COMMENTARY

The impact of functional hypothalamic amenorrhea on women's health

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ABSTRACT

The study's objective is to highlight the issue of Functional Hypothalamic Amenorrhea while taking into consideration any underlying diseases, their treatments, diagnoses, and effects. 38 original and review publications about Functional Hypothalamic Amenorrhea were included after searching PubMed. The most frequent cause of secondary amenorrhea in women of reproductive age is Functional Hypothalamic Amenorrhea. It is a condition that may be reversed and is brought on by stress connected to rapid weight reduction, intensive activity, or traumatic situations. Hormonal factors, including reduced gonadotropin secretion, impaired pulsatile GnRH secretion in the hypothalamus, and altered hormonal activity of the ovaries, form the basis of Functional Hypothalamic Amenorrhea. This condition causes hypoestrogenism, which causes amenorrhea and anovulation by disrupting the menstrual cycle. Long-term hypoestrogenism can be extremely hazardous to overall health and have numerous negative short- and long-term effects. It is important to begin Functional Hypothalamic Amenorrhea treatment as soon as feasible, with a focus on lifestyle changes. Pharmacological therapy shouldn't be started till after that. Importantly, even though therapy is frequently prolonged, the majority of patients recover as a consequence. Patients can avoid a variety of harmful effects on their fertility, cardiovascular health, and bone health, as well as reduce mental morbidity, with effective therapy that is based on multidirectional action.

Key Words: *Hypoestrogenism; GnRH; Hypothalamic amenorrhea*

INTRODUCTION

A deviation in the pulsatile release of Gonadotropin-Releasing Hormone (GnRH) from the brain is the cause of Functional hypot-Hypothalamic Amenorrhea (FHA), which is categorised as hypogonadotropic hypogonadism. The range of hypothalamic-pituitary abnormalities in FHA can be extremely extensive and encompasses a normal-appearing secretion pattern, a greater mean frequency of LH pulses, a lower mean frequency of LH pulses, and the entire lack of LH pulsatility. Reduced gonadotropin secretion therefore influences the ovary's ability to produce estradiol. One of the most frequent reasons of secondary amenorrhea in FHA instances is the disrupted hypothalamic pituitary ovarian axis, which is generally linked to stress, weight reduction, and/or excessive exercise. There are three categories of FHA depending on the triggering factor: exercise-related, stress-related, and weight loss related. Whatever the precise cause, a complicated condition of hypoestrogenism, other endocrinological abnormalities, and metabolic abnormalities brought on by FHA may affect the balance of the whole body.

Epidemiology

About 3% to 5 % of adult women experience secondary amenorrhea, which is defined as three months without period. The American society of reproductive medicine estimates that 3% of FHA instances of primary amenorrhea and 20% to 35 % of cases of secondary amenorrhea are caused by FHA. Female athletes are more likely to experience it. Calculated that amenorrhea affects 30% of women and that modest menstrual abnormalities affect about 50% of women who exercise frequently. Female athlete trio, a grouping of disordered diet, amenorrhea and osteoporosis, was originally identified in 1997.

Differential diagnosis

In each instance, functional hypothalamic amenorrhea should be distinguished from other types of primary or secondary amenorrhea. An evaluation of the gonadotropins and the identification of hypo gonadotropic hypogonadism are the fundamental method for making this difference. A GnRH stimulation test, which in the case of FHA demonstrates a positive response of the gonadotropins to exogenous GnRH, is the primary diagnostic technique when such a diagnosis has been made. With the use of this test, it is simple to distinguish between hypothalamic dysfunction and pituitary illnesses, which also exhibit hypogonadism. It's crucial to rule out genetic and organic conditions when the hypothalamic origin has been identified. The following should be considered as a probable hereditary cause of amenorrhea. Other uncommon disorders with idiopathic hypogonadotropic hypogonadism include Kallman syndrome (marked by anosmia and particular mutations), Prader-Willi syndrome (with distinctive hyperorxia, obesity, and retardation), and others. Congenital disorders are indicated by characteristics like

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delayed puberty, primary amenorrhea and the existence of other symptoms including anosmia, mental retardation, severe obesity, facial dysmorphia, and malabsorption. Imaging analysis may be used to rule out organic illnesses of the hypothalamus, such as neoplasms, sarcoidosis, TB, parasitoids and other infiltrating lesions.

FHA-related hormonal disturbances

As mentioned above, the hypothalamic pituitary ovarian axis is depressed in FHA. The main disease in this characteristic is impaired GnRH and gonadotrophin production, and FHA also has aberrant pituitary hormone secretion. Hypothalamic pituitary adrenal axis activation is a hallmark of FHA and is associated with stressors. This phenomenon is thought to be a key pathogenic element in FHA patients. Adrenocorticotrophin from the pituitary and cortisol from the adrenal glands are secreted at higher rates as a result of hormone (CRH) secretion, and these phenomena are connected to a diminished GnRH drive. There have been reports of elevated cortisol levels in the cerebrospinal fluid and serum in FHA.

In FHA patients, abnormalities in the hypothalamic-pituitary-thyroid axis are also seen. Thyrotropin levels are low to normal, reverse triiodothyronine levels are elevated, and triodothyronine levels are low. Elevated nocturnal serum growth hormone levels and decreased 24 hour prolactin levels are two additional hypothalamic amenorrhea-related results. Low blood levels of insulin, IGF-1 and enhanced insulin sensitivity are characteristics of FHA patients. In addition, testosterone levels in FHA patients are reported to be lower than in healthy controls. Clinically speaking, FHA shouldn't be seen just as a symptom like amenorrhea.

FHA changes in neuroendocrine function

It is extremely difficult to pinpoint the exact processes behind the pathophysiology of FHA. There is evidence that a number of neuropeptides, neurotransmitters, and neurosteroids may be implicated in the pathophysiology of FHA, as well as in the physiological control of GnRH pulsatile secretion. Kisspeptin, neuropeptide Y (NPY), ghrelin, leptin, corticotropin releasing hormone (CRH), b-endorphin, and allopregnanolone should all be given special consideration. A key role in puberty and fertility is played by kisspeptin, which is produced by the KISS-1 gene and its G protein-coupled receptor GPR54. The hypothalamus-pituitary-ovarian axis is activated by the kisspeptin/GPR54 system. The arcuate nucleus of the hypothalamus can be directly stimulated by kisspeptin to secrete GnRH. When exogenous kisspeptin is administered to healthy females, blood levels of LH and FSH rise. Acute kisspeptin administration to FHA-positive women significantly increases the release of gonadotropin.

Energy balance, sexual behavior, and circadian rhythm are all regulated by neuropeptide Y (NPY). NPY has an impact on the hypothalamic area that controls appetite and promotes eating. If the levels of sex hormones, primarily estradiol, are high enough, NPY will cause the creation of GnRH. In hypoestrogenic patients, NPY have an inhibitory impact on GnRH. found that amenorrheic patients had lower basal serum NPY than did menstruation women. Patients with amenorrhea brought on by weight reduction had more NPY and LH peaks than controls. Ghrelin is a peptide that increases hunger but decreases the use of fat. Ghrelin also prevents the hypothalamic-pituitary-gonadal axis, which is what causes amenorrhea to last longer in people who have regained their normal weight. Compared to healthy women, women with FHA had higher ghrelin levels. Exercise-related or underweight amenorrheic individuals have a markedly larger rise of serum ghrelin than those who maintain a steady weight. An important connection between metabolic and hormonal signals and their effects on thereproductive axis is made by the hormone leptin, which is produced from adipose tissue. When compared to eumenorrheic controls of the same age, weight, and body fat, patients with hypothalamic amenorrhea had significantly lower blood leptin concentrations. By influencing both the hypothalamus-pituitary-ovary axis and the hypothalamus-pituitary-adrenal axis, CRH is a key player in the control of reproduction. Stress, whether physical or emotional, causes the CNS to immediately produce more CRH. The release of ACTH and other peptides associated to Pro-opiomelanocortin (POMC), including β-endorphin and β-lipotropic hormone, is then stimulated by CRH in the pituitary. GnRH and gonadotropin release are inhibited by increased glucocorticosteroid production. The processes mentioned point to a particular stress aetiology for hypothalamic amenorrhea.

CONCLUSIONS

FHA is a clinical issue that is underappreciated. It has to do with the severe impairment of reproductive processes, such as anovulation and infertility. This illness affects women's health in a number of ways, including their skeletal system, cardiovascular system, and mental health. Patients have a reduction in bone mass density, which is associated with an elevated risk of fracture. The primary long-term effects of FHA are hence osteopenia and osteoporosis. Endothelial dysfunction and unfavorable lipid profile alterations are examples of cardiovascular consequences.

When compared to healthy persons, FHA patients exhibit considerably greater levels of anxiety, sadness, and sexual dysfunction. To avoid both immediate and, especially, long term medical effects, FHA patients should be accurately evaluated and handled.