

Wolfram Syndrome: Endocrinological Features in a Case Series Study and Review of the Literature

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Abstract

Objective: Wolfram syndrome (WFS) is a rare and complex genetic disorder referred to as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness).

Material & Methods: All insulin dependent diabetic patients presented over a period of 10 years, who had optic atrophy or a positive family history of WFS, were enrolled in the study. Criteria for the diagnosis of WFS were the presence of insulin dependent diabetes mellitus (IDDM) along with optic atrophy unexplained by any other disease and/or some other abnormalities associated with WFS.

Findings: WFS has been diagnosed in sixteen patients, 9 males and 7 females aged 5.5 to 22yr (median age of 13.4 yr). Nine patients (more than half) came from consanguineous marriages. The earliest manifestation of WFS was IDDM (at a median age of 5.4yrs). All patients developed non-autoimmune IDDM before the age of 8 years old. Only two cases were ketoacidotic. Common diabetic complications of proliferative retinopathy, glomerulosclerosis and neuropathy were remarkably absent in our patients even with long-lasting diabetes mellitus. Antidiuretic hormone (ADH)-responsive diabetes insipidus was confirmed by water deprivation test in 8 patients (50%). The incidence of diabetes insipidus in our patients was lower compared to other studies. Growth retardation, as short stature and a weight below the 5th percentile for age and gender, was found in 13 (81%) and 5 (31%) patients respectively.

Conclusion: Early diagnosis and proper treatment aimed at relieving the symptoms and preventing the future complications are of paramount value and importance.

Key Words: Wolfram syndrome, Diabetes mellitus, Optic atrophy, Diabetes insipidus, Deafness

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Introduction

Wolfram syndrome (WFS), also known as DODMOAD, is a rare hereditary neurodegenerative disease. Wolfram in 1938 was first to suggest that diabetes mellitus and optic atrophy might be associated as part of the syndrome^[1]. The acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness) was coined for the most common complications. Many patients also develop urological, neurological and psychiatric illness as part of a progressive neurodegenerative disorder. The pathogenesis of the disease is still unknown. One candidate gene mapped to chromosome 4p and a role of mitochondrial DNA in the pathogenesis of this syndrome has been suggested as evidence for genetic heterogeneity^[2].

Since the first description of this syndrome, there have been about 300 case reports in literature^[3-10]. Our study includes 16 patients affected with WFS derived from both consanguineous and non consanguineous marriages. By investigating the different aspect of clinical manifestation and laboratory examination of these patients, we aimed to provide more information on the disease that may lead to a better elucidation of the pathophysiology and also improvement in the treatment of this devastating disease.

Material & Methods

All insulin dependent diabetic patients presented to our center (inpatient/outpatient) over a period of 10 years, who had optic atrophy or a positive family history of WFS, were enrolled in the study. Criteria for the diagnosis of WFS were the presence of insulin dependent diabetes mellitus along with optic atrophy unexplained by any other disease and/or some other abnormalities unassociated with WFS. For example thiamine responsive anemia with diabetes mellitus and deafness and also Leber hereditary optic atrophy were eliminated.

Thyroid function tests, anti-thyroid peroxidase (ATPO), anti thyroglobulin (ATG)

and islet cell antibodies were measured to evaluate the autoimmunity in this syndrome. C-peptide level (both basal and stimulated) was also measured. Diabetic nephropathy was also assessed by 24 hour microalbuminuria and plasma creatinine in patients who had diabetes mellitus for more than 5 years. Complete blood count (CBC) and RBC indices were measured and in case of anemia a thorough investigation for elucidating the etiology was performed. Patients' height and weight percentiles were measured to evaluate their growth pattern. For every patients included in the study whose basal urine osmolalities were less than 600 mosm kg⁻¹ and specific gravity less than 1.010, we performed a water deprivation test followed by arginine vasopressin administration to diagnose central diabetes insipidus. Blood samples were taken for DNA extraction from all patients as well as their parents and siblings. Although the intention was to study the WFS1 and mitochondrial mutation, unfortunately this was not possible. Our study was approved by the ethical committee of the University and written informed consent of each patient or parent was taken.

Findings

The 16 patients, 9 males and 7 females, belonged to ten families. In seven families only one child was affected with WFS. The other three families had two, three, and four affected siblings in each family. Nine patients (more than half) came from consanguineous marriages. Parental consanguinity was the first degree (parents being cousins) (Table 1). The median age of the patients was 13.4 yrs (range 5.5-22yrs). The sex ratio (male/female) was 1.28. The associated manifestations of WFS are shown with the age of presentation and prevalence comparing to several other studies in table 2.

Diabetes mellitus presented with polyuria and polydipsia or it was diagnosed while family members of the index patient with WFS were screened for the syndrome. The anti-thyroid peroxidase (ATPO), anti thyroglobulin (ATG) and islet cell antibodies were undetect-

Table 1: Demographic characteristics of our patients with WFS

Family No	Patient No	sex	Age at presentation (y)	Consanguinity of parents
1	1	Male	12	No
2	2	Male	9	No
3	3	Male	11	No
4	4	Male	11	No
5	5	Male	20	No
6	6	Female	14	No
7	7	Male	10	No
8	8	Female	11	Yes
	9	Female	13	
	10	Male	5.5	
9	11	Female	8	Yes
	12	Female	18	
	13	Female	19	
10	14	Female	12	Yes
	15	Male	19	
	16	Male	22	

able in all patients. All patients were insulin deficient. Both basal and stimulated C-peptide level was lower than normal ranges. Only two cases were ketoacidotic. One of them died in an attack of diabetic ketoacidosis. The mean of total daily insulin requirement including crystal and NPH insulin was 1.02 unit/kg (range 0.6 to 1.4 unit/kg). Creatinine clearance was in the normal range in all patients. Diabetic nephropathy (e.g. microalbuminuria) was not

observed in any of the patients. Even at older ages, 17 years after the onset of diabetes mellitus, renal complications due to diabetes mellitus were not noticeable.

The diagnosis of diabetes insipidus was confirmed by water deprivation test in 8 patients (50%). All of them were responsive to intranasal anti-diuretic hormone (ADH) treatment. In one family with three cases of WFS (F/12yr, M/19yr, M/22yr), none of the

Table 2: Associated manifestations of WFS with the age of presentation and prevalence comparing to other studies

Study	Complication	Diabetes mellitus	Optic atrophy	Diabetes insipidus	deafness
our study (n=16)	Age* (year)	5.4 (2-8)	9.2 (5-14)	8.5 (5-16)	9.8(3-16)
	Prevalence (%)	100	100	50	75
Barret et al (n=45)	Age* (year)	6 (0.6-16)	11 (0.12-19)	14 (3-40)	16 (5-39)
	Prevalence (%)	100	100	73	62
Sims et al (n=9)	Age* (year)	6.9 (3-9)	8.9 (8-13)	10.2 (7-18)	10.5 (7-15)
	Prevalence (%)	100	100	78	55
Medlej et al (n=31)	Age* (year)	6 (4-12)	9(5-20)	9 (4-26)	16 (7-24)
	Prevalence (%)	100	100	87	64

*Mean age (range)

affected children had DI, despite the presence of all other components of WFS and severe urological involvement.

The weight of 5 patients (31%) was below the fifth percentile for the age and gender. Only one patient had a weight above the 50th percentile. Despite multiorgan involvement, and even years after onset of diabetes mellitus in some patients, weight patterns on growth charts were not influenced. However, the height of 13 patients (81%) was below the 5th percentile for the age and gender. All 3 patients whose height and growth rates were above the 5th percentile were females aged 12 years or younger, their syndrome was recently diagnosed and had only diabetes mellitus.

Discussion

The Wolfram syndrome (WFS) is a rare dysmorphogenetic disease, which affects 1 in every 500,000 young people^[7]. This incidence seems to be greater in consanguineous parents, as in our case series. We cannot estimate the prevalence of WFS in our population. However, it seems that WFS is much more prevalent in our population because of the high prevalence of consanguineous marriages over many generations in our country. The pathogenesis of the disease is still not well known, particularly concerning the causes of the main neurodegenerative anomalies which characterize the clinical feature. Genetic inheritance was not studied in these 16 patients. However, genetic studies by several groups of researchers have provided evidence of genetic heterogeneity^[9,11,12]. Linkage of WFS to markers on chromosome 4p has been reported during the last decade^[2]. However, some experts believe that among the etiologic factors, a mitochondrial alteration as for some dysmorphogenetic anomalies (optic atrophy, deafness and diabetes mellitus) of WFS can not be excluded^[13,14,15]. The wide spectrum of clinical expression, affecting several organs and tissues, suggests the involvement of mitochondrial DNA.

It is possible that mitochondrial function is disrupted because of mutations in a nuclear

gene or that mutation in a nuclear gene deleteriously interact with mitochondrial gene^[16]. Defects in mtDNA have been detected in some studies but were absent in others^[17,18]. More recently a candidate gene (WFS1) was mapped to 4p16.1 and isolated^[19]. In addition, mutations in this gene have been identified in patients affected with WFS^[20-24]. WFS1 encodes a transmembrane protein suggested to play a role in the survival of certain populations of cells, particularly neuronal and endocrine cells^[20,25]. Patients with a second locus WFS2 mapped to chromosome 4q22-q24 did not have diabetes insipidus, but had ulcer in upper gastrointestinal tract and bleeding^[9].

The minimum ascertainment criteria to diagnose WFS are childhood onset (under 15 years of age) diabetes mellitus and progressive optic atrophy, but the presence of these anomalies is not certainly sufficient. These give a positive predictive value for WFS of 83% and negative predictive value of 1%^[7].

The first and the most prominent presenting problem in our patients was diabetes mellitus. Most of them presented with polyuria, polydipsia, and a positive family history of diabetes mellitus, with a minority being diagnosed with diabetic ketoacidosis (DKA). The median age at diagnosis of diabetes mellitus was the second half of the first decade. All of our patients developed diabetes mellitus earlier than the age of 8 years old, showing the early-onset nature of diabetes in this syndrome.

IDDM found as part of WFS differs from classical IDDM in several ways. The component of diabetes mellitus in WFS is non-autoimmune, not prone to either ketosis or diabetic retinopathy and non-HLA linked. Some experts suggested a relation between WFS and HLA-DR2 which are negatively associated in classical IDDM^[4,5,16,26,27]. Postmortem studies have shown a selective loss of beta cells^[28].

Many relatives of Wolfram patients have diabetes mellitus, suggesting that obligate carriers may contribute to the genetic heterogeneity of diabetes in general population^[2].

Of significant importance is that the common diabetic complications of prolifera-

tive retinopathy, glomerulosclerosis and neuropathy are remarkably absent in patients with WFS as compared to people with other forms of juvenile-onset diabetes mellitus. Although there are results in contrast to what was previously reported by some authors concerning the lack of diabetic microvascular complications in WFS, our study supports a lack of such complications in WFS^[7, 29-31].

There is no evidence that tight blood sugar level control slows or alters the progression of wolfram syndrome manifestations.

The association of autoimmune diseases with diabetes mellitus was always negative in all patients showing that diabetes mellitus in Wolfram syndrome is not the result of an autoimmune process, but part of a neurodegenerative disease with incomplete involvement of the pancreas.

DI in WFS is of central type or ADH-responsive. Nephrogenous DI, secondary to urological pathology, maybe a contributory factor to central DI. The persistence of polyuria and polydipsia maybe erroneously attributed to poor control of the DM rather than the presence of DI. A water deprivation test should be applied in all patients with diabetes mellitus who have polyuria and polydipsia even with normal glycemic control. Histopathological and clinical studies demonstrated that this complication is due to atrophy and gliosis of all the supraoptic and paraventricular neurohypophyseal system^[32].

Defective growth hormone secretion is the most frequent alteration documented in a study^[18]. Growth retardation due to GH deficiency is thought to be a result of progressive and atrophic changes in the hypothalamo-hypophyseal regions^[10].

Furthermore diabetes mellitus, diabetes insipidus, hypogonadism and urological abnormalities may be contributory factors to growth retardation. Hypogonadotropic hypogonadism and primary hypogonadism have been frequently found in association with WFS^[7, 26, 33, 34].

Although we have not the opportunity to evaluate the hypothalamo-hypophyseal axis in our patients, the exaggerated prolactin

response to TRH, growth hormone deficiency, temperature dysregulation and corticotropin deficiency reported in literature indicate the neurodegenerative nature of WFS^[18].

Conclusion

Our patients group is one of the greatest in the literature concerning the WFS. It provides more patients for adding to the family of WFS that may lead to a better elucidation of the pathophysiology and clinical manifestation of this syndrome regarding its endocrinological features and hopefully to improvement in means of prevention and treatment of this debilitating disease. Early diagnosis and proper treatment, aimed at relieving the symptoms and preventing the future complications is of paramount value and importance. It is advisable to further evaluate for Wolfram syndrome in all children with diabetes mellitus, especially in those families with more than one child suffering from the disease.

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