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MINI REVIEW

Endocrine and metabolic aspects of the Wolfram syndrome

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Abstract Wolfram syndrome (WS), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness), is a neurodegenerative disease with autosomal recessive inheritance with incomplete penetrance. DIDMOAD is a very rare disease with an estimated prevalence of 1 in 770,000 and it is believed to occur in 1 of 150 patients with juvenile-onset insulin-dependent diabetes mellitus. Additionally, WS may also present with different endocrine and metabolic abnormalities such as anterior and posterior pituitary gland dysfunction. This mini-review summarizes the variable presentation of WS and the need of screening for other metabolic and hormonal abnormalities, coexisting in this rare syndrome.

Keywords Diabetes mellitus · Diabetes insipidus · Amenorrhea

Introduction

Wolfram syndrome (WS), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness), is an infrequent cause of diabetes mellitus. WS derives its name from the physician who first reported the combination of juvenile-onset diabetes mellitus (DM) and optic atrophy (OA) in four siblings. DIDMOAD syndrome was coined with the report of two remaining components of the syndrome: diabetes insipidus (DI) and deafness. WS is a neurodegenerative disease with autosomal recessive inheritance with incomplete penetrance. It is characterized by various clinical manifestations including renal tract abnormalities, gonadal disorders, psychiatric disorders and neurological manifestations, as well as the aforementioned DIDMOAD.

DIDMOAD is a very rare disease with an estimated prevalence of 1 in 770,000, and a carrier frequency of 1 in 3,542 subjects, and it is believed to occur in 1 of 150 patients with juvenile-onset insulin-dependent DM. Juvenile onset DM and OA constitute the main diagnostic criteria for WS, the differential diagnosis of which includes other causes of neurodegeneration. The pathogenesis of the disease still remains unknown. However, recent data indicate a role for the WFS1 gene, mapped to chromosome 4p encoding an endoplasmic reticulum (ER) membrane-embedded protein called wolframin. Wolframin is a hydrophobic and tetrameric protein with nine transmembrane segments and large hydrophilic regions at both termini. Wolframin is expressed in the pancreas, brain, spinal cord, heart, and muscle, and to a lesser degree in the liver and kidneys. In the pancreas, the protein is expressed mainly in β-cells and is absent in the exocrine glands [1, 2]. ER localization suggests that WFS1 protein has physiological functions in membrane trafficking, secretion, processing, and/or regulation of ER calcium homeostasis. A recent study has demonstrated that wolframin is a calmodulin (CaM)-binding protein. It has been shown that CaM targets many cellular proteins to provide a wide range of Ca^{2+} signal transduction [3].

Diabetes mellitus, an invariable finding, is usually the first manifestation to occur and is usually insulin-requiring. The cause of diabetes is insulinopenia secondary to degeneration of β-cells, whereas the autoantibodies usually observed in patients with type 1 diabetes (IA2, anti-GAD, etc.) are absent

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in nearly all patients reported. In addition, gonadal disorders are frequently observed in male patients and rarely in women mostly as mild to moderate menstrual disturbances.

Psychiatric manifestations are particularly diverse, and an increased predisposition for psychiatric disorders has been proposed for heterozygous carriers [4]. Heterozygote carriers of WFS1 gene mutations are proposed to be at increased risk of psychiatric disease on the basis of increased incidence of self-reported episodes or hospitalizations for psychiatric disease [4, 5]. Despite the fact that a few subsequent studies have found an increased incidence of WFS1 gene polymorphisms among patients with psychiatric disorders and suicidality [6, 7], most have found no significant difference compared with controls [8–13].

Morbidity and mortality in WS are high and quality of life is impaired due to neurological and urological complications.

Genetic background

Wolfram syndrome is a very rare disease with an estimated prevalence of 1 in 770,000. The carrier frequency, as previously described, is 1 in 3,542 individuals and its prevalence in children was found to be 1 in 500,000. However, the prevalence varies worldwide with the highest one (1/68,000) reported in Lebanon, probably due to higher rates of consanguinity prevalent in that region [14].

Genetic studies have shown that WS has an autosomal recessive inheritance with incomplete penetrance. Further studies have reported a Wolfram-like phenotype segregated in an autosomal dominant (AD) pattern [15].

According to Strom et al., loss of function mutations on both alleles was demonstrated in 42% of studied families with WS (5 of 12). In the same study, one family with the syndrome was only found to have a heterozygous stop mutation. According to the authors, non-allelic heterogeneity provides an alternative explanation for the clinical manifestations in this particular family [16, 17].

Furthermore, the study of El-Shanti et al. has identified a potential second locus, designed WFS2, which mapped to chromosome 4q22-24 following linkage analysis of three large, consanguineous Jordanian families, containing 16 patients with WS. These patients had additional features to those previously described in WS, such as profound upper gastrointestinal ulceration and bleeding, and absence of diabetes insipidus in all affected family members [18].

Endocrine and other aspects

Diabetes insipidus (DI) is most commonly central, with a prevalence varying between 51 and 87% depending on the study [14, 19, 20]. DI becomes apparent more frequently in the second decade of life [19]. Neuroradiological and postmortem reports in many patients have shown an absence of the normal T1 hyperintensity seen in the posterior pituitary lobe along with gliosis and atrophy of the paraventricular and supraoptic nuclei of the hypothalamus [21–23]. Furthermore, studies of vasopressin secretion in response to stimuli [24] and postmortem studies show accumulation of vasopressin precursors in the paraventricular nuclei [25]. These studies have demonstrated the functional defects in addition to the loss of nuclei. In patients with WS, diabetes insipidus usually develops later (after the appearance of diabetes mellitus), the duration of which is unclear. This highlights the need for surveillance for DI in all subjects with WS regardless of age.

Both primary and secondary hypogonadism have been reported frequently in male patients [14, 19, 26–30]. The reason for the male predominance has not been clearly elucidated. In females, according to earlier studies, ovarian function is normal with only abnormalities in menstruation reported [14, 31]. Therefore, patients with WS who appeared with hypogonadism, menstrual abnormalities, or infertility, at any age, should be investigated.

Medlej et al. reported pituitary hypofunction of probable hypothalamic origin in 15 of 20 patients screened [14]. Deficient growth hormone (GH) secretion was the most common abnormality (9 of 20 patients) followed by deficient corticotrophin secretion (4 of 20 patients) [14]. Patients with WS therefore need to be monitored for growth retardation, which would presumably respond to GH administration. With respect to deficient corticotrophin secretion, the findings of Medlej et al. corroborate with those reported by Marquadt and Loriaux [32]. Thus, the requirement for steroid supplementation in these patients during periods of stress such as severe infection needs to be considered.

WFS1 gene mutations have also been implicated in sporadic progressive autosomal-dominant, low-frequency sensorineural hearing loss (LFSNHL). Mutations in LFSNHL are heterozygous missense mutations that affect only one amino acid and are non-inactivating [33]. This is different from the high-frequency hearing loss seen in patients with WS [34]. Additionally, Einberg et al. have reported a Danish family with AD optic atrophy associated with hearing impairment and impaired glucose tolerance in advanced age, caused by a missense mutation in the WFS 1 gene [15].

Metabolic aspects

Wolfram syndrome constitutes an infrequent cause of diabetes mellitus and its reported prevalence in patients with type 1 DM, varies worldwide from 0.5 to 4.8%. In general, WS is believed to occur in 1 of 150 patients with

juvenile-onset insulin-dependent diabetes mellitus. DM in DIDMOAD is typically of early onset, with an absence of obesity and a low prevalence of ketoacidosis. DM development has been attributed to impaired homeostasis of β-cells, especially increased apoptosis or failure of regenerative processes. In addition, studies have shown that wolframin may help fold a protein precursor of insulin (proinsulin) into the mature hormone that controls blood glucose levels [35].

Although non-autoimmune β-cell destruction is documented in patients with WS, the presence of antibodies is an unusual finding [36]. Nakamura et al. reported a rare case of a Japanese man with WS with positive diabetes-related antibodies, who was found to have a novel mutation of the WFS1 gene. It seems that in the studied subject, two distinct pathophysiological mechanisms leading to DM may be implicated. First, the impaired homeostasis of β-cells due to mutations in the WFS 1 gene which lead to increased apoptosis and/or failure of regenerative processes, and second, autoimmune destruction of β-cells, confirmed by the presence of anti-GAD (glutamic acid decarboxylase antibodies), a finding which differs with studies of human leucocyte antigen (HLA) subtypes among WS patients. They have demonstrated an increased prevalence of HLA DR2, a finding which is different to that observed in type 1 DM [37].

Moreover, Cano et al., the French Wolfram Study Group, compared 26 patients with WS with 52 patients with type 1 DM matched for age at the onset of diabetes. They demonstrated a lower daily insulin requirement and lower glycated hemoglobin A1c (HbA1c) levels, despite a less intensive insulin regimen in patients with WS [38]. Also, studies of Kinsley et al. and Cano et al. have shown decreased prevalence of diabetic retinopathy, nephropathy, and other microvascular complications in patients with WS compared with type 1 DM. These findings were attributed to the persistence of residual pancreatic β-cell activity in these patients [20, 38].

Recommendations for endocrinologists

Wolframin is a transmembrane protein, as previously described, which exists in many organ systems. Due to its multisystem localization, WS may present with variable clinical presentations and multiple organ dysfunction.

Therefore, the clinician facing a case of WS should be aware of two factors:

(1) Before reaching the diagnosis of WS, the following diagnoses should be considered: congenital rubella syndrome, Leber's hereditary optic atrophy, thiamine responsive anemia with DM and deafness, Friedreich's ataxia, Refsum disease, Alstrom syndrome, Lawrence–Moon–Biedl syndrome, and Kearn–Sayre syndrome.

(2) Dynamic tests of pituitary gland should be included:

(a) Insulin tolerant test and LH-RH test (lutenising hormone releasing hormone test) to detect potential anterior pituitary lobe dysfunction.

(b) Posterior pituitary gland function by water deprivation test, at any age, even if the absence of polyuria.

Perspectives and conclusions

The majority of the WFS1 mutations is concentrated on exon 8 and is located in the C-terminal hydrophilic part of the protein [2, 16, 39]. No genotype–phenotype correlation has been identified in patients with WS. The function of WFS1 is unknown and it is difficult to assess or predict the effect of these mutations on protein function and hence their biological relevance. The knowledge of WFS1 gene mutations and protein function is important both for the recognition of treatable complications in Wolfram patients and for the possibility of genetic counseling for the patient and their family members.

In conclusion, this literature mini-review indicates the importance of screening patients suffering from WS for other metabolic and hormonal abnormalities. In particular, we highlight the importance of dynamic endocrine testing to exclude anterior and posterior pituitary gland dysfunction, at any age, post diagnosis of the syndrome.

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