol [108]. We have to consider availability of GnRH infusion pumps, cost of treatment, patients requirements especially if patient presents as a partner of an infertile couple with spermatogenesis in view. Since long term treatment is required even in west mostly testosterone therapy as (injectable esters) is generally preferred for convenience of infrequent injections and cost, DHT is not preferred as it can’t be aromatized to estradiol and hence can’t serve the dual purpose of testosterone esters used for decades now as first line treatment. TN enanthate is one of the cheaper preparations, used at a dose of 200-250 mg once every 2 or 3 weeks. Although these doses depend on age at diagnoses and local practices, Pediatric endocrinologists who see these patients at a younger age, initially prescribe lower doses, gradually increasing for fear of inducing abrupt virilization and bone maturation which could cause behavioral and relational problems. Endocrinologists see adult CHH patients at a later stage when main signs/symptoms are of severe hypogonadism, and usually require full dose. Although two approaches are not comparable patient should be counseled that he will need longterm androgen therapy. Once full virilization has been induced by exogenous testosterone, males whose testes have significantly increased in size (<5%cases) should be revaluated off androgen replacement therapy to identify those with reversible forms [110,111] who no longer require treatment.

Patients who wish to have an increase in testicular volume or fertility in developing countries like ours where most centres don’t have the facilities of infusion pump the approach of combination therapy with initial rFSH with the idea of stimulating proliferation of immature sertoli cells which are

Figure 1 Courtesy ref 73-In a subset of adolescents with IHH (and Kallmann syndrome),mutations in genes that encode critical components of the HPG axis lead to either a lack of GnRH secretion or action. The etiologies in the remaining cases are undetermined. The lack of GnRH action leads to a deficiency of both priming and hormonal secretion of the gonadotropins in the pituitary and of the leydig/theca cells of the gonads. These characteristics of the HPG axis form the physiological basis for the diagnostic tests (indicated in bold face) and typical characteristics (indicated in italic anosmia/hyposmia, small testes, micropenis, cryptorchidism) used to identify patients with a higher likelihood of IHH than CDGP.
### Congenital hypogonadotropic hypogonadism (CHH)

#### Sense of smell in propositus and relatives
- Interview to detect anosmia or deep hyposmia
- If apparently normal olfactometry and/or olfactory bulb MRI

#### NORMAL
- (and without other signs suggesting Kallmann syndrome)

#### Or a syndromic cause in the propositus and/or relatives

#### Normosmic Kallmann

#### Non syndromic CHH

- GNRHR
- KISS1R
- TAC3 and TACR3
- GnRH1

#### No mutation
- (or monoallelic mutation)

#### Or without others signs suggesting Kallmann syndrome

#### Or a syndromic cause in the propositus and/or relatives

#### Normosmic Kallmann

#### Non syndromic CHH

- GNRHR
- KISS1R
- TAC3 and TACR3
- GnRH1

#### No mutation
- (or monoallelic mutation)

#### Figure 2

With permission from Dr. Young courtesy ref79-Molecular studies performed in male patients of CHH categorized on the basis of smell and:
1) MRI, 2) Bimanual synkinesis, tooth agenesis, hearing impairment, renal agenesis, cleft lip/palate, high arched palate, pes cavus, ptosis, absent nasal cartilage, hand/foot skeleton abnormalities and iris coloboma.

3) Step by step strategy based on familial history and putative mode of disease inheritance (pedigree), and the presence of additional clinical anomalies as mentioned above that may direct the geneticist towards a particular Kallmann gene.

4) For instance, KAL1 is analyzed especially in Kallmann men with mirror movements (bimanual synkinesis) and/or for kidney agenesis and/or when the pedigree suggests an X-linked mode of inheritance; whereas,

5) in subjects displaying cleft lip/palate FGFR1 mutations are searched in first line whatever the apparent mode of inheritance.

6) in subjects with monoallelic PROK2 or PROKR2 mutations, search for mutations in other CHH genes to demonstrate a digenic or oligogenic mode of inheritance.

7) Analysis of other large genes mentioned below performed in second line, given their lower or unknown prevalence among normosmic CHH and Kallmann men. Sizes of the genes currently sequenced in CHH patients: GNRH1, three exons; GNRHR, three exons; KISS1R, five exons; TAC3, six exons; TACR3, five exons; KAL1, fourteen exons; FGF8, six exons; FGF8, 18 exons; PROK2, four exons; PROK2, four exons; CHD7, 38 exons; WDR11, 29 exons; NSMF (NMDA receptor synaptosomal signaling and neuronal migration factor—formerly known as NELF), 16 exons.
under control of FSH initial doses of 1.5iu/Kg (180-450u/week ) x2months -2.8yrs Puberty is then initiated with hCG 500iu-4000 iu/week, 1-3times/week sc and after onset of hCG treatment if patient can’t afford can shift to highly purified FSH. Raivio found this induced prepubertal testes growth with increase in serum inhibin B levels, and 6/7 prepubertal boys displayed sperms despite extremely small initial test is primed with rFSH [111].

GnRH treatment is successful in inducing virilization and spermatogenesis in men with IHH; however a small subset of IHH men, fail to reach a normal testicular volume and produce sperm on this therapy [112]. Pitteloud in studying 76 IHH men undergoing GnRH therapy for 12-24 months to define predictors of outcome of long term GnRH therapy concluded anosmia was not an independent predictor, however favorable predictors of achieving an adult testicular size and consequently optimizing spermatogenesis are prior history of sexual maturation, with a baseline inhibin(IB) > 60pg/ml along with absence of crypotorchidism [113].

Further extending this study on GnRH treatment, Sykiotis et al studied 90 patients and classified patients into four groups according to the response obtained to long term physiological pulsatile GnRH release . 1) 67/90 subjects displayed normal expected response, with normal serum T (270-1100ng/dl, LH (4.2-17IU/Land FSH (1.8-14IU/L) and had sperm in their ejaculate and were labeled as typical responders. In rest 23 patients(26%)three distinct patterns were seen 2)10men remained hypogonadotropic and hypogonadal with low normal LH/FSH, serum T, <200ng/dl and no sperm despite GnRH doses upto 800ng/Kg and thus labeled Group 1 with triple defect with GnRH deficiency, pituitary resistance and testicular failure. 3) 8men achieved normal serum T and produced sperms but did so with high LH (>17IU/L and FSH >14IU/L and thus labeled Group 2 with dual defect, GnRH deficiency and testicular resistance. 4) 5men remained azoospermic after atleast 21 months despite achieving normal serum T, LH and FSH and thus labeled Group 3 with GnRH deficiency with azoospermia. Although typical responders showed mutations in all the IHH genes tested, atypical responders displayed mutations exclusively in KAL1 Gene [114]. Although Sinisi et al reported a case with homozygous mutation in PROKR2 gene Val274 Asp which presented as reversible KS along with persistent oligozoospermia [115].

Dwyer 2013 conducted a randomized open label prospective trial to see if there is any benefit of giving recombinantFSH (rFSH) pretreatment for 4 months followed by pulsatile GnRH therapy vs GnRH therapy alone in a group of CHH patients with prepubertal tests (<4ml), no cryptoorchidism, and no prior gonadotropin therapy and found rFSH increased inhibin B levels into normal range (29+9-107+41pg/ml) and doubled testicular volume from 1.1-2.2ml. Histological analysis showed proliferation of sertoli cells (SC) and spermatogonia, a decreased SC to germ cell ratio from 0.74 to 0.35 and SC cytoskeletal rearrangements. Although with pulsatile GnRH similar hormones and significant testicular growth was exhibited, all men receiving rFSH developed sperms in their ejaculate (7/7 vs 4/6in GnRH only group) and showed trends towards higher maximal sperm counts and hence concluded that rFSH not only appears to maximize the SC population, but also induces morphologic changes, suggesting broader developmental roles [116]. This maybe in accordance with the results of study of Pitteloud where he found while studying 25 patients of IHH that when analyzed for degree of pubertal/testicular development (TV < or =3ml)Group 1 men showed sharp increases in serum FSH compared to men with some prior evidence of partial puberty (TV>3ml Group II. Group I exhibited a decreased LH response to GnRH on day1, compared to day1 which did not recover until day5 (1-4 vs 5-7days). GroupII exhibited a robust and equivalent LH response to GnRH throughout 7days of study. The mutations identified were in 4 different locations on genetic studies (DAX1, KAL1, GNRH1, FGFR1) in this cohort. Hence they concluded GnRH deficient men undergoing GnRH induced sexual maturation displayed an inverse responsiveness to GnRH and baseline testicular size and 1 (B) levels. This observation implied that increasing seminiferous tubule maturity represents the major constraint on FSH responsiveness to GnRH in early puberty. In contrast LH responsiveness to GnRH correlated directly with duration of GnRH exposure. Although attenuated pituitary gonadotropin responses were noted in 2 subjects harboring DAX1 mutations it is consistent with their known pituitary defects and this model of IHH helps study the normal physiology of puberty which one can’t disscut out in normal adoselscent boys with intact H-P-G axis [117].

Still controversy exists on the sexuality and intimate relations of men with severe CHH accompanied by cryptorchidism and microopenis [118]. Since there is a negative prognostic value of cryptorchidism and low testicular volume for the future fertility of patients with severe CHH, a trial of earlier gonadotropin therapy during the neonatal or normal pubertal period is warranted and just may prove beneficial, both in terms of testicular hypertrophy and in terms of future fertility [119-122]. Not only do we learn how to manage these patients but these patients of IHH have served as good models to make us understand the role of testosterone, estradiol feedback at hypothalamic and pituitary control of GnRH secretion in human model otherwise.

ROLE OF ESTRADIOL
Trabados studying 91 men of IHH, with 63 controls and 45 patients of Klinefelters syndrome found male hypogonadism in CHH is associated with profound E2 insufficiency which can be overcome by aromatizable androgen (Tenanthane) or combined gonadotropin (FSH-hCG) therapy, but not dihydrotestosterone (DHT) contrary to Klinefelters syndrome [108]. This E2 deficiency is also associated with abnormal bone development, noteenage growth spurt and osteopenia or osteoporosis. Reports that altered E2 production (aromatase loss of function mutations), and responsiveness (E2 receptor inactivating mutations) are associated with adverse skeletal effects in men strongly suggest that E2 are critically important for male sexual development and bone mineral density acquisition [123-125]. Further Rochira reported 4 cases of tall stature without growth hormone deficiency who had a impaired response of GH to GHRH-ARG as compared to normal subjects and who had significantly lower IGFB1 levels as compared to normal subjects and both IGFB1 peak and concentrations were not modified by estrogen therapy in men with aromatase deficiency and concluded insulin as the...
cause of tall stature rather than GH for the marked increase in height due to nonclosure of epiphyses [126]. Besides that for normal physiology, Pitteloud 2008 showed that for Inhibition of LH secretion by T in men aromatization is required for its pituitary effect but not its hypothalamic effect as shown by studying 11 men with GnRH deficiency and 21 normal (NL) men and using ketonozole for medical castration and inhibition of aromatase. They showed that in NL men KC caused a3fold increase in mean LH, which was stable on d6-7 with no add back. Addition of Treated LH levels (34-17IU/L) by slowing GnRH frequency pulses, whereas LH amplitude increased from 6.9 to 12.1IU/L, E2 add back suppressed LH levels from 36.4-19IU/L, by slowing GnRH pulse frequency (11.4-8.6pulses/12h but had no effect on LH amplitude). In IHH men restoring normal T levels caused no suppression of mean LH levels/LH amplitude. E2 add back normalized mean LH levels and decreased LH levels and decreased LH amplitude from 14.7 to 12IU/L and thus concluding both T and E2 have independent effects on LH 2) Inhibition of LH by T requires aromatization for its pituitary but not hypothalamic effect 3) E2 has dual sites of feedback, but its predominant effect is at the hypothalamus [127].

Further since KP10 is a potent stimulator of LH and increases pulse frequency in men and men LH and testosterone levels in normal men there may be a potential role of KP agonists in HH due to KISS 1/KISS1R mutations [128,63]. Although TAC3/TACR3 mutations also are associated with IHH administration of NKB was not accompanied by increase in serum LH and testosterone levels, hence role of NKB doesn't appear to be useful in treating these patients presenting with TAC3/TACR3 mutations [129,130].

CONCLUSION

Despite finding so many early developmental genes like KAL1, FGF8, FGFRI, NELF, CHD7, PROK2, PROKR2, HeSST1, SEMA3A in astudy of a large cohort of GnRH deficient patients (n=397) at the Massachusetts general hospital at least roughly 32% have been linked to at least one gene mutation (when studying all genes including those involved in GnRH function like (KISS1/KISS1R, GnRH/GnRHR/TAC3/TACR3) whereas just for KS mutations in any of the 9 genes identified thus far have been found only in approximately 30% patients [131,132] Suli a lot of controversial issues remain regarding role of PROK signaling as highlighted in [58] regarding absence of PROK receptors on GnRH neurons, mode of inheritance-digenic/oligogenic [133] with presence of PROK2 mutations even in normosmic HH and thus extending the role beyond olfactory bulb development and GnRH neuronal migration and absence of any defect in homoygous mutations while most of human presentations being in heterozygous mutations. Further recently that there may be an ethnic role is highlighted by greater presence of PROKR2 mutations in KS patients from Maghreb as compared to European origin patients (23.3% vs 5.1%) [134]. Further more work needs to be done on other transcription factors as has been shown for SOX10 i.e., loss of function mutations in SOX 10 is associated with KS along with deafness [135]. Similar work needs to be done for other transcription factors in view of genetic overlap of other midline forebrain disorders like SOD and HPE with KS.

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