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KALLMANN'S SYNDROME AND NORMOSMIC ISOLATED HYPOGONADOTROPIC HYPOGONADISM: TWO LARGELY OVERLAPPING MANIFESTATIONS OF ONE RARE DISORDER

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Abstract:	Dear Editor, We are submitting the Letter to the Editor entitled "KALLMANN'S SYNDROME AND NORMOSMIC ISOLATED HYPOGONADOTROPIC HYPOGONADISM: TWO LARGELY OVERLAPPING MANIFESTATIONS OF ONE RARE DISORDER" by the Network Ipogonadismo Centrale (NICe) of the Italian Societies of Endocrinology (SIE), of Andrology and Sexual Medicine (SIAMS), and of Peadiatric Endocrinology and Diabetes (SIEDP). This letter is a position statement by an expert group of basic and clinical scientists (you can find the full list at the end of the letter) that is aimed to affirm the requirement for a revision of the Rare Disease classification by the Italian National Health system that discriminates the patients affected with these two largely overlapping clinical entities (KS and nIHH). Looking forward your decision on this manuscript, I send my very best regards. Yours sincerely, Luca Persani Corresponding Author
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Letter to the Editor

KALLMANN'S SYNDROME AND NORMOSMIC ISOLATED HYPOGONADOTROPIC HYPOGONADISM: TWO LARGELY OVERLAPPING MANIFESTATIONS OF ONE RARE DISORDER

The Network for Central Hypogonadism (Network Ipogonadismo Centrale, NICe) of the Italian Societies of Endocrinology (SIE), of Andrology and Sexual Medicine (SIAMS) and of Peadiatric Endocrinology and Diabetes (SIEDP).*

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Central Hypogonadism (CHg) is a disorder caused by an insufficient GnRH stimulation of an otherwise intact pituitary-gonadal axis. It is also called isolated or congenital gonadotropin-releasing hormone (GnRH) deficiency or Isolated Hypogonadotropic Hypogonadism (IHH). CHg may be either congenital or acquired, and can either be secondary to hypothalamic or pituitary dysfunctions. Isolated CHg is a rare disease with an incidence of 1:8,000 males and 1:40,000 females. It can either be associated with a normal or defective sense of smell, respectively identifying the normosmic CHg (nCHg or nIHH) or the Kallmann's syndrome (KS). Males frequently present with defective androgenization and growth at peripubertal age but micropenis and cryptorchidism may already be evident in the neonatal period, indicating a defective HPG activation during the prenatal development. Females generally present with primary amenorrhea and growth retardation. Additional neurological (e.g., anosmia, bimanual synkinesia) and non-neurological defects (e.g., the midline or kidney defects) may frequently co-exist and be linked to specific modes of inheritance. Indeed, KS was originally described as caused by mutations in a specific X-chromosome gene, *KAL-1* (reviewed in ref. 1), with a consequent altered targeting of olfactory axons and migration of neurons producing GnRH, the key central regulator of the reproductive axis, but this genetic defect was soon found to be present in a minority of the patients. Thus the causal event of the isolated CHg was often missing and the classification of "idiopathic" IHH or CHg was consequently adopted. Nevertheless, the observation of familial cases with variable modes of inheritance (X-linked or autosomal dominant or recessive) soon indicated that IHH or CHg retains a highly heterogeneous genetic component. The application of conventional linkage studies to investigate the genetic basis has proven difficult, because most pedigrees tend to be of small size, since the majority of patients remain infertile in the absence of therapeutic treatment. In the last decade, however, the knowledge on the pathogenesis of CHg has been profoundly deepened thanks to the utilization of animal and cellular models; these, together with the application of modern techniques of genetic investigation, brought evidence of previously unknown genetic determinants of IHH (either nCHg or KS). These new insights have played a significant role

in disclosing the physiological complexities of the HPG axis and therefore in elucidating the pathophysiology of IHH. Association with a multitude of candidate genes has nowadays been identified (1). Some genes are determinant for the correct embryonic differentiation of the GnRH-secreting neurons, such as the receptor-ligand pair FGFR1/FGF8 (Fibroblast Growth Factor Receptor 1; Fibroblast Growth Factor 8), NELF (Nasal Embrionic LH releasing hormone Factor) and HS6HST1 (Heparan Sulfate 6-O-Sulfotransferase 1). Other genes encode the signals essential for the correct migration of the GnRH neurons form their embryonic origin to the hypothalamus, such as the KAL-1, the ligand-receptor complex PROK2/PROKR2 (Prokineticin 2 and its receptor), the CHD7 (Chromodomain Helicase DNA binding protein 7) and SEMA3A (members of the class 3 Semaphorins). Other genes encode the elements of upstream signals contributing to the activation of GnRH neuron, such as the two ligand-receptor couples formed either by the TAC3/TACR3 (Tachykinin 3 and its receptor also named Neurokinin B, NKB, and/or Neurokinin 3 Receptor, NK3) or the KISS1/KISS1R (Kisspeptin1 and its receptor, previously known as GPR54). Finally, candidate genes for IHH also include the GnRH gene itself (GnRH1) and its receptor (GNRHR).

IHH was classically classified into two distinct clinical entities, KS and nIHH. However, such separate classification has been questioned in recent years since these two entities may exist in different relatives within unique familial settings, thus supporting the idea that they may constitute variable phenotypic manifestations of largely common genetic defects (2). On such basis, a novel vision is presently arising in which IHH may be considered as a complex genetic disease characterized by variable expressivity, penetrance and modes of inheritance in which the inability to go through puberty represents the cardinal manifestation. As in multifactorial complex diseases, the pathogenesis of IHH may include the influence of environmental factors, but also the concurrent involvement of SNPs or other genetic defects in two or multiple interacting genes. Indeed, the recent reports of patients carrying pathogenic rare variants in more than one gene have challenged the long-held view of a strictly monogenic disorder. Oligogenicity, which is as frequent as the biallelic defects in a single gene, may partially account for the phenotypic variability of isolated

GnRH deficiency, as demonstrated in a North-American cohort (3) and more recently confirmed in the Italian cohort presently constituted by 394 cases, that have been collected thanks to the collaboration among three different Scientific Societies and numerous referral centers (see Ref. 1).

In conclusion, the more recent genetic studies and genotype/phenotype correlation analyses have clearly confirmed that central hypogonadotropic hypogonadism is a multifaceted genetic disease including anosmic (Kallmann's Sindrome) and normosmic (IHH) phenotypes. Both of these manifestations undergo similar therapeutic protocols for the induction of puberty and fertility, whereas no treatment is so far available for the osmic defect. Therefore, the patients classified with either of these two clinical entities should not be discriminated, and the possibility of a total exemption from clinical expenses given by the Italian National Health System only to patients with the diagnosis of Kallmann Syndrome (Rare Disease code: RC0020) should be extended to the patients with normo-osmic forms of central hypogonadism (nCHg or nIHH).

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DISCLOSURE STATEMENT

The Authors declare no conflict of interest related to this work.

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