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"From Hormonal Imbalance to Heart Health: Unveiling the Impact of Functional Hypothalamic Amenorrhea"

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ABSTRACT

Functional Hypothalamic Amenorrhea(FHA) is a condition with multifactorial pathophysiology affecting the Gonadotropin-releasing hormone secretion. This happens due to the Hypothalamic-pituitary-ovarian(HPO) axis disruption, leading to the persistent cause of amenorrhea. Several factors such as Psychosocial stress, weight loss, diet with calorie restriction, excessive exercise or a combination of these acts as triggers. Young women with FHA often struggle to manage stress and are prone to mood swings, depression and anxiety. Since FHA causes hormonal disturbances, chronic hypoestrogenemia results in a negative influence on growth of bones. Low levels of estrogen inhibits the gene expression of osteoprotegerin and influences the apoptosis of osteoblasts. In addition to this, hypoestrogenemia also delays the formation of bone growth factors and bone remodelling. This in turn reduces bone mineral density, making them more fragile and vulnerable to the risk of fractures. Furthermore it poses risks to cardiovascular health and reproductive well-being. Treatment includes an interdisciplinary approach to address bone health, psychological support, nutritional deficiencies and fertility support. Restoring hormonal imbalance and ensuring overall well-being are the key factors of management.

Keywords: Functional Hypothalamic Amenorrhea(FHA), Gonadotropin releasing hormone, Hypothalamic-pituitary-ovarian(HPO)axis, Hypoestrogenemia, Bone mineral density, Cardiovascular health, Hormonal imbalance.

INTRODUCTION

Functional hypothalamic amenorrhea is a condition that can be reversible, wherein the cessation of menstruation occurs in young women of premenopausal age. [1] It is often characterised by Hypogonadotropic hypogonadism, causing disturbance in the menstrual cycle. The disruption of Hypothalamic-pituitary-ovarian (HPO) axis leads to the diminished secretion of GnRH from the hypothalamus thereby reducing the surge of FSH and LH levels, which results in anovulation and hypoestrogenic state. [2],[3] Compared to primary amenorrhea, FHA is the leading cause of secondary amenorrhea, which is the absence of menstruation for 3 or more consecutive cycles in a woman with normal menstrual history.

Excessive exercise, stress, weight loss, eating disorders are the major components contributing to FHA. Prolonged FHA in women can have lasting effects on bone health, reproductive health, heightened CVS risk and psychological well being.[1],[10]

ETIOPATHOGENESIS

Numerous factors such as environmental stressors, personality traits, psychological disorders, exercise, low body weight, weight loss, and young women in sports have been implicated in the etiology of FHA since Reifenstein defined hypothalamic amenorrhea as a syndrome in which “overt or latent psychological disturbances” disrupt menstrual functioning. Individuals typically report experiencing greater depressed symptoms and having
trouble managing everyday stress.

Amenorrheic athletes experience constant metabolic changes and energy deficit due to greater energy expenditure and caloric restriction from various factors.[11] The term female athlete triad as a clinical syndrome portraying a unique form of Functional Hypothalamic Amenorrhea (FHA) which is characterised by the concurrent existence of three interlinked conditions. This includes amenorrhea, osteoporosis, and a disturbed nutritional intake or eating disorder. These conditions are increasing among competitive female athletes, especially women who are competitive runners and swimmers.[12]

Women with hypothalamic amenorrhea have rare variations in genes linked to idiopathic
hypogonadotropic hypogonadism; this suggests that mutations may play a role in women's varying susceptibility to the functional alterations in GnRH secretion that are specific to hypothalamic amenorrhea. Often they have higher cortisol levels and higher hypothalamic pituitary-adrenal axis activity than women with eumenorrhea. This offers the greatest endocrine evidence that stress desynchronizes the GnRH neural network.

It is crucial to understand the significance of the proper function of the hypothalamic pituitary ovarian axis in maintaining reproductive health. The pituitary gland plays a vital role in this axis by releasing essential hormones called gonadotropins, specifically luteinising hormone (LH) and follicle-stimulating hormone (FSH). These hormones are responsible for regulating the reproductive processes in the body. The secretion of these important hormones is stimulated by the rhythmic and pulsatile action of a hormone called Gonadotropin-

releasing hormone (GnRH) released by the hypothalamus. However, in a condition known as functional hypothalamic amenorrhea (FHA), there is a disruption in the signalling between the hypothalamus and the pituitary gland. This disruption occurs due to insufficient pulsatile serotonin production of GnRH in the hypothalamus. As a consequence, the levels of LH and FSH become insufficient to support the complete growth of ovarian follicles and the normal release of eggs (ovulation) from the ovaries. It is important to address and treat FHA to restore the balance in the hypothalamic pituitary ovarian axis and support reproductive health. This leads to a consequent deficiency in oestrogen. Amenorrhea occurs, if the hypothalamus and pituitary fails to produce adequate gonadotropins i.e. luteinising hormone (LH) and FSH are secreted by the pituitary gland pulsatile stimulation by the hypothalamic GnRH. [13]Occasionally, Hypothalamic Amenorrhea (HA) may be the result of a structural abnormality such as a hypothalamic tumour. If there is no underlying structural abnormality,[14] HA is deemed functional. Various contributory factors to Functional Hypothalamic Amenorrhea (FHA) include stress and chronic diseases. However, most instances of FHA arise due to a relative energy deficit in the body linked with weight loss or physical activity. [15] [13]These include a delayed onset of puberty, cessation of menstruation also known as amenorrhoea, challenges related to fertility and longstanding deficiency of estrogen leading to reduced bone mineral density (BMD). Furthermore, HA can also impose potential risks on sexual, genitourinary health and may even impact cardiovascular health.

Rare number of FHA cases happen without a clearly identifiable precipitant, in which case, it is referred to as idiopathic Hypothalamic Amenorrhea.

HA is classified as functional, FHA is caused by a number of factors such as stress and chronic illness.[16]

The reduction of GnRH, which is primarily caused by factors such as weight loss, exercise, or stress, is a complex process that involves the modulation of various neurosignals affecting the hypothalamic GnRH. They generally can have both inhibitory and stimulatory effects. The activation of the HPO axis, typically triggered by nutritional or other stresses, results in a decrease in GnRH secretion and subsequent alterations in LH pulsatility from the pituitary gland. Several hormonal abnormalities, which consist of low levels of IGF-1, increased cortisol and ghrelin, decreased levels of T3, T4, leptin, and kisspeptin, contribute to the suppression of GnRH observed in patients with functional hypothalamic amenorrhea (FHA). [17] GnRH suppressed by hormonal abnormalities that are associated with FHA including IGF- 1, increased cortisol, increased ghrelin, and decreased T3, T4 , decreased leptin, kisspeptin signals.

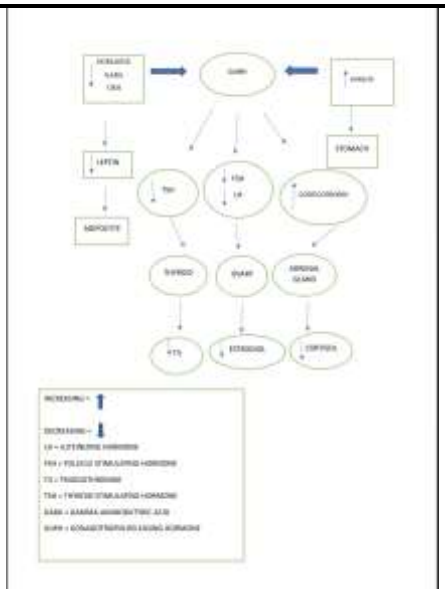

Figure 1: Pathophysiology of Functional Hypothalamic Amenorrhea.

Bone consequences

A substantial deficiency in estrogen substantially impacts the condition of the bone and plays a crucial role in managing the appropriate metabolic activity in the skeletal system. Estrogen provokes the activities of osteoblasts, the cells that are responsible for bone formation, thereby encouraging the production of distinct growth factors. These growth factors encompass Transforming Growth Factor Beta (TGF-β), Insulin-like Growth Factor 1 (IGF-1), and Bone Morphogenetic Protein 6 (BMP6). [18] Estrogen deficiency women with FHA, bone production is decreased due to the osteoblast apoptosis, which results in decreased growth factor formation.[19] The lack of estrogen promotes osteoclast (bone resorption cells) activity by inhibiting the osteoprotegerin gene expression which blocks the inhibition of osteoclast formation. [18]An increased osteoclast further increases the production of RANKL(receptor activator of nuclear factor Kappa B ligand), macrophage – colony stimulating factor (M- CSF), Interleukin – 6(IL- 6), Interleukin -1(IL -1)and tumour necrosis factor alpha (TNF – alpha) which further leads to the bone deterioration[18]

The deficiency of oestrogen resulting from FHA causes severe risk to young women and leads to the development of osteopenia or osteoporosis. Bone mass density (BMD) uses x- ray to evaluate the amount of minerals in the bone including calcium, which is the primary structural element responsible for the bone density.[20]

The condition of Hypoestrogenemia detrimentally influences the absorption process of calcium via the intestine, consequently reducing the availability of calcium required for bone reabsorption[21] and decreases BMD due to low oestrogen results in bone loss in the trabecular bone underscoring the severity of FHA on the skeletal system.[18]

Hypothalamic amenorrhea has a resultant effect of causing hypothyroidism through the suppression of thyroidal axes, thereby influencing the basal metabolic rate. In particular, the levels of triiodothyronine (T3) and thyroxine (T4) have been observed to decline in women afflicted by FHA, while the levels of thyroid-stimulating hormone

remain unaffected.[21]Hypothyroidism impairs the bone formation and growth retardation due to thyroid deficiency on bone metabolism.[22]

Reproductive Consequences

The condition of anovulation, where the ovaries fail to release an oocyte during a menstrual cycle, is closely related to the neurohormonal and hormonal background of Functional Hypothalamic Amenorrhoea (FHA). In particular, the disruption in the regular output of Gonadotropin-Releasing Hormone (GnRH) can negatively influence the consistent release of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH). As a downstream effect, this leads to a significant reduction in estrogen levels, which subsequently results in anovulation.[23]Such disturbance, if it transpires during the onset of puberty, is presented by women as primary amenorrhea – the absence of menstrual periods in a woman by the age of 16. The more prevalent presentation relative to FHA, however, is secondary amenorrhea; a condition that manifests in pubescent girls and women, characterised by the cessation of menstrual periods after they have once been regular.

As per medical analysis articulated by Hind, [23] a correct and apt diagnosis along with subsequent treatment of FHA (Functional Hypothalamic Amenorrhea) is critical due to the potential fertility risks associated with chronic amenorrhea. Based on the research conducted by Devoto and Aravena,[24] it is observed that adolescent females exhibiting hypothalamic dysfunction and menstrual issues may not respond effectively to Clomiphene. However, it should be noted that a poor response to Clomiphene doesn't necessarily imply an unfavourable prognosis in regards to menstruation or fertility.

Mentioned earlier, anovulation is a distinct feature of Functional Hypothalamic Amenorrhea (FHA). It's well recognized that affected individuals cannot conceive spontaneously. Another critical consideration is the long-term impact of untreated hypothalamic amenorrhea on reproductive health. Several complications may arise in girls going through puberty with FHA, including delayed menarche, asynchronous puberty, and underdeveloped secondary and tertiary sexual characteristics. These issues can pose significant barriers to their reproductive health. In adulthood, The identical ailment can result in atrophic alterations in the urogenital mucosa and uterine musculature. In the event of a patient suffering from FHA or a preceding FHA episode becoming pregnant, it is of utmost importance to administer meticulous management throughout their pregnancy owing to the significantly elevated chances of experiencing miscarriage and preterm labor.[25] Additionally, individuals with FHA have the potential to encounter a more intricate and challenging obstetric course, entailing complications such as insufficient weight gain and restricted foetal growth within the womb.

Cardiovascular Consequences

Disorders related to the heart and associated organs are the cause of cardiovascular diseases. The major underlying cause of heart diseases is Atherosclerosis. Women living with functional hypothalamic amenorrhea are prone to cardiovascular disease and are the leading cause of death among women of all ages. Women between the ages of 35-44 years are highly affected by cardiovascular disease.[26] Hypoestrogenism is linked

with accelerated progression of atherosclerosis, premenopausal women presenting with FHA are characterised by hypoestrogenemia. One common and reversible form of FHA in association with energy deficiency is exercise associated amenorrhea (EEA). [27] Coronary and peripheral vessels contain estrogen receptors that permit estradiol to play a regulatory role in vascular function. Estrogen excites the synthesis of nitric oxide (NO) through both genomic and non-genomic effects, leading to the augmented production of endothelial derived nitric oxide, causing vasodilation. [3] The endothelium regulates the artery's fluid equilibrium.A molecule that is generated from the endothelium,nitric oxide is essential for maintaining blood vessels integrity,regulating vascular tone,averting inflammation and platelet aggregation,and slowing down the proliferation of smooth muscle cells. Factors that decrease nitric oxide generation and / or bioavailability promote endothelial dysfunction, which is recognized to be a permissive factor for the development and advancement of atherosclerosis.Estrogen, caloric restriction, and frequent aerobic exercise are all related to higher endothelial nitric oxide synthesis and/ or bioavailability through different pathways.[27]

Psychological Consequences

Adolescent girls and young adult women with FHA are at a higher risk of depression.

Focusing on stress-related to FHA, various types of stress and lifestyle events, which are perceived as traumatic and/or stressful experiences by women. [28]

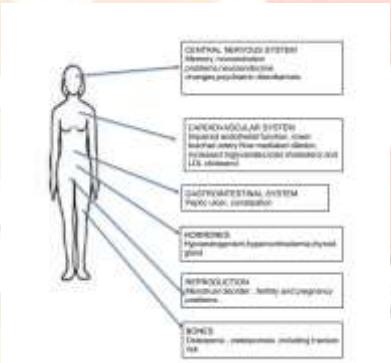

Figure 2: Overall consequences of FHA.

High levels of psychological and physiological stress, which can manifest as anything from coping mechanisms and weight loss to maladaptive behaviour. Heart rate variability (HRV) is a valid indicator of a person's psychological reaction to stress and capacity for environmental adjustment. The autonomic nervous system stimulates the sympathetic (SNS) and parasympathetic (PNS) nervous systems to generate different variations in heart rate variability (HRV) that correspond to the person's psychophysiological reaction to stress. Due to the high levels of PNS activation that FHA patients exhibit under psychological stress, parasympathetic hyperactivation may be a disease sign.[29]

MANAGEMENT

Management of functional hypothalamic amenorrhea requires an interdisciplinary approach, as the condition is reversible and resolves when the underlying cause is addressed. Therefore accurate identification and elimination of the primary cause is important. [1]

To correct the HPO axis functioning, the primary management involves lifestyle modifications for healthy weight gain through a diet with sufficient nutritions and optimising calorie intake.[4]

In female athletes with a healthy weight but low calorie intake may contribute to lower body fat, leading to FHA. Hence a tailored diet to optimise calorie intake and modifications in exercise such as reducing the intensity of exercises can increase energy availability. [8]

Psychological treatment is necessary to address patients with anxiety, depression, disordered eating, improper sleep and psychosocial stress. Cognitive-behavioural therapy(CBT) aims to improve patient conditions and resume normal menstruation.[4]

CBT has significantly reduced nocturnal cortisol levels and improved Leptin levels, thereby promoting metabolic and ovulatory functioning.

In patients with long term FHA, due to low circulating estrogen levels, bones are mainly affected, becoming fragile with reduced bone density. Levels of Calcium and vitamin D should be checked and daily supplements are necessary along with dietary modifications. [5]

After gaining weight, sustaining the same weight for 6 to 12 months is crucial for regular menstruation. If the consistent lifestyle modifications are ineffective, pharmacological considerations for bone mineral density (BMD) are evaluated. [7]

Combined oral contraceptives do not improve bone density hence, transdermal cyclic estrogen-progesterone therapy is preferred as it doesn't affect Insulin like growth factor 1(IGF-1) secretion, an osteoanabolic hormone for short term for individuals with higher risk. [6],[7],[8],[9]

In patients planning for pregnancy, initial weight gain of at least 18.5 kg/m² with >23% body fat is recommended. Later, treatment with pulsatile gonadotropin releasing hormone (GnRH) followed by drugs like Clomiphene citrate for ovulation induction is considered in cases of sufficient endogenous estrogen.[4],[8]

For patients with the complaints of PCOS, Letrozole is preferred over clomiphene due to higher chances of ovulation.[6],[7]

To achieve desired outcome periodic follow-up and examinations are necessary.[1]

CONCLUSION

Functional hypothalamic amenorrhea is a reversible condition and a leading cause of amenorrhea in premenopausal women. The enduring status of hypoestrogenemia not only influences reproductive health but also affects bone health contributing to osteopenia or osteoporosis. It also elevates the risk of CVD. The management should primarily focus on underlying causes, emphasising sustained lifestyle modifications and tailored therapeutic regimen for better outcome. Educating young women and creating awareness serves as a crucial precautionary measure.

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