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An unusual case of Wolfram syndrome 1 with prevalent psychiatric symptoms

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Abstract

Wolfram syndrome 1 (WS1) is an autosomal recessive and neurodegenerative disease characterized by diabetes mellitus, diabetes insipidus, optic atrophy, and deafness. WS1 patients often experience neurological disorders, including brainstem and cerebellar atrophy and cognitive impairment. Psychiatric disorders are found in 60% of WS1 patients, and some of them exhibit suicidal behavior. WS1 is rapidly progressive and has a poor prognosis, leading to early death. The disease is caused by mutations in the WFS1 gene, which encodes a transmembrane glycoprotein called "wolframin." Here, we describe a patient with a severe phenotype of WS1, characterized by a high prevalence of psychiatric symptoms. We also extended our genetic study to some family members of the patient who manifested psychiatric disorders. Our study suggests that WFS1 could be a potential target for studying mental illnesses because it encodes critical wolframin regions, which are believed to be key factors in the development of these diseases. Further research is needed to understand the psychiatric features of WS1 and to increase our knowledge of mental disorders' pathogenesis.

Introduction

In 1938, Wolfram and Wagener first described Wolfram syndrome 1 (WS1; MIM 222300), an autosomal recessive and neurodegenerative disease (1). Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DI DM OA D) are the clinical hallmarks of WS1. The acronym DIDMOADUD has also been suggested to define the WS1 because a high frequency of urinary alterations has been found (2). WS1 patients exhibit a variety of neurological disorders, including brainstem and cerebellar atrophy and cognitive impairment (3-6). Psychiatric disorders were found in 60% of the patients (7-9). WS1 exhibits a broad spectrum of psychiatric symptoms, including mood disorders, seizures, anxiety, depression, and impulsivity (10-12). Among them, a subset of patients exhibited suicidal behavior as a clinical manifestation of WS1 (13-16). The diagnostic criteria for WS1 are: (1) coexistence of the two major criteria (DM and OA); (2) one major criterion with two minor criteria; and (3) two of any of the DIDMOAD manifestations (2). WS1 is a rapidly progressive disease with a poor prognosis, resulting in an early death at a mean age of 30 (3). Respiratory failure is the most common cause of death due to brainstem atrophy. Early diagnosis is crucial for accurate prognosis, avoiding complications, and reducing transmission. Although no current therapy exists, new medications have been developed to slow its progression (17). Numerous studies found that WS1 affected 1 in 770,000 adults (3) and 1 in 500,000 children (18) in the United Kingdom, 1 in 100,000 in North America (19), 1 in 710,000 in the Japanese population (20), and 1 in 68,000 in the Lebanese population (21). WS1 is a genetic disorder with an autosomal recessive inheritance mode. It is caused by mutations in the WFS1 gene, which is situated on the short arm of chromosome 4 (4p.16). WFS1 spans a length of 33.4 kilobases and encodes

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a transmembrane glycoprotein called "wolframin". It consists of eight exons, with exon 8 encoding the majority of the transmembrane region and the carboxy terminus of wolframin (22,23). Wolframin is an 890 amino acid transmembrane glycoprotein located in the endoplasmic reticulum (ER), consisting of nine transmembrane segments and a large hydrophilic region. Several tissues, including the heart, lung, placenta, pancreatic cells, and brain tissue, express WFS1 at high levels (24,25). The pattern of WFS1's expression is variable because it is low during intrauterine development and progressively increases until maturity. Wolframin expression is highly correlated with neuronal differentiation and is associated with decreased cerebral volume and abnormalities in the medulla and cerebellum (26). WFS1 mutations, primarily inactivating, cause around 90% of WS1 cases (17). Numerous WFS1 mutations, including pathogenic, presumably pathogenic, and uncertainly significant variants, are concentrated in the largest exon 8 (22, 23). The frequency of heterozygotes for WFS1 mutations ranges from 0.31 to 1 percent. It has been found that the WFS1 heterozygotes have an increased risk of developing psychiatric disorders (7). The large number of mutations, associated with clinical complexity and limited patient numbers, makes it difficult to correlate genotype and phenotype in WS1.

Case report

A 24-years-old man was born at full term following a pregnancy without complications and with no early developmental abnormalities. His mother was 28 years old, and his father was 30 years old when he was conceived. His parents were unrelated, and he was the third of four children. Both his father and sister had a history of psychiatric disorders. The patient's father, a 55-years-old man, suffered from irritability, insomnia, mood fluctuations, and alcoholism. Due to his impulsive aggression and irritability, his relationships with family members were severely damaged. The patient's sister, a young woman of 19, suffered from episodes of severe sleep deprivation, behavioral alterations, extreme irritability, and alcohol consumption. She also experienced long periods of severe depression and two attempted suicides.

The first months of the patient's life were normal. At 10 months, the patient began to walk and speak, and by 18 months, he was able to formulate short sentences. Later on, he had difficulty speaking and writing at school, but no therapy had been administered. At the age of 7, he was diagnosed with insulin-dependent, non-autoimmune DM, and 3 years later, with DI. At the age of 11, he had a gradual loss of almost all his vision due to bilateral OA. Simultaneously, he had a period of behavioral problems characterized by increased psychomotor activities, bossy behavior, an increase in speech productivity, and an elated mood. These symptoms were all resolved with pharmacological therapy. However, later on, the patient stopped his medication, and thus, he experienced a depressive episode. He was hospitalized several times because the control of DM was poor; in fact, he failed to comply with glucose monitoring, insulin treatment, and dietary guidelines. During one of these hospitalizations, the patient was diagnosed with hypothyroidism. At age 13, he made his first impulsive attempt at suicide. At age 16, he was admitted to a psychiatric clinic because he fluctuated between phases of increased psychomotor activity, increased speech production, euphoric mood disturbances, marked irritability, and phases of intense melancholy. The patient was released from the hospital with a diagnosis of bipolar disorder type 1. His therapy included sertraline and fluoxetine, but, after one year of improvement, he stopped it. As a result, he experienced a relapse of a depressive episode and a second suicide attempt. Therefore, additional serotonergic reuptake inhibitor therapy was administered. Two years later, a diagnosis of cerebellar ataxia was made. The magnetic resonance imaging (MRI) scans revealed diffuse atrophy of the opto-chiasmatic regions, cerebrum, cerebellum, and brain stem. Finally, the coexistence of DM, OA, DI, and neuropsychiatric disorders led to a diagnosis of WS1.

WFS1 genetic analysis

Genetic testing was performed to confirm the suspicion of WS1. DNA from the proband, his sister, and his parents was extracted from whole blood using the High Pure PCR Template Preparation Kit (Roche, Mannheim, Germany). Unfortunately, blood samples from other family members were not available. The coding regions and exon-intron boundaries of WFS1 (OMIM:626201; NM_006005.3) were amplified using polymerase chain reaction (PCR) with previously described primers (27). The amplified samples were sequenced automatically using an automated fluorescent sequencing method (Big Dye Terminator Kit v1.1, Applied Biosystems). The ABI PRISM sequencing instrument 3730 (Applied Biosystems) was utilized to separate the amplified products. Sequencing both DNA strands of three distinct PCR products was used to confirm all genetic variations. The sequence variants were considered mutations if they (a) caused a non-conservative amino acid substitution, (b) were absent in 300 ethnically matched control chromosomes, and (c) affected phylogenetically conserved residues. Other DNA variations that did not meet these criteria were categorized as polymorphisms.

Bioinformatics

HGMD (http://www.hgmd.cf.ac.uk/ac/index.php), Exac (http://exac.broadinstitute.org/), EVS (http://evs.gs.washington.edu/EVS/), dbSNP (https://www.ncbi.nlm.

nih.gov/projects/SNP/), and Varsome (https://varsome.com/) were used to assess the novelty of each found WFS1 mutation. Many computational analyses were carried out, namely Mutation Taster, Sift, and Polyhen2, which classified the variants as "disease-causing," "damaging," and "probably damaging," respectively, in order to better determine the potential pathogenic effects of mutations on WFS1 functionality.

Genetic testing showed that our WS1 patient was a [c. 532_537del6 (R178_Q179del) + c. 1673G>A (R558H)] heterozygote compound. His sister and his father were heterozygotes for c. 532_537del6 (R178_Q179del) deletion, and his mother was a heterozygote for c. 1673G>A (R558H) missense mutation.

Discussion

In the case described above, the WS1 patient was a R178_Q179del /R558H heterozygous compound in which the expression of a deletion and of a missense mutation of WFS1 resulted in a severe phenotype of WS1 characterized by the onset of DM at the age of 7, DI at the age of 10, bilateral OA at the age of 11, and neurological complications at the age of 18. In addition, the patient exhibited writing and reading difficulties in primary school and progressive severe psychiatric disorders beginning at age 11. He attempted suicide at the ages of 13 and 17 years old. It could be believed that the diagnosis of WS1, a progressive, incurable, and fatal disease, had caused the patient's psychiatric symptoms. In our case, however, psychiatric alterations such as mood disorders and impulsive and aggressive behavior had manifested almost simultaneously with DM, DI, and OA. Moreover, both the patient's father and sister abused alcohol and exhibited psychiatric disorders. The sister also suffered from prolonged episodes of severe depression and attempted suicide twice. We believe that, in our case, a genetic cause of the familial recurrence of mental illness cannot be ruled out. Our WS1 patient was identified by molecular analysis of the WFS1 as a heterozygote compound harboring both the R178_Q179del deletion inherited from the father and the c.1673G>A (R558H) missense mutation transmitted from the mother. The patient's sister, who displayed severe psychiatric symptoms, had the WFS1 R178_Q179del deletion in a heterozygote state, but WS1 did not affect her. The mother, who had a c.1673G>A (R558H) WFS1 heterozygote missense mutation, did not exhibit any psychiatric symptoms. The genetic variations found in the patient and in two members of his family were localized in nucleotide sequences of WFS1, which encode for critical wolframin regions. The R178_Q179del deletion resulted in an alteration of the hydrophilic terminus of wolframin, while the c.1673G>A (R558H) missense mutation disrupted the protein's sixth transmembrane domain.

It has been suggested that psychiatric disorders found in WS1 patients and in WFS1 mutation heterozygotes are the result of altered intracellular calcium dysregulations and cell signaling disruptions caused by specific mutations in WFS1 that alter the structure of wolframin (28). Since the finding of specific causative mutations in the WFS1, a lot of progress has been made in understanding the WS1 and its related symptoms, such as psychiatric disorder (9). Heterozygosity for WFS1 mutations has been shown to be an important risk factor for psychiatric disorders. In an interesting study, Swift et al. showed that carriers with only a copy of the WFS1 mutation exhibited a 26-fold higher risk of psychiatric hospitalization than non-heterozygotes (7,12). Moreover, a wide range of psychiatric signs and symptoms, such as thoughts of suicide, aggressive behavior, and bipolar disorders, were found in patients who were homozygotes or compound heterozygotes for the WFS1 mutations and in their first-degree relatives (12,20). Few studies with contradictory results have been performed on the behavioral and cognitive aspects of patients with WS1. Nickl-Jockschat et al. (29) and Chaussenot et al. (5) identified psychiatric symptoms (including anxiety, aggression, and mood swings) and learning difficulties in these patients. Nevertheless, some studies found severe psychiatric symptoms in WS1 patients but not behavioral disorders (30,31). Due to the high prevalence of psychiatric disorders in WS1 patients and their relatives, it has been suggested that WFS1 plays a crucial role in the regulation of emotions and, thus, could be a potential target for the study of psychiatric disorders. Recent studies described patients suffering from severe depression, schizophrenia, bipolar disorder (BD), and attempts at suicide who had mutations in the WFS1 but not the clinical key features of the WS1 (32). The finding of WFS1 mutations in psychiatric patients without WS1 has suggested a potential association between the WFS1 mutations and psychiatric symptoms, as well as their utility as biomarkers and predictors for some psychiatric disorders (33). Although the specific role of wolframin remains unclear, mutations in WFS1 have been found to affect many cellular pathways crucial for efficient cell signaling. These mechanisms include intracellular calcium signaling and its downstream effects, ER stress, normal mitochondrial functionality, as well as neurotransmitter synthesis and release (34). Alterations in these complicated pathways have been proposed as key contributors to the development of several mental illnesses (32).

Conclusions

The patient described in this report exhibited biallelic severe mutations in the WFS1 gene, a missense mutation (R558H), and a deletion (R178_Q179del). These genetic variants cause a severe phenotype of WS1, characterized by a high prevalence of psychiatric disorders. Several studies showed that WS1 patients have an increased risk of

developing mental illness. Given the reported high frequency of mental disorders and suicide in Wolfram syndrome 1, it is imperative to regularly evaluate the mental health status of WS1 patients and provide appropriate therapy. Further studies are needed to examine the psychiatric features of Wolfram syndrome 1 and to increase, thus, our knowledge of the pathogenesis of mental disorders.

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