Wolfram syndrome: Phenotypic heterogeneity and novel genetic variants in the *WFS1* gene

Síndrome de Wolfram: heterogeneidad fenotípica y nuevas variantes genéticas en el gen WFS1

Wolfram syndrome (WS) is a neurodegenerative disease, first described in 1938 by Wolfram and Wagener.[1] It is a rare autosomal recessive disorder, with a prevalence of 1/770,000 in the United Kingdom, 1/710,000 in Japan and 1/100,000 in North America.[2,3] WS is estimated to occur in 1/150 cases of juvenile-onset insulin-dependent diabetes *mellitus* (DM),[4] which is usually its first manifestation.[3,5]

Type 1 and type 2 variants have been identified, caused by mutations in *WFS*1 and *CISD2* genes, respectively, the former being the most common.[6,7] WS type 1 is also known as DIDMOAD (Diabetes Insipidus, Diabetes *Mellitus*, Optic Atrophy, and sensorineural Deafness).[3] *WFS-1* gene encodes wolframin, a protein expressed in the pancreas (mainly in beta-cells), brain, spinal cord, muscle, heart, and to a lesser degree kidneys and liver.[4] It plays an important role in the regulation of endoplasmic reticulum and calcium homeostasis.[2] Juvenile-onset DM and OA are the main criteria for WS, as mutations in the *WFS1* gene induce cellular apoptosis in the pancreatic beta-cells, neurons and in a variable spectrum, in other endocrine and non-endocrine organs.[8]

Our aim is to report two patients with insulin-dependent DM due to WFS1-related WS, with different presentation forms. These cases illustrate the broad and heterogeneous spectrum of clinical manifestations of WS and its progressive course.

The first case refers to a 21-year-old man who presented at the age of 6 with diabetic ketoacidosis. DM-related antibodies (anti-glutamic acid decarboxylase, anti-islet cells and anti-insulin) were not detected but random C-peptide was low (0.2 ng/mL, RR 0.78–5.19), and he was started on insulin therapy. During childhood, delayed psychomotor development and learning disability were noted. At 7 years of age, due to visual complaints, he was referred to the ophthalmology outpatient clinic and, while diabetic retinopathy was excluded as expected, bilateral optic atrophy was diagnosed. There was no remarkable family history but genetic testing was performed, considering the early-onset complex phenotype, revealing compound heterozygous variants in the *WFS1* gene: c.482G>A (p.Arg161Gln) in exon 5 (previously not described and predicted to be pathogenic in the bioinformatic analysis) and c.1066T>C (p.Ser356Pro) in exon 8. He presented polyuria, diluted urine, thirst and nocturnal enuresis. He was started on desmopressin, with clinical improvement, so it was gradually increased to 0.12 mg three times a day. Due to maintaining nocturnal enuresis and exacerbation of urinary urgency and incontinence, he was started on oxybutynin (up to 5 mg twice a day) for suspected neurogenic bladder. At 17 years of age, he presented acute kidney injury associated with hydronephrosis, which resulted in chronic kidney disease and chronic urinary catheterization. Delayed puberty was also found and the investigation revealed compensated hypergonadotropic hypogonadism and normal karyotype (46, XY). Treatment with testosterone has not been needed yet. In recent years, glycemic control has been out-of-target due to the difficulty in performing adequate basal/bolus regimen according to carbohydrate counting, even with his mother's help.

The second case is a 55-year-old man with a past medical history of learning difficulties since childhood, and visual impairment since adolescence. In his 20s, enuresis was noted and at the age of 26 years he was diagnosed with DM due to the onset of polydipsia and polyuria; DM-associated antibodies were negative. Two months later, he was started on insulin therapy due to persistent hyperglycemia under oral glucose-lowering agents associated with weight loss and low random C-peptide (0.1 ng/mL). Over the years, glycemic control has been out-of-target, and he developed bilateral non-proliferative retinopathy. At 50 years of age, he was referred to the ophthalmology outpatient clinic due to increased visual impairment and bilateral optic atrophy was diagnosed. Brain MRI showed cerebellar and brainstem atrophy, and he was thus referred for neurological evaluation. Gait ataxia was seen, with an otherwise unremarkable neurological examination. He underwent formal neuropsychological evaluation which confirmed multidomain mild cognitive impairment. He had three siblings also with DM, one of them bearing severe visual impairment of unknown etiology, but he had no contact with them and evaluation was not possible. Next generation sequencing panel for Leber's hereditary optic atrophy was performed and turned out negative. Genetic sequencing of the *WFS1* gene was then carried out, disclosing two compound heterozygous genetic variants: c.548 T>C (p.Met183Thr) in exon 5 (previously not described and predicted to be pathogenic in the bioinformatic analysis) and c.1066 T>C (p.Ser356Pro) in exon 8, and he was then referred to genetic counseling. He was also evaluated at the Psychiatry clinic due to severe anxiety and self-injurious behaviors; he was treated with risperidone, mirtazapine and fluoxetine, with little benefit. Over the years, his psychiatric condition and glycemic control aggravated. He died at home at 56 years of age, due to unknown cause.

We describe two cases of WS with previously unknown genetic variants, with heterogeneous phenotypic presentation and clinical progression. Unlike the first patient with a typical presentation at puberty, the major manifestations of WS were delayed in the second patient. He was more than 50 years old, although a life expectancy shorter than 30 years has been described.[9] No genotype-phenotype correlation has been identified in WS so far.[5,10] Beyond DIDMOAD, these cases also demonstrate multisystemic manifestations of WS, such as renal tract abnormalities, subclinical gonadal failure, psychiatric conditions and neurological symptoms,[2,5] which can be challenging to manage. Despite a different etiopathogenesis from autoimmune DM,[5] these patients require an approach similar to type 1 DM.[9]

There is no effective therapy for several symptoms of WS, which can be life-threatening.[10] Considering the poor quality of life and early mortality,[4,9] usually by respiratory failure due to bulbar disfunction, a timely diagnosis may improve the management of WS and delay the complications of out-of-target glycemic control,[9] as well as the proper referral of these patients and their relatives to genetic counseling. The coexistence of early-onset DM and visual impairment, espe-

cially in the absence of DM-related antibodies, should alert to the possibility of WS and the active search of other symptoms seen in these patients. Out-of-target glycemic control favors neurodegeneration,[11] and effective treatment of DM may prevent or delay the complications and improve overall prognosis. However, glycemic control is very demanding in patients who have little capacity to deal with that without relatives' help, usually in those with neurologic and psychiatric symptoms.

These cases highlight how devastating WS can be, and the need to keep a low diagnostic threshold for genetic testing, even if family history is negative or unclear. Furthermore, multidisciplinary team management is paramount, in order to manage the different manifestations of this disorder and improve patient quality of life and prognosis.

Ethical standards

Written informed consent for publication was obtained. The publication of the manuscript was approved by the Local Ethical Committee.

Authors' contributions

JLF and VC drafted the manuscript and contributed equitably. All authors were involved in critical revision of the manuscript and have approved the final version of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

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