Male hypogonadotropic hypogonadism in various genetic disorders

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Abstract

Introduction and purpose: Male hypogonadism is diagnosed in patients with total testosterone under 9-12nmol/L (250-350ng/dl) in serum which is associated with numerous symptoms which can severely lower the quality of patients life. Due to the cause and associated levels of gonadotropins it can be divided to hypergonadotropic and hypogonadotropic hypogonadism. Hypogonadotropic hypogonadism occurs far less often, but it's considered to remain underdiagnosed. The purpose of this study is to review most of the inborn diseases that involve hypogonadotropic hypogonadism as one of their components.

Current state of knowledge: Patients with Kallmann syndrome constitute the majority of confirmed hypogonadotropic hypogonadism cases, however due to variable epidemiological data and differing diagnosing processes the exact incidence cannot be estimated – it ranges from 1 in 85 000, to 1 in 5000 males and about 3-4 times less often in women. Other conditions that can occur with hypogonadotropic hypogonadism are Isolated Gonadotropin-Releasing Hormone deficiency, Gonadotropin disorders, Prader-Willi Syndrome, some pleiotropic syndromes like CHARGE syndrome, Patau syndrome, Pfeiffer syndrome, Hartsfield syndrome, Waardenburg syndrome, Bardet-Biedl syndrome, or other syndromes. The evaluation and treatment of some of these conditions does not involve hypogonadism or other gonadal disorders due to short lifespan, which cause the underestimations in hypogonadism morbidity.

Conclusions: Regardless of lower incidence of hypogonadotropic hypogonadism compared to hypergonadotropic type, endocrinologists should stay aware of its under-diagnosis and actively search for signs of low gonadotropic hormones and gonadotropin-releasing hormone levels in hypogonadal patients.

Key words: Hypogonadism; hypogonadotropic; testosterone; genetic disorder; Kallmann syndrome

Introduction and purpose

Hypogonadism is a condition defined as sex hormones deficiency in males and females. Classification marks out two types of hypogonadism – hyper- and hypogonadotropic. Focusing on men, the state of substantially low testosterone level (total testosterone under 9 – 12 nmol/L (250-350 ng/dl) [1]) in morning serum, reduced spermatogenesis with high levels of gonadotropins such as luteinising hormone (LH) and follicle-stimulating hormone (FSH) belongs to the first type (primary hypogonadism) which is caused by testicular failure. When it comes to the second group (secondary hypogonadism) the main issue lays in the dysfunction of hypothalamus and/or pituitary gland, which causes decrease in level of serum testosterone and spermatogenesis impairment. Serum LH and FSH levels in this type are decreased or in a lower range of normal laboratory values [2][3].

Due to the low number of people who undergo diagnostics, it is very difficult to estimate the number of males suffering from hypogonadism in the general population.. However it was estimated that 40% of men over 45 years old and 50% men in their 80s are suffering from hypogonadism [4]. Some studies showed that hypergonadotropic hypogonadism is more frequent, as 12,3 males per 1000 are diagnosed with various types of this disease annually (in the United States). On the other hand it was estimated that 1-10:10 000 patients suffer from hypogonadotropic hypogonadism. Secondary hypogonadism can be caused by congenital or acquired abnormalities, when it comes to inborn factors 2/3 of them are linked to Kallmann syndrome and 1/3 have different etiology [5].

As mentioned before, hypogonadotropic hypogonadism is induced by different causative factors. Starting from delayed pubertal development in children, where the hypothalamic-pituitary-gonadal (HPG) axis does not work properly - the main risk factors are chronic diseases (such as inflammatory bowel disease, celiac disease or hypothyroidism) which make up a large part (20%) of all the causes. Malnourishment, excessive exercise and psychological problems with strong negative emotions can be a part of the issue as well [6].

Hyperprolactinemia, pituitary lesions (for example tumour, granuloma or abscess), drugs (opiates, alcohol abuse), anabolic steroids, severe illness or pituitary irradiation, trauma or surgery are other factors having negative impact on HPG axis[2][5]. It has been reported that hypogonadism can be viewed as another important component of metabolic syndrome [7]. 1/3 of young men (14-35 years old) with obesity have lower levels of testosterone and relatively decreased amount of gonadotropic hormones but still within the normal range, indicating secondary hypogonadism [8]. Congenital hypogonadotropic hypogonadism can be isolated (isolated deficiency of gonadotropin/ gonadoliberin) or with other developmental defects. For example secondary hypogonadism with anosmia or hyposmia is known as Kallmann syndrome [9]. Patients who suffer from Prader-Willi syndrome, CHARGE syndrome or Waardenburg syndrome manifest with hypogonadotropic hypogonadism as well [10][11].

Symptoms of secondary hypogonadism can vary according to one's age and level of testosterone[2]. Men who suffered from it before puberty, clinically demonstrate eunuchoid proportions, delayed formation of secondary sexual characteristics, high-pitched voice, small testes, prostate and penis [12]. Post-puberty males show low libido, erectile dysfunction, infertility, low bone density, reduced body mass, depression and metabolic syndrome[13][5].

Complications of hypogonadotropic hypogonadism can have a highly negative impact on patients' lives. The main trouble is infertility as lower levels of testosterone disrupt spermatogenesis [5]. The sex steroid deficiency in congenital secondary hypogonadism leads to low bone density which can cause osteoporosis and make bones prone to fractures [14]. According to some studies, males with isolated hypogonadotropic hypogonadism with reduced levels of testosterone in serum are more vulnerable to diabetes and coronary heart disease [15].

The main aim of the treatment is to focus on restoring fertility, if possible. In connection with defects in hypothalamus and pituitary gland the substitution of gonadotropin and gonadoliberin in secondary hypogonadism is a preferable solution to testosterone replacement therapy, although it's expensive and not very accessible [16]. However the third option is helpful in supporting proper puberty and processes such as developing primary and secondary sexual characteristics [5].

The goal of this paper is to review genetic disorders that can be manifested by hypogonadotropic hypogonadism.

Current state of knowledge

Kallmann Syndrome

Kallmann syndrome (KS) is the most common type of gonadotropin releasing hormone (GnRH) deficiency and most common hypogonadotropic hypogonadism as well. Exact prevalence of KS is unknown, it's been estimated to affect 1 in 5000 boys and about 5 times less girls [17]. Those numbers vary depending on the population – according to the study conducted in Finland the prevalence of the defect is about 1 in 48 000 people (1 in 30 000 in males and 125 000 in females) [18]. The studies on military recruits in France revealed the prevalence of 1 in 10 000 males [19], and 1 in 85 000 males on Sardinian conscripts [20].

Presence of anosmia or hyposmia (lack or significantly lowered ability to smell) is specific to Kallmann syndrome. This relation was proven to occur due to common embryonic precursors

of olfactory and GnRH-releasing neurons which are parts of neural crest as well as ectoderm [21], [22]. Far over 20 different genetic mutations were identified [23] that can disrupt processes of migration and differentiation of those precursor cells, of which the most known are KAL1 (anosmin 1 protein) [24], FGF8 pathway proteins genes [25]–[27], CHD7 gene (chromodomain helicase DNA binding protein 7)[28], [29], or SOX10 gene [30]. As a result the olfactory nerve cells and GnRH-producing nerve cells are misplaced and cannot correctly perform, which leads to hypogonadotropic hypogonadism with anosmia, although exact pathological mechanism isn't known.

Coexisting hypogonadotropic hypogonadism and anosmia is enough for KS clinical diagnosis, although the disease can present with various other anomalies, such as facial dysmorphia (cleft lip and/or palate [25], [31], [32], hypodontia [25], [33]), congenital ptosis [34], [35], hear impairment [31], [32], abnormal ocular muscles activity [36], [37], renal agenesis[34], [38], or corpus callosum agenesis [25], [39].

The treatment of KS is currently the same as hypogonadism. There are no therapeutic options available for treating anosmia.

Prader – Willi Syndrome

Prader–Willi syndrome (PWS) is a genetic disorder that has an estimated prevalence of 1 in 10 000 to 25 000 live births [40], ranging from 1 per 8 333 in rural regions of Sweden [41], 1 per 15 830 in Australia [42], 1 per 17 482 in Japan [43], to 1 per 45 000 in UK [44]. Such differences, although seem to largely differ between populations of certain countries, likely come as a result of using different methods of identification of affected individuals. PWS mostly occurs in the Caucasian population, with both sexes affected equally [45].

The disease is caused by a deficiency in function of genes located on chromosome 15, locus 15q11-q13 due to deletion, from which scientists differentiated two types, according to breaking points: type 1 between breaking point (BP) I and III, consisting of more genes, and type 2, between BP II and III. Other types of mutations are uniparental disomy of chromosome 15 and imprinting defect, of which the most common is paternal deletion accounting for approximately 60% of cases, UPD 15 – 36%, and imprinting defect – 4% [46][47]. If such deletion occurs in the maternal chromosome, it causes Angelman Syndrome (AS). 15q11-q13, also called the Prader-Willi critical region (PWS/AS region), contains several genes, such as MKRN3, MAGEL2, NDN, SNURF-SNRPN, and a cluster of snoRNA long non-coding repetitive genes, the one main being SNORD116[48].

The key features of individual affected by PWS are: craniofacial and hand abnormalities, hypogonadotropic hypogonadism, growth hormone deficiency causing short stature, hypotonia in infancy, intellectual disability, development delay and hyperphagia that leads to obesity in early childhood [49]. Clinically PWS is divided into two stages: the first one during the perinatal and infancy period, when symptoms such as infantile hypotonia, poor sucking reflex leading to feeding problems, temperature instability, strabismus, hearing impairment, and hypopigmentation are present, also hypogonadotropic hypogonadism with hypogenitalism or primary gonadal failure. In the infancy LH and FSH levels are normally elevated [50]. The second stage is distinguished when between ages 2-6 the affected person demonstrates hyperphagia and food-seeking behavior that, if not controlled, could lead to morbid obesity associated with type 2 diabetes and dyslipidemia [51][52][49][53]. In later stages of life patients seem to have an increased risk of developing psychiatric disorders, such as bipolar syndrome or psychosis [54]. At the onset of puberty testosterone in males as well as

estrogen in females remain low to normal. Males are thought to be infertile, females could potentially become pregnant, with late first period at an average age of 20 [50].

There are three categories of diagnostics criteria for PWS: major counted for one point, minor for half, and supportive with the latter not given any points. Major criteria consist of such features as: improving over the age hypotonia, characteristic facial features, hypogonadism, hyperphagia, and abnormalities in the PWS/AS region. The minor criteria are composed of e.g. decreased fetal movement, behavioral problems, hypopigmentation, viscous saliva. In children 3-years-old and younger five point are required to diagnose a patient with the disease, four of them should be major. Patients older than 3 years old need eight points with five of them being major to confirm the diagnosis [55].

Currently, there is no causal treatment for PWS, however, through the therapy consisting of hormone substitution, strict diet, mental health support, and physiotherapy, patients can be protected from the development of life-threatening symptoms [56][57]. In vitro research suggests that potentially knocking out ZNF274 and restoring the expression of silent maternal alleles could lead to developing a healthy cell population [58].

Isolated Gonadotropin-Releasing Hormone deficiency and Gonadotropin disorders

Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD) is a part of congenital hypogonadotropic hypogonadism [59]. GnRH is a 10-amino acid neuropeptide, produced in the preoptic area of hypothalamus as it is the first hormone excreted in the hypothalamic-pituitary-gonadal (HPG) axis. It is released by axon terminals of the median eminence and it stimulates anterior part of pituitary gland to pulsatile secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH). Both hormones has great impact on sex steroids synthesis and gametogenesis [60]. The deficiency in GnRH production, secretion or action can lead to delayed puberty in younger patients and even infertility in adults causing extremely decreased quality of life [61]. Isolated disorders in LH and FSH secretion can be the cause of hypogonadotropic hypogonadism as well.

We can divide congenital hypogonadotropic hypogonadism in two types. First one is normosmic IGD (nIGD) which refers to 40% of all. Men who suffer from IGD and anosmia or hyposmia (Kallmann syndrome) are the second group and make up 60% of total [62]. There are no publications showing the exact number of patients with nIGD.

Many genes stay unknown as mostly oligogenic etiology is hard to investigate. However some genes characteristic for nIGD were described. Some of mentioned: GNRH1, GNRHR, KISS1, KISS1R (GPR54), TAC3, and TACR3. There are several common genes for Kallmann syndrome as well as nIGD as well, such as CHD7, FGFR1, FGF8, FGF17, NSMF, HS6ST1,PROKR2, PROK2 and WDR11 [62][63][64].

Prepubertal as well as postpubertal patients who are suspected to have nIGD show a normal clinical picture of hypogonadotropic hypogonadism and lowered level of testosterone, LH and FSH in serum [65]. After physical examination and basic biochemical tests, the next step is pituitary MR, however in recent years GnRH stimulation test is also evaluating due to accurate differentiation between hypothalamus and pituitary dysfunction [66]. There are several other tests which are recommended for diagnosis, such as prolactin level, measurement of Sertoli cell markers inhibin 1, amount of AMH (Anti Mullerian Hormone)

and hCG stimulation tests [67]. The last part of diagnosis is the smell test, such as University of Pennsylvania Smell Identification Test (UPSIT) [68]. If these trials show dysfunction of GnRH production or secretion, as well as its incorrect action and normal sense of smell, we can conclude nIGD. At risk relatives of families with X-line and autosomal recessive inheritance can have genetic tests only if pathogenic variants are known, prenatal testing is also available [62].
nIGD treatment does not vary from basic hypogonadotropic hypogonadism therapy [62].

Pleiotropic genetic syndromes

Pleiotropy is a phenomenon, which concerns one gene mutation that has many effects on unrelated tissues and features [69]. Congenital hypogonadotropic hypogonadism (CHH) can occur as a part of many syndromes, which pathogenesis is based on pleiotropy. Types of mutations involve gain or loss of function, dominant negative or haploinsufficiency. Some pleiotropic genes can be modified by other genes due to oligogenic inheritance of CHH [70].

CHARGE syndrome is a genetic autosomal dominant disease. Due to some studies on patients with that condition, the most frequent defect occurs in genes of chromodomain helicase DNA-binding 7 (CHD7) [71][72]. Its role is to supervise proper migration of multipotent neural crest cells, which form into multiple tissues, including genitourinary structures [72]. Studies show that the most common mutation type (because 75%) are nonsense and frameshift [71]. It is fairly prevalent syndrome as annually 1:10 000 – 15 000 patients will be diagnosed. CHARGE is an acronym which first letters stand for: Coloboma ocular, Heart defects, Atresia, Retardation of growth, Genitourinary anomalies and Ear abnormalities. Gonadal defects are mostly related to the hypogonadotropic hypogonadism, which mostly occur with anosmia, same as in Kallmann Syndrome [73]. Hormone replacement therapy or gonadoliberin therapy are among treatments implemented in patients with CHARGE syndrome [74].

Patau syndrome was clinically described in 1960 by Dr Patau [75], who connected congenital clinical symptoms such as: microcephaly and intrauterine malformations, with trisomy of chromosome 13. The most common defects concern: facial changes as cyclopia, cleft lip and/or plate and small ears. Central nervous and cardiovascular systems remain affected as well. Further organs with impairment functions are lungs, kidneys, liver and genitals [77]. More than 50% of patients suffer from hypospadias, cryptorchidism and micropenis which can accompany hypogonadotropic hypogonadism [78]. When it comes to epidemiology it is the third most common trisomy, after Down and Edwards syndrome. The frequency is estimated at 0,5:10 000 [76].

Another condition connected to CHH is **Pfeiffer syndrome** [79]. It is an autosomal dominant disease caused by mutation in fibroblast growth factor receptors (FGFR)-1 (chromosome 8p) and FGFR-2 (chromosome 10q) [80]. It is a highly rare syndrome which affects up to 1 person in 100 000 annually [81]. People who suffer from Pfeiffer syndrome demonstrate skull deformations, mostly "cloverleaf skull". Acrocephaly and brachycephaly are observed. Proptosis, hypertelorism, and broadened thumbs are commonly seen as well. Hypogonadotropic hypogonadism may occur, but it is not always related to that condition [79][81].

Hartsfield syndrome is a rare congenital disease, which is also caused by mutation in the FGFR-1 gene that has heterozygous (autosomal dominant) or biallelic (autosomal recessive) variants [83]. Clinically it consists of two core dysfunctions: holoprosencephaly spectrum and

ectrodactyly spectrum [82]. For the final recognition patient should also present cleft lip or cleft palate [84]. Brain malformations such as corpus callosum agenesis, absent septum pellucidum, absent olfactory bulbs, and vermian feeding difficulties are the most frequent. Eye and cardiac malformations, as well as endocrine problems for example hypogonadotropic hypogonadism and central diabetes insipidus are also seen[85][82][84].

Subsequent congenital condition is known as **Waardenburg syndrome** (WS). It affects 1:40000 patients annually [86] and is related to autosomal dominant SRY Box 10 (SOX10) gene mutation which is also seen in Kallmann syndrome [87]. There are four main types of WS which are recognized in connection with major and minor criteria. So that patients with type 1 WS present 2 major criteria or 1 major and 2 minor. Type 2 concerns one's with 2 major criteria, and does not show dystopia canthorum. Individuals with type 3 and 4 meet the same criteria as type 1, however type 3 protrudes from musculoskeletal malformations, and type 4 - Hirschsprung disease. The last type differs from the rest as it is inherited recessively. So the major criteria for WS are: congenital hearing loss, dystopia canthorum[88] and pigmentary defects in skin, eyes and hair, due to lack of melanocytes [86]. Some studies showed that WS can occur with hypogonadotropic hypogonadism, however it is not highly common for that disease [89].

Bardet-Biedl syndrome (BBS) is a rare, autosomal, recessive disorder with severe multiorgan impairment. The prevalence of this disease varies from 1 in 140 000 to 1 in 160 000 in North America and Europe to even 1 in 13 500 in Kuwait. [90] BBS in the past was associated with Laurence-Moon-Biedl syndrome, but from 1920 it is described as a separate disorder. [91]

Currently, there are at least twenty genes (BBS1-BBS20) known that are leading to the abnormal structure and impaired functioning of primary cilia, which play a key role in sensory perception and various signaling pathways. Due to defective cilia, intercellular communication is disturbed, which contributes to many congenital defects and disease symptoms. BBS is associated with five fundamental characteristics including retinitis pigmentosa, polydactyly, obesity, hypogonadism and mental retardation. [92], [93] Hypogonadism is being reported frequently in BBS. Most researchers indicate that hypothalamic–pituitary dysfunction is responsible for hypogonadism. On the other hand, there are opinions that its cause is primary testicular atrophy. [94]–[97]

The divergent clinical features and varying age of onset often complicates the diagnosis of BBS. It is observed that in most cases the first stage of the disease diagnosis occurs when the patient reports the ophthalmologists for his ocular distress. Genetic diagnosis of BBS is complicated due to lack of gene-specific disease symptoms. However, it is gradually becoming more accessible with the invention of multigene sequencing technologies. Treatment of BBS is largely limited to symptomatic management. [91], [92]

There are many congenital pleiotropic syndromes that can cause hypogonadotropic hypogonadism. Interestingly many genes that occur in pleiotropic conditions, such as CHD7, FGFR1,SOX10, cause Kallmann syndrome as well [98].

Other syndromes

Trisomy 18, also known as **Edwards syndrome** (ES), is the second most common autosomal aneuploidy after trisomy 21. Several studies have shown that the estimated incidence ranges from 1 in 3 000 to 1 in 10 000 live births, with a predilection for females. [99]–[103] While

thirty years ago this disease was considered as a lethal anomaly, the latest literature documents that there is 50% chance of survival beyond one week, 8–25% of infants may reach their first birthday, and up to 10% are reported to survive up to several years. [104], [105]

Phenotype of patients results from full, mosaic or partial trisomy 18q. [99], [100] An extra chromosome (94% of cases), effect of invalid segregation of chromosomes in meiosis or postzygotic mitosis, is most often of maternal origin. [106]–[108] A small percentage of cases (<5%), called mosaic ES, occur when only some of the body's cells have an extra copy of chromosome 18. A piece of this chromosome translocates to another chromosome before or after conception. In such cases symptoms range from early mortality to apparently phenotypically normal adults, in which the mosaicism is detected after the diagnosis of complete trisomy 18 in a child. [109]–[112] In the partial trisomy form (<2%) only a segment of the long arm of the chromosome 18 is present in triplicate, often resulting from a balanced translocation or inversion carried by one parent. [102], [113] Most of the studies indicate that the critical fragment for the ES phenotype is that extending from q11.2. [114], [115]

Trisomy 18 is characterized by a diverse clinical picture with involvement of all organs and systems. The most frequent phenotypic characteristics consist of: prenatal growth deficiency, specific craniofacial features (microcephaly, micrognathia, hypertelorism), malformations of the thorax, abdomen, limbs, internal organs (kidney, heart, esophageal defects), marked psychomotor and cognitive developmental delay. [116]–[119] Studies also point to failed embryonic migration of neuroendocrine GnRH1 cells from the nasal epithelium to the forebrain. This disrupted migration of neuroendocrine GnRH cells is responsible for hypogonadism. Although hypogonadotropic hypogonadism is not commonly reported, due to the short life expectancy, cryptorchidism and micropenis are common in affected men [120].

The above features of trisomy 18 are very typical, therefore they are rarely misdiagnosed with other diseases. Symptoms diagnosed during ultrasonography have to be confirmed with a karyotype test showing either partial or complete trisomy of the chromosome 18. Suspicion of ES can also be done by biochemical analysis – showing reduced levels of human chorionic gonadotropin.[121] Moreover to detect ES there are used other techniques such as the fluorescent in situ hybridization (FISH), the comparative genomic hybridization (CGH) or sequencing of fetal DNA molecules in the maternal blood. [122], [123]

Septo-optic dysplasia (SOD), also known as de Morsier syndrome, is a rare congenital disorder of brain malformations. Recent studies gave a reported incidence of 1,9/2,5 in 100 000 in Europe, with equal sex distribution. However, in retrospective regional study conducted in Canada the annual incidence reached even 53 in 100 000. [124], [125] The etiology of SOD is not fully explained, it is thought that it can be caused by viral infections, environmental teratogens and vascular or degenerative damage. Other factors include parental age, parity, alcohol and substance abuse, smoking, antenatal bleeding or ethnicity. [126] The classical triad of symptoms of this syndrome includes: optic nerve hypoplasia, agenesis of the pellucidum septum and corpus callosum and hypoplasia of the hypothalamo-pituitary axis. [127] Hypogonadotropic hypogonadism is thought to be conditioned by pituitary failure. Studies indicate that genetic factors are also involved in this condition. It is reported that SOX2 and WDR11 aberrations induce a wide range of symptoms, such as hypogonadotropic hypogonadism, pituitary hypoplasia, combined pituitary hormone deficiency. [128]
Cases with major anomalies may be diagnosed prenatally by ultrasound, while others appear later in infancy or childhood with the diagnosis of vision disability and growth failure leading to a final diagnosis of septo-optic dysplasia. Despite the fact that SOD is incurable, many of

its symptoms can be improved thanks to the adapted approach, consisting of hormonal exchange, corrective ophthalmic surgery and neuropsychological support. [127], [129]

Conclusions

Results of many studies accompanied by the abundance of clinical experience of many specialists in various fields of medicine brought us much knowledge about hypogonadotropic hypogonadism and its etiology, effects and the diseases it can be a symptom of. Although in a lot of different diseases a diagnosis of any type of hypogonadism doesn't matter clinically due to short lifespan of affected individuals, the discoveries of this particular one allowed to further investigate the pathophysiology of this defect, raise awareness, and as a result helped in developing potential treatment in the future. Regardless of all of those findings hypogonadotropic hypogonadism needs further research in order to increase said knowledge and disease detectability.

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