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Case Report

Patient with Martin-Bell syndrome and premenstrual syndrome, tendency for obesity from puberty

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Abstract

Background: *Fragile X* syndrome (FRA X) is the most common cause of inherited moderate intellectual disability. The cause of FRA X syndrome is a dynamic mutation in the *FMR1* gene (located on the X sex chromosome—long arm, position 27.3, between base pairs 147 911 951 and 147 951 125). **Case(s):** A patient born in 1993 along with her mother was referred to the Department of Developmental Age Gynaecology and Gynaecological Sexology of the Obstetrical Clinical Hospital at the Poznań University of Medical Sciences (Poland) because of existing recurrent menstrual cycle disorders and recurrent genital inflammation. From her history since childhood, this patient had fluctuating body weight with a tendency for overweight and obesity. Contact with the patient was difficult, she was reluctant to answer questions during the medical interview. There is a family history of intellectual disability. The patient required continuous gynaecological and psychiatric care, diet therapy, physical activity was recommended, which had a beneficial effect on the patient's somatic and mental health. **Conclusions:** The diagnosis of fragile X syndrome involved not only the patient but also her family in a very broad interdisciplinary approach, also in terms of genetic counselling. Additional problems with cycle disorders, genital inflammation and weight disorders mean that the patient will still require gynaecological and psychiatric care, diet therapy, and physical activity has been recommended, which has a beneficial effect on the patient's somatic and mental health.

Keywords: Martin-Bell syndrome; Diagnosis; Patient

1. Introduction

Fragile X syndrome (FRA X), or fragile X syndrome (*Fra X*, *FRA X*, *Martin-Bell* syndrome) was first described by James Purdon Martin and Julia Bell in 1943 [1] as a genetic disorder characterised by an intellectual decline of varying degrees with behavioural symptoms sometimes overlapping those of characteristic autism [2]. FRA X syndrome is the most common cause of inherited moderate intellectual disability affecting 1/4000 men and 1/7000 women.

The cause of fragile X syndrome is a dynamic mutation in the *FMR1* gene located on chromosome X (long arm, position 27.3, between base pairs 147 911 951 and 147 951 125). It is a dynamic mutation involving duplication of a segment of the gene with a sequence of three CGG nucleotides. Between 65 and 200 repeats is a so-called pre-mutation, usually not giving disease symptoms but tending to “elongate” in subsequent generations. More than 200 re-

peats is a full mutation that produces symptoms in all affected boys and in about half of the girls [3–6].

Fragile X syndrome belongs to a group of diseases caused by trinucleotide repeats.

Fragile X syndrome is associated with a phenomenon known as Sherman's paradox in that the risk of the disease occurring in siblings of an asymptomatic carrier is significantly lower than in their grandchildren and great-grandchildren.

FMRP protein, encoded by the *FMR1* gene, is necessary for the proper development of synapses between the neurons responsible for such processes as learning and memory. A lack causes delayed maturation of the neurons, but probably does not damage them or lead to their death, which raises the chance of developing drugs to alleviate the symptoms of the disease, even in adults.

The syndrome is inherited similarly to X-linked disorders, associated with a dominant gene with limited penetrance.



The disease can only manifest if the abnormal version of the gene is passed on to the offspring by the mother. For women with the defect, half of their sons have a high risk of mental retardation, and for daughters the risk is moderate (30–50%, mainly due to physiological inactivity of one of the X chromosomes). A man who carries a pre-mutation of the *FMR1* gene will pass it on to all his daughters (but not to his sons, since male sex develops from the Y chromosome), but they will not show any symptoms of the disease. However, they will pass on to their children a defective gene with an even higher number of CGG trinucleotide repeats, increasing the risk of developing the disorder [7].

One in 259 women is a carrier of the mutated *FMR1* gene, but to accurately determine the risk of the disease in a family with a history of mental retardation, one must visit a genetic counselling clinic.

2. Case study

In 2005, the Department of Developmental Age Gynaecology and Gynaecological Sexology of the Obstetrical Clinical Hospital at the Poznań University of Medical Sciences (Poland) was visited by a female ER patient born in 1993 along with her mother because of existing and recurrent menstrual cycle disorders: irregular cycles with abundant, painful menstrual periods preceded by menstrual tension syndrome and a problem of recurrent persistent inflammation of the genitals and urinary tract. From the patient's mother's history, there had been weight fluctuations since childhood with a tendency for overweight and obesity (currently Body Mass Index (BMI) 28, one year earlier 29). Contact with the patient was difficult from the beginning, she was reluctant to answer questions related to her medical history—those questions were mainly answered by the patient's mother. She was observed to be very shy, with difficult eye contact (family history of intellectual disability—genetic and psychiatric tests were referred).

Gynaecological examinations with ultrasound and laboratory tests were applied. Hypothalamic-pituitary-ovarian axis disorders; recurrent functional changes in ovaries, vaginal biocenosis disorders were found. Somatic development in line with her sex and age.

Anti-inflammatory therapy, probiotic therapy, oestrogen and progesterone therapy, Nonsteroidal anti-inflammatory drugs (NSAIDs) were used. Therapy continued. Low carbohydrate diet and increased physical activity were also recommended.

The patient was diagnosed with FRA X syndrome—broken chromosome, Martin-Bell syndrome within the autism spectrum, which significantly affects the functioning of the now adult lady Emergency Room (ER) limiting her earning possibilities. The patient still requires gynaecological and psychiatric care, diet therapy, recommended physical activity, which has had a positive effect on the patient's somatic and mental health.

3. Discussion

Phenotypic features in patients with broken X chromosome syndrome vary with age such as:

- mental development disorders—broad spectrum: from problems with speech at preschool age and schooling to profound disability (85% of patients have an IQ between 20–70); symptoms are more severe in men;
- shyness, difficult eye contact;
- in some cases, symptoms similar to ADHD (*attention-deficit hyperactivity disorder*) and autism also appear (autoimmunity, hand flapping);
- reduced muscle tone.

In addition, patients are also more likely to have additional medical conditions i.e., [8,9]:

- cardiac murmurs, mitral valve leaflet prolapse syndrome;
- chronic sinusitis and middle ear infections;
- gastro-oesophageal reflux;
- epileptic seizures—in 25% of patients;
- mood disorders.

Individuals carrying the *FMR1* premutation after the age of 50 may develop a condition called Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) resembling Parkinson's disease ataxia, tremor, balance disorders, memory loss) [10,11].

The first symptoms—reduced muscle tone, sensory disturbances—are not characteristic and are usually not associated with this condition. Psychomotor development is often normal or slightly abnormal until preschool or school age, when communication problems or intellectual deficiencies become apparent.

The diagnosis of fragile X syndrome involves not only the patient but also the family in a very broad interdisciplinary approach, such as with genetic counselling. The full spectrum of symptoms observed in FRA X syndrome should be characterised, along with the increased risk of the condition, and of being a carrier, should be strongly emphasised to members of the patient's extended family. In addition, it is important to stress the need for DNA testing of the proband's siblings, especially if they show learning difficulties or behavioural disorders. If the proband is male, the mother is the carrier of the permutation [12].

There is currently no proven causal treatment. Symptomatic treatment is advisable, including care from a speech therapist and child psychologist, therapy for sensory integration, hyperactivity or aggressive behaviour.

The patient described still requires family care despite her adult age. Apart from psychiatric care, the patient requires strict gynaecological care due to a strongly expressed premenstrual syndrome. Furthermore, weight fluctuations have been observed—overweight with a tendency for obesity since puberty—poor eating habits with an excess of carbohydrates. Bulimia has not been diagnosed. BMI since observation was close to 30, and the following year 27, which is related to the restriction of carbohydrates in the diet

and undertaking physical activity, although unfortunately still insufficient (running, walking, gymnastics). In educational activities, the patient was informed that the lack of physical activity and improper diet would have a significant impact on the development of overweight and obesity, which in turn is associated with the risk of type 2 diabetes. Muscular effort increases the transport of glucose from the blood and extracellular space to the cells of working muscle. This process occurs independently of the action of insulin. Exercise reduces insulin resistance, i.e., increases the sensitivity of muscle cells to insulin. Physical activity also has a beneficial effect on the lipid profile and promotes the reduction of body weight. In the case of obese and overweight patients, in addition to increasing physical activity, it is recommended to reduce daily caloric intake by 500–1000 kcal per day—this is what the dietary recommendations for the described patient aim at. Movement and diet are also important to reduce symptoms associated with premenstrual syndrome [13].

Premenstrual syndrome (*syndroma tensionis praemenstrualis*, PMS (Premenstrual Syndrome) is a syndrome of emotional, behavioural and physiological symptoms occurring a few days to two weeks before menstruation and disappearing at the end of bleeding [14]. It is an interdisciplinary problem—psychological, gynaecological, endocrinological, sexological and psychiatric.

Taking into account the diagnostic criteria, PMS occurs in 2.5–5% of girls and women, but it should be remembered that the symptoms that are a component of this syndrome can be experienced by as many as 40–80% of girls and women.

Patients with premenstrual syndrome present a range of mood disorders and physical and psychological symptoms that are noticeable in the luteal phase and disappear in the follicular phase of the menstrual cycle, in the absence of other psychiatric or medical disorders that could be the cause of the condition. The main symptom, irritability, and other disturbances occur in such severity that they interfere with some aspects of women's life (especially sexual) and usually persist for 10–14 days each month.

The basic elements for the diagnosis of premenstrual syndrome are [15,16]:

- the need to determine prospectively the time of onset of symptoms;
- occurrence of at least a 30% increase in the severity of symptoms in the luteal phase compared with the follicular phase;
- an additional criterion is that psychiatric illnesses have been excluded in these women, that they are not using oral contraception and that they have regular monthly cycles.

The pathophysiology of premenstrual syndrome is still unclear and the causes may be multifactorial. In the case of the patient described, it overlaps with fragile X chromosome syndrome (FRA X). It is believed that premenstrual

syndrome is a consequence of a decrease in progesterone secretion in the second phase of the sexual cycle leading to a decrease in the progesterone/oestrogen ratio. The theory of fluid retention suggests that oestrogens induce increased synthesis of angiotensinogen in the liver, leading to increased production of aldosterone which directly affects sodium retention and potassium loss. It has also been found that the mediocre increase in prolactin levels during the second phase of the sexual cycle, is possibly due to disturbances in the synthesis or secretion of dopamine and serotonin in the central nervous system. Dopamine has been shown to exert a direct natriuretic effect on the kidneys, and serotonin is responsible for hypersensitivity [17,18].

Treatment modalities for PMS have undergone significant changes in the last decade. Although the pathophysiology of the syndrome has not been fully elucidated, effective therapy is possible for most patients based on correct diagnosis.

Any woman who notices an increase in her symptoms should consult her doctor. This is necessary in order to exclude other diseases, whether internal, neurological or gynaecological, which may cause similar symptoms. It is important to distinguish between a typical premenstrual syndrome and perimenopausal complaints, the primary cause and not the effect, which can be stress, anxiety, depression, emotional disorders, family or work problems. The internal and gynaecological examination is aimed at finding possible organic changes, e.g., after gynaecological operations, after births or miscarriages, suffering from other organic diseases of the reproductive organs. The simplest method is the measurement of basal body temperature performed daily, just after waking up throughout the menstrual cycle, performing a so-called cyto-hormonal smear taken from the vagina, a cervical mucus crystallization test or determining the level of sex hormones—ovarian and pituitary—in blood serum [18–20].

People with milder premenstrual syndrome symptoms may try non-pharmacological methods, i.e., increasing physical activity (aerobics, walking) to relax and loosen the body, eating meals rich in calcium (dairy products, whole grain cereals, poultry, bananas, fish, brown rice), large amounts of fibre, limiting the intake of sweets, salty snacks, carbonated drinks, coffee and tea, and drinking at least 2 litres of water a day instead. In addition, it is recommended to consume products containing tryptophan (dark chocolate, bananas, milk, white cheese), which is a precursor for serotonin [21–23]. Vitamin D, not only under the influence of the sun (skin synthesis) but also through the consumption of food products (mushrooms—boletes, chanterelles, fish—mackerel, tuna, salmon, eggs, yellow cheese) which can help alleviate PMS. Adequate sleep, especially in a sufficiently darkened room, has a beneficial effect on progesterone levels and is an invaluable ally in the fight against stress.

With more severe premenstrual complaints, and especially in full-blown premenstrual dysphoric disorder (PMDD), non-pharmacological approaches generally fail and should not be used as the sole management for longer than 3 months. After this period, pharmacotherapy should be considered by using antidepressants from the SSRI (serotonergic) group, nonsteroidal anti-inflammatory drugs (naproxen and mefenamic acid). Breast swelling and tenderness can be relieved by vitamin E, given only in the second half of the cycle, and gammalinolenic acid (e.g., in evening primrose oil). Some studies have shown the benefits of taking calcium carbonate at a dose of 1200 mg per day during three monthly cycles. However, there is no evidence of the effectiveness of supplementing magnesium, manganese and other micronutrients. The significant effectiveness of contraceptive use has also not been confirmed [24,25].

Treatment options include administration of [26,27]:

- gestagens in the second half of the cycle (day 17–26), e.g., didrogesteron (10 mg/day) or progesterone (50 mg 1 time/day);
- ovulation-inhibiting contraception;
- prolactin inhibitors, when the predominant symptom is mastodynia with abdominal complaints and a tendency to oedema, e.g., bromocriptine (½-1 tablet), from day 14–28 of the cycle;
- diuretics as an adjunct to therapy or as an exclusive treatment when oedema and weight gain are the predominant symptoms, e.g., hydrochlorothiazide 12.5–25 mg/day;
- vitamin A, B (especially B6), D and E complex.

In the case of the described patient, in the face of irregular menstrual periods preceded by premenstrual syndrome and pain, additional gynaecological treatment included oestrogen/gestagen therapy with drospirenone, NSAIDs and prophylactic probiotics.

It should be emphasised that the symptoms of broken chromosome syndrome in Mrs ER were not expressed as extremely as in literature. In childhood, disruptions in contact with family and peers, lowered mood and learning problems (especially in science subjects) were observed. Mrs ER has, however, completed secondary education. She still has strongly expressed mood lowering, recurrent premenstrual syndromes and libido—no sexual partner. From the history provided by the patient's mother, the patient's childhood was evidenced with weight fluctuations with a tendency for overweight and obesity. The patient still requires gynaecological care, psychiatric care, diet therapy, physical activity was recommended, which is beneficial for the patient's somatic and mental health. In addition to psychiatric care, the patient still requires close gynaecological care due to a strongly expressed premenstrual syndrome, with the hope that with the use of typical medications for this syndrome, there is an improvement.

A change in diet and the fact of undertaking increased physical activity are also important in improving the pa-

tient's general condition.

4. Conclusions

The diagnosis of fragile X syndrome involved not only the patient but also her family in a very broad interdisciplinary approach, also in terms of genetic counselling. Additional problems with cycle disorders, genital inflammation and weight disorders mean that the patient will still require gynaecological and psychiatric care, diet therapy, and physical activity has been recommended, which has a beneficial effect on the patient's somatic and mental health.

Author contributions

KPR and GJB and PM analyzed the data; WK, MPK and KWS and MM performed the review and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final draft.

Ethics approval and consent to participate

Informed consent was obtained from all subjects involved in the study.

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Conflict of interest

The authors declare no conflict of interest. KP-R is our Reviewer Board, given his role as Reviewer Board, had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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