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Case Report

Wolfram Syndrome; Case Series Report at the "National Medical Center 20 De Noviembre ISSSTE"

Eduardo Sagarnaga-Quezada[1*], Alma Vergara-López[1]
[1]Department of Endocrinology, CMN "20 de Noviembre", Institute of Security and Social Services of State Workers, Mexico City 03229, México

***Corresponding Author:** Eduardo Sagarnaga-Quezada
Department of Endocrinology, CMN "20 de Noviembre", Institute of Security and Social Services of State Workers, Mexico City 03229, México

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Abstract: Wolfram syndrome it's a rare autosomal genetic disease. Also, kwon as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness). Its classified as one of infancy onset diabetes mellitus non autoimmune causes, its presentation generally happens at an early age; other characteristics of the disease are insipidus diabetes, optic atrophy, neurosensorial deafness, psychiatric alterations and other neurodegenerative disorders.

Keywords: Wolfram syndrome, WSF1, CISD2, endoplasmic reticulum disease, diabetes.

INTRODUCTION

Wolfram syndrome was originally described by Donald J. Wolfram and H. P. Wagener in 1938 in a report of various family members which presented with diabetes mellitus and optic atrophy, with subsequent development of ataxia, deafness and incontinency [3]. Later in 1998 the WSF1 gene was identified [4]. Estimated incidence is 1 per 100,000 habitants in the United States of America, and an incidence of 770,000 per habitants in the United Kingdom, an estimate of 1% of the total population are porters [5]. Its estimated that 1 of every 150 patients with early development of diabetes suffer from this syndrome [6]. Its classified by the ICD-11 as one rare cause of diabetes mellitus with the subcategory 5A16.1 [1]. Most of this patients will die from respiratory failure secondary to bulbar degeneration. The mean age of death is 30 years, most of them at an age of 25 to 49 years [7].

CLINICAL CASES

Case 1

Woman referred from an outpatient hospital from a second level hospital at 17 years of age. History: paternal grandfather died from an ischemic cerebral vascular event, paternal grandmother and both maternal grandparents diagnosed with type 2 diabetes, 2 younger siblings with a history of diabetes and hearing loss diagnosed at 2 and 4 years of age. Menarche at 11 years of age, regular cycles. Diabetes mellitus diagnosed at 2 years of age due to polydipsia and polyuria in treatment with insulin, basal bolus schedule; optic atrophy diagnosed at 8 years of age, depressive disorder in pharmacological treatment at 14 years of age, neurogenic bladder requiring permanent bladder catheterization, bilateral hypoacusia diagnosed and diabetes insipidus with adequate response to treatment with desmopressin diagnosed at 16 years of age, assessed by ophthalmology who confirms bilateral partial optic atrophy. Diagnosis of subclinical hypothyroidism at age 17 without requiring pharmacological treatment, with recurrent urinary tract infections. At the age of 21, a lesion in the right upper right quadrant of the right breast was removed with histopathological findings of fibroadenoma.

A molecular study for WFS1 was performed on the patient, as well as on her parents, and WFS1 was found by PCR amplification and sequencing, in exons 4 and 8 variant: c.409 424dup (p.Val142Glyfs*110) c.1078 _1083del (p.Cys360_Thr 361) compound heterozygote; in father carrier variant: c.409_424dup (p.val142glyfs*110), mother carrier variant: c.1078_1083del (p.cys360_thr 361 del). Subsequently,

a study was performed on siblings in whom the same variants identified were confirmed.

Case 2

Male with history of; fatal ischemic cerebral vascular event in paternal grandfather, paternal grandmother and both maternal grandparents diagnosed with type 2 diabetes, 2 sisters diagnosed with Wolfram syndrome. At the age of 16 years old with a history of diabetes mellitus diagnosed since 2 years of age in treatment with basal insulin bolus, sensorineural deafness since 10 years old requiring the use of hearing aids due to bilateral sensorineural hearing loss since 22 years old; development of neurogenic bladder requiring a urinary catheter at the age of 21 years old. At the age of 23, migraine with aura was diagnosed by the neurology department, who started treatment with topiramate 25 mg per day. Sequencing and PCR amplification of WSF1 showed exons 4-8, variant Val142-Gly110 / Cys360-Thr361 compound heterozygous, same mutation found in her sisters.

Case 3

Woman referred at 22 years of age from a second level hospital. History of paternal grandparents and maternal grandmother with type 2 diabetes, father with type 2 diabetes, 4 healthy siblings, another brother with hearing pathology not studied. Menarche at 15 years of age, regular cycles. Diabetes mellitus diagnosed at 5 years of age, started treatment with NPH insulin, later on basal and bolus insulin. At 14 years of age, bilateral partial optic atrophy was diagnosed. Primary hypothyroidism diagnosed at 16 years of age treated with levothyroxine. Peripheral neuropathy not associated with hypoglycemia identified at 18 years of age, treated with gabapentin. At the age of 18 she was diagnosed with bilateral hypoacusia, at the age of 20 she developed neurogenic bladder requiring intermittent catheterization and diabetes insipidus requiring treatment with desmopressin. Depressive disorder was diagnosed at 21 years of age. Sequencing and PCR amplification was performed with the finding of a biallelic WFS1 gene mutation confirming Wolfram syndrome.

ETIOLOGY

It is generally caused by loss-of-function mutations in the WSF1 gene which consists of 33.4 kilobases and 8 exons, responsible for coding the wolframin protein located on chromosome 4p16.1, [8] generally located in exon 8, however, mutations have been described in exons 3,4,5 and 6, mostly by substitution of a base pair (missense) although there are described cases of mutation with premature termination of the encoded protein (nonsense) [9, 10]. Wolframin is a transmembrane protein of the endoplasmic reticulum involved in secretion, movement, processing and regulation of calcium in the endoplasmic reticulum; this protein consists of 890 amino acids with a molecular weight of 100 kilodaltons and is made up of 9 transmembrane hydrophobic segments and terminal hydrophilic portions at both ends [4]. Its mutations cause accumulation of poorly processed protein residues that subsequently cause apoptosis by overcoming the cell's ability to dispose of these products [9,4].

This protein is highly expressed in the hippocampus, amygdala, olfactory bulb, heart and pancreatic beta cells. In the latter it downregulates transcription factor 6 alpha (ATF6α) which is related to endoplasmic reticulum stress as well as endoplasmic reticulum stress response elements (ERSE), stabilizes the E3 ubiquitin ligase HDR1 suppressing the endoplasmic reticulum stress signaling chain, [11] and has also been linked to proinsulin processing as well as insulin release [12, 13]. Wolframin also interacts with the beta 1 subunit of the sodium/potassium ATPase, and could therefore alter the activity of the latter [14]. Wolframin also acts as a calmodulin regulating calcium storage in the endoplasmic reticulum with consequent alteration of cytosolic calcium and subsequent alteration of mitochondrial activity (inhibition of mitochondrial fusion, decreased mitochondrial mobility and mitochondrial destruction) with consequent reduction in ATP levels [15].

A variant of Wolfram syndrome known as Wolfram syndrome type 2 caused by a mutation on chromosome 4q22-24 of the autosomal recessive CISD2 gene, this gene encodes a zinc-finger protein of the endoplasmic reticulum that also plays a role in calcium homeostasis, called ERIS (endoplasmic reticulum intermembrane small protein), this protein is expressed in pancreas and brain and is localized between the mitochondrial outer membrane and the endoplasmic reticulum membrane, it is involved in glucose and calcium regulation, insulin sensitivity and autophagocytosis. This syndrome unlike WSF1 does not present with diabetes insipidus or psychiatric disorders but presents with ulcers and upper gastrointestinal tract bleeding as well as disorders in platelet aggregation [4].

CLINICAL MANIFESTATIONS

Non-autoimmune insulin-dependent diabetes is the first manifestation in the majority of cases, presenting on average at 6 years of age, [16] in these patients microvascular complications are less frequent and if they occur their progression is slower. Unlike autoimmune diabetes, this occurs at younger ages, most cases have negative antibodies, a characteristic is that these patients present residual insulin secretion, they are associated with longer periods of remission, lower total insulin requirements and a higher incidence of severe hypoglycemia [4,17,18]. Optic nerve atrophy manifests with loss of peripheral vision and color vision, usually observed at 11 years of age, [16,20] optic atrophy is progressive and progresses to complete blindness in

most patients within 8 years of diagnosis with a range of 1 to 25 years [16].

Diabetes insipidus presents in most patients (73%) [7] usually by 14 years of age, loss of neuronal bodies in supraoptic nuclei has been observed, as well as altered vasopressin processing [6]. Sensorineural deafness is present in 62% of the cases, it has a slow evolution and most of the time it is asymptomatic, the main characteristic is the deafness towards high frequency sounds [4,7]. It presents on average at the age of 12 and a half years [19, 21]. Multiple psychiatric and neurological symptoms have been described; neurological manifestations occur in up to 62% of patients from the age of 16 years on average, the most common being cerebellar truncal ataxia, dysarthria and dysphagia, central apnea due to brain stem involvement, this being the main cause of death in these patients [4,20]. Psychiatric disorders are found in up to 60% of patients; depression, psychosis and sleep disturbances are the main manifestations. A greater suicidal tendency than in the general population has been described [4,7,22,23].

Urological alterations, mainly bladder disorders, consist of bladder atony or sphincter dyssynergia; these complications can occur at any stage of the disease in up to 58-62% of patients [7]. Both hypogonadotrophic and hypergonadotrophic hypogonadism have been described mainly in male patients, although the reason for this distribution is unknown [24]. Different gastrointestinal alterations have also been described, mainly intestinal dysmotility, gastroparesis, incontinence, although these are less frequent than other clinical manifestations [4].

DIAGNOSIS

For diagnosis are considered the criteria used by OPHTARA (Reference Centre for Rare Diseases in Ophthalmology) and WSRA (Wolfram Syndrome Research Alliance), with major criteria: A) diabetes mellitus presentation before 16 years of age and B) optic atrophy presentation before 16 years of age. Minor criteria; a) diabetes insipidus, b) diabetes mellitus after 16 years of age, c) optic atrophy after 16 years of age, d) sensorineural deafness, e) neurological symptoms (ataxia, epilepsy, cognitive impairment), f) urinary tract abnormalities, g) loss-of-function mutation in an allele in the WFS1 or CISD2 genes or family history of Wolfram syndrome. The diagnosis is established with 2 major, 1 major and 2 minor criteria or 2 identified mutations in the WSF1 or CISD2 genes.

DISCUSSION

Wolfram syndrome is a rare disease that is generally underdiagnosed and difficult to manage due to the wide range of clinical manifestations that require a multidisciplinary team approach and treatment. These patients will present multiple complications throughout their lives and have a life expectancy much lower than the general population, in our case series we can observe multiple manifestations of the disease most of them at an early age, not every patient develops every single manifestation of the disease's spectrum, however all of our patients develop diabetes mellitus, neurosensorial deafness and some type of urological pathology (table 1). However, early diagnosis and treatment improves both the quality of life and life expectancy of these patients. A higher incidence of hypoglycemia has been observed in these patients, as well as a lower incidence of diabetes complications, so less strict glycemic control goals could be considered in this population. The WSRA (Wolfram Syndrome Research Alliance) has multiple clinical trials of experimental drugs in which recently diagnosed patients could be considered for enrollment.

Table 1: Clinical Manifestatios of Wolfram Syndrome and Its Presentation by Age

	Case 1	**Case 2**	**Case 3**
Current Age	23	24	27
Diabetes Mellitus	2	2	5
Optic Atrophy	8	-	14
Diabetes Insípidus	16	-	20
Deafness	16	10	18
Urological	14	21	20
Psiquiátric	14	-	21
Neurológic	-	23	18
Hypogonadism	-	-	-
Primary Hipothiroidism	17	-	16
Identified Mutation	WFS1, exons 4 and 8, variants: Val142-Gly110 / Cys360-Thr361	WFS1, exons 4 and 8, variants: Val142-Gly110 / Cys360-Thr361	WSF1

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Conflict of interest

The authors declare that there are no conflicts of interest at the time of publication of this article.

REFERENCES

1. Urano, F. (2016). Wolfram Syndrome: Diagnosis, Management, and Treatment. *Current diabetes reports, 16*, 6.
2. Pallotta, M. T., Tascini, G., Crispoldi, R., Orabona, C., & Mondanelli, G. (2019). Wolfram syndrome, a rare neurodegenerative disease: from pathogenesis to future treatment perspectives. *Journal of Translational Medicine, 17*, 238.
3. Cárcamo Fonfría, A., Santos-Bueso, E., Benitez Del-Castillo, J. M., & Porta-Etessam, J. (2018). A new mutation in a patient with Wolfram syndrome. *Neurologia, 33*(9), 618-619.
4. Rigoli, L., Bramanti, P., Di Bella, C., & De Luca, F. (2018). Genetic and clinical aspects of Wolfram syndrome 1, a severe neurodegenerative disease. *Pediatric Research, 83*, 921–929.
5. Swift, M., & Swift, R. G. (2000). Psychiatric disorders and mutations at the Wolfram syndrome locus. *Biol Psychiatry, 47*(9), 787-93.
6. Mohd Ashraf, G., & Dilafroze, B. (2009). Current developments in Wolfram syndrome. *J Pediatr Endocrinol Metab, 22*(1), 3-10.
7. Sharath, K. (2010). Wolfram syndrome: important implications for pediatricians and pediatric endocrinologists. *Pediatric Diabetes, 11*(1), 28–37.
8. Collier, D. A., Barret, T. G., Curtis, D., Macleod, A., Arranz, M. J., Maassen, J. A., & Bundey, S. (1996). Linkage of Wolfram Syndrome to Chromosome 4pl6.1 and Evidence forHeterogeneity. *Am.J. Hum. Genet, 59*, 855-863.
9. Go Lee, A., Ashwini, K., Subdhaa, T., & Al Othman, B. (2022). Wolfram Syndrome. American Academy of ophtalmology.
10. Hardy, C., Khanim, F., Torres, R., Scott-Brown, M., Seller, A., & Poulton, J. (1999). Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. *Am J Hum Genet, 65*(5), 1279-90.
11. Yamada, T., Ishihara, H., Tamaru, A., Takahashi, R., Yamaguchi, S., Takei, D., & Tokita, A. (2006). WFS1-deficiency increases endoplasmic reticulum stress, impairs cell cycle progression and triggers the apoptotic pathway specifically in pancreatic beta-cells. *Hum Mol Genet, 15*(10), 1600–1609.
12. Fonseca, S. G., Fukuma, M., Lipson, K. L., Nguyen, L. X., & Allen, J. R. (2005). WFS1 is a novel component of the unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic beta-cells. *J Biol Chem, 280*, 39609–39615.
13. Lemaire, K., & Shhuit, F. (2012). Integrating insulin secretion and ER stress in pancreatic β-cells. *Nat Cell Biol, 14*, 979–981.
14. Sütt, S., Altpere, A., Reimets, R., Visnapuu, T., Loomets, M., Raud, S., & Salum, T. (2015). Wfs1-deficient animals have brain-region-specific changes of Na+, K+-ATPase activity and mRNA expression of α1 and β1 subunits. *J Neurosci Res, 93*(3), 530–537.
15. Cagalinec, M., Liiv, M., Hodurova, Z., Hickey, M. A., Vaarman, A., & Mandel, M. (2016). Role of mitochondrial dynamics in neuronal development: mechanism for Wolfram syndrome. *PLoS Biol, 19*, e1002511.
16. Barrett, T. G., Bundey, S. E., Fielder, A. R., & Good, P. A. (1997). Optic atrophy in Wolfram (DIDMOAD) syndrome. *Eye, 11* (Pt 6), 882-8.
17. Rohayem, J., Ehlers, C., Wiedemann, B., Holl, R., & Oexle, K. (2011). Diabetes and neurodegeneration in Wolfram syndrome: a multicenter study of phenotype and genotype. *Diabetes Care, 34*(7), 1503-10.
18. Cano, A., Molines, L., Valéro, R., Simonin, G., & Paquis-Flucklinger, V. (2007). 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, 30*(9), 2327-30.
19. Barrett, T. G., Bundey, S. E., & Macleod, A. F. (1995). Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet, 346*(8988), 1458–63.
20. Scolding, N. J., Kellar-Wood, H. F., Shaw, C., Shneerson, J. M., & Antoun, N. (1996). Wolfram Syndrome: Hereditary Diabetes Mellitus with Brainstem and Optic Atrophy. *Ann Neurol, 39*(3), 352-60.
21. Lesperance, M. M., Hall, J. W., San Agusrin, T. B., & Leal, S. M. (2003). Mutations in the Wolfram Syndrome Type 1 Gene (WFS1) Define a Clinical Entity of Dominant Low-Frequency Sensorineural Hearing Loss. *Archives of Otolaryngology—Head and Neck Surgery*, 129(4), 411–420.
22. Chaussenot, A., Bannwarth, S., Rouzier, C., & Vialettes, B. (2011). Neurologic features and genotype-phenotype correlation in Wolfram syndrome. *Ann Neurol, 69*(3), 501-8.
23. Crawford, J., Zielinski, M. A., Fisher, L. J., Sutherland, G. R., & Goldney, R. D. (2002). Is there a relationship between Wolfram syndrome carrier status and suicide? *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 114*(3), 343-6.
24. Toppings, N.B., McMillan, J. M., Au, P .Y. B., Suchowersky, O., & Donovan, L. E. (2018). Wolfram Syndrome: A Case Report and Review of Clinical Manifestations, Genetics Pathophysiology, and Potential Therapies. *Case Reports in Endocrinology, 2018*, Article ID 9412676.
25. Lafusco, D., Zanfardino, A., Piscopo, A., Curto, S., Troncone, A., & Chianese, A. (2022). Metabolic Treatment of Wolfram Syndrome. *Int. J. Environ. Res. Public Health, 19*(5), 2755.