Wolfram Syndrome 1

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Wolfram syndrome 1 (WS1) is a rare neurodegenerative disease transmitted in an autosomal recessive mode. It is characterized by diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and sensorineural hearing loss (D) (DIDMOAD). The clinical picture may be complicated by other symptoms, such as urinary tract, endocrinological, psychiatric, and neurological abnormalities. WS1 is caused by mutations in the *WFS1* gene located on chromosome 4p16 that encodes a transmembrane protein named wolframin. Many studies have shown that wolframin regulates some mechanisms of ER calcium homeostasis and therefore plays a role in cellular apoptosis.

Keywords: Physiology ; Epidemiology ; Wolfram syndrome 1 ; Genetics ; neurophysiopatology

1. Introduction

Wolfram syndrome 1 (WS1; MIM 222300) is a rare autosomal recessive neurodegenerative disease first described in 1938 by Wolfram and Wagener [1]. The main clinical features are diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and deafness (D), hence the acronym DIDMOAD. However, WS1 is frequently complicated by other symptoms, such as urinary tract, endocrinological, psychiatric, and neurological abnormalities [2][3]. Early-onset non-autoimmune insulin-dependent DM and bilateral OA are key clinical criteria for the diagnosis of WS1 [1]. WS1 is a rare type of DM and has been included in subcategory 5A16.1 of the International Classification of Disease (ICD-11) [4]. Prognosis is poor, as the clinical course of WS1 is rapidly progressive and leads to a premature death of patients at the mean age of 30 years (25–49 years). The main cause of death is respiratory failure due to brainstem atrophy [5][6]. There are currently no therapies for WS1. However, careful clinical follow-up and supportive care can be helpful for relieving severe and progressive symptoms of WS1.

2. Epidemiology of WS1

WS1 is a very rare neurodegenerative disease. Epidemiological studies showed a prevalence of 1 in 770,000 [5] and 1 in 500,000 in children [7] in the UK; 1 in 100,000 in North America [8]; 1 out of 710,000 in the Japanese population [9]; and 0.74 out of 1,000,000 in the Italian population [10]. The highest prevalence of WS1 is of 1 in 68,000 in the Lebanese population [11] and of 1 in 54,478 in a population from a small area of Sicily (Italy) [12], probably due to the high rates of consanguinity in these populations [11][12]. The frequency of the WS1 carriers is not well known. However, a study in the UK population showed that WS1 carrier frequency was 1/354 [5].

WS1 is frequently not recognized early, as insulin-dependent non-autoimmune DM is the first clinical manifestation. It has been found that the prevalence of WS1 in patients with DM ranges from 0.57% in the UK [5] to 4.8% in the Lebanese population [11]. Zmyslowska et al. found that in pediatric insulin-dependent DM populations, WS1 was diagnosed with a delay of at least 7 years as WS1 patients were initially misdiagnosed as having type 1 DM [13]. Moreover, Lombardo et al. found that WS1 had a prevalence of 1 in 22.3 in Sicilian (Italy) patients with juvenile-onset, insulin-dependent DM aged <30 years [12].

3. Genetics of Wolfram Syndromes

The human WS1 gene (WFS1) was identified in 1998 [14][15]. It is located on chromosome 4p16, consists of eight exons, and encodes wolframin, a transmembrane glycoprotein of 890 amino acids (aa) in the endoplasmic reticulum (ER). Wolframin consists of nine transmembrane segments and a large hydrophilic region at both ends [16]. *WFS1* is highly expressed in brain tissue, pancreatic β-cells, heart, lung, and placenta [17]. Thus far, over 200 mutations have been found in the *WFS1* gene, and most of them are in exon 8 (https://www.ncbi.nlm.nih.gov/clinvar/, accessed on 10 February 2022) [18]. The region of exon 8 encodes the transmembrane and C-terminal domain of wolframin, which is important for the functionality of this protein [14][19]. *WFS1* mutations are frequently inactivating (nonsense or frameshift) [18], and most of

them are transmitted in an autosomal recessive mode. However, autosomal dominant mutations have been found in WS-like diseases, such as *WFS1*-related non-syndromic low-frequency sensorineural hearing loss (LFSNHL) [20][21]. Specifically, *WFS1* mutations have been also implicated in non-syndromic hearing loss DFNA6/14/38 [22]. The great number of *WFS1* mutations, the complexity of the clinical picture of WS1, and the small number of patients (30–60 patients) do not allow a genotype-phenotype correlation [18]. De Heredia et al. analyzed both genetical and clinical data from 412 WS1 patients published since 1998 and found 178 mutations in *WFS1* [23]. The mutations were classified according to their effect on *WFS1* expression, and it was suggested that patients with mutations causing absent wolframin production were more likely to have earlier onset diabetes mellitus, and perhaps earlier onset of optic atrophy, than patients with residual wolframin expression. Rigoli et al. studied 44 WS1 patients of Italian ethnicity and 1 Arab male (Morocco). Mutations were subdivided into three groups according to predicted functional consequences, as the high genetic heterogeneity of *WFS1* complicated genotype-phenotype correlations [10]. WS1 patients with nonsense mutations and frameshift and/or multiple amino acid insertion/deletions in both alleles resulting in absence of wolframin were included in group 1. Group 2 consisted of WS1 patients with missense mutations and/or single amino acid insertions in both alleles. Most of *WFS1* variants included in group 2 result in milder degradation of wolframin than those in group 1. Compound heterozygous WS1 patients with mutations not found in groups 1 and 2 were included in group 3. It was found that the age of onset of DM, D, and DI but not of OA differed between the three groups. Furthermore, the survival time of patients in group 1 tended to be shorter than that of patients in the other groups. The type of clinical manifestations of the WS1 patients was not different among the 3 groups. The results of the study in Italian patients suggest that there may be a genotype-phenotype correlation in WS1. The genetic and clinical study of a larger number of WS1 patients could elucidate the pathogenetic mechanisms of WS1 [10].

A second rare and neurodegenerative type of WS has been described, namely WS2, which is transmitted in an autosomal recessive mode. WS2 is caused by mutations in CDGSH iron-sulfur domain-containing protein 2 (*CISD2*) gene, which maps to chromosome 4q22-q23 and consists of three exons [24]. *CISD2* encodes the zinc-finger protein named “small intermembrane endoplasmic reticulum protein” (ERIS), which is highly expressed in tissues such as pancreas and brain [25]. Although the function of ERIS is not fully known, it has been found that it transfers iron to the mitochondria and thus is important for the regulation of iron and reactive oxygen species (ROS). Furthermore, ERIS plays a central role in the regulation of mitochondrial homeostasis and exchanges between ER and mitochondria and in the activation of autophagy and apoptosis [26]. The clinical features that characterize WS2 are still not completely established, as there are few affected subjects. The main symptoms of WS2 are ulcers of the upper intestine, mucocutaneous bleeding, and defective platelet aggregation, which are pathognomonic of WS2 and which are absent in WS1 [27][28]. They have been found in over 90% of patients affected by WS2. Therefore, they are useful clinical criteria for a differential diagnosis with WS1. Juvenile onset DM, variable degrees of OA, high-frequency sensorineural hearing impairment, DI, neurological and psychiatric abnormalities, endocrine disorders, and impaired renal function have also been reported. OA is progressive and is associated with loss of ganglion cells, but it is milder and less progressive than that of WS1. It has been suggested that optic nerve involvement is consistent with a diagnosis of optic neuropathy and not of optic atrophy [28].

4. Physiology and Pathophysiology of WS1

Wolframin is in the endoplasmic reticulum (ER) membrane, which plays a key role in the ability of cells to properly fold and post-translate secretory and the ER transmembrane proteins [29][30][31]. Mutations in *WFS1* cause an accumulation of misfolded proteins in the ER and therefore ER stress. High levels of misfolded proteins stimulate the unfolded protein response (UPR), which induces transcriptional and translational events that restore ER homeostasis. When ER stress is chronically persistent due to physiological processes (biosynthesis post-prandial of insulin) or to pathological processes (cancer, inflammatory diseases, viral infection, gene mutations), the UPR stimulates cell apoptosis. [17][29][31][32][33]. For this reason, high levels of ER stress found in WS1 cause apoptosis of pancreatic cells and alterations of neuronal cells [33].

UPR activates three transmembrane proteins located in the ER that function as sensors of stress: inositol-requiring protein 1 (IRE1), protein kinase RNA (PKR) -like ER kinase (PERK), and activating transcription factor 6 (ATF6). These transducers play a key role in survival adaptation and cell death processes. Moreover, some studies have found that, under physiological conditions, ER chaperones, such as immunoglobulin binding protein (BIP), maintain their luminal domains in a state of inactivity. BIP is released to facilitate the folding of accumulated proteins when high levels of UPR occur in ER [34][35][36].

Under conditions of physiological stress, IRE1 oligomerization and autophosphorylation occurs [37]. Subsequently, the RNase domain of IRE1 induces a splice of the X-binding protein 1 (XBP-1) mRNA because of which a transcriptionally active mRNA (sXBP-1) is formed. sXBP-1 is activated to XBP-1, a transcription factor. After translocation to the nucleus,

XBP-1 upregulates some UPR target genes to re-establish protein homeostasis and activate cellular protection. Under pathological conditions, hyperactivation of IRE1 with consequent apoptosis is found. Moreover, IRE1 affects the biosynthesis of insulin: in hyperglycemia, it induces β cell homeostasis and thus an improvement in pro-insulin biosynthesis [38].

The transmembrane PERK protein is also involved in intricate mechanism of ER stress. Indeed, it activates the phosphorylation of eIF2alfa, a eukaryotic initiation translation factor 2alfa. The role of eIF2alfa is to decrease ER biosynthetic activity and to enhance the translation of both ATF4 transcription factor and apoptosis-antagonizing transcription factor (AATF) mRNAs. ATF4 activates genes involved in amino acid transport and metabolism, glutathione biosynthesis, and antioxidant responses. Moreover, ATF4- ATF3-CHOP axis promotes apoptosis. Thus, under conditions of pathological ER stress, apoptosis is induced by the continuous activation of these factors. On the other hand, AATF promotes the survival of cells [39].

ATF6 is the third important regulator of the UPR response. BIP dissociation, induced by ER stress, promotes translocation of ATF6 to the Golgi apparatus. Here, the cleavage of ATF6 occurs by means of some proteases with subsequent formation of a cytosolic active transcription factor. Upon activation, ATF6 translocates to the nucleus where it improves protein folding, processing, and degradation activity by upregulating ER transcriptional homeostatic factors. A regulatory role of ATF6 in lipid biosynthesis has also been described [40][41][42].

The intricate pathway of UPR is negatively regulated by *WFS1*. Under physiological ER stress, *WFS1* negatively regulates ATF6, reduces the activation of the ER stress response element of the ER (ERSE) promoted by ATF6, and induces the stabilization of E3 ubiquitin ligase HRD1 (HMG-CoA reductase degradation protein) and thus the suppression of stress signals. [17]. Conversely, in WS1, the hyperactivation of ATF6 promotes both the expression of genes involved in apoptosis, such as CHOP, ATF4, BIP, and sXBP1, and the reduced gene expression of insulin. Moreover, wolframin regulates the calcium release and absorption mechanisms in the ER. It is a calmodulin (CaM) with several functions, including the interaction with many cellular proteins and the regulation of the Ca2 + signal transduction processes involved in apoptosis [43]. High levels of ER stress have been shown to cause alterations in mitochondrial function, thus suggesting that WS1 could be a mitochondrial disease [44]. Recently, a link between ER stress, increased cytosolic Ca2+levels, impairment of mitochondrial dynamics, and inhibition of neuronal development in *WFS1*-deficient neurons has been described [45][46]. In healthy cells, *WFS1* is linked to neuronal calcium sensor 1 (NCS1) and inositol 1,4,5-trisphosphate receptor (IP3R) to induce transfer of Ca2+ between ER and mitochondria. In *WFS1*-deficient cells, a severe decrease of NCS1 levels was found, which causes a reduction of ER-mitochondria interactions and transfer of Ca2+ [47]. Therefore, there is a strong causal link between ER stress, alterations in cytosolic levels of Ca 2+ and in mitochondrial dynamics, and developmental delay in *WFS1*-deficient neuronal cells [45]. In this intricate pathogenic mechanism, the alterations of mitochondria-associated ER membranes (MAMs) play an important role [48][49]. MAMs are dynamic domains of interaction between mitochondria and ER in which several proteins involved in UPR are located. The role of these proteins is to stabilize the structure of MAMs and to facilitate the functional dialogue between ER and mitochondria. Indeed, MAMs facilitate the transfer of Ca2 + between ER and mitochondria mainly through IP3R [46][49]. According to these observations, Cagalinec et al. suggested that a “mitochondrial phenotype” in WS1 patients could be due to severe alterations of mitochondrial dynamics caused by even mild ER stress [46]. Zmyslowska et al. studied a human WS cell model in which skin fibroblasts reprogrammed into induced pluripotent stem cells (iPS) and then into neural stem cells (NSCs) were subjected to induced ER stress. The analysis of the proteins involved in mitochondrial function showed a down-regulation of the subunits of the respiratory chain complexes, an upregulation of the proteins involved in the Krebs cycle, and mechanisms of glycolysis in WS NSC cells. These alterations were not found in the control cells. These data have shown that severe mitochondrial damage resulting in functional and morphological alterations of mitochondria plays a key role in the pathogenesis of WS1 [50].

Finally, *WFS1* was found to regulate the function of the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), an important protein implicated in β-cell ER calcium homeostasis [51][52].

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