

Wolfram syndrome: A case report

Síndrome de Wolfram: Um relato de caso

Síndrome de Wolfram: Reporte de un caso

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Abstract

Wolfram Syndrome is an autosomal recessive disease linked to the short arm of chromosome 4. The main clinical features are diabetes mellitus and optic nerve atrophy, as well as central diabetes insipidus, ataxia, sensorineural deafness and changes in the urinary tract. Other symptoms may be present, but less common. The harms in the life of its carriers are profound, due to the degenerative and non-remissive nature of the syndrome. The present study aims to report the case of a female patient, 23 years old (2020), born in Alfenas - Minas Gerais - Brazil, with the Wolfram Syndrome, as well disclose more knowledge about the syndrome. In addition, we address the need for interaction between different health professionals to minimize the suffering experienced by people with the disease and their families.

Keywords: Wolfram syndrome; Psychiatry; Optic nerve, Diabetes Mellitus; Epilepsy.

Resumo

A Síndrome de Wolfram é uma doença autossômica recessiva ligada ao braço curto do cromossomo 4. As principais manifestações clínicas são diabetes mellitus e atrofia do nervo óptico, além de diabetes insípido central, ataxia, surdez neurosensorial e alterações do trato urinário. Outros sintomas podem estar presentes, mas menos comuns. Os prejuízos na vida de seus portadores são profundos, devido ao caráter degenerativo e não remissivo da síndrome. O presente estudo tem como objetivo relatar o caso de uma paciente do sexo feminino, 23 anos (2020), natural de Alfenas - Minas Gerais - Brasil, com a Síndrome de Wolfram, bem como divulgar mais conhecimentos sobre a síndrome. Além disso, abordamos a necessidade de interação entre os diversos profissionais de saúde para minimizar o sofrimento vivenciado pelas pessoas com a doença e seus familiares.

Palavras-chave: Síndrome de Wolfram; Psiquiatria; Nervo óptico, Diabetes Mellitus; Epilepsia.

Resumen

El síndrome de Wolfram es una enfermedad autosómica recesiva ligada al brazo corto del cromosoma 4. Las principales características clínicas son diabetes mellitus y atrofia del nervio óptico, así como diabetes insípida central, ataxia, sordera neurosensorial y alteraciones del tracto urinario. Pueden estar presentes otros síntomas, pero menos comunes. Los daños en la vida de sus portadores son profundos, debido a la naturaleza degenerativa y no remisiva del síndrome. El presente estudio tiene como objetivo reportar el caso de una paciente de 23 años (2020), nacida en

Alfnas - Minas Gerais - Brasil, con el Síndrome de Wolfram, así como divulgar más conocimientos sobre el síndrome. Además, abordamos la necesidad de interacción entre diferentes profesionales de la salud para minimizar el sufrimiento que experimentan las personas con la enfermedad y sus familias.

Palabras clave: Síndrome de Wolfram; Psiquiatría; Nervio óptico, Diabetes Mellitus; Epilepsia.

1. Introduction

In 1938, four siblings were examined, finding the presence of diabetes mellitus and optic atrophy; one of them developed neural symptoms and the others developed almost complete blindness and deafness (Wolfram & Wagner, 1938; Barret & Bunday, 1997). Subsequently, these symptoms were called Wolfram syndrome (WFS), a very rare neurodegenerative autosomal recessive disease, with symptoms such as diabetes mellitus type I (Lu et al., 2014), insipid diabetes, optic atrophy and some neurological deficits (Barret & Bunday, 1995; Barret & Bunday, 1997; Urano, 2016)

The prevalence is close to 1/770,000 and can start in infancy (Hershey et al., 2012), adolescence or adulthood. Clinically, Wolfram syndrome is characterized by the association of diabetes mellitus type I in the first decade of life (Hershey et al., 2012) and optic atrophy; some patients present insipid diabetes and some level of neurosensory deafness (Bespalova et al., 2001). Other less common signs include atony of the urinary tract (Barret & Bunday, 1995), ataxia, peripheral neuropathies, dementia, psychiatric disturbances and/or seizures, depression, verbal and physical aggression, intestinal problems, renal disturbances, central respiratory insufficiency and apnoea, myocardiopathy, anaemia and late sexual development. Neurological symptoms include cognitive impairment, nystagmus, anosmia, lack of tendon reflexes in the extremities, epilepsy, dysphagia, polyneuropathy and central sleep apnea (Zmylowska et al., 2014; Urano, 2016), juvenile diabetes and optic atrophy are the most important findings for a clinical diagnosis of WFS (Barret & Bunday, 1997).

In molecular terms, WFS is a recessive autosomal hereditary disease (Barret & Bunday, 1997; Shang et al., 2014; Urano et al., 2014) involving at least two genes, WFS1 and WFS2 (Inoue et al., 2008) with about 150 known mutations. WFS1 encodes for wolframin, which is expressed in the endoplasmic reticulum and is associated with calcium homeostasis via a mechanism that has not yet been elucidated (Barret & Bunday, 1997), loss of WFS1 function is responsible for low frequency sensorineural hearing loss (Bespalova et al., 2001) and the main features of WFS. WFS2 encodes for iron sulphur domain-containing protein 2 and seems to be associated with neural and muscular atrophy and accelerated aging in mice (Chen et al., 2009) as well as autophagy (Chang et al., 2010).

Dysfunction of the endoplasmic reticulum and mitochondria is commonly observed in WFS (Chang et al., 2010; Urano, 2016). Indeed, dysfunction of the endoplasmic reticulum is associated with many chronic diseases such as diabetes, atherosclerosis, inflammatory bowel disease and neurodegeneration (Ozcan & Tabas, 2012). Currently, there is no efficient therapy targeting the endoplasmic reticulum, therefore are not consolidated drug therapy for cited disturbs. Specific to WFS (Urano, 2016), insulin is used for diabetes treatment. Moreover, studies have shown that dantrolene seems to prevent endoplasmic reticulum stress in humans and rodents and may have utility in WFS (Lu et al., 2014).

Some studies have cited the importance of studying WFS to elucidate the mechanism of pancreatic β -cell dysfunction in diabetes (Shang et al., 2014; Urano, 2014; Urano, 2016). Certainly, a diagnostic multidisciplinary team with physicians and other health professionals well-informed in the treatment of WFS could alleviate suffering and ameliorate the life quality of these patients (Urano, 2016) and to avoid an early stress that plays an important role in the future mental illness (Teixeira et al., 2020), in this case for a patient with mental problems. The definitive diagnostic of the WFS performed by genetic characterization, which is expensive for patients, particularly in developing countries, so in these cases, a clinical diagnosis is prevalent. Additionally, clinical follow-up and family involvement are very important to improve patient quality of life.

There are many problems with involving WFS patients in society, but even more difficult is the absence of medical knowledge about this disease; addressing this is the main objective this case report. As the late delivery of specific treatment for WFS could cause suffering, more information about the clinical details of WFS would be helpful. Here, we provide a case report of a patient with WFS in Brazil to inform medical professionals about this disorder.

2. Methodology

In an internship a medical student knew the patient. A patient presenting the Wolfram Syndrome was studied via anamneses, image techniques, karyotype, blood test. She is housed in Varginha-MG where she is frequently submitted to clinic examination because the metabolic problems and psychiatric problems.

The mother signed the free consenting and permitted the anamnesis of the patient and contributed with information about the historic and patient's behavior.

All recommendations of the ethics proceedings about clinic trials and human care were followed in the contact with patient. We took care for a female author to talk about the personal sexual behavior with the patient. This work was previously submitted to Ethics Committee in the Federal University of Goiás under the number 953854

3. Results

We report the case of a 23-year-old single woman, born in Varginha, Minas Gerais, Brazil. She is the daughter of a young consanguineous fifth degree cousin couple, probably contributing to the syndrome, as it is known that WFS mutations are inherited as an autosomal recessive trait.^{5,8} The father presents a history of epilepsy. The mother is healthy but suffered a spontaneous abortion in the first trimester of pregnancy; uterine curettage was not necessary.

The patient has two maternal half-brothers, both male and healthy, and four paternal half-brothers (two women and two men), one of them with hearing loss and the remaining healthy. Several cases of epilepsy in close relatives were reported. During the pregnancy of the patient, the mother reported recurrent asthma and infection of the urinary tract. Analysis of the prenatal ultrasound showed no alterations in the patient. The patient was born via Caesarean, at term, weighing around 2450 g and was sent home together with her mother. Neonatal screening was normal, and she developed precociously, with adequate neuropsychomotor development.

Around 3 years of age, she was diagnosed with diabetes mellitus type 1; no causes other than genetic were investigated. Around 14 years of age, an ophthalmologic evaluation indicated bilateral optic atrophy. The patient also presented urinary and faecal incontinence, and deafness was determined for high frequencies of sound.

The patient has shown difficulties in learning and abnormal behavioral in relation to colleagues. For males, she always believes that they want some kind of sexual relations, and she is extremely jealous of females. When younger, at around 10 years of age, when she had a hypoglycemia crisis, she became physically aggressive with those around her.

A recent physical examination identified weight (80 kg), height (1.72 m) and head circumference suitable for age and sex, with a high nasal root, high and square nasal bridge, bulbous nose tip, well-marked nasolabial filter, fine upper lip, small teeth, micrognathia, clinodactyly of the fifth digit of the hands and feet, enlarged hallux, toenail abnormalities, Tanner M5P5, and normal heart sounds via auscultation; however, the patient has reported tachycardia and bradycardia. The patient shows an altered libido with a tendency for excitation; for instance, shows some euphoria in the presence of men and, according to her mother/caregiver, she fantasizes about contact with men. She currently has a boyfriend, but she betrays him when possible.

4. Discussion

Into the features of the Wolfram Syndrome, was observed moderate intellectual disabilities (ICD 10 F71.1), complicated by overlapping psychotic symptoms (ICD 10 F06.2), with features of mental automatism, magical thoughts, lability of humour and dysphoria. This information was provided to the authors by the mother, who cited behaviour compatible with psychosis that was corroborated by examination using observations under neuropsychology perspective (Aversi-Ferreira et al., 2019; Luria, 1981). The authors observed average alterations in cognition (ICD 10 F71.1) such as difficulty multiplying different numbers; however, for equal numbers, she responded correctly. She usually asks about the date as 'today is what number?'. She constantly corrects her mother's mistakes regarding memories and incorrect words which demonstrated problems linked to frontal lobe problems by difficulties to correct the actions of thought (Luria, 2015; Luria, 1981).

She is currently treated with oxcarbazepine 300 mg three times a day, valproic acid 250 mg three times a day, clonazepam 2 mg at night, macrodantin 100 mg at night for urinary tract infection prophylaxis, puran (Monday to Friday 50 mg in the morning; Saturday and Sunday 75 mg in the morning), desmopressin 10 µg in four nasal applications at night, NPH insulin 3x day (46 IU in the morning, 18 IU a midday, 12 IU at night) and regular insulin according to her glucose value.

The purpose of this case report, beyond providing information on WFS for anamnesis, is to highlight the possible errors in the diagnosis of this disorder because the scarce knowledge about this disease by health professionals, indeed, seems to be necessary a post formation of psychiatrists for a better preparation to attend some kind of patients (Silva et al., 2020).

One example occurred when the patient pretended to be deeply asleep and did not wake up with any stimulus (it was reported that the patient's brother put ice in her hand in order to disturb her, but she did not move). Afraid of this being a serious illness, the patient's mother took her to the local hospital, where tests were performed, showing no disturbances. She only 'woke up' when an endovenous placebo was offered. Up to the time of the interview, the patient continued to take this placebo when experiencing similar conditions. It was also reported that the patient has hallucinations such as talking to a dead uncle, has an imaginary boyfriend and makes up events that did not occur. She barely writes and speaks.

In general, her sleep is disequibrated and decompensated, with clonic convulsions (ICD G40.3) and myoclonic movements in the limbs in most common mild crises and generalized movements of extension in deeper crises. During mild crises, she does not lose consciousness, but in the deeper ones she does.

Associated with her deregulated sleep, an event occurred when the patient was sleeping excessively and no showing reactions, but it seemed that she was listening, according to her mother. In the hospital, the doctors thought that she was pretending, but oxygenation and a physical examination indicated the absence of motor responsiveness. The patient was conducted to the emergency room without her mother, although the mother had presented a document from a psychiatrist stating the need for the mother's presence for all medical proceedings. The mother said that she had confidence in the medical team, but she did not receive communication about the proceedings. After the proceedings, the mother entered the room and saw blood on the bed sheet and the patient complained about throat pain. It appeared that gastric lavage had been performed to remove the possible presence of drugs.

The above cited situation is an example of the problems that the patients and their families are suffering by the deinstitutionalization of the individual with mental illness in Brazil (Batista, Barbosa & Silva, 2020).

5. Conclusion

Being a rare syndrome, the lack of preparation of the health team in relation to how to proceed with the patient's condition is understandable. However, this cannot be a reason for the team to have neglected the mother's guidance regarding

the state in which the patient was found. Therefore, our aim is to show the importance of always maintaining a good doctor-patient relationship in order to avoid possible physical and psychological damage to both the patient and his/her family.

This kind of case report could indicate other researchers to write cases about rare syndromes for elucidate the health professionals to follow the correct way for treatments and to indicate the correct expert to avoid, at least, the suffering of the patient and family.

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