Male acquired hypogonadotropic hypogonadism: Diagnosis and treatment

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Abstract

Acquired hypogonadotropic hypogonadism (AHH), contrary to congenital hypogonadotropic hypogonadism (CHH) is characterized by postnatal onset of disorders that damage or alter the function of gonadotropin-releasing hormone (GnRH) neurons and/or pituitary gonadotroph cells. AHH thus prevents the establishment of gonadotropin secretion at puberty, or its post-pubertal maintenance. Thus, postnatal AHH may prevent the onset of puberty or appear during pubertal development, but it usually emerges after the normal age of puberty. Although pituitary tumors, particularly prolactinoma, are the most common cause, sellar tumors or cyst of the hypothalamus or infundibulum, infiltrative, vascular, iron overload and other disorders may also cause AHH. Pituitary surgery and head trauma or cranial/pituitary radiation therapy are also usual causes of AHH. The clinical manifestations of AHH depend on age of onset, the degree of gonadotropin deficiency, the rapidity of its onset and the association to other pituitary function deficiencies or excess. Men with AHH have less stamina, decreased libido, erectile dysfunction and strength, and a worsened sense of well being leading to degraded quality of life. The physical examination is usually normal if hypogonadism is of recent onset. Diminished facial, body hair and muscle mass, fine facial wrinkles, gynaecomastia, and hypotrophic testes are observed in long-standing and complete AHH. Spermatogenesis is impaired and the volume of ejaculate is decreased only when gonadotropins and testosterone levels are very low. Men with AHH may have normal or low serum LH and FSH concentrations, but normal gonadotropin values are inappropriate when associated with low serum testosterone. In the majority of AHH patients, serum inhibin B is “normal”. The decrease of this sertolian hormone indicates a long-standing and severe gonadotropin deficiency. Symptoms, usually associated with significant testosterone deficiency in men with AHH, improve with testosterone replacement therapy. Replacement therapy is often simple, using an injectable testosterone ester as first line treatment. Fertility can be restored rather quickly, provided there is no independent primary testicular damage and the partner is fertile.

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Résumé

Les hypogonadismes hypogonadotrophiques acquis après la puberté (HHA) sont plus souvent et plus efficacement diagnostiqués actuellement. Bien que les causes les plus fréquentes soient les adénomes hypophysaires, en particulier les prolactinomes, ainsi que d’autres processus tumoraux de la région, il ne faut pas oublier que d’autres étiologies peuvent être en cause comme les processus infiltratifs ou les surcharges tels que respectivement les hypophysites ou l’hémochromatose. À côté des classiques lésions chirurgicales et radiothérapeutiques de la région sellaire, une origine post-traumatique est de plus en plus recherchée. Les manifestations cliniques de l’HHA dépendent de la profondeur et de la durée du déficit gonadotrope. Un des meilleurs signes cliniques est la perte de la libido qui est malheureusement souvent négligée par le malade ou son médecin. Cette baisse de la libido s’accompagne parfois ou est confondue avec des troubles de l’érection mais une dysfonction érectile avec une libido conservée est assez rarement en rapport avec un déficit en testostérone. L’examen clinique peut être sans particularité quand l’HHA est récent. La diminution de la pilosité et du volume testiculaire tout comme la diminution des masses musculaires n’interviennent que lorsque le déficit gonadotrope est ancien et profond. L’exploration hormonale montre habituellement une baisse importante de la testostérone totale sérique associée à une baisse des gonadotrophines mais ces dernières peuvent demeurer dans l’intervalle des valeurs de référence pour l’âge. La mesure de l’inhibine B, non nécessaire au diagnostic, est le plus souvent normale, mais décroit lorsque le déficit en gonadotrophines est profond et prolongé. La baisse importante de la testostérone circulante chez les hommes atteints d’HHA explique l’efficacité cliniquement évidente de l’androgénothérapie sur l’ensemble des symptômes liés à l’hypogonadisme.

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1. Definition and causes

Acquired hypogonadotropic hypogonadism (AHH), contrary to congenital hypogonadotropic hypogonadism (CHH) [1,2], is characterized by postnatal onset of disorders that damage or alter the function of gonadotropin-releasing hormone (GnRH) neurons and/or pituitary gonadotroph cells. AHH thus prevents the establishment of gonadotropin secretion at puberty, or its post-pubertal maintenance [3–6]. Postnatal AHH may prevent the onset of puberty or appear during pubertal development, but it usually emerges after the normal age of pubertal development (Fig. 1).

2. Clinical features

The clinical manifestations of AHH depend on the age of onset, the severity and duration of gonadotropin deficiency, and whether or not other pituitary hormone deficiencies are also present. Symptoms of hypogonadism may be masked by pituitary hormone hypersecretion that is clinically predominant, as in acromegaly and Cushing’s disease for example.

One reliable clinical sign of post-pubertal acquired hypogonadism is a loss of libido [4,6], often overlooked by the patient or doctor. This loss of sexual desire is often accompanied by or confused with erectile dysfunction, but erectile dysfunction with preserved libido is rarely due to a significant testosterone deficit or, therefore, with AHH [7]. At interview, men with AHH sometimes mention a reduced frequency of shaving and a loss of drive.

Physical examination is poorly informative in recent onset AHH, and the findings may also be influenced by other pituitary deficits. Thus, palor or loss of pubic and axillary hair is more common in patients with associated adrenal insufficiency that completes the androgen deficiency [8].

The decrease in testicular volume and muscle mass is inconsistent [4,6], only occurring when the gonadotropin deficiency is long-standing and severe [5]. Thus, more than 50% of men in whom AHH occurs after puberty and who have low testosterone levels have normal testicular volume (Young unpublished data).

Hypothalamic-pituitary damage occurring before or during pubertal development, respectively, results in absent pubertal development or blocked pubertal maturation manifested by a more or less complete increase in testicular volume, without virilization (Fig. 2).

3. Hormonal investigations

Hormone assays in this setting show a variable but often significant decrease in serum total testosterone [4–6]. Measurement of bioavailable testosterone does not generally provide additional diagnostic information [9], and standard assays of free testosterone are unreliable for diagnostic purposes [10]. One exception is investigation of the gonadal axis in men with acromegaly who may, in the absence of hypogonadism related to a microadenoma [11], have “low” total testosterone due simply to the decrease in SHBG carrier protein [12]. In these patients with GH hypersecretion, measurement of bioavailable testosterone or calculation of the free testosterone index, together with the interview and physical examination, may be useful for deciding whether or not androgen replacement therapy is appropriate [12]. This particular diagnostic problem requires further study.

In patients with AHH, the fall in serum total testosterone is associated with lower circulating levels of the gonadotropins LH and FSH, but the latter may remain within the range of reference values for age, which is inappropriate given the fall in serum testosterone levels. This characteristic profile makes it easy to differentiate AHH from acquired primary testicular hypogonadism, where levels of FSH and, to a lesser extent, LH are high [2]. One exception is the patient with an FSH-secreting gonadotroph adenoma, in whom the dissociation between high FSH and low LH will draw attention [13]. In doubtful cases, pituitary MRI will readily identify a gonadotropin macroadenoma.

Estradiol deficiency is a lesser-known characteristic of male hypogonadotropic hypogonadism [9]. It explains the bone loss leading to osteoporosis [14–16], in the absence of replacement therapy, and also the insulin resistance associated with AHH [17].

Serum inhibin B assay is not necessary for positive diagnosis of AHH, as levels are often normal [6], only falling when the

Fig. 1. Schematic view of the activation of the hypothalamic-pituitary testicular axis across fetal and postnatal life in male human. During fetal, early neonatal and pubertal development, pulsatile hypothalamic secretion of gonadotropin-releasing hormone (GnRH) (a) stimulates pituitary gonadotropin biosynthesis and secretion (b) that, in turn, stimulates testicular steroid and peptidic hormones production (c). Onset of postnatal conditions responsible for acquired hypogonadotropic hypogonadism (AHH) can occurs before and during pubertal development but, in the majority of patients, after the pubertal activation of gonadotropin secretion. Adapted from [1].
gonadotropin deficiency is severe and long-standing [2,5]. This inconsistent decrease matches the loss of testicular volume; thus, Sertolian peptide is more useful as a marker of the severity of gonadotropin deficiency than as a diagnostic tool [2].

An increase in anti-müllerian hormone (AMH) has also been described in men with AHH [18], but it is smaller than that seen in men with CHH [19]. It reflects the decline in testicular testosterone impregnation. Given its complex regulation (in opposite directions) by FSH and intratesticular testosterone [20], its clinical interpretation is far from simple. Therefore, measurement of this gonadal peptide should be reserved for clinical research purposes.

When the clinical findings point to AHH, it is crucial to investigate all anterior pituitary functions in order to determine whether it is isolated or part of an array of multiple pituitary deficits or even pan hypopituitarism. If pituitary MRI shows an expansive process, pituitary investigations are also important to detect symptomatic or subclinical hormone hypersecretion, and especially hyperprolactinemia.

4. Other investigations

MRI of the hypothalamic-pituitary region is essential for the etiologic diagnosis of AHH, as it can visualize a tumor or infiltrative process. If no pituitary tumor or infiltrative process is visible, particularly when AHH is isolated, hemochromatosis should be ruled out by assaying serum iron and the transferrin saturation coefficient. AHH secondary to early iron overload of gonadotroph cells by blood transfusions in patients with blood diseases may lead to pubertal failure [21]. In this case the etiology is obvious, AHH secondary to juvenile hemochromatosis can prevent pubertal development and mimic CHH if the gonadotropin deficiency is early and complete, or occur during the late second or third decade after full or partial early puberty [22–24]. AHH associated with hemochromatosis due to HFE mutations occurs later, between the ages of 40 and 60, coinciding with the onset of liver fibrosis and diabetes [25,26].

5. Etiology

The multiple causes of AHH are classified into three groups (Table 1) [21–50]:

- functional impairment, which is generally reversible and frequently drug-related or due to nutritional deficiency, with no detectable hypothalamic-pituitary lesions; it sometimes reveals a systemic disorder;
- organic disorders, mainly represented by pituitary adenomas but also by other hypothalamic-pituitary tumors or infiltrative processes;
- iatrogenic insults secondary to surgery or radiotherapy of the sellar region are also common causes of AHH; this group includes post-traumatic causes, that are increasingly sought.

6. Treatment of hypogonadism

Treatment must of course target the underlying cause. However, contrary to some medical antitumoral treatments (cabergoline, somatostatin analogs), pituitary surgery and/or radiotherapy frequently perpetuates or even aggravates gonadotropin deficiency. AHH sometimes persists despite the reduction or eradication of the causal tumor or infiltration. Chronic androgen replacement therapy is therefore generally necessary. The first objective is to correct the symptoms of testosterone deficiency and the morbid consequences of sex steroid deficiency described above [2,51–54]. These goals can
In whom IM administration of testosterone enanthate is poorly tolerated or contraindicated. Finally, non-esterified testosterone can be administered percutaneously in the form of a gel or patch [53]. The use of these products in AHH is limited in France by their high cost, their non-refunding by the health insurance system, and the need for daily applications, which again probably undermines adherence to this chronic treatment.

Androgen therapy in men with AHH or CHH is essentially empirical, given the lack of validated clinical trials [1,2]. It is particularly noteworthy that, despite its long-standing use, the schedule of testosterone enanthate administration required to optimize the risk-benefit ratio has not yet been determined in clinical studies [54]. Similarly, no large studies have been conducted to evaluate the safety of long-term androgen therapy in men with acquired hypogonadism.

Treatment monitoring is also empirical and focuses on signs of overdose, such as aggressiveness, hypersexuality, polycythemia or prostate enlargement (digital rectal examination, with or without ultrasonography and PSA tumor marker assay) [53].

7. Management of infertility

Only a minority of men who develop AHH at an early age seek treatment for infertility. The more frequent onset of AHH in men who have already had children means that investigations of the gonadotrope axis, and particularly testicular exocrine involvement, are often limited. This infertility is related to a decrease in sperm production that may lead to the onset of secretory azoospermia which, fortunately, is inconsistent [4,6,55,56]. Semen analysis will be the first investigation in a man with AHH on androgen replacement therapy who wishes to have children. If the results are normal, which is possible in case of partial gonadotropin deficiency [4,6,55,56], initial management will focus on a possible cause of infertility in the patient’s partner. In case of partial (oligo) spermia or complete (azoospermia) failure of spermatogenesis, and when no cause of infertility is found in the partner, treatment will begin with gonadotropin administration. In the absence of comparative studies showing the superiority of a particular treatment, the protocol will be adapted from those found to be effective in open studies in patients with AHH ([1] and references in this article). The use of human chorionic gonadotropins, by subcutaneous injection (less painful and as effective as the intramuscular route) at doses of 1500 IU two or three times a week, can largely restore intratesticular testosterone concentrations [57], leading to qualitatively and quantitatively normal spermatogenesis. This treatment normalizes circulating testosterone levels, meaning that exogenous testosterone administration can be stopped. Small studies have shown that in partial AHH (normal or slightly reduced testicular volume), single-agent therapy with this product can restore normal sperm production [58]. When the deficit is more severe and testicular volume is very small, FSH must be added [1]. The doses used range from 75 IU twice a week to 150 IU three times a week, subcutaneously. It must be repeated that no particular protocol has proven its superiority, and that the different FSH preparations are similarly effective.

be reached by using an aromatizable androgen such as testosterone. In France, we use a relatively inexpensive testosterone ester such as testosterone enanthate, which provides adequate substitution when injected intramuscularly (IM) at a dose of 250 mg every 2 to 4 weeks [2,51–54]. The use of testosterone undecanoate makes it possible to extend the interval between IM injections to 2 or 3 months [53], but this formulation is very expensive and is not refunded by the French health insurance system, limiting its use. Treatment efficacy is assessed empirically, mainly on clinical grounds [54]. Testosterone values vary widely depending on the sampling date relative to the last injection. Thus, when circulating testosterone is measured during the first week after testosterone enanthate injection, the serum concentration will be supraphysiological, suggesting overdosing, while during the third week it will be below the reference range, suggesting underdosing. However, these variations do not seem to affect most patients’ well being. In the minority of patients who are affected by large testosterone fluctuations, the unit dose may be reduced empirically, with more frequent injections of smaller amounts.

Testosterone undecanoate can also be used orally in the form of two 40-mg capsules three times a day to obtain minimal androgen coverage [53]. Because of this frequent dosing, which may undermine adherence, this form of androgen therapy is generally held back as a second-line option for patients in whom IM administration of testosterone enanthate is poorly

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<tr>
<td>Etiology of acquired hypogonadotropic hypogonadism [21–50].</td>
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<tr>
<td><strong>Tumors of the hypothalamic-pituitary region [27]</strong></td>
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<tr>
<td>Craniohypophyseal adenoma [28]</td>
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<td>Pituitary adenomas [29,30]</td>
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<td>Dysgerminomas, chilomas</td>
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<td>Pituitary metastases or lymphoma [31,32]</td>
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<td>Sellar meningiomas</td>
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**Hypothalamic-pituitary infiltrative process** |
- Hemochromatosis [21–26] |
- Hypophysitis or infundibulitis [33,34] |
| Sarcoïdosis [35] |
| Histioctytesis [36] |

**Iatrogenic or traumatic** |
- Surgery of the hypothalamic-pituitary region [27,28] |
| Pituitary, brain or pharyngeal radiotherapies [37–40] |
| Head injury [41] |

**Functional** |
- Hyperprolactinemia (microadenoma or extrapituitary causes) [29,42] |
- Nutritional deficiency (anorexia nervosa, chronic disease, excessive physical activity) [43,45] |
- Hypercortisolism (pituitary microadenoma or extrapituitary origin) [46] |
| Feminizing tumors [47,48] |
| Endogenous progesterone and 17-hydroxyprogesterone excess secondary to congenital adrenal hyperplasia due to 21 hydroxylase deficiency |
| Drug-related causes (androgens, anabolic steroids, estrogen-progestagens, GnRH agonists, corticosteroids, opioids) [49,50] |

| Idiopathic |
| Hypophysitis? Genetic origin? Injury? [4,6,33,34] |

GnRH: gonadotropin-releasing hormone.
AHH is distinguished from congenital forms of HH by the relatively rapid correction of azoospermia, after 4 to 6 months [1]. Similarly, the sperm count frequently normalizes, which is rare in CHH [1]. It appears that conception (the main therapeutic objective) will occur more rapidly when the pretreatment testicular volume is close to normal. The use of inhibin B as a prognostic marker, as proposed in congenital forms [59], has not been specifically evaluated in sufficient numbers of patients with AHH. Occasionally, in extreme cases of testicular hypotrophy, a very low or undetectable levels of inhibin B should draw attention to the possibility of primary testicular damage independent of the gonadotropin deficiency.

In conclusion, positive diagnosis of AHH is rarely difficult when supported by a combination of significantly reduced circulating total testosterone and non-elevated gonadotropin levels. MRI is the key to identifying the cause (tumor growth or infiltration). If MRI is normal, a metabolic or functional cause should be sought.

Replacement therapy is often simple, using an injectable testosterone ester. Fertility can be restored quickly, provided treatment is started early. MRI is the key to identifying the cause (tumor growth or infiltration). If MRI is normal, a metabolic or functional cause should be sought.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


