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Review Article

Diabetes mellitus, and neuropsychiatric features in Wolfram Syndrome 1

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Abstract

Wolfram syndrome 1, an autosomal recessive and neurodegenerative disorder, is characterized by diabetes insipidus, diabetes mellitus, optic atrophy, deafness, and other disorders such as neuropsychiatric issues, abnormalities in the urinary tract and endocrinological alterations. The clinical course of WS1 is fast-progressing, with patients who die at a mean age of 30 years. Respiratory failure is the most prevalent cause of death due to brainstem atrophy. Approximately 90% of WS1 cases are caused by mutations in the WFS1 gene, which codes for wolframin, a transmembrane glycoprotein. Here, we will focus on two clinical features of WS1: diabetes mellitus, and neuropsychiatric disorders. Diabetes mellitus in WS1 is insulin-dependent, non-auto-immune, and has clinical features that differ from the most common diabetes mellitus. Neurological disorders in WS1 patients include brain atrophy, the absence of a posterior pituitary signal, and reduced synaptic connections. Approximately 50% of WS1 patients manifest psychiatric symptoms during early adulthood including severe depression, psychosis, sleep abnormalities, verbal impulsivity, and physical aggression. The etiology of these symptoms remains unclear, and typically makes WS1 more difficult to treat. This study will also include an update on recent findings on the role of WFS1 mutations in the pathogenesis of neuropsychiatric disorders in patients affected by Wolfram syndrome.

Introduction

In 1938, Wolfram and Wagener (1) first defined Wolfram syndrome 1, an autosomal recessive and neurodegenerative disorder (WS1; MIM 222300). WS1 is characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DI DM OA D). The International Classification of Diseases (ICD-11) has subclassified WS1 as an uncommon type of diabetes (2). Additionally, neuromuscular pathology with biochemical abnormalities in muscles, as well as central neurodegenerative changes, has been documented (3,4). A wide range of neurological and psychiatric symptoms, such as brainstem and cerebellar atrophy, cognitive impairment, seizures, anxiety, and depression, has been found in WS1 patients (5,6,7,8). Other symptoms, such as anomalies in the urinary system and endocrinological alterations, typically make WS1 more difficult to treat (9). Given the high incidence of renal abnormalities in WS1, the acronym DIDMOADUD has been proposed (10). As WS1 is characterized by many clinical features, (1), it has been suggested that WS1 can be diagnosed in the following cases: (1) coexistence of the two major criteria (DM + OA); (2) one main criterion together with two minor criteria; and (3) two of any of the DIDMOAD manifestations (10). The clinical course of WS1 is fast progressing, and patients die early at a mean age of 30 years (25-49 years), making the prognosis poor. Respiratory failure is the most prevalent cause of death as a result of brainstem atrophy (5). WS1 is a painful illness for patients and their families. Thus, early diagnosis is essential for enabling accurate prognostication, avoiding complications, and reducing the transmission to further progeny.

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Although there is no therapy for this devastating disease at present, intriguing new medications have been developed to slow its progression (9).

In this review, we will describe the main characteristics of the WFS1 gene, and we will focus on the diabetes mellitus as well as on the neuropsychiatric features of Wolfram Syndrome 1.

Epidemiology of WS1

The prevalence of WS1 is extremely low, with rates of 1 in 770,000 (5) in adults and 1 in 500,000 (13) in children in the United Kingdom; 1 in 100,000 (14) in North America; 1 in 710,000 in the Japanese population (15); and 1 in 68,000 (16) in the Lebanese population. The highest frequency, 1 in 54,478, was found on a small Sicilian-populated area of Italy (17). Due to their high rates of consanguinity, the Lebanese and Sicilian populations may have a higher prevalence of WS1 (16,17). The carrier frequency in the United Kingdom was 1/354 (5).

The initial symptom of WS1 is non-autoimmune insulin-dependent DM. A study have been shown that WS1 patients can be misdiagnosed as patients with the more common insulin-dependent DM (18). Numerous studies have provided variable estimates on the prevalence of this syndrome among patients with DM, with estimates ranging from 0.57% in Lebanon to 4.8% in the United Kingdom. (9). In the study by Zmyslowska et al., it was found that the diagnosis of WS1 in pediatric patients with insulin-dependent DM was delayed by a minimum of 7 years. Furthermore, it was observed that almost all of WS1 patients were often misdiagnosed as having the most frequent insulin-dependent type 1 DM (18). Lombardo et al. described a Sicilian population (Italy) with juvenile-onset, insulin-dependent DM aged 30 years in which WS1 had a relative prevalence of 1 in 22.3. In WS1 patients with nonconsanguineous parents, the frequency was 1 in 51.2 (17).

Genetics of Wolfram syndromes

WS1 is an autosomal recessive disease that is caused by homozygous or compound heterozygous mutations in the WFS1 gene (19). It spans 33.4 kb, is located on the short arm of chromosome 4 (4p.16), and produces the transmembrane glycoprotein known as wolframin. WFS1 includes eight exons and can produce 15 distinct transcripts. Exon 1 is non-coding. Exons 2–7 are small coding exons, while exon 8 encodes most of the transmembrane region and the carboxy terminus of wolframin (19,20) (Figure 1). Many mutations in the WFS1, such as pathogenic, likely pathogenic, and uncertainly significant variants,

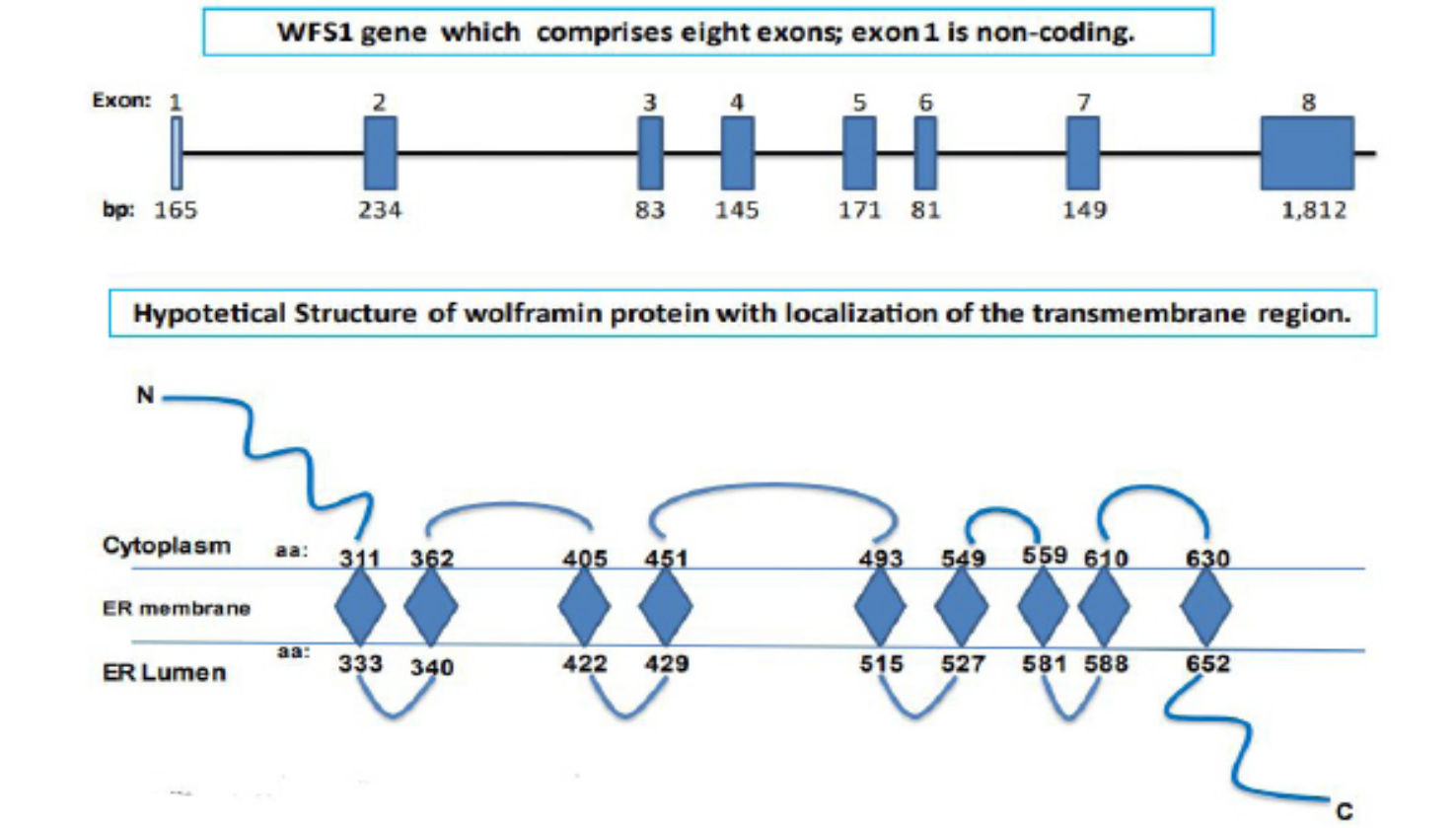

Figure 1: *WFS1 gene and wolframin sructures.*

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are localized in exon 8, which is the largest exon (20,21). There are just a few pathogenic or potentially pathogenic variants in the other regions of WFS1(9). The mutations are mostly inactivating (nonsense or frameshift) (9) and cause around 90% of WS1 cases. The large number of WFS1 mutations, the complexity of the WS1 clinical picture, and the limited number of patients (30–60 patients) do not allow a correlation between genotype and phenotype (22). It has been hypothesized that WS1 patients with mutations resulting in absent wolframin production were more likely to develop DM earlier than patients with mutations resulting in residual wolframin expression (11,22,23).

Some authors proposed to divide the WFS1 mutations according to their effect on the functionality of wolframin. In Group 1, there were WS1 patients with nonsense mutations, frameshifts, and/or a large number of insertions or deletions of amino acids in both alleles, indicating they lacked wolframin. Group 2 consisted of WS1 patients who had biallelic single amino acid insertions or missense mutations.Most WFS1 mutations in group 2 caused a slower degradation of wolframin compared to those observed in group 1. The WS1 patients assigned to group 3 were compound heterozygotes of WFS1 mutations that were not found in either group 1 or group 2 (22).

An Italian study on 45 WS1 patients showed that the onset ages of DM, D, and DI, but not of OA, varied between the three groups. Additionally, patients in group 1 often had shorter survival times than patients in the other groups. The findings on Italian patients indicate a possible relationship between the genotype and phenotype of WS1 and suggest that this genetic approach be applied to a larger number of patients (11).

The frequency of heterozygosity for WFS1 mutations was observed to vary between 0.31% and 1.0% (5). Furthermore, the heterozygous subjects had high risks of developing psychiatric disorders (23).

Low-frequency sensorineural hearing loss (DFNA6/14/38) (24), autosomal dominant optic atrophy with hearing impairments (25), and autosomal dominant DM (26) are additional WFS1-related diseases that have been reported. Furthermore, single nucleotide polymorphisms (SNPs) at the WFS1 locus may make some subjects more predisposed to type 2 DM (27).

A small percentage of cases of WS are caused by sequence variations in the CISD2 gene (also known as WFS2) or other unidentified genes (10). Wolfram syndrome 2 (WS2) is inherited in an autosomal recessive mode (19, 28), and it is characterized by bleeding upper intestine ulcers, abnormal platelet aggregation, diabetes insipidus, and psychiatric abnormalities. CISD2 is expressed in several tissues, including the brain and pancreas, and it is mapped to chromosome 4q22–q24 (29). It produces a small, 135 amino acid (aa) protein known as ERIS (endoplasmic reticulum intermembrane small protein), which is found in ER membranes connected to mitochondria. ERIS distributes dynamically between the ER and mitochondrial outer membrane (30). It plays a key role in the modulation of glucose homeostasis and insulin sensitivity (31), calcium homeostasis (29), and autophagy (32).

Although CISD2 does directly interact with wolframin, it has been suggested that WS1 and WS2 may represent a continuum of clinical symptoms because WFS1 and CISD2 reside in the same pathway (33).

WFS1 and WS1

WFS1 produces wolframin, a transmembrane glycoprotein that has 890 amino acids (aa) and is found in the endoplasmic reticulum (ER). Nine transmembrane segments characterize the structure of wolframin, which also has a large hydrophilic area at both ends (21). Heart, lung, placenta, pancreatic cells, and brain tissue all have significant levels of WFS1 expression (34). The wolframin transmembrane and C-terminal domain, which are crucial for this protein's functions, are encoded in the region of exon 8 (19,34). The expression of the human WFS1 protein is low throughout the fetal stage (14–16 weeks) and gradually rises over time until it reaches a plateau in maturity (35). Like how it starts in the dorsal striatum and amygdala during late embryonic development, mouse WFS1 mRNA expression in the forebrain also expands to other brain regions after birth (36). WFS1 mRNA expression is highly correlated with neuronal differentiation. Even at the earliest stage of clinical symptoms, reduced cerebral volume and specific abnormalities in the brainstem and cerebellum are associated with WS1 (37).

Wolframin is located in the ER and plays a key role in posttranslational modifications, folding, and assembly of newly produced proteins, such as insulin, calcium storage, redox regulation, steroid synthesis, and apoptosis (34,38,39,40).

Wolframin, ER stress and apoptosis

Mutations in WFS1 cause unfolded protein response (UPR) activation and an accumulation of misfolded proteins, a condition named “ER stress”. The UPR is a network of signaling pathways that reduce stress, produce proteins for survival, and restore ER equilibrium through transcriptional and translational events (38). In the ER, three transmembrane proteins that act as stress sensors are activated by UPR: inositol-requiring protein 1 (IRE1), protein kinase RNA (PKR)-like ER kinase (PERK), and

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activating transcription factor 6 (ATF6). These transducers are crucial in processes involving cell death and survival adaptability. Moreover, some studies have found that, under physiological conditions, ER chaperones, such as immunoglobulin-binding protein (BIP), are inactive. BIP is released to facilitate the folding of accumulated proteins when high levels of UPR occur in the ER (41,42,43).

Under conditions of chronically excessive stress such as physiological processes (biosynthesis post-prandial of insulin) or pathological processes (cancer, inflammatory diseases, viral infection, gene mutations), UPR is unable to reduce stress levels or restore homeostasis, resulting in an increased susceptibility to apoptosis (34,38,44). This mechanism has been implicated in the pathogenesis of WS1, in which the high levels of ER stress cause alterations of brain cells and pancreatic cells that undergo apoptosis (44).

The release and absorption of calcium in the ER also affect cellular death. The loss of WFS1 function causes a widespread disruption of intracellular Ca2+ homeostasis, which affects Ca2+ signaling both in the resting state and during stimulation, as shown by recent studies on beta cells, neurons, and patient-derived fibroblasts (45, 46,47). Wolframin is a calmodulin (CaM), that interacts with a wide range of cellular proteins and regulates several Ca2+ signal transduction processes. WFS1, thereby regulates the storage of cellular ER calcium levels and, as a result, cell apoptosis (44). Mutations in WFS1 disrupt the regulation of cytosolic Ca2+ homeostasis, which in turn alters the dynamics of mitochondria. Particularly, a wolframin deficit or absence induces a cascade of ER stress that alters the IP3R calcium channel. As a result, there is a disturbance in the cytosolic Ca2+ balance, which in turn affects mitochondrial dynamics (inhibited mitochondrial fusions, altered mitochondrial trafficking, and increased mitophagy) (47). Finally, low ATP levels caused by mitochondrial changes alter neuronal development. Some studies showed that the alterations of mitochondria-associated ER membranes (MAMs) play a significant role in this complex pathogenic mechanism (48). Several proteins implicated in UPR are found in MAMs, which are dynamic areas of interaction between mitochondria and the ER. These proteins stabilize MAM structure and facilitate functional communication between the ER and mitochondria. IP3R is the primary mechanism by which MAMs improve Ca2+ transport between the ER and mitochondria (48). Several studies have suggested that a “mitochondrial phenotype” in WS1 patients could be due to severe alterations of mitochondrial dynamics caused by even mild ER stress (47). 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 neural stem cells (NSC) (49). Thus, severe mitochondrial damage resulting in functional and morphological alterations of mitochondria may provide a rationale for explaining the clinical features of WS1. Therefore, a full understanding of this mechanism may lead to the identification of potential therapeutic targets for WS1 and neuropsychiatric diseases (49).

Wolframin and insulin-dependent and non-autoimmune diabetes mellitus

The first clinical manifestation of WS1 is almost always non-autoimmune and non-HLA-linked insulin-dependent DM, and it is often diagnosed in childhood at an average age of 6 years (range: 3 weeks to 16 years). This type of diabetes might easily be misdiagnosed as type 1 DM (T1DM) when it manifests early. Therefore, the diagnosis of WS1 can be delayed for several years (18). WS1 must be suspected when DM has extremely long periods of remission, is antibody-negative, and does not start with ketoacidosis. Moreover, insulin-dependent DM of WS1 differs from more frequent type 1 DM because of earlier identification, lower ketoacidosis prevalence, fewer positive autoantibodies, a longer remission duration, and a higher incidence of severe hypoglycemia. The crises of severe hypoglycemia are caused by a disruption in ER function, resulting in neurologic damage. It was found that microvascular complications, especially microvascular retinopathy, are less common than in type 1 DM, as hyperglycemia occurs when there is a high level of ER stress (50). Microvascular signs are infrequent and don't progress as rapidly as the more common insulin-dependent DM (51,52). Not much is known about the degree of metabolic control (based on HbA1c level) and insulin requirement compared with T1DM patients. WS1 is characterized by a persistence of insulin secretion that causes the progression of DM to complete insulin deficiency less quickly than common DM (52). Many patients require insulin therapy. WS1 nonautoimmune insulin-dependent DM has lower daily insulin requirements and mean HbA1c levels as compared to more common T1DM. It is crucial to understand the clinical distinctions between the DM of WS1 and the more prevalent T1DM, as an incorrect diagnosis of WS1 could have life-threatening consequences for WS1 patients (52). Wolframin has a key role in the development of DM in WS1. Most likely, wolframin is needed for embryogenesis, namely in the pancreas' development. According to Xu et al.'s study, the Wfs1 protein is probably localized into the mesenchyme in the mouse pancreas. Some authors found that Wfs1-deficient (Wfs1KO) cells exhibited fewer pancreatic islets versus heterozygous (Wfs1HZ) or wild-type (WT) mice. Therefore, Wfs1KO pancreatic islets secreted less insulin than WT and Wfs1HZ islets. This Wfs1 deficiency thereby

caused a steadily declining cell mass, disruption of the pancreatic islet architecture, and a considerable reduction in insulin production (53). Wolframin is a protein that is highly expressed in pancreatic islet cells and may help in the folding of proinsulin, a protein that serves as a precursor to the hormone insulin that controls blood glucose levels (54). In Wfs1-deficient mice, an increase in insulin requirement was associated with an increase in apoptosis, which suggested that WFS1 regulated β cell survival (55). In Wfs1-deficient mice, less insulin and more proinsulin were found, indicating altered insulin pathways (56). Wolframin's localization in pancreatic secretory granules contributes to the prohormone of insulin processing. Thus, in WS1 patients, wolframin deficiency causes progressive loss of cells, decreased glucose tolerance, delayed cell cycle progression, and activation of ER stress/UPR, all of which contribute to the development of nonautoimmune insulin-dependent DM (57).

Neurological disorders

Several regions of the brain of WS1 patients have abnormalities, as shown by neuropathological postmortem case studies (58). In vivo neuroimaging allowed early identification of generalized brain atrophy (cerebellum, medulla, and pons), the absence of a posterior pituitary signal, and a reduced signal from the optic nerve in patients (59). Mice wolframin mRNA and protein are highly expressed in the brain from infancy to early adulthood. In the supraoptic nucleus and the magnocellular nucleus of mice, Wfs1 mRNA expression has been found to be rather consistent during development, but it declines in postnatal life (36). Moreover, a study conducted on rats documented a significant upregulation of Wfs1 mRNA and protein expression in specific regions of the limbic system, namely the amygdaloid area, hippocampal CA1 region, olfactory tubercles, and superficial layer of the piriform allocortex (60). The Wfs1 expression initiation pattern in the mouse forebrain was examined using mRNA in situ hybridization. A protein found in the synaptic vesicles, encoded by the synaptophysin (Syp1) gene, was studied as a marker of neuronal growth and synaptic connections (36). Syp1 expression was initiated during the early phases of brain development before Wfs1 expression, which did not begin until all brain structures were mature and reached the adult pattern three weeks postnatally. Indeed, in the early stages of brain development, Wfs1 expression was either nonexistent or extremely low. Thus, it has been suggested that WFS1 may be independently regulated during the postnatal period and that its function may be to preserve the brain from neurodegeneration (36).

Widespread brain atrophy in the late stage of WS1 was found in some studies (37). However, it is unknown at what stage in the disease's progression these brain abnormalities appear or whether specific brain areas and tissue types are more or less vulnerable. Hershey et al. found that the WS1 patients had a smaller intracranial volume, mainly of gray matter, accompanied by alterations in the microstructural integrity of white matter in the brain trunk and in the brain. These alterations were also found in the younger patients, who had the mildest symptoms (37). These findings suggested that even at the earliest stage of clinical symptoms, WFS1 mutations correlate with reduced intracranial volume as well as specific alterations in the brainstem and cerebellum. This pattern of anomalies provides a significant new understanding of the pathogenesis of WS1 by showing that wolframin has a considerable impact on early brain development in addition to later neurodegenerative effects. Therefore, the pathogenetic mechanisms behind the neurodegeneration of WS1 are extremely complex since abnormalities of the brain may be a result of two different pathological processes, both neurodegenerative and neurodevelopmental.

The expression of WFS1 has also been associated with other neuropsychiatric disorders. An interesting study suggested that heterozygotes for WFS1 mutations have a high risk of mood disorders (61-63) and an increased risk of suicide (64). Studies have suggested that the crucial function of WFS1 mutations in the onset of neuropsychiatric disorders in WS1 patients could also be used to better understand the pathogenesis of additional neurological disorders, such as Alzheimer's (AD) (65-67). Chronic stress induced by WFS1 mutations would contribute to the neurodegenerative processes associated with such diseases. In fact, it has been found that the depletion of wolframin induced prolonged ER stress and impaired the degradation and clearance of tau aggregates in Alzheimer's disease. (67). So, wolframin would play a key role in the neurodegenerative mechanisms underlying both WS1 and AD and might be a potential therapeutic opportunity for neurodegeneration and dementia.

Neuropsychiatric complications have been frequently found in WS1 patients. Neurological symptoms can also occur in the early years of life and were observed in 62% of WS1 patients. Other studies, however, found a much higher prevalence of neurological disorders, reaching up to 70% (11). Generally, the onset of neurological disorders occurs before the age of 16. The average age of onset is 30 years, with a range of 5 to 44 years. Nevertheless, it has been shown that there are subclinical neurological signs even in the early stages of the disease, namely during late puberty.

Thus, the onset of neurological symptoms seems to start at an earlier age (6), in contrast to previously reported cases (5). de Heredia et al. found that WS1 patients usually

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develop neurological symptoms within the age range of 10 to 30 years, with a median onset age of 23 years. The authors suggested that there are two distinct peaks in the onset of symptoms, which occur at the ages of 13 and 30, respectively (22).

Ataxia and dysphagia

The most common neurological symptom (45%) of WS1 is ataxia of the trunk due to abnormalities in the cerebellum. Fifteen of the forty-five examined patients with WS1 showed truncal or gait ataxia. Therefore, it has been recommended that the WS1 patients receive neurological counseling at least once or twice a year (68).

Brain stem atrophy

According to some studies, in 54% of WS1 patients, magnetic resonance imaging (MRI) revealed alterations in the brain trunk, the posterior region of the hypothalamus, and the cranial nerves (59,69). Although these findings are interesting, there is currently no evidence of a correlation between neuroimaging data and the clinical features of WS1 (59).

Due to brain stem atrophy, central apnea frequently causes death, and the WS1 patients could need a tracheostomy (5). Hence, both polysomnography and overnight oximetry are required as follow-up tests.

Other neurological anomalies include peripheral neuropathy (39%), cognitive impairment (32%), epilepsy (26%), dysarthria, dysphagia, and nystagmus (10%). Swallowing therapy can prevent serious complications such as aspiration pneumonia. In some cases, esophageal dilatation and esophagomyotomy are useful (70).

Autonomic neuropathy occurs frequently in WS1 patients, appearing as orthostatic hypotension, anhidrosis, hypo- or hyperidrosis, constipation, gastroparesis, or disturbances in thermoregulation (hypo- or hyperthermia). A history of headaches was also reported in the WS1 patients (6). Dysphagia and respiratory failure are the most common causes of death. (5,71).

Neurological abnormalities may also involve the urinary tract, leading to neurogenic bladder with hydroureter, urinary incontinence, and frequent infections. Patients exhibiting these symptoms must have a urodynamic examination, which may identify incomplete bladder evacuation or bladder atony (6).

Psychiatric disorders

Many WS1 patients, approximately 50%, manifest various psychiatric signs during early adulthood (average beginning age of 20.5 years) (72). However, some authors suggested that psychiatric symptoms may not be present in the early stages of WS1 but may appear later (73). Variability in the age of onset of psychiatric symptoms can be attributed to continued neurodegenerative processes; consequently, cognitive, and psychiatric symptoms would be observed in the later stages of WS1 disease. The etiology of these psychiatric symptoms remains unclear, as it is still unknown if these symptoms arise from the stress associated with a chronic illness, the presence of pathogenic mutations in the WFS1 gene, or a combination of both factors. The prevalence of psychiatric disorders in WS1 has not been fully investigated. However, it seems that almost 60% of WS1 patients suffer from psychiatric symptoms (11). Psychiatric disorders, including severe depression with suicide attempts, psychosis, sleep abnormalities, verbal impulsivity, and physical aggression, may exacerbate the clinical picture in WS1 patients (5,9). A recent study showed that 77% of WS1 patients exhibited anxiety as their most prevalent symptom. Significantly high frequencies of mood disorders, neurodevelopmental disorders, and sleep-wake disorders were found among the WS1 patients. Particularly, there appeared to be an increased risk of anxiety and obsessive-compulsive spectrum disorders in WS1 (73). An interesting study found that sixty percent of WS1 patients had a history of severe psychiatric disorders, such as depression, psychosis, confusion, memory loss, dementia, irritability, frustration, and impulsive violence. Twenty-five percent of these patients were "very severe", with 12 of them requiring hospitalization and 11 attempting suicide. The age range for the first attempted suicide or hospitalization was 15 to 32 years (70). The WS1 patients respond generally to conventional therapie. Multidisciplinary care is urgently required for the management and follow-up of WS1 patients who have made suicide attempts. Previous studies have proposed that smell- and sleep-related symptoms could be useful as potential markers for monitoring patients affected by psychiatric disorders (73). Generally, patients with WS1 show no signs of cognitive decline. However, Chaussenot et al. found that in a group of 59 WS1 patients, cognitive impairment was the third symptom (32%), following cerebellar ataxia and peripheral neuropathy (11).

Although heterozygous carriers don't show any symptoms, they are at a high risk of developing a variety of symptoms linked to the WFS1 genetic variants (23,61,74). In a study, etherozygous WFS1 mutations were associated with deafness and an increased risk of developing type 2 diabetes (75). Metabolic diseases, psychiatric disorders, and even suicidal thoughts were all linked to WFS1 heterozygosity (64). Swift et al. found that 10 of 11, hospitalized relatives of WS1 patients were heterozygous WFS1 mutation carriers. These results showed that WFS1 heterozygotes exhibit a 26-fold higher risk of psychiatric hospitalization than non-

heterozygotes. According to recent studies, Due to the high prevalence of psychiatric disorders in WS1 patients and their relatives, WFS1 could be a potential target for the study of psychiatric disorders (62). There are numerous difficulties in explaining the pathogenesis of psychiatric disorders in WS1 patients. Animal models studies suggested that wolframin impairs some brain areas (such as medial prefrontal cortex, temporal lobe, hippocampus, and amygdala) associated with stress responses, anxiety, and depression (76-78). Deficient Wfs1 mice exhibited behavioral features analogous to anxiety, sadness, and posttraumatic stress disorder phenotypes as WS1 patients (74,79). In some studies, cross-sectional neuroimaging scans of WS1 patients showed small brainstem and cerebellar volumes, as well as insufficient axon myelination. Longitudinal studies revealed an unusual decrease in the volume of ventral pons white matter and a decrease in the volume of cerebellar cortex gray matter over time, as well as signs of altered neurodevelopment and neurodegeneration (80,81). The causative process by which the WFS1 gene induces neuropsychiatric symptoms remains uncertain despite numerous performed studies. However, it has been found that ER stress plays a significant role in this pathogenetic mechanism, resulting in a failure in the regulation of emotions (82).

Sleep disturbances

Sleep disturbances were reported in WS1. WS1 patients, as well as their parents, may have a high frequency of sleep-related issues, including snoring, heavy breathing, bed wetting, and excessive tiredness, when compared to healthy subjects. Furthermore, a significant proportion of WS1 patients in adolescence and adulthood met the criteria for hypersomnolence disorders (73).

The relationship between sleep disorders and WS1 remains unclear, as it is unknown whether these sleep issues are primarily associated with WS1 or if they are caused by comorbid chronic diseases such as type 1 DM or diabetes insipidus, which could increase the frequency of nocturnal urine and disrupt sleep patterns (83). It is crucial to understand the involvement of wolframin in sleep regulation because the prevalence of heterozygous WFS1 mutations is approximately 1% of the population and its potential impact on psychiatric disorders is high (23,61,63). A large number of breathing disorders during sleep, particularly obstructive sleep apnea (OSA), was found in WS1 patients. Both adults and children with WS1 had much higher rates of OSA than the general population (e.g., 29.4% vs. 2-7%) for adults, and 100% vs. 1-5% for children (83). It has been hypothesized that the high rate of OSA in the WS1 population may contribute to disease progression (83,84).Moreover, it has been found an association between a high apnea hypopnea index (AHI) and increased disease severity (84). Sleep dysfunction in WS1 may be linked to regional neuropathology, including decreased brainstem and cerebellar volumes (37,85). It has been hypothesized that WS1 patients could be more vulnerable to sleep disturbances due to the activation of ER stress, which is associated with sleep disorders. This vulnerability may be related to wolframin's crucial function in preventing ERstress-induced apoptosis (86;87). Some studies have shown that the sleep-modulating activity of Wfs1 requires dopamine. Furthermore, it has been found that Wfs1 loss reduces the sleep via altering ER-mediated calcium homeostasis, which modulates neuronal activity and neurotransmitter release. These results emphasize the role of dopamine and dopamine receptor neurons in WFS1-associated sleep disorders (88). Previous studies have hypothesized that sleep disorders (73,83) and impaired olfactory and gustatory perception (73,89) might be useful as potential early-stage markers for WS1.

Conclusion

A multidisciplinary approach is required for the successful management of WS1, a rare, neurodegenerative and lethal disease affecting many different organs and systems. A early diagnosis reduces morbidity and death by avoiding and treating complications. WS is a monogenic model for research on diabetes, neurodevelopment, and neurodegeneration. Moreover, it has been referred as a prototypical disorder related to ER stress and as a crucial regulator of cellular homeostasis and intracellular Ca2+ signaling. Recent studies have suggested a strong association between endoplasmic reticulum dysfunction and several metabolic disorders, including type 1 and type 2 diabetes, as well as neurodegenerative and psychiatric diseases, atherosclerosis, inflammatory pathologies, and cancer. An early diagnosis of WS1 is crucial for enhancing morbidity and decreasing mortality. Furthermore, genetic counseling is required in affected families. Understanding the relationships between ER stress, cytosolic Ca2+ alterations, mitochondrial dynamics, and neurodevelopment in WS1 could be helpful for the development of new therapies for WS1.

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