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Case Report

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Functional hypothalamic amenorrhea remission, with spontaneous pregnancy after behavioral modifications

Abstract

Functional Hypothalamic Amenorrhea (FHA) is a disorder that generates a state of chronic anovulation due to a low calorie intake and high energy expenditure through intense physical activity. This energy deficit induce several hormonal changes that lead to decreased secretion of gonadotrophin releasing-hormone (GnRH) and luteinizing hormone (LH), resulting in a chronic state of hypoestrogenism and infertility. Loss of bone mineral content and delayed puberty may also arise from such condition depending on patient´s age. Herein we present a case of a patient with HFA that was reversible through behavioral modifications, resulting in spontaneous pregnancy.

Keywords: amenorrhea, athletes, hypogonadism, exercise

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Abbreviations: FHA, functional hypothalamic amenorrhea; LH, luteinizing hormone; GnRH, gonadotrophin releasing-hormone

Introduction

The practice of high-intensity physical exercises has grown exponentially over the years. Despite the various health benefits that physical activity has, when performed strenuously associated with a strict diet, the calorie deficit can negatively impact body functioning and hormonal balance.[1–3] Hypothalamic amenorrhea is a disorder that generates a state of chronic anovulation. This disorder is common in high-performance female athletes, as well as patients with anorexia nervosa, whose rigid diet and low weight maintenance affects the hypothalami-pituitary-ovary axis by suppressing GnRH pulses and decreasing LH and FSH secretion, generating a state of hypoestrogenism, menstrual cycle irregularities and infertility. It is also believed that high levels of stress have the same effect over the axis, collaborating to this condition.[4–6] Moreover, several other consequences of this condition arise, such as late menarche, infertility and loss of mineral bone density.[1] Herein, we report a case of such condition, with spontaneous pregnancy after change in lifestyle and increased calorie intake. An informed consent was obtained from the patient.

Case report

A 35year old woman presented to Endocrinology clinic for secondary amenorrhea evaluation and infertility; she reported that menses were irregular for about 18 months, and developed amenorrhea over the last 6 months. She had no comorbidities, had no regular medication use, although she was on regular use of omega-3 fatty acids (EPA/DHA 2000mg per day) on her own account; she denied use of androgenic steroids. Patient was a physical education instructor, very concerned about healthy eating and body image; she claimed that her routine was a 10km run everyday, cross-fit training 5 times a week, and began a very low carbohydrate intake for 2years (under 50grams/day). Physical exam was unremarkable; no hirsutism or signs of virilization, galactorrhea was absent, thyroid was normal, as well as vital signs. A bioimpendance for body composition was performed, and revealed Height=166cm, Weight=57kg, in which 35% was defined as muscle, 15% fat (with visceral fat level of 2-normal <9).

Laboratory exams showed an Estradiol level of 30pg/ml, Total testosterone of 17ng/dl, Prolactin of 8ng/mL, Follicle Stimulating Hormone (FSH) of 7.9UI/L and Luteinizing Hormone (LH) of 12.7UI/L, with a normal thyroid function and late night salivary free cortisol. Trans vaginal ultrasound was unremarkable, showing normal ovaries and endometrial echo complex thickness of 8mm. With a laboratory finding of central hypogonadism, a Clomiphene citrate stimulation test was performed: for 5 days, a daily dose of 50mg was taken by the patient, and on the 14th day, laboratory exams were performed, revealing: FSH 2UI/L, LH 17UI/L, Progesterone 0, 51ng/ml, and estradiol 1,888pg/ml. A magnetic resonance (MR) of the hypophysis/hypothalamus was performed, but was also, unremarkable. A whole body composition analysis revealed a normal bone mineral content. We, then, raised the hypothesis of functional hypothalamic amenorrhea and suggested she increased carbohydrate intake for about 250g, and lowered physical activity level for only 45min a day, alternating aerobic and resistance activities. After only 75 days of lifestyle change, patient had a spontaneous menstrual flow, and became pregnant on the next month.

Discussion

The causes of amenorrhea are basically divided between organic and functional causes. Organic is that which is directly related to a well-established anatomic pathology, such as uterine agenesis, hypothalamic/hypophysary tumors, Asherman's syndrome, among other causes; they may be related to congenital or acquired conditions. Hypothalamic amenorrhea is classified as functional due to its association with behavioral and nutritional factors, and the absence of structural injuries, which determines a potential reversibility with the correction of such underlying factors.[6,7] Among the consequences

of such a situation, attention is drawn to infertility, which is related to chronic anovulation. Other problems related to the chronic hypoestrogenic state standout, such as osteopenia and osteoporosis, which increases the risk of bone fractures, especially in high-performance athletes and delayed puberty, in cases of young athletes.1 In fact, the female athlete´s triad is defined as a calorie deficit associated with loss of bone density and menstrual cycle dysfunction.[6]

The diagnosis of hypothalamic amenorrhea is predominantly clinical, perceived by the absence of menstrual cycles for more than 6 months or for more than 3 cycles in women whose cycles were previously regular. In the specific cases of hypothalamic amenorrhea in athletes, it is also noticed the low weight and important calorie intake restriction. In order to establish the diagnosis of functional amenorrhea, organic causes must be ruled out, requiring detailed physical examination and clinical history, associated with imaging and biochemical tests.[2,6,7] The correct amount of energy for the body is what allows the performance of metabolic processes such as thermoregulation, locomotion, reproduction, growth and general homeostasis; all of this is made possible by adequate hormonal secretion.[2] In response to the energy deficit resulting from low intake and high energy expenditure, there is a reduction in basal metabolism, in order to preserve energy. A great part of this phenomenon is due to the described reduction in serum T3 and IGF-1, due to growth hormone resistance.[6]

Moreover, reductions in leptin, and kisspeptin, two well established GnRH tropic factors, occur in theses patients, mostly due to the low carbohydrate intake and low body fat–most important tissue responsible for leptin secretion, which in turn, will activate kisspeptin neurons, to stimulate GnRH secretion.[6] Furthermore, an increase in ghrelin secretion from gastric chamber is resultant from low nutrients ingestion; this will in turn stimulate central NPY/Agouti-related peptide neurons, which are potent GnRH supressors.[8] Also, increased tonus of Corticotrophin Releasing Hormone (CRH) is also responsible for GnRH suppression, as well as an increased cortisol secretion; this functional hypercortisolism state demonstrates the chronic stress condition induced by such behavior.[6]

Treatment relies mainly on behavioral modifications, though there are pharmacological approaches when bone mineral loss is present, or fertility is the focus. Regarding regulation of menstrual cycles, the administration of combined hormonal contraceptives should be avoided, as this may mask the condition, leading the patient to assume that condition has resolved.[5] Main focus on FHA is weight gain, nutritional adjustments and decrease energy expenditure, as this will resolve energy deficit and revert pathophysiological events.[1,5] Although restoration of energy balance is key, drug therapies with metreleptin or naltrexone have been studied, and might represent future targets for clinical investigaton.[9] The use of Clomiphene Citrate to induce ovulation in patients with hypothalamic amenorrhea is controversial, and, in principle, should be reserved for those patients with vestigial estrogen levels. As an option, ovulation can be induced by the use of exogenous GnRH or gonadotrophins–however, fertility should only be attempted in patients with a body mass index (BMI) over 18 kg/m^2, as low BMI seems to be related to premature birth, low birth weight and pregnancy losses.[5] Management of bone mineral loss in this situation is troublesome; there is evidence that the use of hormone replacement therapy in patients with hypothalamic amenorrhea may attenuate bone loss, but with no recovery of the previously loss. The use of Parathyroid hormone analogs is controversial, but may induce bone mass gain in conditions of severe osteoporosis.[5,6]

Conclusion

Hypothalamic amenorrhea is a common condition in female athletes with dietary restrictions, in which the energy deficit suppresses the secretion of hormones that regulate reproduction and growth, generating consequences such as infertility, amenorrhea and osteoporosis. In our case, patient presented amenorrhea and anovulation that was not reversible with the use of clomiphene citrate; behavioral changes was successful measure to resume menstrual cycles and ovulation, achieving a spontaneous pregnancy.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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