Case Report

WOLFRAM SYNDROME: A GENETIC ANALYSIS OF 2 BROTHERS

Marcella Nara Nunes, MD; Ana Carolina Duarte Esperidião, MD; Maria Luiza Mendonça Pereira Jorge, PhD; Paulo Tannus Jorge, PhD

ABSTRACT

Objective: Wolfram syndrome (WS) is a rare, autosomal recessive, progressive disease associated with considerable morbidity, even for heterozygous individuals. Our aim was to describe the cases of 2 brothers with WS and emphasize the importance of this syndrome as a differential diagnosis for autoimmune type 1 diabetes.

Methods: Two cases of WS were studied by reviewing medical files and performing clinical and imaging examinations and laboratory tests, including *WFS1* gene sequencing.

Results: The patients were 2 brothers who were both diagnosed with early onset diabetes mellitus (DM) and were found to have bilateral optic nerve atrophy during screening for chronic complications. In investigating other manifestations of the syndrome, both brothers were found to have diabetes insipidus (DI), moderate hypoacusis, and urinary tract alterations. In addition, there were personal and family histories of psychiatric problems. WS was confirmed through genetic sequencing by a homozygous mutation of the *WFS1* gene.

Conclusion: Early diagnosis of WS is important for improving patient prognosis, anticipating associated complications, and enabling timely genetic counseling for family members. **(AACE Clinical Case Rep. 2015;2:e96-e99)**

Abbreviations:
DI = diabetes insipidus; **DIDMOAD** = diabetes insipidus, diabetes mellitus, optic atrophy, deafness; **DM** = diabetes mellitus; **MRI** = magnetic resonance imaging; **WS** = Wolfram syndrome

INTRODUCTION

Wolfram syndrome (WS) or DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness) is progressive, neurodegenerative disease with an autosomal recessive mode of inheritance, and its estimated incidence is 1 our of 770,000 live births (1,2).

The minimum criterion for detecting WS is an association between early onset diabetes mellitus (DM), generally before the age of 10, and bilateral optical atrophy occurring before the age of 20. DM without autoimmunity is the first manifestation of WS, and although there is selective, progressive loss of beta cell function, the cells that produce glucagon and somatostatin are preserved. WS has lower prevalence of chronic complications than classical autoimmune type 1 DM, and ketoacidosis occurs only infrequently during WS evolution (1,3-5). Bilateral optic nerve atrophy is progressive affecting mainly the peripheral vision, but a recent histopathologic study of retinal and optic nerves demonstrated both central and peripheral involvement. The initial symptoms are very mild and include reduced visual acuity and color vision loss. The median onset of blindness is a median of 8 years after the diagnosis of optic atrophy (5-10). Around 70 to 75% of affected patients develop diabetes insipidus (DI), which is typically diagnosed around the age of 15. DI is usually the central type, which is confirmed by a neuroradiologic absence of T1 hyperintensity of the posterior pituitary lobe on magnetic resonance imaging (MRI), along with gliosis and atrophy of the paraventricular and supraoptic nuclei of the hypothalamus (5). The diagnosis of WS may be delayed because its symptoms are confounded with those of poorly controlled

Submitted for publication April 23, 2014
Accepted for publication October 1, 2014
From the Department of Endocrinology, Universidade Federal de Uberlândia (UFU), Uberlândia, Minas Gerais, Brazil.
Address correspondence to Dr. Marcella Nara Nunes; Pará Street, 1720 - Federal University of Uberlandia - Department of Medical Clinic; 38.400-902 - Uberlândia, MG, Brazil.
E-mail: marcellanara@hotmail.com
DOI:10.4158/EP14178.CR

autoimmune type 1 DM (1,5,8,9). Approximately two-thirds of patients experience some degree of neurosensory auditory loss, initially of high frequencies and progressing to lower frequencies (1-3).

Another problem related to DIDMOAD is atony of the urinary tract, which leads to dilatation of the upper portion and bladder dysfunction. This may result from impairment of the nerve fibers of this region (1,3,6). A variety of neurological signs and symptoms can be cited, such as ataxia, peripheral neuropathy, crises of apnea, losses of the senses of taste and smell, hemiparesis, and myoclonus (5,6,10). A high prevalence of psychiatric disorders has also been reported in individuals with WS and among heterozygous individuals. Approximately 60% of WS patients experience episodes of severe depression or psychosis along with compulsive physical and verbal aggression. There is no direct correlation with suicide among homozygous individuals (11,12), but even heterozygous individuals with mutations in the *WFS1* gene have an eightfold greater chance of being hospitalized due to psychiatric disorders than do individuals with 2 normal copies of the gene. Furthermore, they are at greater risk of developing neurosensory low-frequency deafness and type 1 DM (9,11,12).

The differential diagnosis includes autoimmune type 1 diabetes, and the main differences between diabetic patients with WS and patients with autoimmune type 1 DM are highlighted in Table 1. Others differential diagnoses include Leber optic nerve atrophy, anemia responsive to thiamine with DM, and deafness. The association between diabetes and optic nerve atrophy may also occur in Friedreich ataxia, Refsum disease, Alström syndrome, Lawrence-Moon syndrome, and Kearns-Sayre syndrome (2-4).

CASE REPORTS

The patients were 2 brothers from a family of 3 children of nonconsanguineous Caucasian parents. The mother presented a psychiatric abnormality (as reported by the father) that had been characterized as schizophrenia, but no abnormalities had been identified in the father or the patients' sister. The mother and sister were never evaluated by our team because they live in another city and did not come for a consultation, even when we explained the importance of this approach. There was no family history of type 1 DM. The clinical diagnosis was confirmed in both brothers; bidirectional sequencing of the DNA of the *WFS1* gene identified the homozygous mutation c.1243_1245delGTC. In a previous investigation of antibodies against pancreatic cells (anti-glutamic acid decarboxylase antibodies), both brothers were found to be negative. As the other family members had no clinical suspicion of WS, sequencing of the *WFS1* gene was not carried out due to the cost of the test.

Case 1

The first patient was a 20-year-old male with a previous diagnosis of autoimmune type 1 DM that had been made at age 3. Despite poor metabolic control, he did not have any history of diabetic ketoacidosis. In an ophthalmological examination with fundoscopy, bilateral atrophy of the optic nerve was found, but there were no signs of diabetic retinopathy. The hypothesis of DIDMOAD was raised, and routine urine tests showed that the urine osmolality was low, even with glycosuria, and there were signs of polyuria and polydipsia. Renal ultrasonography showed bilateral ectasia of the renal pelvis and notable urinary residues in the bladder. Through audiometry and imitanciometry, moderate hypoacusis was detected, with bilateral neurosensory auditory loss of 4,000 Hz. Brain MRI showed bilateral reduction of the optic nerve signal (Fig. 1); atrophy of the hypothalamic region, brainstem, cerebellum, and cerebral cortex; and an absence of the normal T1 hyperintensity from the neurohypophysis (Fig. 2). In addition, the patient developed depressive moods that were treated with antidepressant medication.

Table 1
Comparative Features Between Wolfram Syndrome and Autoimmune Type 1 Diabetes

Characteristic	Wolfram syndrome	Autoimmune type 1 diabetes
Islet autoantibodies	Negative	Positive in >80% of cases
Ketoacidosis	Rare	Common
Fundus exam	Pale appearance or bilateral atrophy of optic nerve Diabetic retinopathy is rare	Diabetic retinopathy may be present
Urinalysis	Low urine osmolality Glycosuria may be present	Normal urine osmolality Glycosuria may be present
Insulin dose required	Satisfactory control with a less intensive regimen	Intensive regimen
Impaired hearing	Slowly progressive, high-frequency sensorineural hearing loss	No symptoms

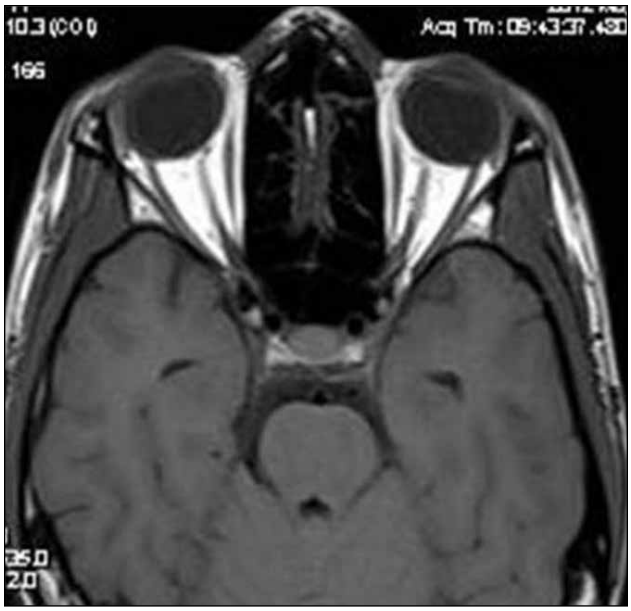

Fig. 1. Magnetic resonance image showing optic nerve atrophy.

Case 2

The patient was a 18-year-old male who had been diagnosed with type 1 DM at the age of 6. He had classical symptoms of polyuria, polydipsia, and elevated glycemia but no history of ketoacidosis despite unstable disease control. While he did not have visual impairments, fundoscopy showed bilateral pallor of the papillae and left-sided perinerve atrophy. There were no signs of diabetic retinopathy. Routine urine tests showed that the urine density was also low in this patient. Renal ultrasonography showed thickening of the bladder wall with notable urine residues. Audiometry showed moderate hypoacusis. Brain MRI did not reveal signs of optic atrophy or any other abnormalities, possibly due to the fact that the optic nerve damage was incipient, as demonstrated by the fundoscopic examination. As mentioned above, this patient was diagnosed with diabetes at the age of 6. Because he is the younger brother, it is possible that the optic atrophy was in an early stage at the time of examination.

DISCUSSION

Patients with WS usually require a less rigorous insulin schedule. Despite this, detailed urologic, ophthalmologic, psychiatric, and audiologic evaluations are warranted, even in asymptomatic individuals. Regular re-evaluation at the typical age of appearance of these features appears prudent. Bladder dysfunction can be managed with clean intermittent catheterization and anticholinergic agents to prevent urinary tract infections. Central DI should be screened for by assessing urine sodium and osmolalities. DI is treated with vasopressin supplementation.

Mutations in 2 genes have been associated with WS were identified. In the WS1 group, the anomalies are mostly missense mutations in the *WFS1* gene (4p16.1) coding for wolframin, a protein located in the endoplasmic reticulum that plays a role in calcium homeostasis. In the WS2 group, the gene responsible the mutated gene is *CISD2*, which codes for CDGSH (iron sulfur domain-containing protein 2). The characteristics are similar to those of WS1, except they do not develop DI and they have a greater risk of bleeding. Mutations in the *CISD2* gene have only been identified in 3 consanguineous families, whereas mutations in the WFS1 gene are responsible for most WS phenotypes (10,13-16).

Like the majority of WS cases, our patients had mutations in the *WFS1* gene, which leads to a defect in wolframin, a protein that is expressed most abundantly in the brain, pancreatic beta cells, and heart. Wolframin is important in cell apoptosis, given that it regulates calcium in the endoplasmic reticulum, and defects in this protein may be associated with pancreatic beta cell loss and neuronal degeneration in WS (1,4,5).

Genetic analysis can provide information regarding on mutation type. Patients with noninactivating mutations, considered missense, have a "milder" phenotype than patients with inactivating mutations (nonsense, frameshift, deletion, or insertion). The age at onset of DM is also related to the type of mutation: 11 and 7.3 years for noninactivating and inactivating mutations, respectively (14). Our findings are compatible with descriptions in the literature related to mutations in *WFS1* and the time taken for symptoms to appear, as well as the psychiatric characteristics presented by the mother who carried the mutation (9,14,15). A cohort study of patients with WS reported that the mean time for diabetes to appear was 6 years (3). Microvascular complications are rare and develop more

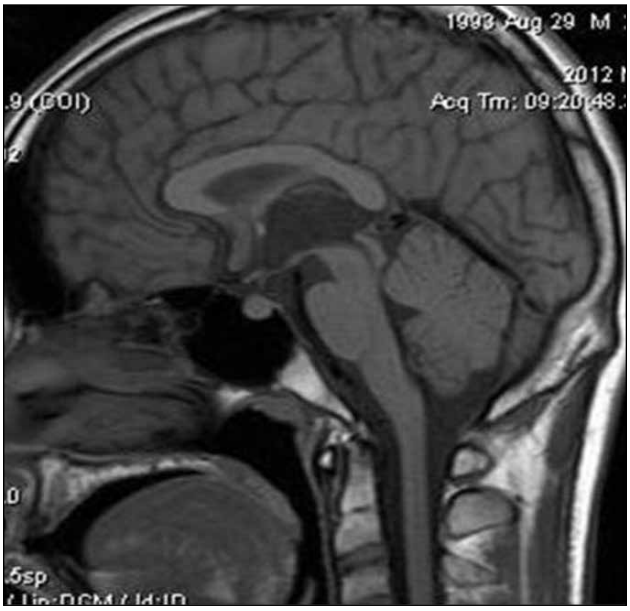

Fig. 2. Magnetic resonance image showing signal loss of the neurohypophysis and cerebellar atrophy.

slowly than in cases of type 1 DM, despite poor metabolic control. There have been few explanations for the low prevalence of microvascular complications and the variety of signs and symptoms in WS cases. Some authors have suggested that more severe phenotypes are related to mutations in the carboxy terminal of the protein associated with deafness or to inactivating mutations linked to an earlier onset of DM (1,3,9,14).

CONCLUSION

WS is a rare genetic cause of DM, and an early diagnosis of this condition becomes important as it helps clinicians anticipate associated complications and consequently reduces the morbidity and mortality. Early diagnosis also enables genetic counseling, and follow-up should be extended to first-degree family members in view of the greater risk of psychiatric disorders and DM among individuals with heterozygous *WFS1* gene mutations. This condition should be suspected in patients with a diagnosis of type 1 DM who are negative for antibodies, who have a history of premature death among siblings or a family history of WS, or those presenting with both type 1 DM and deafness (1,14-16). In such cases, it is important to investigate consanguinity in the parents and refer the patients for ophthalmologic evaluation while bearing in mind that not all childhood diabetes is type 1 diabetes.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Ribeiro MRF, Crispim F, Vendramini MF, Moisés RS.** Síndrome Wolfram: da definição às bases moleculares. *Arq Bras Endocrinol Metab*. 2006;50:839-844.
2. **Naderian G, Ashtari F, Nouri-Mahadavi K, Sajjadi V.** A case of wolfram syndrome. *J Ophthalmic Vis Res*. 2010;5:53-56.
3. **Barrett TG, Bundey SE, Macleod AF.** Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet*. 1995;346:1458-1463.
4. **Boutzios G, Livadas S, Marinakis E, Opie N, Economou F, Diamanti-Kandarakis E.** Endocrine and metabolic aspects of the Wolfram syndrome. *Endocrine*. 2011;40:10-13.
5. **Kumar S.** Wolfram syndrome: important implications for pediatricians and pediatric endocrinologists. *Pediatric Diabetes*. 2010;11:28-37.
6. **Hershey T, Lugar, HM, Shimony JS, et al.** Early brain vulnerability in Wolfram syndrome. *PLoS One*. 2012;7:e40604.
7. **Conart JB, Maalouf T, Jonveaux P, Guerci B, Angioi K.** [Wolfram syndrome : clinical and genetic analysis in two sisters]. *J Fr Ophtalmol*. 2011;34:543-546.
8. **Boettcher C, Brosig B, Zimmer KP, Wudy SA.** The subtle signs of Wolfram (DIDMOAD) syndrome: not all juvenile diabetes is type 1 diabetes. *J Pediatr Endocr Met* 2011;24:71-74.
9. **Gasparin MR, Crispim F, Paula SL, et al.** Identification of novel mutations of the WFS1 gene in Brazilian patients with Wolfram syndrome. *Eur J Endocrinol*. 2009; 160:309-316.
10. **Rigoli L, Di Bella C.** Wolfram syndrome 1 and Wolfram syndrome 2. *Curr Opin Pediatr.* 2012;24:512-517.
11. **Swift RG, Sadler DB, Swift M.** Psychiatric findings in Wolfram syndrome homozygotes. *Lancet* 1990;336:667-669.
12. **Crawford J, Zielinski MA, Fisher LJ, Sutherland GR, Goldney RD.** Is there a relationship between Wolfram syndrome carrier status and suicide? *Am J Med Genet*. 2002;114:343-46.
13. **Rigoli L, Lombardo D, Di Bella C.** Wolfram syndrome and WFS1 gene. *Clin Genet*. 2011;79:103-117.
14. **Aloi C, Salina A, Pasquali L, et al.** Wolfram syndrome: new mutations, different phenotype. *PLoS One*. 2012;7:e29150.
15. **Xu O, Qu H, Wei S.** Clinical and molecular genetic analysis of a new mutation in children with Wolfram syndrome: a case report. *Mol Med Rep*. 2013;7:965-968.
16. **Al-Sheyyab M, Jarrah N, Younis E, et al.** Bleeding tendency in Wolfram syndrome: a newly identified feature with phenotype genotype correlation. *Eur J Pediatr.* 2001;160:243-246.
17. **Cano A, Molines L, Valéro R, et al.** Microvascular diabetes complications in Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness[DIDMOAD]: an age- and duration-matched comparison with common type 1 diabetes. *Diabetes Care*. 2007;30:2327-2330.