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Congenital hypogonadotropic hypogonadism in females: Clinical spectrum, evaluation and genetics

Hypogonadisme hypogonadotrope chez la femme : clinique, exploration et diagnostic génétique

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Résumé

Les hypogonadismes hypogonadotrophiques congénitaux (HHC) sont une cause bien connue de défaillance du développement pubertaire chez la femme. Chez la grande majorité des patientes, le tableau clinique résulte de la sécrétion insuffisante et concomitante des deux gonadotrophines hypophysaires LH et FSH qui empêchent un fonctionnement normal ovarien endocrine et exocrine cyclique après l’âge d’activation pubertaire de l’axe gonadotrope. Dans des cas exceptionnels mais intéressants, elles peuvent découler d’un déficit électif d’une des gonadotrophines FSH ou LH par anomalie génétique de leur sous-unité β spécifique. La prévalence de l’HHC, estimée à partir de séries hospitalières est considérée comme deux à cinq fois moins importante chez les femmes par rapport aux hommes atteints de ces maladies. Cette fréquence est probablement sous-estimée du fait d’un diagnostic insuffisant des formes avec développement pubertaire partiel. Les formes isolées ou apparemment isolées (i.e., syndrome de Kallmann avec anosmie ou hyposmie non exprimée spontanément par les patients) de ces maladies sont découvertes le plus souvent pendant l’adolescence ou à l’âge adulte devant un développement pubertaire absent, incomplet ou apparemment complet mais avec quasi constamment une aménorrhée primaire. Dans une minorité de cas et surtout dans les formes familiales des causes génétiques à transmission autosomique ont été retrouvées. Il s’agit dans ces cas de mutations de gènes affectant le fonctionnement de la cascade de signalisation hypothalamo-hypophysaire impliquée dans la sécrétion normale de LH et FSH (mutations de GnRHR, GnRH1, KISS1R/GPR54, TAC3, TACR3) et qui sont toujours associées à des déficits gonadotropes congénitaux isolés, avec olfaction normale et non syndromiques. Des cas de mutations de FGFR1, plus rarement de son ligand FGF8, ou de PROKR2 ou son ligand PROK2 ont été mis en évidence chez des femmes atteintes de syndrome de Kallmann ou de son variant hyposmique ou normosmique. Dans les causes syndromiques complexes (mutations de CHD7, anomalies de la leptine et de son récepteur, syndrome de Prader-Willi, etc.) le diagnostic de la cause de l’HHC est actuellement le plus souvent suspecté ou posé avant l’âge de la puberté du fait des signes cliniques associés mais dans quelques rares cas des causes syndromiques peu symptomatiques peuvent initialement se présenter à l’adolescence comme des HHC isolés non syndromiques ou des syndromes de Kallmann.

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Abstract

Congenital hypogonadotropic hypogonadisms (CHH) are a well-known cause of pubertal development failure in women. In a majority of patients, the clinical spectrum results from an insufficient and concomitant secretion of both pituitary gonadotropins LH and FSH that impedes a normal
Congenital hypogonadotropic hypogonadism (CHH) results from abnormal gonadotropin secretion and is characterized by a complete or partial lack of pubertal development that is caused mainly by defective GnRH production or release by the hypothalamus, or by a primary gonadotropic cell dysfunction in the pituitary. The prevalence of CHH, evaluated from 1/10,000 to 1/4000 in males, was reported to be between two and five times less frequent in females. These values mainly established by specialized teams belonging to teaching hospitals (Fig. 1) are probably underestimated compared to the real frequency of CHH in the general population of women as a consequence of recruitment biases. CHH is revealed in the majority of female teenagers and women by primary amenorrhea. The classical hormonal signature of CHH is a low level of circulating sex steroids, together with low or “normal” levels of FSH and LH.

1. Clinical presentation

In women, CHH is revealed in by primary amenorrhea in more than 90% of cases. Breast development is highly variable but it is absent in a minority of cases. Indeed, it is often present and sometimes almost normal. Similarly, pubic hair may be absent, sparse or even normal. These partial forms, in majority not referred to hospital contribute to explaining the underestimated prevalence of this condition in women. In a very mild form, CHH can be restricted to isolated chronic anovulation, whereas estradiol secretion is adequate for...
Primary amenorrhea
(whatever breast development is)

- Serum LH, FSH, Estradiol: Low or in « normal range acyclic »
- Normal prolactin
- Normal pituitary, thyroid and adrenal functions
- Normal circulating iron and transferrin saturation coefficient
- Normal hypothalamus and pituitary MRI

Exclude functional hypothalamic amenorrhea:
- Low BMI, eating disorders, body composition (low fat)
  - Excessive physical activity
- Offactometry
  - (and/or olfactory bulbs MRI)
- Detailed familial survey:
  - Hypogonadism ?
  - Infertility ?
  - Anosmia ?
  - Hyposmia ?
  - Associated non reproductive non olfactory signs ?
- Isolated CHH or Kallmann: Molecular Genetic analysis
  (see Fig 4)

Fig. 3. Steps to overcome before achieving the diagnosis of congenital hypogonadotropic hypogonadism (CHH) in women or female teenagers referred for primary amenorrhea.

endometrial development and therefore associated with the existence of a single menstruation (primosecondary amenorrhea) or even chronic oligomenorrhea or a positive progestin withdrawal test [3]. These attenuated forms have also been described in women having conceived spontaneously [7].

One challenge in women with sporadic CHH, normal olfactory and hypothalamopituitary MRI and no identified mutation is the differential diagnosis of functional hypothalamic amenorrhea [1,8,9]. In women referred for primary amenorrhea and with a hormonal profile suggesting HH but without anosmia or hyposmia or identified genetic anomalies, the diagnosis of CHH must therefore only be considered with care, after ruling out underweight, eating disorders, excessive physical activity, and chronic underlying conditions (Fig. 3) [1,8,9]. When body weight or BMI are at the lower limit of normal, body fat measurement can also be useful to screen for functional hypothalamic amenorrhea in this context.

Finally, the presence of non-reproductive non-olfactory additional disorders, including mirror movements, palate anomalies, renal agenesis (ultrasoundography), hearing impairment (audiometric testing), and tooth agenesis, should be carefully searched in these female patients and, whenever possible, their first-degree relatives, because such anomalies can direct the clinicians and geneticist towards particular genetic forms of the disease [10] (Kallmann syndrome or more complex syndromic causes) in which genetic counseling is mandatory.

2. Evaluation

Serum estradiol concentrations are often low in women with CHH [1–6], sometimes below the detection limit. They seem to correlate with breast development: indeed, in the absence of breast development, circulating estradiol concentrations are undetectable while estradiol is detectable with a sensitive assay when breast development exceeds stage B2. A similar relationship exists between pubertal development and pituitary gonadotropin concentrations: the latter are often very low or undetectable in the absence of breast development, while in patients with stage B3 or B4 breast development, they can reach values close to those observed in the early follicular phase of women with normal cycles (Fig. 3). As in males with CHH, the GnRH test have a poor diagnosis value to make a positive diagnosis in females and serves more to confirm the severity of congenital gonadotropin deficiency [11], which in fact is often already clinically perceptible (reflected by the degree of breast development). Thus, the GnRH test provides no extra diagnostic information relative to baseline gonadotropin levels evaluated with modern assays [1]. In addition, it cannot show whether the gonadotropin deficiency is hypothalamic or pituitary in origin: for instance, the results of GnRH test can be negative in profound hypothalamic gonadodropin deficiency and positive in partial pituitary deficiency [1–6,11].

Before making a firm diagnosis of isolated congenital gonadotropin deficiency, all antepituitary functions must be investigated in order not to miss hyperprolactinemia, global anterior pituitary insufficiency, or an associated endocrine disorder that may be part of a syndromic form of CHH (Fig. 3).

On the same way, in the absence of anosmia or other associated signs suggesting a syndromic cause, primary juvenile hemochromatosis may mimic CHH and be a real differential diagnosis [12]. It is therefore useful to rule out iron overload, given the therapeutic implications in this disorder. Primary juvenile hemochromatosis can be ruled out by measuring serum iron and the transferrin saturation coefficient.

3. Imaging

Pelvic sonography is useful for determining the size of the uterus [13–15], which reflects estrogen impregnation, as well as endometrial thickness, ovary size and the number and size of ovarian follicles [13–15], that may correlate with the severity of gonadotropin deficiency [3].

MRI of the brain and olfactory bulbs is useful in CHH. Although the findings are nearly always normal in isolated normosmic CHH, MRI can rule out an expansive, infiltrative or malformative disorder of the hypothalamopituitary region. MRI can also be used to analyze the olfactory bulbs and furrows in a search for signs of Kallmann syndrome.

4. Genetics

Identification of genetic abnormalities related to CHH over the last 2 decades has provided important insights into the pathways involved in the development, maturation and function of
the reproductive axis. In women, mutations of *FGFR1*, *PROK2*, *PROKR2* and *FGF8* have been found specifically in Kallmann syndrome, a disorder in which CHH is related to abnormal GnRH neuron ontogenesis and is associated with anosmia or hyposmia [6,10–18] (Fig. 4).

In fact, in females as in males, the CHH phenotype is usually tightly linked to an isolated deficiency of gonadotrophin secretion. These patients, who have no clinical abnormalities, associated signs or hormone deficiencies independent of the deficiency in gonadotrophin and sex steroids, have isolated CHH [1]. Such cases are occasionally due to genetic alterations affecting GnRH secretion: mutations in *GNRH1* [5], *GPR54/KISS1R* [19,20] and *TAC3* and *TACR3* [21–23] or the GnRH sensitivity of gonadotropic cells: GNRHR [1,4,24,25] (Fig. 4).

Since more than 20 years, we have learned a great deal from a number of genotype-phenotype published studies: so, we know now the clinical features of patients with *GnRHR* gene mutations where both genders are highly variable, even in the same kindred [1]. On the same way, whatever the mutations, it has been clearly established that the spectrum of the reproductive phenotype in women with CHH, is much broader than originally anticipated (Fig. 5). There is no doubt that, these findings have changed our old oversimplified view of the disease.

Finally, we must be aware that a minority of female patients with Kallmann syndrome or a syndromic form of CHH may also initially appear to have isolated CHH. Close clinical, familial and genetic studies can correct the diagnosis, which is particularly important for genetic counselling [1,26].

**Conflicts of interest**

Aucun.

**References**


