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Case Report

Wolfram Syndrome: The Importance of a Multisystemic Approach in Early Diagnosis

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Abstract

Purpose: To report two clinical cases of a patient with Wolfram Syndrome.

Case Reports: Case 1, 22 years old, female, manifested by onset in childhood of diabetes mellitus (4 years old), low visual acuity (LVA) at 14 years old, and central diabetes insipidus (17 years old) and later bilateral sensorineural deafness and neurological disorders. Case 2, 23 years old, female, at 5 years of age, she starts with diabetes mellitus, LVA (17 years old) evolving later with bilateral sensorineural deafness. Both cases present biomicroscopy and applanation tonometry within normal limits; the visual field examination reveals, in both cases, absolute scotoma with a small central island of vision.

Conclusion: The essential features for the diagnosis are the presence of early-onset diabetes mellitus and optic atrophy. These two reported cases draw attention to the professional's expertise in establishing the association between their main characteristics, favoring early clinical diagnosis, thus enabling better multidisciplinary follow-up.

Keywords: Wolfram syndrome; Optic atrophy; Diabetes mellitus; Visual acuity.

Abbreviations

WS: Wolfram Syndrome; DIDMOAD: Diabetes Insipidus, Diabetes Mellitus Optic Atrophy and Deafness; LVA: Low Visual Acuity

Introduction

Wolfram syndrome (WS) is a rare, autosomal recessive, progressive neurodegenerative condition that was first described in 1938 by Woftram and Wagner [1,2].

The presence of early-onset diabetes mellitus (first decade of life) and optic atrophy (second decade) are fundamental characteristics for the diagnosis of WS. Classic findings can be characterized by the acromion DIDMOAD (diabetes insipidus, diabetes mellitus optic atrophy and deafness). When present, these criteria give a positive predictive value of 83% and a negative predictive value of 1% [3,4].

There may be other systemic alterations, but less frequently, such as ataxia, nystagmus, neurogenic bladder, ataxia, cataracts, diabetic retinopathy, glaucoma, gonadal atrophy and predisposition to psychiatric diseases [5,6].

About three hundred cases have been reported in the global literature, with most presenting the incomplete form of the syndrome [7,8]. In this article, two case reports with all the classic symptoms of the syndrome followed up at a Tertiary Hospital in the Federal District, Brazil, will be described. We emphasize the patients' consent to voluntarily participate in the study and this only started after signing the free and informed consent form.

Case Reports

Case 1

TAB, 22 years old, female, diagnosed with diabetes mellitus at the age of 4, presents a history of low visual acuity (LVA) that started at the age of 14, progressing to bilateral sensorineural deafness and neurological disorders and later diabetes insipidus was detected core at age 17. The diagnosis of Wolfram syndrome was performed by genetic testing identifying the presence of the WFS1 gene. On the current ophthalmologic examination, he has a best visual acuity of 20/80 in both eyes.

Case 2

MFSA, 23 years old, female, diagnosed with diabetes mellitus at 5 years old, evolving with LVA at 17 years old and later presenting bilateral sensorineural hearing loss. At the current ophthalmological examination, he has better visual acuity of counting fingers at 2 meters in the right eye and counting fingers at 50 cm in the left eye.

In both cases, biomicroscopy and tonometry were within normal limits. The visual perimetry examination also showed the same alteration in cases 1 and 2, with absolute scotoma with a small central island of vision and color retinography (Figure 1) with papillary pallor 4+/4+ associated with the absence of visualization of the nerve fiber layer.

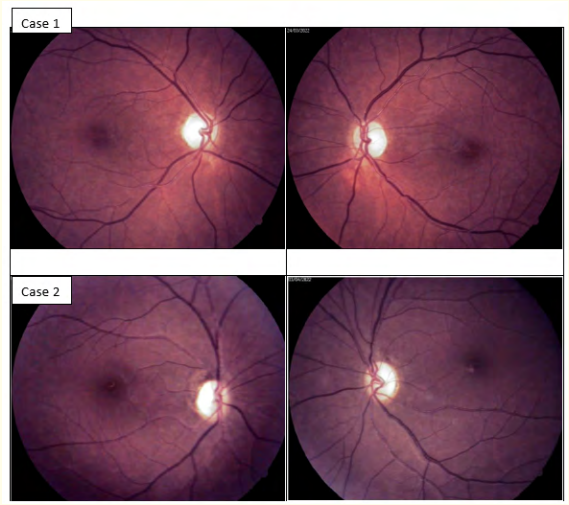

Figure 1: Color retinography demonstrating pallor of the 4+/4+ papilla associated with the absence of visualization of the nerve fiber layer.

Discussion

WS is a disease characterized by the presence of diabetes insipidus (73%), diabetes mellitus (100%), optic atrophy (100%) and deafness (62%) [5,9]. It has an estimated prevalence of 1:100,000 in children and 1:770,000 in adults, and approximately 15,000 to 30,000 people are affected worldwide [9]. The pathophysiology is still not well known, but genetic studies have shown mutations in the WFS1 gene on chromosome 4, this gene encodes a protein of the endoplasmic reticulum membrane, wolframine. The alteration in this protein increases the stress on the endoplasmic reticulum, compromising the cell cycle [10].

Patients with WS present a progressive, slow and symmetrical decrease in visual acuity around the second decade of life. Although diabetes mellitus appears very early, the evolution is also gradual and with fewer complications such as classic microvascular alterations and diabetic ketoacidosis. Visual impairment is related to loss of nerve fiber layer and pallor of the optic disc. Hearing loss is also slow and progressive, postponing the correct diagnosis [6,7].

The symptoms of the condition vary according to the age of the patients, with diabetes mellitus appearing at around 6 years of age, while optic atrophy is evident from 11 years of age. Deafness, for the most part, appears at the age of 15, and approximately 65% of patients will already have this deficiency by the age of 30 [6,8].

Evaluation with complementary examination demonstrates in the evoked visual potential impairment in the maculo-occipital pathway, in the visual perimetry with absolute scotoma with small central island of vision or only absolute scotoma [4,11,12].

WS has an unfavorable prognosis, as most patients have severe neurological impairments and have a reduced life expectancy. So far, there is no treatment available for the condition. The average life expectancy for these patients is 35 years [8].

Thus, as it is a systemic pathology with slow progression, with nonspecific findings, specialists need to have comprehensive clinical knowledge, highlighting the need for a holistic and longitudinal approach to the patient, involving a multidisciplinary team, with different specialties such as pediatrics, otorhinolaryngology, endocrinology, physiotherapy, among others [6-8].

Conclusion

SW neurodegenerative condition, autosomal recessive, rare with estimated prevalence between 1:770,000 - 1:100,000 cases. Among the essential characteristics for the diagnosis are the presence of early-onset diabetes mellitus (first decade) and optic atrophy (second decade), consistent with the cases in question. When present, these criteria give a positive predictive value of 83% and negative predictive value of 1% for SW. Other frequent but not obligatory findings are diabetes insipidus, neurological disorders and deafness. These two reported cases draw attention to the professional's expertise in establishing the association between their main characteristics, favoring early clinical diagnosis, thus enabling better multidisciplinary follow-up.

Conflict of Interest

None.

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