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CASE REPORT

Wolfram syndrome – Clinical diagnosis of rare multisystemic condition

Síndrome de Wolfram – Diagnóstico clínico de condição rara multissistêmica

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ABSTRACT

Wolfram Syndrome consists of a neurodegenerative pathology of genetic character, also known by the acronym DIDMOAD that translates the main findings of this disease, Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness. The article report the case of a patient diagnosed clinically with this syndrome in a general ophthalmology out patient clinic. Considering that patients with this genetic alteration have more than one cranial nerve affected by the disease and clinical history without meningitis or other neurological alterations, one has to think about rare alterations, as is the case with this syndrome. From the diagnosis, the WRUS questionnaire was applied in consultation, which all owed the comparation of the patient with concepts obtained internationally available in the literature.

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

RESUMO

A Síndrome de Wolfram consiste em uma patologia neurodegenerativa de caráter genético, também conhecida pela sigla DIDMOAD que traduz os principais achados dessa doença, Diabetes Insipidus, Diabetes Mellitus, Atrofia Óptica e Surdez. O artigo visa relatar o caso de um paciente diagnosticado clinicamente com essa síndrome em um ambulatório geral de oftalmologia. Tendo em vista que os pacientes portadores dessa alteração genética apresentam mais de um par craniano afetado e quadro clínico sem histórico de meningite ou outras alterações neurológicas, tem-se que pensar em alterações raras, como é o caso dessa síndrome. A partir do diagnóstico, aplicou-se o questionário WRUS em consulta, o qual permitiu a comparação do paciente abordado com dados obtidos internacionalmente disponíveis na literatura.

Descritores: Síndrome de Wolfram/diagnóstico; Atrofia óptica; Diabetes mellitus; Acuidade visual.

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Introduction

Wolfram syndrome (WS) was first described in 1938 by Wolfram and Wagener. The researchers classified it as a hereditary syndrome characterized by the presence of diabetes mellitus and optic atrophy, both acquired early in life. Subsequent descriptions added diabetes insipidus and deafness to the syndrome, which develop in approximately 73 and 62% of patients, respectively.[1]

Thus, the pathology was also named DIDMOAD, the initials of the main clinical findings, being diabetes insipidus, diabetes mellitus, optic atrophy and deafness.[2] Optic atrophy and diabetes mellitus are considered minimum diagnostic criteria.[3]

In the Syndrome, visual acuity loss is commonly defined as a symmetric high frequency loss, with a relatively slow degenerative progression occuring in the second or third decade of life.[2] But diabetes mellitus progresses slowly with fewer complications such as microvascular alterations, diabetic ketoacidosis, and blood sugar oscillation when compared to patients with type 1 diabetes due to another etiology. The auditory loss tends to be slowly gradual, and affects mainly the high frequencies between 250 and 2000 Hz resulting in late diagnoses.[4]

WS results in a deregulation of calcium homeostasis in the Endoplasmic Reticulum (ER) which stores this ion and is able to identify abnormal protein conformations and direct them to degradation. However, by autosomal recessive genetic mutations, ER loses this ability and accumulates aberrant proteins, which triggers a stress response leading to apoptosis of neuronal cells and pancreatic beta cells, and is responsible for the clinical alterations seen in this syndrome. Therefore, WS ends up integrating a secondary mitochondrial aspect.[5]

This syndrome is considerably rare, with phenotypic diversity associated with symptoms that by themselves are diagnoses of specific pathologies. The objective of the present report is to illustrate a clinical presentation of WS in order to improve its diagnosis.

Clinical Case

Patient K.Z.C., male, 13 years old, reported low visual acuity five years ago, with progressive worsening and intensifying one year ago, making him use a magnifying glass in school, despite optical correction at the onset of symptoms with the use of corrective lenses. As previous history, he reported insulin-dependent diabetes mellitus for about 4 years, as well as hypoacusis and daltonism. K.Z.C. had no intercurrences during birth, which was a cesarean surgery at 38 weeks, as well as he does not have any positive family history. So far, there is no retardation of neuropsychomotor development nor previous history of neurological diseases.

Laboratory tests were requested: Glycated hemoglobin: 7.6%, the others - Vitamin B12, Serum Copper and Magnesium were within the limits of normality, ruling out other possible metabolic disorders.

The ophthalmologic examination showed visual acuity: 20/80 in both eyes (BE) with correction. Tonometry 13/12 mmHg. Fundoscopy: rare microaneurysms, and pallor of the optic nerve in BE (Figure 1). Ectoscopy and ocular motility without alterations.

Exame físico neurológico: ramo coclear do VIII par craniano (Vestibulococlear) comprometido. Coordenação, equilíbrio, sensibilidade, força, marcha e reflexos superficiais e profundos sem alterações.

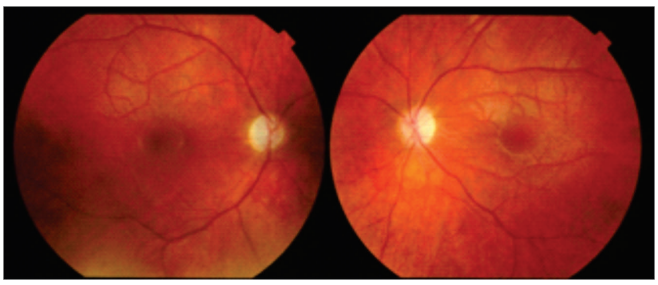

Figure 1: Fundoscopy showing pallor of the optic nerve in BE and microaneurysms.

Neurologic physical examination: cochlear branch of the VIII cranial pair (Vestibulocochlear) involved. Coordination, balance, sensitivity, strength, gait, and superficial and deep reflexes without alterations.

The patient had undergone Ocular Angiography and Optical Coherence Tomography (OCT) two years before at another service, which showed no alterations.

Therefore, the first diagnostic impression was of a condition of retinal dystrophy and metabolic disorder. Then, a new OCT (Figure 2) was requested, compatible with losses in the nerve fiber layer (NFL).

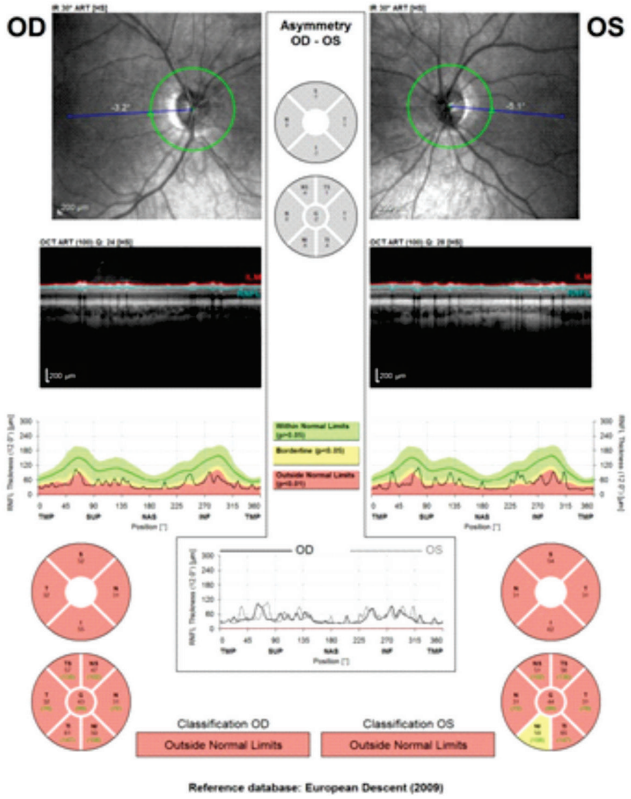

Figure 2: OCT showing losses in the layer of nerve fibers in BE.

In addition, a new OCT was performed using the Spectralis Heidelberg® device with a scanning protocol for the nerve fiber layer (NFL), which showed a preserved ganglion cell layer and loss of the nerve fiber layer in the four quadrants in BE, with normal excavation (Figure 3).

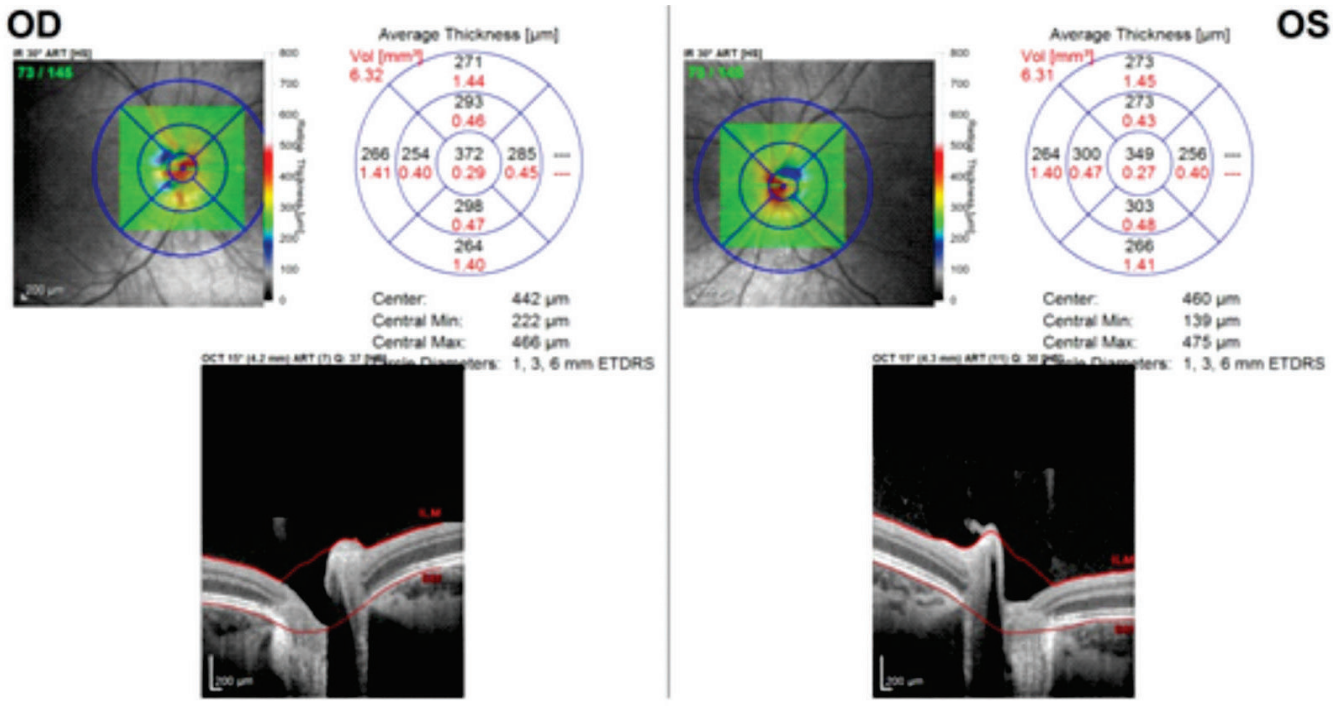

Figure 3: OCT representing normal excavation in BE.

The final approach was to request a genetic test to search for mutations in the WFS1 gene by the sequencing technique. The analyzes carried out in said test identified two possibly pathogenic variants for WS in heterozygosis in exon 8 of the WFS1 gene. The patient is under follow-up in an ambulatory specialized in low vision.

Discussion

Among the hereditary optic atrophies, there is a heterogeneous group of diseases described as bilateral optic atrophy, with the main ones being: Optic atrophy of the Kjer type, Behr syndrome and WS. The latter presents autosomal recessive inheritance, presenting between 5 and 21 years of age, diffuse and severe optic atrophy, and systemic abnormalities besides DIDMOAD, such as short stature,[6] and all of them were found in the patient in question.

WS is considered to be a rare neurodegenerative disease that is closely related to genetic alterations,[7] and its incidence is 1 case in 770,000 of the general population.[8]

The diagnosis of WS is clinical, using mutational analysis with genetic testing to strengthen the clinical conclusion. The minimum criteria for diagnosis are: Diabetes mellitus (DM) and optic atrophy, both with onset before 15 years of age, with positive predictive value of 83%, and negative of 1%.[4]

The symptoms of the pathology are related to the average age of the patients, with diabetes mellitus onset at 6 years, whereas the optic atrophy is evidenced from 11 years of age. in the majority of cases, deafness starts at age 15, and at age 30 approximately 65% of patients will already have this deficiency.[9]

Although the patient in the study has diabetes mellitus, diabetic papillitis does not fit the case since it is characterized by telangiectasia on the papilla surface, or by discreet optic nerve dysfunction.[6] However, the patient presented only pallor in the optic nerve.

The characteristic image in patients with nerve fiber layer loss is of well-defined optic disc margins, decreased fibers in the retina assuming a mottled pattern, small indefinite vessels, and incomprehensible retinal details. The diffuse loss of the retinal fibers is difficult to detect, especially when bilateral,(10) compatible with the patient studied.

The prognosis of the syndrome is restricted as a result of the majority of patients dying prematurely with severe neurological deficiencies. To date, no treatment is available. The average life expectancy for these patients is 35 years.[5]

In the patient in question, the WURS scale (Wolfram Unified Rating Scale) was applied to individually evaluate the severity and diversity of WS symptoms, focusing on previously known neurodegenerative disorders, allowing a reliable and valid measurement of the severity of the case. Thus, it is possible to evaluate the progression of the disease, and establish the most appropriate intervention for each patient. WURS shows its relevant predictive value by quantifying and qualifying patients' quality of life, which is considered to be the most relevant parameter for clinical trials, according to the Food and Drug Administration (FDA).[8]

The scale consists of a behavioral and a physical evaluation, the latter comprising two parts: one requiring the evaluation of a physician, and the other requiring the evaluation of the parents (Table 1).[8]

Each item in the physical domain gains a score of 0 – 4, with zero corresponding to the absence of symptoms, and four to the presence of symptoms with the greatest severity. In the behavioral domain, the score goes from 0 – 3, following the same line, with zero being a normal behavior, and three the presence of a disorder of greater severity. Thus, the median, standard deviation, and score range were developed in WURS according to a study carried out

with 12 participants. (8) These values are represented in table 2, along with the values found for the patient in question.

The patient's score on this scale was calculated from the physical domain, first with low visual acuity of 20/80 in BE seen at first appointment, with no optical correction, representing a high impact on the patient's life, and allowing the sum of 3 points. In addition, the hypoacusis presented was considered, being this one of small intensity and adding only 1 point. Finally, the behavioral domain was assigned 1 point for stereotyped/repetitive behaviors, which were present in the patient as circular movements of the hands, but which were sporadic and controllable. Thus, the final sum represented 4 points.

With the present report, we emphasize the importance of the clinical knowledge from general to specialized, with an approach of the patient as a whole, since he had already been treated and followed by three other specialties (pediatrics, otorhinolaryngology, and endocrinology) that addressed only isolated pathologies, delaying the definitive diagnosis.

Table 1
WURS Domains and Items for physical and behavioral evaluations

Domain WURS	Items	Maximum Score
Physical – medical evaluation	(1) Speech Clarity, (2) Reproduction of Abnormal Repetitive Sounds, (3) Protrusion of the Tongue, (4) Visual Acuity, (5) Hearing, (6) Passive Movement of Arms, Legs and Neck, (7) Tonus of Arms and Legs, (8) Repetitive sounds with the hands, (9) Maximum Dystonia (10) Normal Spontaneous Movements, (11) Gait, (12) Trunk Stability, (13) Traction Test by Retropulsion Heel (14) Motorized Tics or Stereotypes, (15) Myoclonus, (16) Resting Tremor, (17) Tremor with Posture or Action Held, (18) Dismetria, (19) Korea of appendicular muscles (20) Tandem Walk	124
Physical - parent's evaluation	(1) Temperature regulation, (2) Bladder control, (3) Intestinal control	12
Behavioral	(1) Sad Mood, (2) Apathy, (3) Anxiety, (4) Aggression Against Others (5) Aggression Against Self, (6) Stereotyped / Repetitive Behaviors (7) Compulsions, (8) Hearing Hallucinations, (9) Obsessions	54
Total score	Sum of physical and behavioral evaluations	190

Table 2
Comparison between values found in the WURS scale for the studied patient and data found in the literature

Dommain WURS	Median	Minimum	Maximum	Patient reported
Physical evaluation	5	0	29	4
Evaluation Behavioral	3.5	0	14	1
Total score	11.5	3	40	4

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