Hypothalamic amenorrhea: From diagnosis to therapeutical approach

Aménorrhée hypothalamique du diagnostic à l’approche thérapeutique

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Résumé

Parmi les aménorrhées secondaires, l’aménorrhée hypothalamique (HA) est celle qui ne s’associe à aucune cause endocrinienne ou systémique manifeste. L’HA est essentiellement liée à des éléments de stress variés affectant le contrôle neuroendocrinien de la reproduction. En pratique clinique, l’HA est surtout associée au stress métabolique, physique ou psychologique. Le stress est une réponse adaptative de l’organisme à travers tous ses systèmes homéostasiques à des stimuli externes ou internes qui activent des voies physiologiques spécifiques ou non. L’HA survient en général après exposition à des conditions ou des situations de stress sévères tels que : un régime, un entraînement intensif, ou des événements émotionnellement intenses, toutes situations qui peuvent entraîner une aménorrhée avec ou sans perte de poids. L’HA est une aménorrhée secondaire correspondant à un diagnostic d’exclusion. En fait, le diagnostic repose essentiellement sur une bonne anamnèse. L’HA doit être explorée en fonction de l’histoire clinique de la patiente, de la survenue des ménarches, de la périodicité menstruelle, du moment et des modalités de survenue de l’aménorrhée ; il faut exclure toutes les maladies endocriniennes ou métaboliques (en général le diabète) ainsi que les affections systémiques. Il est nécessaire d’identifier toute situation stressante induite par un deuil, des problèmes familiaux, professionnels, une perte de poids ou des troubles du comportement alimentaire, un surentraînement physique. Des investigations endocriniennes peuvent être proposées bien qu’elles ne soient pas spécifiques ; aucun paramètre ne permet de poser le diagnostic de façon absolue car l’HA est en grande partie dépendante de la réponse individuelle et adaptative au stress. Cet article a pour but de donner des perspectives diagnostiques et des stratégies thérapeutiques potentielles.

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Mots clés : Aménorrhée hypothalamique ; Stress ; GnRH ; Perte de poids ; Bêta-endorphines ; Aménorrhée hypogonadotrope ; Hypoestrogénie

Abstract

Among secondary amenorrheas, hypothalamic amenorrhea (HA) is the one with no evidence of endocrine/systemic causal factors. HA is mainly related to various stressors affecting neuroendocrine control of the reproductive axis. In clinical practice, HA is mainly associated with metabolic, physical, or psychological stress. Stress is the adaptive response of our body through all its homeostatic systems, to external and/or internal stimuli that activate specific and nonspecific physiological pathways. HA occurs generally after severe stressed conditions/situations such as dieting, heavy training, or intense emotional events, all situations that can induce amenorrhea with or without body weight loss and HA is a secondary amenorrhea with a diagnosis of exclusion. In fact, the diagnosis is essentially based on a good anamnestic investigation. It has to be investigated using the clinical history of the patient: occurrence of menarche, menstrual cyclicity, time and modality of amenorrhea, and it has to be excluded any endocrine disease or any metabolic (i.e., diabetes) and systemic disorders. It is necessary to identify any stressed situation induced by loss, family or working problems, weight loss or eating disorders, or physical training or agonist activity. Peculiar, though not specific, endocrine investigations might be proposed but no absolute parameter can be proposed since HA is greatly dependent from individual response to stressors and/or the adaptive response to stress. This chapter aims to give insights into diagnosis and putative therapeutic strategies.

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Keywords: Hypothalamic amenorrhea; Stress; GnRH; Weight loss; β-endorphin; Hypogonadotropic amenorrhoea; Hypoestrogenism

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1. Introduction

Among secondary amenorrheas, hypothalamic amenorrhea (HA) is the one with no evidence of endocrine/systemic causal factors, mainly related to various stressors affecting neuroendocrine control of the reproductive axis. The disappearance of menstrual cyclicity is related to a dysfunction of hypothalamic signals to the pituitary gland, resulting in a failure of the ovarian function with no ovulation. The term “hypothalamic” refers to the hypothalamus, an area at the base of the brain that acts as a “hormone control center” for the many biological functions and activities and among them is the control of the reproductive functions and ovarian function.

Typically, HA is also indicated as functional hypothalamic amenorrhea (FHA) since this condition and disorder no systemic causal factors, no endocrine disease (such as thyroid or prolactin [PRL] dysfunctions), and no central nervous system (CNS) disease or lesion such as tumor or trauma. FHA occurs with a random frequency not different throughout the fertile life, as reported in a group of randomly sampled postmenarcheal women [1,2]. In fact, this disorder is not limited to a restricted period of a woman’s reproductive life but may occur at any age.

2. Neuroendocrine disorders in menstrual cyclicity

In clinical practice, HA is mainly associated with metabolic, physical, or psychological stress. Stress is the adaptive response of our body through all its homeostatic systems, to external and/or internal stimuli that activate specific and nonspecific physiological pathways. FHA generally occurs after severe stressed conditions/situations such as dieting, heavy training, or intense emotional events, all situations that can induce amenorrhea with or without body weight loss [2,3]. A specific correlation exists between loss of weight and amenorrhea [3] when loss of weight is below a critical point and the ratio between fat and muscular mass is severely reduced, and loss of menstrual cyclicity is a typical occurrence. In fact, after dieting as well as during intense training of dancers or runners (excessive consumption of energies), amenorrhea is a frequent symptom [4]. Indeed, the low ratio may be due both to high energy consumption and reduced food intake, since the best performance in athletics is also linked to an equilibrium between lean mass (i.e., muscles) and body weight, where body weight is usually kept at the lower levels. Psychological stressors such as emotional, familial, or working problems may have a negative impact on food intake. Reduced food intake can induce amenorrhea through specific metabolic signals, which amplify the stress response to fasting [5]. Associated with psychological stressor(s) recorded as heavy negative event(s), many patients often show affective disorders (neuroticism, somatization, anxiety) and this mix of situations leads to the disruption of the hypothalamus–pituitary function controlling the ovarian function [6]. These cascades of situations negatively affect gonadotropin-releasing hormone (GnRH) release and the reproductive axis, activating or inhibiting hypothalamic and/or extrahypothalamic areas in the brain as well as acting in the periphery. In particular, one of the key events of this modulatory action is played by neurotransmitters and neuropeptides produced in the central nervous system. The central nervous system (CNS) and networks are sensitive to external and internal environmental change (light–dark cycle, temperature), as well as to cognitive, social, cultural, and emotional events. Each of these signals may become stressor when acute changes occur, and through integration with the hormonal signals they can stimulate while adapting responses [2].

On the basis of what has been described above, the ovarian failure typically occurring in patients affected by HA represents the adaptive mechanism to stress, so that the reproductive axis activity is reduced/blocked. Such a blockade of the reproductive function is reversible but it occurs in such critical conditions that reproduction is not considered essential for the survival of those women. Poly- or oligomenorrhea are some intermediate steps that can anticipate the occurrence of the amenorrheic condition, which is the last and worst stage of this clinically adaptive response to stress.

3. Physiopathology of stress-induced hypothalamic amenorrhea

HA [7–9] is a model of hypogonadism characterized by several neuroendocrine aberrations that occur after a relatively long period of exposure to a repetitive and/or chronic stressor(s) so as to affect the neuroendocrine hypothalamic activity [10,11] as well as the release of several hypophyseal hormones [2,9,11–15]. The reproductive axis is severely altered in these patients and both the opioid and dopaminergic systems have been proposed as potential mediators of stress-related amenorrhea in humans [16,17]. As demonstrated in experimental studies in monkeys and rats, the common response to stressors is the increase of adrenocorticotropic hormone (ACTH) and cortisol plasma levels that activate lipolysis and glycogenolysis-like compensatory mechanisms. In animals, it has been demonstrated that the intraventricular injection of corticotropin-releasing hormone (CRF) reduces GnRH and luteinizing hormone (LH) release [18,19]. Since the corticotropin-releasing hormone (CRF) is the specific hypothalamic stimulating factor for ACTH, elevation of ACTH in response to stress is anticipated by the elevation of CRF stimulation. Evidence of a central site of action for CRF in blocking GnRH-induced LH release is demonstrated by the fact that CRF antagonists reverse the stress-induced LH decrease in rats [18]. CRF elevation as an adaptive response to stress is also responsible for the increase of central β-endorphin (βEP) release (Fig. 1).

This last is probably the most important peptide of the endogenous opioid peptides (EOPs) family and is a potent inhibitor of GnRH-LH secretion. Because of this evidence a connection has been suggested between the activation of the hypothalamic–pituitary–adrenal (HPA) axis and the stress inhibition of the hypothalamus–pituitary–gonadal (HPG) axis [12]. Since naloxone, a specific opioid receptor antagonist, is able to counteract the CRF-induced LH secretory blockade [20], opioid peptides have been considered the key factors in the stress-induced inhibition of the HPG axis. Moreover, the stress-induced hyperactivation of the CRF–ACTH–adrenal axis is able to deter-
mine an exaggerated secretion of cortisol from the adrenal glands. Such a situation induces higher cortisolemia in patients affected by HA and negatively modulates adrenal response to stress. In fact, it has been reported that these patients, though showing hypercortisolemia in basal condition, resulted in having a reduced response to exogenous ACTH stimulation [21]. Such data confirmed that though in baseline conditions the adrenal gland is overstimulated, the maximum response of cortisol to external stimuli remains the same. This means that the delta, which is the difference between the maximal cortisol response to the stimulation and the baseline level before the stimulation, is reduced. Clinically, this means that the adrenal gland produces a lower amount of cortisol when the stressed situation hits (Fig. 2).

Among the hormones deeply involved in the modulation of the CNS, there are also neurosteroids. The term ‘neurosteroids’ was introduced by Robel and Baulieu in 1987 [22]. These steroids are synthesized in and/or act on the CNS. Main representatives of the neurosteroids include pregnenolone, pregnenolone sulfate, allopregnanolone, dehydroepiandrosterone and dehydroepiandrosterone sulfate [22]. Specific pulsatile release of allopregnanolone was found in healthy women during the menstrual cycle. Our group [23,24] demonstrated higher levels of this neurosteroid in women in the luteal phase of the menstrual cycle. In other words, allopregnanolone secretion is coupled only to a hyperactivated adrenal function in patients suffering for hypothalamic amenorrhea [24,27]. Meczekalski et al. [28] reported blunted allopregnanolone response to CRH in women with hypothalamic amenorrhea. This research may indicate that reduced sensitivity and expression of CRH receptors may be responsible for such response in women with hypothalamic amenorrhea [27,28].

Peripheral hormonal signals, such as glucocorticoid hormones or PRL, are also activated by stress and are able to act as stress-induced hormonal signals. In fact, cortisol itself exerts a suppressive effect on GnRH-stimulated LH release [29] and such action mainly takes place at the pituitary level but it cannot be concluded that an additional negative effect may be present in extrapituitary areas, indirectly inhibiting LH secretion [30]. Also, PRL increases and responds to external stimuli such as emotional and physical events as well as internal rhythms such as sleep. This mechanism has been extensively studied in the rat [31] and is mediated by the activation of several stimulating factors like thyrotropin releasing hormone, vasoactive intestinal peptide, oxytocin, or by the failure of the dopaminergic control that antagonizes prolactin. The final result of stress-related hormone responses is a negative effect both on gonadotropin secretion and gonadal steroid biosynthesis.

The fact that patients suffering for FHA have low weight or exaggerated weight loss induce specific adjustment in the metabolic pathways, not only for the consistent reduction of the fat mass but for the significant reduction of insulin, leptin and NPY plasma levels. Indeed, these hormones can heavily affect reproductive function since all of them are able to modulate directly and/or indirectly the reproductive axis [27]. Insulin modulates both ovarian and hypothalamic functions, similarly to NPY and leptin, inducing direct stimulation on GnRH secreting neurons [27]. The significant reduction of these hormones due to the consistent reduction of the fat mass (that reduces leptin synthesis) and to the low glucose availability (most of it is quickly metabolized as soon as is introduced with eating) that maintain low insulin levels, induce low NPY levels. It is interesting to remember that NPY directly modulates GnRH production through leptin mediation within the hypothalamus [27].

4. Hormonal profile in hypothalamic amenorrhea

HA is a secondary amenorrhea sustained by reduced LH plasma levels, in great part activated by stress-induced endogenous opioid hypertone. Typically, in these HA patients, FSH plasma levels results to be normal. Regarding LH plasma levels,
women affected by HA are usually characterized by two possible situations:

- normogonadotropinism, with LH more than 3 mU/mL;
- hypogonadotropinism, with LH equal or less than 3 mU/mL.

These are not two distinct kinds of HA but just the evolution of the same HA, from normal normogonadotropic levels to hypogonadotropic levels, due to the growing blockade of the hypothalamus-pituitary function(s).

Usually, in hypogonadotropic patients, LH pulsatile secretion is characterized by a pulse amplitude significantly reduced while pulse frequency is higher than what can be observed in eumenorrheic women [9]. In some HA patients, LH pulses can only be observed during the night as in prepuberal girls. In addition, LH response to exogenous GnRH may be lower than that in women with normal menstrual cycles. These abnormalities of hypophyseal hormones secretory pattern deeply influence ovarian activity, inducing the blockade of follicular maturation and the typical condition of hypoestrogenism. In these women, most of the circulating estrogens derive from peripheral conversion of androgens, especially in the muscle tissue. The hypoestrogenic condition, especially if present for several months up to 1 year, might induce metabolic consequences, affecting, in particular, specific tissues such as bone tissue. In fact, bone mass peak might be affected and reduced so that showing osteopenia may expose the patient to the risk of reduced bone mass density during fertile life and perimenopausal period, which results in a major risk of pathological fractures.

Hypoestrogenism also induces the increase of total cholesterol, VLDL, LDL, and triglyceride levels and the reduction of sex hormone binding globulin (SHBG) synthesis and release. This latter event can induce a higher rate of unbound androgen, which is biologically active. This condition of relative hyperandrogenism can easily induce the occurrence of mild/severe hirsutism and acne.

When stressed conditions are chronic, the HPA axis might be activated at higher levels for a long time interval. It can frequently be observed that in a discrete group of patients with HA, there might be high and steady levels of cortisol, higher than 25 mg/L. Chronic activation of adrenal pathways determines a lower response of adrenal gland to endogenous as well as exogenous ACTH (i.e., ACTH stimulation test) in amenorrheic women than in eumenorrheic women, and this is due to the fact that in HA patients the adrenal gland is already highly activated and the adrenal response to ACTH cannot be higher than what has been observed as the maximal response [25]. In HA, PRL levels are normal or lower than in women with normal cyclicity, and this can be explained by the dopaminergic hypertone that inhibits PRL secretion. Moreover, in women with HA, and in particular in women with anorexia or with excessive restrictive feeding, hypothyroidism with low plasma levels of fT3 and fT4 and a relative increase of TSH plasma levels are frequent.

These features characterize the so-called “low fT3 syndrome,” where fT3 is reduced due to the fact that “reverse” T3, the biologically inactive analogue of fT3, is produced in a higher amount [29]. The reverse T3 is not able to induce metabolic effects on the cells and this is a defensive system, especially for patients with feeding restriction or excessive energy consumption. In addition, the thyroid gland shows that lower basal metabolism is also reduced and limits the energy dispersion for heat production. In fact, these patients typically have cooler skin and wear heavy dresses in comparison to the other (eumenorrheic) subjects.

5. Diagnostic approach

HA is a secondary amenorrhea with a diagnosis of exclusion. In fact, the diagnosis is essentially based on a good anamnestic investigation. The clinical history of the patient (occurrence of menarche, menstrual cyclicity, time and modality of amenorrhea) has to be investigated. Any endocrine disease or any metabolic (i.e., diabetes) and systemic disorders are excluded and it is important to identify any stressed situation induced by loss, family or working problems, weight loss, or eating disorders, resulting from physical training or agonist activity. All these are the main causal factors of stress-induced HA. Obviously, a clinical check is important for evaluating weight and body composition, computing body mass index (BMI = weight in kg/height in m2), looking for physical signs of weight loss/anorexia like deterioration, hirsutism, hypoproteinemia, hypothyrominemia, thin skin, and face and legs edema (these latter are induced by hypoproteinemia). It is important to exclude other kinds of amenorrhea such as hyperandrogenic amenorrhea (the signs are acne, hirsutism, seborrhea), hyperPRL (the signs are galactorrhea, cephalalgia), and visual disorders (that lead to the suspicion of pituitary micro/macro adenomas). It is of relevance the evaluation of the hormonal profile in the baseline condition, especially LH, FSH, estradiol, androgens (testosterone, androstenedione, DHEA, DHEAS), cortisol, prolactin, thyroid hormones (TSH, fT3, fT4), and thyroid autoantibodies (anti-TPO, anti-TG, and anti-TSHr). The hepatic function, total proteins, albumin, sideremia, amylase, and lipid profile must also be evaluated.

Though most of the diagnostic approach can be performed with a simple baseline determination, in some cases, additional investigation might be more helpful to better study the physiopathological condition for that single patient. These kinds of exams can be done in specific centers where the dynamic endocrine stimulation tests can be organized. Among them, the most useful are: the pulsatility study of LH and FSH (sampling every 10–15 min for 4–6 h) to assess the gonadotropin profile and to classify the type of LH pulses and the type of amenorrhea (normo- or hypogonadotrophic); the GnRH test (using a bolus of 10 μg of GnRH) to evaluate LH and FSH pituitary responses; and the naloxone test (using the infusion of 10 mg of naloxone cloridrate) to assess whether the opioidergic tone is responsible of the gonadotropin dysfunction. In women with stress-induced HA, LH response to naloxone infusion is considered positive when LH is increased more than two times the baseline levels [30]. It is also necessary to mention that a negative response does not exclude the presence of the opioidergic hypertone since this might be so high that the...
amount of naloxone infused is not effective in counteracting it.

6. Therapeutic strategies

The approach to HA must always be considered as stereo-
scopic, in the sense that more than one factor is always involved
in the genesis of the functional blockage of the reproductive sys-
tem. Therefore, more than one therapeutical approach might be
needed.

If eating disorders are present, it is important to reduce the
negative modulation/action induced by starvation, energy
imbalance, and/or training as well as all the psychological dis-
turbances. Obviously, it is very important to increase the quality
of food with more proteins in the diet and probably psychological
support might be suggested.

In case opioidergic hypertone is suspected as one of the patho-
genetic mechanisms of HA, the therapeutic administration of
an opioid receptor blocker, such as naltrexone chloride, might be
proposed. Naltrexone is usually administered at a dose of
25–50 mg/die per os for several weeks (up to 3–6 months). Some
clinical trials have reported the occurrence of menstrual cyclicity
within 2–6 months [30]. It is important to note that a higher rate
of success has been demonstrated in patients that are responsive
to the naloxone test [31].

Another possible therapeutic strategy is the use of acetyl-
L-carnitine (ALC). In fact, ALC has been reported to act on the
central cholinergic, serotonergic, and dopaminergic sys-
tems [32–34] and to modulate some neuronal activities. For
this reason, ALC administration is used to improve the cen-
tral nervous activities in patients affected by dementia [35] and
some studies [31] showed that ALC modulates HPG axis func-
tion in hypogonadotrophic patients. Indeed, six months ALC
administration at the dose of 1-2 g/die was able to induce the
increase of both LH and PRL plasma levels and the LH pulse
amplitude. The effect on PRL in hypogonadotrophic amenor-
rhea supports the positive modulation of ALC either directly
on pituitary function or through the increased estrogen milieu
[31]. Indeed, ALC administration has been reported to increase
GnRH induced LH response in rats [36] as well as in women
[31]. These observations support the fact that ALC is active in
those hypothalamic areas involved in the activation/maturation
of the hypothalamus-pituitary axis. It has been proposed that
these effects might be due to the fact that carnitine derived
from ALC increases the amount of the intra-mitochondrial car-
nitine, improving the transportation of free fatty acids in Krebs’s
cycle. This observation might explain the higher rate of success
on patients with hypogonadotropic HA and weight loss and/or
high-energy consumption.

Among the mediator(s) of opiateergic and/or dopaminergic
systems [31,37–40] in HA, a role has also been proposed for
gamma-aminobutyric acid (GABA), an important modulator of
the physiological response to stress or anxiety [41]. In fact,
various acute and chronic stressors have been shown to pro-
duce a rapid decrease in the activity of GABAergic pathways
in primates and in humans [42,43]. The fact that stress and
anxiety stimulate both the secretion of corticotropin-releasing
factor (CRF) and modulate GABAergic neurons, suggests a pos-
sible functional interaction between these two systems. Indeed,
GABAergic or benzodiazepine receptor-mediated mechanisms
inhibit CRF release [44] and anxiolytic benzodiazepines can
reverse or antagonize in experimental animals several CRF-
meditated behavioral effects that are thought to be related to stress
[45,46]. Few years ago a neurotropic compound, pivagabine
(PVG), a hydrophobic-4 aminobutyric acid derivative [47] has
been shown to exert specific effects on stress-induced activi-
tries in rats [47,48]. Experimental data also showed specific
inhibitory actions of PVG on some behavioral parameters in rats
exposed to various stressors [49] probably acting indirectly on
GABA receptor type A (GABAA) [42,43]. Since PVG prevents
the reduction of hypothalamic contents of CRF and its discharge
from hypothalamic neurons [50] in rats, it has been supposed that
PVG might modulate the adaptive response to stress. When
PVG was administered to a group of patients with HA specific
modulation of GH, ACTH and cortisol secretions were observed
[51]. These data sustained the role of anti-stress activity of this
compound in patients with highly activated HPA axis [52] and
quite often in the presence of a disturbed metabolic balance
[53], all of them being causal factors of the reproductive failure
of these patients. In addition, PVG has been reported to reduce
anxiety and depression in postmenopausal women [54] Prob-
ably, PVG modulates the release of hypothalamic CRF and/or
pituitary ACTH, and this last observation is in agreement with
the fact that the increased GH release might also be related to the
PVG-induced decrease of the CRF hypothalamic tone. In fact,
CRF is involved in GH regulation and acute CRF administra-
tion inhibits GHRH-induced GH secretion probably through a
higher somatostatin release [51,55].

In conclusion, FHA is quite a complex syndrome. Diagnos-
tic criteria are not so easy to identify since any other systemic
causal factors that might be the basis of the amenorrheic condi-
tion have to be excluded. It must be kept in mind that all kinds
of stressors (physical, metabolic, and psychological) are always
deeply and tightly involved in the genesis of the reproductive
failure and it is almost impossible to exclude their combination.
This means that FHA needs a stereoscopic approach and diagno-
sis, with a balanced analysis of all clinical and anamnestic data.
Endocrinological as well as gynecological and psychological
evaluation are important, thus confirming that the gynecolo-
gist needs to be well trained in fields close to gynecology or
reproductive medicine such as internal medicine and psychol-
ogy.

Conflict of interest statement

None.

References

type, and etiology of menstrual disorders in the age group 12-19 years.


