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Hypothalamic amenorrhea: From diagnosis to therapeutical approach

Aménorrhée hypothalamique du diagnostic à l'approche thérapeutique

A.D. Genazzani [a,*], E. Chierchia [a], S. Santagni [a], E. Rattighieri [a], A. Farinetti [b], C. Lanzoni [a]

[a] *Department of Obstetrics and Gynecology, Gynecological Endocrinology Center, University of Modena and Reggio Emilia, Via del Pozzo 71, 41100 Modena, Italy*
[b] *Department of General Surgery, University of Modena and Reggio Emilia, Modena, Italy*

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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.

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.

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

* Corresponding author.
E-mail address: algen@unimo.it (A.D. Genazzani).

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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 activity 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 extra-hypothalamic 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 agents 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 adrenocorticotropin 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 hypothalamus–pituitary–adrenal (HPA) axis and the stress inhibition of the hypothalamus-pituitary–gonadal (HPG) axis [12]. Since naloxone, a specific opiod receptor antagonist, is able to counteract the CRF-induced LH secretory blockade [20], opiod 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-