Endokrynologia Polska
DOI: 10.5603/EP.a2021.0038
Volume/Tom 72; Number/Numer 4/2021
ISSN 0423–104X, e-ISSN 2299–8306

Wolfram syndrome: Portuguese research

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Abstract

Introduction: Wolfram syndrome (WFS) is a neurological and endocrinological degenerative disorder, also known as DIDMOAD (Diabetes Insipidus, early-onset Diabetes Mellitus, progressive Optic Atrophy, and Deafness) syndrome. It is an autosomal recessive disorder, mostly involving the Wolfram syndrome 1 gene (*WFS1*). The phenotypic pleiomorphism, rarity, and molecular complexity complicate the follow-up of these patients.

Material and methods: We aimed to describe the clinical characteristics and the follow-up of 11 patients with this disorder. We retrospectively analysed all WFS patients diagnosed between 1990 and 2020 in the Centro Hospitalar São João, a tertiary hospital in Northern Portugal.

Results: Eleven patients were included. Four patients had all 4 components of DIDMOAD. The presentation was diabetes mellitus (DM) in 9 patients, optic atrophy (OA) in another patient, and diabetes insipidus (DI) in another one. The median age of DM and OA diagnosis was 6 and 14 years, respectively. Nine patients had diabetes mellitus, and the other 2 patients had impaired glucose tolerance. All patients had OA. Four patients presented DI, all of them diagnosed in adolescence. Four patients had hearing impairment, 5 had urological abnormalities, 5 had neurological disorders, and 8 had psychiatry disorders. Eight patients had a broad spectrum of recessive mutations in *WFS1*.

Conclusion: The information obtained in this study can facilitate further research in an attempt to improve prevention strategies for this devastating disease. **(Endokrynol Pol 2021; 72 (4): 353–356)**

Key words: *Wolfram syndrome; diabetes mellitus; diabetes insipidus; optic atrophy; deafness*

Introduction

Wolfram syndrome (WFS), also known as DIDMOAD, is a rare inherited disease first described in 1938 by Wolfram and Wagener [1, 2]. It is characterized by diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and deafness. Urological, psychological, and neurological comorbidities may also be present.

Wolfram syndrome is very rare. Its prevalence has been estimated at 1 in 770,000 individuals in the UK, 1 in 500,000 in Germany, 1 in 710,000 in the Japanese population, and 1 in 68,000 in the Lebanese population. The highest prevalence, of 1 in 54,478, is in a small district in a Sicilian population [2–6]. The high prevalence of WFS in Lebanese and Sicilian populations could be due to the high rates of consanguinity in these populations [7, 8].

Because WFS is a progressive disorder, and affected individuals experience a wide spectrum of symptoms during their lifetimes. The lifespans of affected individuals are generally shortened as a consequence of neurological and psychiatric problems, such as central respiratory failure, food aspiration, and suicide. Currently, no therapeutic intervention is known to alter the progression or the life expectancy of the affected individuals [9].

Several loss-of-function mutations of the Wolfram syndrome 1 gene (*WFS1*) have been described in patients with WFS [4]. *WFS1*-deficient mice have glucose intolerance associated with loss of pancreatic beta cells. The gene product of *WFS1* is an endoplasmic reticulum embedded protein, which has been implicated in various cellular functions such as insulin secretion and processing, cell cycle regulation, unfolded protein response, and cAMP production [10–15]. On the other hand, *WFS1* mutation was not identified in some patients, providing evidence of genetic heterogeneity for this disease. A specific mutation in a second gene (*WFS2*), also known as *CISD2*, has been described in affected Jordanian families [16].

The natural history of WFS has been characterized in different populations, mainly Asian populations, and there are few singles in occidental European populations.

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Material and methods

We retrospectively analysed all WFS patients diagnosed between 1990 and 2020 in the Centro Hospitalar São João, a tertiary hospital in Northern Portugal.

We screened a total of 14 patients who were eligible for our study due to the fact that they had diagnostic clinical criteria and identification of *WFS1* mutations. One patient clinically suspected of WFS was excluded because he had no genetic confirmation, and 2 patients with clinical and genetic confirmation were excluded because they had no follow-up in our hospital in adult life.

Demographic data, clinical presentation, including signs and symptoms, and their onset age, family history, and genetic analysis were retrospectively abstracted from clinical records.

Descriptive statistics were expressed for quantitative data by the median. They were presented for categorical data as the number and percentage.

Results

Our population comprised 11 WFS patients, with 7 females (63%) and a median current age of 23 years (range 12–34 years). Two patients were siblings. The patients' clinical features are summarized in Table 1. Four patients (36.3%) had all 4 components of DIDMOAD. OA was present in all patients. Diabetes mellitus was present in 9 (81.8%) patients, and the other 2 patients had impaired glucose tolerance (IGT) rather than DM. Eight patients (72.7%) presented with psychiatric disorders. Urological abnormalities were present in 5 of the 11 patients (45.4%). Five patients also had neurological disorders. Four patients (36.4%) had insipidus diabetes, and 4 patients (36.4%) also had hearing impairment. One patient presented a rheumatological disorder: undifferentiated arthritis in need of biological treatment.

The first clinical manifestation of the disease occurred at a median age of 7 years (range 2–15 years), all of them in paediatric age, and consisted of diabetes mellitus in 9 patients (81%), OA in another patient, and DI in another one. The median age of DM, OA, DI, and urological disorders at onset was 6 (range 2–11 years), 14 (range 5–30 years), 13 (range 10–16 years), and 10 (range 8–10 years), respectively. Hearing loss (HL) developed at the median age of 8 years (range 6–15 years).

Nine patients have diabetes and are currently treated with insulin, in a median dose of 0.7 units/kg/day. The current median HbA_{1c} is 7.5% (range 7–9.5%). Mild hypoglycaemia was found in all patients, and non-proliferative retinopathy was found in 1 patient who had had diabetes for 20 years.

Optic atrophy was bilateral and progressive in all patients, and presented as hypoplasia, visual field defect, and colour blindness — all of them diagnosed in paediatric age.

Three patients presented DI, all of them diagnosed in adolescence. Urological abnormalities including residual urine in the bladder and urinary incontinence were established by imaging examinations in 5 (45.4%) of the 11 patients.

All patients had mutations in *WFS1*. Eight patients (72.7%) had a broad spectrum of recessive mutations in *WFS1*. Three patients (27.2%) had mutations in only 1 allele. Ages at onset of DM in patients with recessive *WFS1* mutations were lower than those in patients with 1 mutation in only 1 allele.

Two patients had changes in brain MRI at this time, which showed atrophy of the cerebellum and brain stem, 1 of them with recent hospitalization in intensive care for acute respiratory failure. The overall survival rate was 100% at the time of follow-up, and the age of patients ranged from 12 to 34 years.

Table 1. *Demographic features of the patients and detailed clinical presentations*

Case nº	Onset age [yrs]	Sex	DM/IGT	OA	DI	HL	UD	ND	PD
1	8	M	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	3	F	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	3	F	Yes	Yes	No	No	Yes	No	Yes
4	6	M	Yes	Yes	No	No	No	No	Yes
5	7	M	Yes	Yes	No	No	No	No	Yes
6	7	F	Yes	Yes	No	No	No	Yes	Yes
7	6	M	Yes	Yes	No	No	No	No	No
8	14	F	Yes	Yes	Yes	Yes	Yes	No	Yes
9	15	F	Yes	Yes	No	No	No	No	No
10	11	F	Yes	Yes	Yes	Yes	No	Yes	Yes
11	6	F	Yes	Yes	No	No	Yes	Yes	No

M — male; F — female; DM — diabetes mellitus; IGT — impaired glucose tolerance; OA — optic atrophy; DI — diabetes insipidus; HL — hearing loss; UD — urological disorder; ND — neurological disorder; PD — psychological disorder

Discussion

In this study, we retrospectively described the clinical features of 11 WFS patients from a single centre in the last 30 years.

Diabetes mellitus was the most common clinical feature in our cohort, in accordance with previous studies. Non-auto-immune insulin-dependent DM is the first manifestation of WFS, but there is a great diagnostic delay from the onset of diabetes to the diagnosis of the syndrome. Zmyslowska et al. found that *WFS1* was diagnosed with a delay of at least 7 years, and that all *WFS1* patients were primarily misdiagnosed as having insulin-dependent type 1 DM [17]. This could be a limitation of our study.

Microvascular complications are rare, and they do not progress as quickly as in the type 1 DM. *WFS1* non-autoimmune insulin-dependent DM is characterized by a daily insulin requirement and a mean HbA_{1c} lower than in type 1 DM, because in *WFS1* the residual insulin secretion lasts longer than in type 1 DM. In our sample, we verified the same tendency. Non-autoimmune insulin-dependent DM of WFS begins in preschool-age without ketoacidosis, it is antibody-negative, and has surprisingly long periods of remission. Therefore, WFS must be suspected in these cases [18–20].

Optic atrophy is usually present in the diagnosis of WFS. In these patients, OA occurs in the first decade; it is progressive and often leads to blindness. It begins at an average age of 11 years (6 weeks to 19 years) with reduced visual acuity and loss of colour vision [2, 18]. The median age of diagnosis of OA in our patients was 14 years. Hence, in WFS patients, an annual eye examination is essential, including visual acuity, colour vision testing, fundoscopy, visual field, and optical coherence tomography scan. The monitoring of the efficacy of potential therapy can be performed by visual evoked potentials [6].

In WFS patients, diabetes mellitus usually occurs in the first decade of life, OA is diagnosed during the early second decade, DI and HL during the second decade, and urological and neurological abnormalities during 10–30 years [21–23], as in our study.

Generally sensorineural deafness presents at an average age of 12–16 years (range 5–39 years) and is a feature seen in 62% of WFS patients [2, 9]. This disorder affects high frequencies first and progresses relatively slowly [2]. Pennings et al. found that in WFS females, hearing loss was more prevalent than in *WFSF1* males [24]. However, in other studies, no gender differences in the degree of deafness were found [2, 25]. In our study, we found that 2 females and 1 male presented this disorder. The follow-up of this disorder in WFS patients includes an audiometry test every year or every 2 years [6].

Neurological complications and psychiatric disorders are frequent in WFS patients. In our study, the incidence of neurological complications was 45%. The most common symptom is cerebellar ataxia, as in our study. Headache has also been reported in WFS [4] — 5 patients in our study presented headache. These patients should be evaluated yearly or twice a year by a neurologist.

Urinary tract problems are another major clinical challenge for Wolfram syndrome patients, affecting 60–90% of this population [26]. Hydroureteronephrosis, urinary incontinence, and recurrent infections are common signs of neurogenic bladder. The median age of onset of urological manifestations is 20 years, although numerous patients develop the symptoms at 10–20 years of age [6, 28]. We reported urological abnormalities in 45.4% of patients.

Frequently (up to 20–30%) WFSF patients are affected by episodes of severe depression, psychosis, smell and sleep abnormalities, or organic brain symptoms, as well as impulsive verbal and physical aggression, while *WFS1* heterozygotes may be predisposed to psychiatric illness. Usually, cognitive and psychiatric symptoms begin in the later stages of the disease [4, 26–28]. In our case, we found a high number of patients with this pathology, given that up 72% of our patients presented psychiatric disorders from adolescence onwards.

Genetic analysis should be considered as an effective method to assist diagnosis and genetic consultation [6]

Wolfram syndrome has high morbidity and mortality, without effective treatment, and the median age of death is around 30 years (range 25–49). Respiratory failure or dysphagia due to brainstem involvement are common causes of mortality [6, 29]. In our case, thus far the survival rate is 100%, with the age of patients ranging from 12 to 34 years.

More studies are necessary to better manage this devastating disease and to guarantee the patients a better quality of life and longer life expectancy [30].

Conclusions

The information obtained in this study can facilitate further research in an attempt to improve prevention strategies, as well as treatments for this devastating disease.

In the author's opinion, Wolfram syndrome, as a multisystemic progressive disease requiring rapid diagnosis, should be followed up in tertiary hospital centres, by a multidisciplinary team. Special care should be taken in the transition into adulthood follow-up, taking into account that the greatest worsening of the disease occurs from the third decade of life.

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