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INSUFICIÊNCIA OVARIANA PREMATURA DA SÍNDROME DO X-FRÁGIL: É HORA DE REAVALIAR A TRIAGEM?

FRAGILE-X SYNDROME PREMATURE OVARIAN INSUFFICIENCY: IS IT TIME TO REAPPRAISAL ITS SCREENING?

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ABSTRACT
Premature ovarian insufficiency is idiopathic in 90% of cases and fragile x syndrome occurs in 2% of sporadic cases, chiefly in pre mutation carriers. It can be a devastating diagnosis since prevents them of childbearing. Current guidelines recommends pre mutation carrier screening for women with a family history of fragile x syndrome-related disorders, intellectual disability, or unexplained premature ovarian failure, when they consider pregnancy, although several phenotypes exist. This article describes fragile x syndrome ovarian insufficiency with migraine and depression, as well as reappraisal its management. A 35 year-old woman had migraine and regular menses since menarche until premature ovarian insufficiency appeared after oral contraceptive withdrawal, at 33 year-old. The FSH values varied from 10 to 165 mUI/mL. As her father start having ataxia after 55 years-old, she performed molecular study, which showed 94 repeat CGG. However, she could not spontaneous childbearing, because the anti-Müllerian hormone value was 0,16ng/dL. This made her so depressive to the point of seeking psychiatric treatment. This supports a differentiated approach through early pre mutation carrier screening and monitoring of ovarian function, aiming at pregnancy, or the institution of hormone therapy when necessary.

RESUMO
A insuficiência ovariana prematura é idiopática em 90% dos casos e a síndrome do x frágil ocorre em 2% dos casos esporádicos, principalmente em portadores de pré-mutação. Pode ser um diagnóstico devastador, uma vez que os impede de ter filhos. As diretrizes atuais recomendam o rastreamento de pré-mutação para mulheres com história familiar de distúrbios relacionados à síndrome do X frágil, deficiência intelectual ou insuficiência ovariana prematura inexplicada, quando consideram a gravidez, embora existam vários fenótipos. Este artigo descreve a insuficiência ovariana na síndrome do X-frágil com enxaqueca e depressão, bem como uma reavaliação do seu manejo. Mulher, de 35 anos apresentou enxaqueca e menstruação regular desde a menarca até o aparecimento de insuficiência ovariana prematura após a suspensão do anticoncepcional oral, aos 33 anos. Os valores de FSH variaram de 10 a 165 mUI / mL. Como seu pai começou a ter ataxia após os 55 anos, ela fez um estudo molecular, que mostrou 94 CGG repetidas. No entanto, ela não conseguiu engravidar espontaneamente, pois o valor do hormônio anti-Mülleriano foi de 0,16ng / dL. Isso a deixou tão deprimida a ponto de procurar tratamento psiquiátrico. Isso dá suporte a uma abordagem diferenciada por meio de triagem precoce de portadores de mutação e monitoramento da função ovariana, visando a gravidez, ou a instituição de terapia hormonal, quando necessário.
Key words: fragile x syndrome, premature ovarian insufficiency, infertility, anti-Müllerian hormone, follicle-stimulating hormone.

INTRODUCTION

Fragile X Syndrome, the main form of inherited intellectual disability, is caused by trinucleotide repeat expansion cytosine – guanine – guanine (CGG) in Fragile X Mental Retardation 1 gene (FMR1), located on chromosome X. These individuals carry the full mutation, composed of more than 200 CGG expansions, which are usually accompanied by hype methylation of the promoted region, with consequent absence of FMRP protein. Expansions above the normal number, between 45-200 repetitions, characterizes the pre-mutation (PM) , which is associated with high risk of Fragile X- associated tremor/ataxia syndrome (FXTAS) in men over 50 years of age, and Fragile X- associated primary ovarian insufficiency (FXPOI).

Premature Ovarian insufficiency (POI) is a rare, complex and poorly understood clinical syndrome that leads to estrogen secretion deficiency and anovulation. It is defined as oligo\amenorrhea before the age of 40, for at least four months of duration, associated with two dosages of follicle stimulating hormone (FSH) greater than 25 UI\L, measured at 1 month interval [2]. POI is commonly referred to as premature menopause, but both are clinically distinct. Menopause is defined as permanent and irreversible cessation of menstruation for at least one year and results from the depletion of functional primordial follicles. In POI, ovarian function is intermittent and unpredictable for several years. Hormonal fluctuations and sporadic ovulation occur in 50% of cases, even allowing pregnancy in 5 to 10% of cases[3],[4].

POI affects approximately 1% of general population. SXF is an uncommon cause, occurring in 2% of sporadic cases. The clinical picture may range from infertility to symptoms of hypoestrogenism. Its diagnosis can be devastating, both due to emotional disorders related to infertility and the significant morbidity resulting from hypoestrogenism, such as osteoporosis, coronary cardiovascular disease and cognitive decline[5],[6]. Therefore, the relevance of the theme lies in the prognostic impact of FXPOI, which requires a differentiated approach through early screening and monitoring of ovarian function, aiming at pregnancy, or the institution of hormone therapy (HT), when necessary.

The objectives of the present study are to describe a case of FXPOI and to reappraisal screening and therapeutic approach.

A Caucasian, nulliparous, unmarried woman, aged 36 years, presented at the Endocrinology outpatient clinic of Álvaro Alvim Hospital, Faculty of Medicine of Campos dos Goytacazes, complaining of premature menopause. She reported as having menarche at 12 years old, her menses were regular, and she took combined oral contraceptive from 24 to 33 years of age, when it was withdrawn. Ten months later, she presented oligo menorrhea, followed by polimenorrhea, mastalgia, irritability and headache, similar to a premenstrual syndrome. She reported migraine and depression for a long period of time, which were treated with metoprolol and duloxetine 60 mg daily, respectively. She did not have any intercourse prior to the menstrual irregularity, and denied galactorrhea, weight loss, hirsutism, acne, personal history of thyroid dysfunction and diabetes. She reported that her father begun presenting ataxia after 55 years of age, and a paternal aunt had premature menopause. At physical examination, body weight and height were 59 kg and 163,5cm, respectively; body mass index was 22 kg/m, and blood pressure, 120/80 mmHg. There was no galactohrrea and the thyroid was normal. Transvaginal ultrasonography was requested, and blood from a peripheral vein was collected for hormone measurements, karyotype and real time-polymerase chain reaction (RT-PCR) for FMR1 gene.

RESULTS

Laboratory tests showed fluctuations of FSH, luteinizing hormone (LH) and Estradiol (E2) values from July, 2016 to April, 2018. Thyroid stimulating hormone (TSH) and prolactin (PRL) Values were normal, anti-adrenal anti- tyro-peroxidase (TPO) antibodies were negative and anti-Müllerian hormone (AMH) level was low. These results are shown in table 1.

Table 1. Hormonal dosage values from July 2016 to April 2018.

Dates	FSH	LH	E2	AntiTPO	Inibhin B	Antiadrenal	PRL	AMH	Progesterone (Luteal phase)
07/08/2016	16,2	78,02	<11,8	—	—	—	—	—	—
07/19/2016	69,5	43	75,4	40,4 (<35)	—	—	—	—	—
08/22/2016	10,4	14,2	257,5	—	—	—	—	—	—
08/24/2017	34,6	40,8	122	29	4,91	—	11,6	0,16	0,5
04/24/2018	34	11,8	73	37,3	—	<1:10	—	—	—

The karyotype was 46, XX [50] and the RT-PCR of FMR1 gene showed 94 CGG repeats. The sonographic test showed a normal uterus and ovaries, fine and regular endometrium with thickness of 0,4 cm. Bone mineral density was normal. Oral micronized progesterone was prescribed (200 mg daily for 12 days a month). She became so depressed with this diagnosis that came back to the psychiatrist, who changed duloxetine for deslaflaxine.

DISCUSSION

Normal ovarian function results from a continuous process which begins with primordial germ cell formation and proliferation through the development of follicular units during fetal life. It extends into adulthood and is characterized by steady follicular loss or atresia that ends with the menopause. The ovarian function declines mainly after 35-years of age. POI results from inadequate formation of follicular pool in utero, or an abnormally fast depletion of this pool during post-natal life, or both[1]. Genetic influences determines the size of the primordial follicle pool, impact on the rate of its atresia and the age at menopause[4].

The FMR1 gene is located at Xq 27.3 and encodes FMRP protein, which is important for brain and ovarian development. The CGG repeat expansion in the 5´-untranslated region is followed by to hyper methylation of its promoter region, leading to transcriptional silencing of the FMRP. As a result, toxic mRNAs are transcribed and accumulate in the granulosa cells, as was demonstrated in adult knockout females. They sequester specific RNA-binding proteins, such as Sam68, DGCR8 and DROSHA, leading to accelerated follicular atresia and resistance of the ovaries to gonadotropins, through 'down regulation' of their receptors, as exactly shown in PM carriers. The accumulation of these mutant mRNAs in the CNS disrupts the synapses, favoring the appearance of ataxia and essential tremor in PM carrier males, as described in the patient's father[1], [9], [10]. Recently, other comorbidities have been associated with PM, such as primary hypothyroidism, migraine, depression and anxiety[11], [12].

POI is idiopathic in 90% of cases, being the remainder attributed to genetic and auto immune diseases and iatrogenic[4],[7]. POI occurs in 2% of sporadic cases, in 15% of familiar cases and up to 35% of PM carries[7],[8]. After ruling out pregnancy, a minimal routine of investigation includes serum FSH, PRL and TSH determinations. Anti-TPO and anti-adrenal antibodies should be ordered upon confirmation of high FSH values. Other causes are hypogonadotrophic hypogonadism due to intensive physical activity, and policystic ovary syndrome[7]. In the case described, there was no mention to sexual intercourse prior to the menstrual irregularity nor signs of hyperandrogenism, or a significant weight loss. PRL and TSH were normal. As anti-TPO and anti-adrenal antibodies were negative, the hypothesis of autoimmune disease was excluded. A history of premature menopause in her paternal aunt, the beginning of ataxia in her father at 55 years old, the pr/esence of migraine and emotional disturbances directed the diagnosis to FXPOI. The patient presented 94 CGG repeats, what is in agreement with the literature, since POI specially affects carriers from 80 to 99 repeats[1],[9]. In a cohort of 101 Brazilians, 14 presented POI (13,9%) between13 and 38 years of age and of these females, 10 had relatives with PM, and 5 presented early menopause. It is not yet known why the full mutation carriers don´t manifest POI[13].

Ovarian function gradually progresses from an occult stage to a biochemical phase, until reach the final stage of overt POI. The former is characterized by regular menses, but subfertility, low values of AMH and normal FSH. In the second phase, menses are still regular, but the FSH increases until the last one, which is marked by irregular menses and menopausal FSH levels[7]. Furthermore, low ovarian reserve (FXDOR) precedes FXPOI, what can be seen early in the occult stage through AMH dosage, before FSH increase[14]. Another advantage of AMH over FSH is that the former can be assayed at any phase of the menstrual cycle, and not only in the follicular phase. Abed et al compared both hormones in fertile and infertile women and observed that sensitivity and specificity of AMH were of 100% in the diagnosis of POF, while those of FSH were 93,3% and 88%, respectively[15]. This was also shown even in carriers of more than 30 CGG repeats [15].

The oral contraceptive use may mask its presentation, as it happened with this case. As shown in table 1, she presented fluctuations of FSH and estradiol levels, together with unpredictable menses from 33 to 35 years old. However, her bone mass was normal, probably due to the protective effect of the combined contraceptive use for a long time.

FXPOI is an overwhelming diagnosis, chiefly for women who have not childbearing, and evolved to premature menopause, which begins earlier than general population and increases the risk of cardiovascular disease, osteoporosis and cognitive decline[4],[16]. The management depends on the age at diagnosis, risk of expansion in the next generation, ovarian reserve and patient´s preference. Genetic

counseling should be offered and encompass calculation of risk of expansion, according to the number of CGG repeats and those of AGG interruptions. For women who don´t want childbearing, oocyte or embryo cryopreservation should be offered. For who wants childbearing spontaneously, a preimplantation genetic diagnosis should be performed to avoid the transfer of an embryo with abnormal CGG. However, as most of the PM carriers < 100 repeat CGG are resistant to controlled ovarian hyper stimulation and to the success to assisted reproductive technology (ART), some centers suggest egg or embryo donation (10), which also prevents the transmission of this disorder. This procedure is also offered when the overt POI has happened, and fertility preservation was missed (4).Unfortunately, when the patient thought in childbearing, she was already 35 years old, AMH was 0,16 ng/dL and FSH was higher than 165 mUI/L. These factors render conception difficult, with low rate of oocyte retrieval through in vitro fertilization procedures (10). Besides, the risk of expanding the CGG repeat a full mutation and intellectual disability in the offspring made her give up of childbearing spontaneously. All these factors worsened her depression to the point of seeking psychiatrist again. Despite the limitations of a spontaneous pregnancy, a promising research has been done to improve the production of gamete from ovarian tissue by activating the AKT pathway in vitro (IVA). Residual follicles became active in 6 of the 14 patients (43%), and after IVF the pregnancy was achieved (17).

The HT is recommended as soon as the menopausal symptoms appear, like hot flashes, vaginal dryness, insomnia, irritability, and may extent until 51 years old (2, 4). It reduces the risk of osteoporotic fractures (18), cognitive decline (19) and cardiovascular disease (20). Percutaneous or oral 17β-estradiol in monotherapy (for hysterectomized women), or in combination with micronized progesterone or didrogesterone for those with intact uteri are preferable (2, 4, 7). As the patient presented estradiol level of 73 ng/dl and no menopausal symptoms, only micronized progesterone prescribed, what ameliorate her insomnia and menstrual irregularity. As her BMD was normal, she was advised to maintain regular physical activity, take 25 (OH)D 7000 IU a week, and calcium intake in 1200 mg a day (21).

A limitation of this study was due to the fact that the patient's father did not perform the RT-PCR to diagnose FXTAS, which has been inferred by the onset of ataxia at 55 years old.

Finally, we would like to emphasize that the American College of Obstetricians and Gynecologists recommends PM carrier screening for women with a family history of FXS-related disorders or intellectual disability only when they consider pregnancy, are pregnant, or present an unexplained POI (22). Although a repeat lower than 44 CGG be considered normal, some studies have shown increased risk of ovarian senescence when it exceeds 29 CGG (23, 24), and the AMH dosage is more sensitive than the FSH for the diagnosis of FXDOR (25). Thus, we propose a change in the current guidelines, through the FXS screening for all women in reproductive age, who wants to childbearing, since most of PM carriers menstruate regularly and may not have familiar history of SXF- related disorders (26). If more than 29 CGG repeats be present, AMH and FSH should be made periodically. This would avoid FXPOI and allow them a family planning, as childbearing earlier or fertility preservation options.

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