Neuroendocrine and metabolic aspects of functional hypothalamic amenorrhea

BLAŻEJ MĘCZEKALSKI, AGNIESZKA PODFIGURNA-STOBA

Abstract

Functional disorders of the hypothalamus are the most common reason for amenorrhea. Psychogenic stress, undernutrition and excessive exercise are frequently associated with functional hypothalamic amenorrhea (FHA). It is a nonorganic endocrine disorder characterized by the impairment of gonadotropin-releasing hormone (GnRH) pulsatile secretion. The incidence of FHA ranges from 15% to 55% of the secondary amenorrhoeas. This condition is determined by the spectrum of GnRH-luteinizing hormone (LH) disturbances. Patients with the diagnosis of FHA are characterised by low mean frequency of LH pulses, complete absence of LH pulsatility, normal-appearing secretion pattern or higher mean frequency of LH pulses. Many neuropeptides play an essential role in the physiological regulation of GnRH pulsatile secretion and some of them such as corticotropin-releasing hormone (CRH) and kisspeptin may be involved in the pathophysiology of FHA. FHA can be also viewed as important metabolic problem. Hypoestrogenism associated with FHA can be correlated with negative impact on skeletal and cardiovascular system. Patients with FHA are characterized by limited peak bone mass formation and increased risk of osteopenia and osteoporosis. Further studies on the short-term and long-term, cardiovascular and skeletal system consequences of hypoestrogenemia in women with hypothalamic amenorrhea are recommended.

Key words: functional hypothalamic amenorrhea, corticotropin-releasing hormone, kisspeptin, bone loss, cardiovascular system

Introduction

Functional hypothalamic amenorrhea (FHA) is the most common cause of secondary amenorrhea [1]. It is related to the disturbance of pulsatile gonadotropin-releasing hormone (GnRH) secretion [2]. FHA is a reversible and non-organic disorder associated with weight loss, severe stress or excessive exercise [1]. These stressfull factors can react negatively on hypothalamic-pituitary–ovarian axis.

The hypothalamus is responsible for hormonal regulation of the reproductive system. It is situated on the base of the brain in the diencephalon. Moreover, the hypothalamus is the main center of a number of physiological processes such as food intake, body temperature, sexual function and sleep regulation.

Many neurotransmitters and neuropeptides released in the central nervous system (CNS) in the cerebral cortex, suprahypothalamic centers and hypothalamus, are responsible for neuroendocrine controlling of the reproductive axis [3].

Neurohormone GnRH discovered by Schally in 1971 [4] plays an essential role in the regulation of reproductive functions. It is released in a pulsatile manner in the arcuate nucleus located in the hypothalamus. The center where GnRH secretion is located is called the GnRH pulse generator. Appropriate functioning of the hypothalamus-pituitary-ovary axis is regulated by the precise frequency and amplitude of GnRH pulses. GnRH pulses occur every 60–90 minute in the follicular phase and every 120–360 minute in the luteal phase of the menstrual cycle [5].

The main cause of FHA is related to disturbed GnRH pulsatile secretion at the hypothalamus. GnRH pulse dysregulation causes diminished pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This may result mainly in low ovarian synthesis of estradiol, amenorrhea and anovulation in women. Diagnostic criteria for hypothalamic amenorrhea include amenorrhea for at least 3 months with very low serum LH levels (less than 5 mIU/ml) [6].

There are a lot of neuromodulators and neurotransmitters regulating GnRH pulsatile secretion such as neuropeptide Y (NPY), corticotropin-releasing hormone (CRH), kisspeptin, leptin, ghrelin and beta-endorphin. Numerous of these modulators play an essential role in the pathophysiology of FHA, which is related to GnRH release disturbance. Role of corticotropin-releasing hormone and kisspeptin in neuroendocrine aspects of FHA is described in this article.

Neuroendocrine aspects of functional hypothalamic amenorrhea

Corticotropin-releasing hormone

CRH was first identified in 1981 by Vale [7]. It is a peptide consisting of 41 amino acids produced mainly by supraoptic, paraventricular and arcuate nuclei in the hypothalamus. Intestines, gonads and placenta are responsible for peripheral production of CRH [8].
CRH plays an important role in regulation of reproduction by modulating the hypothalamus–pituitary–adrenal axis as well as the hypothalamus-pituitary–ovary axis. Moreover, this peptide is responsible for the coordination of immune, inflammatory mechanisms, the response to stress, and the initiation of preterm and term labor [9].

CRH plays an essential role in the pathophysiology of hypothalamic amenorrhea. This peptide inhibits the electrophysiological activity of the GnRH pulse generator. The direct and indirect impact of CRH on GnRH suppression is observed [10]. Moreover, CRH stimulates endorphin production, which simultaneously inhibits the GnRH release [11].

Concentrations of cortisol were examined in patients suffering from functional hypothalamic amenorrhea [12]. Hypercortisolemia in amenorrheic women was confirmed, which suggests the possible role of CRH oversecretion. This finding indicates increased activity of the hypothalamic–pituitary–adrenal glands system in hypothalamic amenorrheic women [12]. The activation of the hypothalamic–pituitary–adrenal axis by chronic psychogenic or metabolic factors is responsible for reducing GnRH pulsatility [13].

Berga's group [14] discovered, that CRH levels in cerebrospinal fluid in FHA and eumenorrheic patients were similar. Additionally, the β-endorphin concentration in cerebrospinal fluid was lower in FHA than in control subjects [14].

Moreover, diminished ACTH and cortisol response to CRH in amenorrheic patients has been described [15]. Additionally, a similar attenuated response was determined in patients with anorexia nervosa or depression, where endogenous CRH hyperactivity was also found [16]. Presumably, impaired expression and reduced sensitivity of the CRH receptor is the main reason for such blunted ACTH and cortisol response to CRH found in amenorrheic women [17]. Future directions in FHA treatment may include the use of CRH antagonists [18].

**Kisspeptin**

The identification of GPR54, a G protein-coupled receptor and kisspeptin, the ligand for GPR54 has played an important role in understanding the reproduction process.

A 54 amino acid peptide called kisspeptin is encoded by the KiSS-1 gene. The name of this gene and its product, kisspeptin has been given by researchers working at the Pennsylvania State College of Medicine in Hershey, famous for its chocolate "Hershey’s Kisses" [19].

Initial studies have shown the GPR54/kisspeptin system implication in tumor biology. KiSS-1 gene is thought to be a metastasis suppressor gene, producing inhibiting tumor progression kisspeptins [20, 21].

Kisspeptin/GPR54 system has been indicated as a key regulator of puberty and reproduction [22, 23]. This system activates the GnRH release, initiates the puberty and regulates the menstrual cycle. Kisspeptin is thought to be a recently discovered tool of controlling the hypothalamus-pituitary-gonadal axis and a novel tumor marker in gestational trophoblastic neoplasia [24].

The exact mechanisms by which kisspeptin activates GnRH release and also what initiates the process of puberty are still not well known. Kisspeptin effect on GnRH secretion suggests important kisspeptin role as main controller of the hypothalamic-pituitary-gonadal axis [24]. The Kiss-1/GPR54 system is thought to be an essential excitatory for normal pubertal development. However, whether this system is the initial trigger of puberty process remains still an open question [24].

It is thought, that connection between metabolic status, kisspeptin and reproduction regulation might exist. During energy insufficiency at puberty, significant decrease in KiSS-1 mRNA expression at the hypothalamus is observed [25]. This might be the proof that body energy status plays an essential role in the hypothalamic kisspeptin system. Kisspeptin neurons in the states of undernutrition are responsible for the suppression of puberty and reproduction disturbances [25].

**Metabolic aspects of functional hypothalamic amenorrhea**

**Peak bone mass and FHA**

Peak bone mass (PBM) can be defined as maximal amount of bone mineral occurred during skeletal growth [26]. PBM has crucial role for proper skeletal function and particularly for osteopenia and osteoporosis prevention. Approximately 40% of PBM density is achieved during puberty period [26]. PBM reached by males is 30% higher than this formed in females. Therefore females are more threatened by osteopenia and osteoporosis than males. Final formation of PBM occurs approximately at age 25-30 [27].

Many endogenous and exogenous factors contribute to PBM formation. Nutritional factors, especially calcium intake may be important in determining PBM [28]. Calcium deficiencies in young people can account for a 5 to 10 percent difference in PBM and can increase the risk for hip fracture later in life. Sex steroid (estrogen, androgen) and growth hormone (GH), insulin growth factor 1 (IGF-1) are regarded as main hormones affecting PBM formation [29]. The level of physical activity can also contribute to PBM [30]. Moderate physical activity has positive impact on PBM formation and bone mass density [31]. However excessive weight loss or strenous exercise may lead to hypothalamic amenorrhea. When this problem occurs at the peripubertal time the main
consequence is related to decrease of PBM formation. Generally, the majority of women suffer from hypothalamic amenorrhea at the time when PBM is formed. Therefore from this point of view in patients with hypothalamic amenorrhea the most characteristic feature is problem with limited PBM formation.

**Hormonal factors related to osteopenia and osteoporosis in FHA**

Patients with functional hypothalamic amenorrhea suffer from decrease of bone mineral density (BMD) in comparison to age-matched healthy controls [32, 33]. It results not only from disturbed PBM formation but also from BMD loss. Apart from nutritional factors, which are very important, because are related also to proper calcium intake, hormonal factors are of crucial significance. The most important is to understand how estrogen influence bone metabolism. This influence is multifactoral and is mainly related to antiresorptive estrogen action [34]. Estrogens stimulate synthesis of the main growth factors such as transforming growth factor beta – TGF-beta, bone morphogenetic protein 6 – BMP6 and insulin-like growth factor 1 – IGF-1. Estrogens are also responsible for 1,25 (OH) D3, GH and progesterone expression receptors increase [35]. Estrogen action on bone is even broader. Estrogen can exert influence on: inhibition of RANKL production (receptor activator of nuclear factor kappa B ligand). RANK-RANKL system is a mediator in osteoclasts formation in response to known stimuli. Estrogen increase osteoprotegerin gene expression (inhibitor of osteoclasts formation) and decrease of proresorptive cytokines synthesis: macrophage-colony stimulating factor (MCSF), interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-alpha – TNF-α [36].

Patients with hypothalamic amenorrhea are characterized by profound hypoestrogenism. It results from disturbances in pulsatile GnRH secretion, what causes impairment of gonadotropin secretion and in turn decreases of ovarian steroidogenesis. Minimal serum estradiol levels which exert positive impact on bone metabolism is more than 40 pg/ml. As we know serum estradiol levels in hypothalamic patients is below this range and in the majority of cases is below 20 pg/ml. Patients with FHA are characterized by mild hypercortisolism [37, 38]. It results from higher CRH secretion; increased frequency of secretory bursts and increases cortisol halflife [39]. Hypercortisolism inversely correlates with bone formation markers in hypothalamic patients [40, 41].

Other factors which are responsible for bone mass density in hypothalamic patients include: low serum insulin like growth factor 1 (IGF-1) levels, low dehydroepiandrosterone sulfate (DHEAS-S) levels, vitamin D3, deficiency, low free testosterone levels [42].

There are observations that BMD decrease in patients with hypothalamic amenorrhea is lower than in anorexia nervosa [40]. Patients with exercise related amenorrhea and associated weight loss are particularly threatened by BMD decrease [32]. The most important point is these patients with this disorder have increased fracture risk.

Term "female athlete triad" is the term, which describes a combination of three conditions: disordered eating, amenorrhea and osteoporosis [43]. It was first described by the American College of Sports Medicine (ACSM) Meeting in 1997 [44]. Not all patients have all three components of the triad, and new data are beginning to emerge that even having only 1 or 2 elements of the triad greatly increases these females long-term morbidity [45]. The ACSM, in their 2007 positional stand, further defined low BMD as a history of nutritional deficiencies, hypoestrogenism, stress fractures, and/or other secondary clinical risk factors for fracture together with a BMD Z-score between −1.0 and −2.0, and osteoporosis as "secondary clinical risk factors for fracture" with a Z-score −2.0 [46].

**Cardiovascular system**

Estrogen deficiency influence on cardiovascular risk factors in postmenopausal women is well established. Hypoestrogenism in this group of women has a multifactorial impact listed below: impaired bioactivity of nitric oxide (NO), endothelial dysfunction, perturbation in autonomic function, activation of renin-angiotensin system, increased oxidative stress, changes of factors involved in inflammatory and coagulation/fibrinolitic cascade, changes in lipid profile [47].

There are limited data on the hypoestrogenism influence on cardiovascular function in young women with FHA. One of the study revealed, that patients with hypothalamic amenorrhea are characterized by atherogenic lipid profile [48] and another study did not find such phenomenon [49]. Important aspects concern endothelial function in women with FHA. Yoshida et al. [50] found negative association between soluble vascular adhesion molecule 1 (marker of vascular inflammation) and flow-mediated dilatation (FMD) in hypothalamic patients and controls. No differences between other markers of inflammation (cellular adhesion molecule-1, C-reactive protein, tumor necrosis factor α-TNF α, interleukin-6 (IL-6) in both groups. O'Donnel revealed that hypothalamic amenorrhea in physically active women is characterized by paradoxical changes in cardiovascular function, including endothelial dysfunction [49]. It is difficult to present summary on the aspect of cardiovascular function in patients with FHA, because the number of published studies is very limited. Further studies on the short-term and long-term, cardiovascular consequences of hypo-
estrogenism in women with hypothalamic amenorrhea are recommended.

Conclusions

FHA is a nonorganic endocrine disorder characterized by the impairment of gonadotropin-releasing hormone (GnRH) pulsatile secretion. FHA is characterized by profound hypoestrogenism due to described hypothalamic cause.

FHA discloses as a very often and serious medical condition. The pathophysiology of the disorder is not well known and both the diagnosis and the therapy could be difficult. Only better and more precise information of functional hypothalamic amenorrhea and its’ patomechanism explanations of neuropeptide aberrations could approach us to this complicated disorder.

The main metabolic impact FHA patient is related to negative effect on bone metabolism. Hypoestrogenism and undernutrition in FHA patients causes limitation in PBM formation, loss of bone mineral density leading to osteopenia and osteoporosis. Subsequently, this status increases the risk of pathological fractures. Hypoestrogenism in FHA patients can have also negative impact on cardiovascular system through influence on endothelial function and lipid profile.

Despite many serious consequences, functional hypothalamic amenorrhea is often underestimated as a clinical problem. Diagnosis, treatment and prevention metabolic consequences of FHA is of crucial clinical significance.

References

et al. (2005) Changes in hypothalamic Kiss-1 system and restoration of pubertal activation of the reproductive axis by kisspeptin in undernutrition. Endocrinology 146(9), 3917-25.


