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FUNCTIONAL DISORDER OF THE HYPOTHALAMUS AS A CAUSE OF PRIMARY AMENORRHEA

DESORDEM FUNCIONAL DO HIPOTÁLAMO COMO CAUSA DE AMENORRÉIA PRIMÁRIA

TRASTORNO FUNCIONAL DEL HIPOTÁLAMO COMO CAUSA DE AMENORREA PRIMARIA

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ABSTRACT
Functional hypothalamic amenorrhea (FHA) occurs when the hypothalamic-pituitary-ovarian sequence is suppressed due to an energy deficit usually caused by stress, weight loss, excessive exercise and disordered eating, leading to hypogonadism. The diagnosis is of exclusion, and a clinical examination with complementary blood and imaging tests must be performed. Treatment aims to correct the causes, guide adequate nutrition and physical activity. The combined estrogen can be used to restore menstrual cycles and preserve bone mass. We present the case of a 21-year-old patient with primary amenorrhea and hypogonadotropic hypogonadism, with a history of stress linked to low self-esteem, intense ballet activity during puberty and rigidity in eating. Physical examination showed complete pubertal development and low body mass index (16.9 kg/m2). Decreased serum levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), and normal levels of prolactin (PRL), thyroid stimulating hormone (TSH). Bone densitometry showed osteoporosis of the femur and lumbar spine. After weight restoration, physical activity monitored by a professional, and prescription and combined oral hormone therapy, the patient started menstrual cycles.

KEYWORDS: Amenorrhea. Emotional stress. Case report. Hypothalamus. Adolescent.

RESUMO
A amenorreia hipotalâmica funcional (FHA) ocorre quando a sequência hipotálamo-hipófise-ovário é suprimida devido a um déficit energético geralmente causado por estresse, perda de peso, exercício excessivo e alimentação desordenada, levando ao hipogonadismo. O diagnóstico é de exclusão, devendo ser realizado exame clínico com exames complementares de sangue e de imagem. O tratamento visa corrigir as causas, orientar alimentação adequada e atividade física. O estrogênio combinado pode ser usado para restaurar os ciclos menstruais e preservar a massa óssea. Apresentamos o caso de uma paciente de 21 anos com amenorreia primária e hipogonadismo hipogonadotrófico, com história de estresse associado à baixa autoestima, intensa atividade de balé na puberdade e rigidez alimentar. O exame físico mostrou desenvolvimento puberal completo e baixo índice de massa corporal (16,9 kg/m2). Níveis séricos diminuídos de hormônio luteinizante (LH) e hormônio folículo estimulante (FSH) e níveis normais de prolactina (PRL), hormônio estimulante da tireoide (TSH). A densitometria óssea mostrou osteoporose do fêmur e coluna lombar. Após a recuperação do peso, atividade física monitorada por profissional e prescrição e terapia hormonal oral combinada, a paciente iniciou os ciclos menstruais.

PALAVRAS-CHAVE: Amenorreia. Estresse emocional. Relato de caso. Hipotálamo. Adolescente.

RESUMEN
La amenorrea hipotálmica funcional (FHA) se produce cuando la secuencia hipotálamo-hipófisis-ovário es suprimida debido al déficit energético causado generalmente por el estrés, la pérdida de peso, el exceso de ejercicio y la alimentación desordenada, provocando el hipogonadismo. El diagnóstico es de exclusión, y debe realizarse un examen clínico con análisis de sangre complementarios e imágenes. El tratamiento tiene como objetivo corregir las causas, y orientar una

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dieta adecuada y actividad física. Los estrógenos combinados pueden utilizarse para restablecer los ciclos menstruales y preservar la masa ósea. Presentamos el caso de una paciente de 21 años con amenorrea primaria e hipogonadismo hipogonadotrófico, con antecedentes de estrés asociado a baja autoestima, intensa actividad de ballet en la pubertad y rigidez alimentaria. La exploración física mostró un desarrollo puberal completo y un índice de masa corporal bajo (16,9 kg/m2). Disminución de los niveles séricos de la hormona luteinizante (LH) y de la hormona estimulante del folículo (FSH) y niveles normales de prolactina (PRL), hormona estimulante del tiroides (TSH). La densitometría ósea mostró osteoporosis en el fémur y la columna lumbar. Tras la recuperación del peso, la actividad física controlada por un profesional y la prescripción y terapia hormonal oral combinada, la paciente comenzó a tener ciclos menstruales.

PALABRAS CLAVE: Amenorrea. Estrés emocional. Informe de un caso. Hipotálamo. Adolescente.

INTRODUCTION

Amenorrhea is defined as the absence of spontaneous menstruation in women of reproductive age. It affects approximately 3-4% of the female population. The absence of menarche at 13/14 years old in girls who have not yet developed sexual characteristics or at 15/16 years old in those with developed secondary sexual characteristics is considered primary amenorrhea and should be investigated (GOLDEN AND CARLSON, 2008; KLEIN *et al*., 2019).

Alteration in the hypothalamic-pituitary axis can lead to amenorrhea with hypogonadotrophic hypogonadism. Amenorrhea due to hypothalamic causes is caused by a deficiency in the secretion of gonadotropin-releasing hormone (GNRH), produced in the hypothalamus and acting on the anterior pituitary gland to stimulate the secretion of gonadotropic hormones, LH and FSH. These act on the ovaries by stimulating the secretion of estrogen and progesterone. With GNRH deficiency, there will be LH and FSH deficiency (PROMOÇÃO E PROTEÇÃO DA SAÚDE DA MULHER ATM, 2024). Functional hypothalamic amenorrhea (AHF) occurs when the hypothalamic-pituitary-ovarian sequence is suppressed due to energy deficits from stress, weight loss, excessive exercise, or disordered eating (GORDON *et al*., 2017).

The main causes of primary amenorrhea can be divided according to the compartments involved, as shown in Table 1.

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Table 1: Main causes of primary amenorrhea according to the compartments involved:

HYPOTHALAMUS / PITUITARY GLAND (Hypogonadotropic hypogonadism)	OVARY (Hypergonadotropic hypogonadism)	OUTPUT TRACT (Eugonadism)
• Constitutional delay in growth and development • Functional amenorrhea • Eating disorders, amenorrhea in athletes • Kallmann syndrome • Hyperprolactinemia • S. Sheehan • Isolated gonadotropin deficiency • Menarche delay	• Primary ovarian insufficiency • Gonadal dysgenesis (Turner syndrome, other dysgenesis) • Polycystic ovary syndrome (PCOS) • Post-treatment QT, RXT • Autoimmune oophoritis.	• Imperforate hymen • Transverse vaginal septa • Utero-vaginal agenesis • Synechiae, • Ashemann's Syndrome

The diagnosis is suspected when the patient has amenorrhea, compatible clinical history, decreased or normal gonadotropin levels and estradiol lower than 50 pg/ml in the absence of organic diseases of hypothalamic or pituitary origin (GORDON *et al*., 2017; LIU AND BILL, 2008; Gibson *et al*., 2020). Consequences of delayed puberty, infertility and impact on bone mass due to chronic hypoestrogenism with increased risk of osteoporosis and fractures.

The present article is a case report of a 21-year-old female patient with primary amenorrhea due to a functional hypothalamic disorder caused by stressful situations.

METHODOLOGY

A descriptive study of the case report type was carried out, in which the medical records were reviewed, clinical history was understood, imaging and laboratory tests were analyzed, and the diagnostic methods to which the patient was submitted were recorded.

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CASE REPORT

Patient, 21 years old, comes to the hebiatric service accompanied by her mother, complaining of never having menstruated and dissatisfaction with her body due to the small size of her breasts. She reports having started pubertal development at the age of 13. At 14 years of age, she presented relationship difficulties, weight loss due to restrictive diet and ballet practice with exhaustive training until 17 years old when she entered college. She was followed up with a psychologist with little improvement in her condition. At the age of 19, due to the absence of menarche, she sought medical assistance and, after organic disease was ruled out, she was medicated with combined hormonal therapy in the form of a transdermal patch (norelgestromin 203 µg/day + ethinylestradiol 33.9 µg/day). She had mild bleeding with the medicine and stopped after 2 months of use due to severe breast pain and gastrointestinal symptoms.

In use of vitamin D and vitamin B12.

On physical examination: Weight 45.1 kg and height 1.63 m Body mass index (BMI): 16.9 kg/m2. Mild acne, absence of hirsutism, complete pubertal stage (M4, P4 and axillary).

Tests: blood glucose: 74.30 mg/dL, albumin: 5.10 g/dL, ferritin 68.70 ng/dL, sodium: 140 mEq/L, potassium: 4.60 mEq/L, magnesium: 2.10 mg /dl, phosphorus: 3.64 mg/dl, calcium: 10.52 mg/dl, serum zinc: 80.3 ug/dl, vitamin B12: 692 pg/ml, 25-hydroxyvitamin D: 32.1, IGF- 1 Somatomedin C: 119 µg/L (VR 117-323), 17 hydroxyprogesterone: 94.0 ng/dl, total testosterone :41 ng/dL (VR 12-60), DHEA-S: 172 µg/dl; prolactin: 8.74 ng/nl, 17 beta estradiol: 69 pg/ml, TSH: 1.65 IU/ml (VR 0.34-5.6), free T4: 1.02 ng/dl (VR 0, 75-1.8), LH: 2.3 mIU/ml and FSH: 5.81 mUL/ml. Anti-GliadinIgG and IgA antibodies= normal

Image: X-ray of the hand and wrist revealed a bone age of 16 years (chronological age of 19 years). X-ray of the sella turcica and MRI of the skull were normal. Pelvic ultrasound: uterine volume = 14 cm3; ovary D: 3 cm3 and ovary E: 4 cm3. Bone densitometry showed osteoporosis in the femur and spine (Table 2).

Table 2: Bone densitometry results of a 21-year-old patient with hypothalamic amenorrhea:

	BMD (g/cm2)	**T (DP)**	**% young adult**	**Z (DP)**	**% same age**
Lumbar spine:	0.738	-3.7	63%	-3.0	67%
Femur:					
Femoral neck:	0.621	-3.0	60%	-2.7	62%
Total femur:	0.625	-3.0	62%	-2.5	65%

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Conduct: referred to nutritionist and psychologist. Sequential combined hormonal therapy was prescribed (2 mg estradiol valerate + 0.25 mg orally levonorgestrel) for 2 cycles, and oral vitamin D supplementation 10,000 IU/week was kept. After discontinuation of the medicine, the patient had a menstrual delay of 40 days. Medroxyprogesterone acetate 10mg orally was prescribed for 5 days with a positive response and a combined contraceptive containing drospirenone (ethinylestradiol 20µg+ drospirenone 3mg orally) was prescribed for acne improvement.

After 6 months of treatment and nutritional follow-up, the bioimpedance exam revealed a body fat of 20.13, weight gain to 53 kg with a BMI of 20 kg/m2, confirming diagnosis of functional hypothalamic primary amenorrhea.

DISCUSSION

The diagnosis of FHA can be challenging in adolescents, as it is a time when the hypothalamic-pituitary-ovarian (HPO) axis is developing (GORDON *et al.,* 2017). Adolescence represents a process that leads to the formation of body image, sexual integration and maturation. This biological and psychological transformation can be considered a stressor in this period. There are not many studies on the association of psychological aspects in FHA and its prevalence in adolescence, although clinical observation in the last decade has shown an increase in its incidence (BOMBA *et al*., 2007) Studies describe that the suppression of the HPO axis may be due to psychological stress, disordered eating, weight loss and excessive physical exercise (GORDON *et al*., 2017; KLEIN AND POTH, 2013).

A case of primary amenorrhea associated with stress factors such as intense ballet activity during puberty, low self-esteem and low BMI was presented. Thus, the diagnosis of FHA was suggested by the clinical history and complementary exams performed without any abnormality. This clinical investigation with complementary exams in the patient of the report is justified by studies that state that primary or secondary amenorrhea must be evaluated for other causes before a diagnosis of FHA is made. The evaluation consists of anamnesis, physical examination, laboratory investigations and radiological imaging tests (GIBSON *et al*., 2020). The diagnosis of FHA is one of exclusion when ruling out organic diseases and diseases of the hypothalamus, pituitary and ovary axis (GORDON *et al*., 2017; LIU AND BILL, 2008; GIBSON *et al*., 2020).

Physical activities performed by women, aiming at competitive excellence, can lead to changes in the menstrual cycle and even suspension of menstruation. Several mechanisms have been described in order to explain exercise-related amenorrhea, particularly those related to the action of beta-endorphins (TRAVASSOS *et al*., 2017).

According to Martins (MARTINS, 2002) the peak of bone mass is determined by genetic factors, contributing 60 to 80% of the bone mineral content of adults. The author states that lifestyle-related factors influence the remaining 20 to 40%. Among these, ballet practice for a period of 40 hours per week, hormonal status, BMI and food, present in the patient at puberty. Intense physical activities according to Maimoun *et al.* (MAÏMOUN *et al*., 2016) generates stressor mechanisms with

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metabolic changes that can be intermittent or chronic, leading to a decrease in body fat to maximize performance. Adolescent and adult female athletes are at risk of overtraining and/or with insufficient food intake, which can have consequences for endocrine function, particularly in the hypothalamic-pituitary-gonadal axis.

In 2017, the American College of Obstetricians and Gynecologists revised the definition of the female athlete triad. The revised criteria are low energy availability with or without disordered eating, menstrual dysfunction, and low bone density. The review states that an individual does not need to show clinical manifestations of all components of the female athlete triad simultaneously for diagnosis (COMMITTEE OPINION No.702, 2017). The triad occurs when energy intake does not adequately compensate for exercise-related energy expenditure, leading to adverse effects on reproductive, bone and cardiovascular health. The triad effect is more significant in the health of adolescent athletes than in adults because adolescence is a critical time for the accumulation of bone mass (KELLY AND HECHT, 2022). Furthermore, early diagnosis and early intervention can prevent long-term consequences. Some consequences may be irreversible if not diagnosed and treated (LOVELESS, 2017; DAILY AND STUMBO, 2018).

Furthermore, the patient had a BMI of 16.9, which according to the WHO is classified as low weight (HURRIA *et al.,* 2010). Although this low weight is associated with caloric intake restriction, the patient cannot be diagnosed with anorexia nervosa because she does not have a disturbance with her own weight (SENA, 2014). Low weight and reduced body fat reserves imply one of the causes of the development of amenorrhea. In addition, poor caloric intake results in a negative energy balance, which associated with the high energy expenditure of excessive training can cause menstrual disorders (PARDINI, 2001; WILLIAMS *et al*., 2001). Despite the absence of the patient's diagnosis of anorexia nervosa, it is recognized that the percentage of body fat (%BF) is a good predictor of menstrual recovery in women who have this disorder and increasing the %BF by just one unit can increase the chance of menstruation by 15 to 20%. Still, despite the scarcity of data, a cutoff point of %BF approximately equal to 21% was suggested as the minimum for the resumption of menstruation (TRABOULSI *et al.,* 2019). After the beginning of the treatment, the restoration of the patient's weight (53kg) and nutritional status of eutrophic (20kg/m²) according to BMI 19, as well as %BF= 20.13, which reveals the importance of monitoring the anthropometric and nutritional assessment and the clinical evolution of the patient in relation to regularization of your menstrual cycle.

The patient reported low self-esteem with social isolation and weight loss, with adolescents who presented FHA having a higher incidence of subclinical eating disorders, psychosomatic discomfort and mild depressive traits. The subclinical eating disorder of these adolescents was of a “restrictive type” and was in contrast to reports of adults with bulimic symptoms. These data can be explained as a possible evolution and differentiation of subclinical eating disorders in adult life. In fact, restrictive traits seem to represent a specific phenotype in adolescent girls with FHA. This may depend on the models of beauty and success that our society proposes and to which adolescents are susceptible (BOMBA *et al*., 2007).

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In addition, regarding the patient's causal component, the fact of being bullyed at school, social isolation and anxiety may also have favored FHA. The onset of amenorrhea can be observed in stressful situations (BOMBA *et al*., 2007). According to Fourman (FOURMAN AND FAZELI, 2015), FHA is responsible for the reproductive dysfunction observed in malnutrition, excessive exercise, severe emotional stress and chronic disease. During periods of extreme physical, nutritional, or emotional stress, the HPA (hypothalamic-pituitary-adrenal) axis is activated and inhibits the HPO (hypothalamus-pituitary-ovarian) axis at various levels. At the hypothalamic level, CRH suppresses GnRH secretion, and women with FHA have higher mean plasma cortisol levels of 24 hours compared to controls, and cortisol, the end product of the HPA axis, suppresses reproductive function at hypothalamic levels, pituitary and uterine. Therefore, the correlation between the HPA and HPO axes promotes the development of amenorrhea as a functional adaptation to stress.

At normal puberty, gonadotropin-releasing hormone (GnRH) is released by the hypothalamus in a pulsatile manner, stimulating synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. In patients with FHA, GnRH secretion is suppressed, LH pulsatility is impaired, and total LH and FSH levels are reduced, as was the case with the patient in the report. Therefore, it is classified as a form of hypogonadotropic hypogonadism, which results in a hypoestrogenic state (Gibson *et al*., 2020). Without the presence of estrogen, the ovary cannot stimulate follicles, nourish an egg, and release it into the fallopian tube for fertilization. In this way, endometrial thickening is also avoided, as the lack of cyclical changes in estradiol and progesterone concentrations leads to the abolition of the endometrial lining (GROOTHUIS *et al*., 2007). Since an ovulation is one of the main features of the disease, patients with this condition cannot get pregnant spontaneously (TORBATI *et al*., 2017). In contrast, increased secretion of corticotropin-releasing hormone (CRH) results in increased secretion of adrenocorticotropin from the pituitary and cortisol from the adrenal glands. Thus, high concentrations of serum and cerebrospinal cortisol can be found in FHA (PARDINI, 2001).

The reduction in bone mineral density (BMD) is due to the low level of estrogen and results in diffuse bone loss observed in the trabecular bone, highlighting the severity of FHA in the skeletal system. It is estimated that the average BMD of a young woman with only six months of hypoestrogenemia is equivalent to that of a 51.2-year-old woman (VALDES-SOCIN *et al*., 2014).

The primary goal for women with FHA is to normalize energy status, and therefore weight, similarly through dietary modifications and/or exercise training (GIBSON *et al*., 2020).

In this case, given the diagnosis, one of the treatments instituted was follow-up with a nutritionist and guidance regarding the practice of physical activity. According to Chou (CHOU and MANTZOROS, 2018), since the endocrine dysfunction described is mainly in response to a state of chronic energy deficit, management focuses on addressing this underlying cause. Treatment focuses on weight rehabilitation and involves a multidisciplinary approach, including psychological, medical and nutritional aspects. Thus, the change in diet and physical training and a multidisciplinary approach were relevant for this case.

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In addition, the patient adjusted the amount of calcium through food and supplemented vitamin D, which in an adequate intake, as well as maintaining serum levels within normal parameters, are essential for the maintenance and reduction of bone densitometry (BMD) loss, decreasing the probability of developing osteoporosis, and reducing falls and fractures. (ALMEIDA, 2019)

In this case of functional hypothalamic amenorrhea, the use of the transdermal patch was initially instituted, but due to intolerance there was no adherence (GORDON *et al*., 2017). Suggests the short-term use of transdermal E2, cyclic oral progestin therapy (no oral contraceptives or E2 ethinyl) in adolescents and women who has not returned to menstruation after a reasonable attempt at nutritional, psychological, and/or modified exercise intervention. According to Febrasgo (TENSÃO PRÉ-MENSTRUAL – CRITÉRIOS PARA DIAGNÓSTICO, 2018) in cases of hypoestrogenism in adult women, replacement with conjugated estrogens or estradiol by different routes, and in women with a uterus, the addition of progestogen is necessary to prevent endometrial cancer. When hypoestrogenism results from reversible situations, estrogen-progestational replacement can be performed concurrently with specific treatment for the cause, until ovarian function is reestablished.

CONCLUDING REMARKS

Functional hypothalamic amenorrhea is a diagnosis of exclusion, so the investigation of the causes becomes essential. Physiological changes associated with food restriction, intense physical exercise and psychological stress that occur during puberty can lead to hormonal dysfunctions that, if prolonged, can result in negative impacts on bone, cardiovascular, mental and reproductive health. Emphasizing the need for early intervention. However, more studies are needed to better understand the influence of stressors in adolescence that lead to functional hypothalamic amenorrhea and better treatment effectiveness.

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