Title: Repetitive Suicidal Behaviors in a Case With a New Mutation of Wolfram Syndrome; A Jump From the Gene to The Behavior

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Abstract:

Wolfram syndrome (WS) is a rare autosomal recessive neurodegenerative disease with variable symptoms including neuropsychiatric manifestations. A 26-year-old man was reported with classic symptoms of WS and repetitive psychiatric hospitalizations and at least 16 suicidal attempts. The genetic study demonstrated a novel homozygous stop-codon mutation on the WFS1 gene. This special type of mutation may be related to repetitive suicidal behaviors in this case of WS. Psychological support should be a routine practice in patients with WS.

Keywords: Wolfram Syndrome, Suicidal Behavior, Gene Mutation, WFS1 Gene
Introduction

Wolfram syndrome (WS), a rare autosomal recessive neurodegenerative disease, was first described by Wolfram and Wagener in 1938 (1, 2). This syndrome is characterized by Diabetes Insipidus (DI), Diabetes Mellitus (DM), Optic Atrophy, Deafness (DIDMOAD), ataxia, urinary tract complications, and psychiatric manifestations that present in 60% of cases. (3-5) Wolfram syndrome shows a variety of psychiatric symptoms such as mood disorders and impulsivity (6-9). Among these, some of them reported suicidal behavior as a clinical feature of WS (4, 10-13).

Wolfram syndrome is caused by mutations in the the WFS1 gene. The WFS1 gene is located on chromosome 4p16 (14) and encodes Wolframin, one of the membrane glycoproteins of Endoplasmic Reticulum(ER) that prevents ER stress-related apoptosis and regulates calcium channel activity. Wolframin is expressed in the liver and also brain regions such as the hippocampus (15-18) which may contribute to some of its psychiatric disturbances. To date, more than 357 mutations of the WFS1 gene have been documented in the Human Gene Mutation Database (HGMD). (19)

Some authors have proposed a genotype-phenotype correlation despite the similarity between different cases (20). However, it is not yet confirmed whether there is any correlation between these mutations and psychiatric manifestations including suicidal attempts (10).

In this article, we describe a 26-year-old man with a new mutation of Wolfram syndrome with repetitive suicidal behaviors and psychiatric hospitalizations added to a brief review on the connection of suicidal behaviors and Wolfram Syndrome.

Case presentation

A twenty-six -year-old-male was taken to the emergency room with an altered level of consciousness because of a suicidal attempt by injecting 150IU NovoRapid® insulin at December 2019. After initial management, he was admitted to the psychiatry ward of Rasoul-Akram hospital, affiliated by Iran university of medical sciences, for his depressed mood and suicidal ideation. Medical records revealed that he is a known case of Wolfram syndrome. In his past
psychiatric history, he had several suicidal attempts both impulsive and planned, and several episodes of depression, poor drug compliance after remission despite thorough psychoeducation, and frequent medication response failure despite temporary symptom relief. There was a negative substance history except for opium which he gave up 8 years ago. His family history was negative for any mental illnesses and suicide in first degree relatives except for opium addiction in both his parents.

He was accidentally diagnosed to have DM at age three, then he progressively lost nearly all of his vision at age 11 when he gave up his education. He had recurrent hospitalizations for his uncontrolled DM. During one of them at age 16, psychotherapy was recommended for him because of his aggressive behaviors. Two years later at 18 years old, he committed his first impulsive suicidal attempt, after a fight with his brother.

His first psychiatric admission was at age 20 due to a depressive episode with DM as its precipitating factor. He was treated with sertraline and fluoxetine (concurrently). Despite getting better, after 1 year, he interrupted medication for an unknown reason which was the trigger for the relapse of the second depressive episode. However, he didn’t use any medication until age 24. At age 24, he developed headaches and committed the second suicidal attempt. Another selective serotonergic reuptake inhibitor medication was initiated. Looking for the cause of headache, the neurologic examination revealed bilateral optic atrophy, cerebellar ataxia, and bilateral sensorineural hearing loss. Brain magnetic resonance imaging (MRI) was also requested that showed diffuse atrophy in the cerebrum, cerebellum, and brain stem, in addition to an incidental finding of a 2-cm cavernous malformation in the left frontal lobe (figure 1). In addition, diabetes insipidus (DI) was also diagnosed according to lab data. Based on cumulative findings of DM, DI, optic atrophy, sensorineural hearing loss, and neuropsychiatric manifestations, he was finally diagnosed with WS. The diagnosis was confirmed with genetic testing.

Genomic DNA of the patient was extracted from peripheral blood leukocytes and genetic studies were performed by PCR-Sequencing of the coding regions and exon–intron boundaries of the WFS1 gene. (Primer sequences are given in Suppl Table 1). Molecular analysis of the WFS1 gene revealed a homozygous c.493C> T mutation which alters a glutamine amino acid to premature
stop codon at codon 165(p.Q165X) leading to truncation of Wolframin protein (figure 2). The p.Q165X mutation had not been reported previously and Both parents were heterozygous carriers of this mutation.

After about 6 months he committed a serious suicidal attempt (the third one) by insulin injection that caused hospitalization. He received sertraline for depression and desmopressin for DI. But again, despite symptom recovery; he interrupted his medication for an unknown reason. Around 6 months later, he was admitted for depression and suicidal ideation and was treated with escitalopram and buspirone. Two months later he had a severe major depressive episode while taking escitalopram. So he was admitted and received electroshock therapy. Thereafter, the depressive episode recovered but he developed severe headaches that did not respond to analgesics.

After discharge, he committed three suicidal attempts and regressed to a depressed mood, mentioning despair of pain relief as the main reason for suicide. He had at least another eight planned suicidal attempts mostly by insulin injection during the last year. They were all treated at home and did not lead to hospitalization as his family became more experienced in managing his suicide attempts.

In his current hospitalization, he was treated with fluoxetine, gabapentin, and sodium valproate for depression and migraine headaches. He was discharged with partial remission of headache and depression. The follow-up visit within one year of the last hospitalization demonstrated some transient suicidal ideas but no additional suicidal attempt (figure 2).

Discussion

We described a novel stop gain mutation in the WFS1 gene in a young man with repetitive suicidal behavior. He had at least 16 reported suicide attempts between the age of 18 to 26.

In addition, the genetic study revealed a novel homozygous stopgain mutation as c.493C>T (p.Q165X) in the WFS1 gene. This variation has not been reported in control databases, such as
the 1,000 Genomes Project, Exome Variant Server, Exome Aggregation Consortium, dbSNP Database, or literature.

In this case, the classic symptoms of WS including endocrine, ophthalmologic, and neurologic manifestations were conducted before the emergence of most of the suicidal attempts. One may assume that these later manifestations are reactive to the diagnosis of a non-treatable disease, at least in this case. However, the psychiatric symptoms including mood disorder and impulsive and aggressive behaviors were begun simultaneously with other symptoms. In one study, the psychiatric hospitalizations, suicide, and subjective complaints of mental illness were compared between family members of WS and Ataxia-Telangiectasia which revealed more frequency in the blood relatives of the former syndrome, significantly (21). As both disorders are non-treatable diseases with some common manifestations, this was against the assumption of the reactive nature of psychiatric manifestation of WS. In addition, there are several other case reports which suggest the probable relationship between WS gene and suicide. To our knowledge, before this case, there are at least sixteen patients with confirmed WS in the literature who had suicidal behavior (4, 10, 13).

There are some genetic studies on the contribution of the WFS1 gene in suicides. In a controlled study, Crawford et al. found no increased incidence of WFS1 carrier in 100 patients with completed suicides (7). In contrast, in another study the frequency of 611R/611R genotype, one of the three most common variants of exon 8 mutation in WFS1, in suicide victims was much higher than controls and the score of impulsivity and novelty seeking were also significantly higher in this group (8). The contrary results were reported by Zalsman et al. They found an association between H611R polymorphism and mood disorders but aggression/impulsivity and suicidal behavior did not find such association (22). However, based on some indirect data analysis, Swift et al. declared that the carriers of WS gene have a greater than the eightfold risk for psychiatric hospitalization or suicide (21). Several years later, Swift and his colleagues calculated that heterozygote individuals for WS gene had even more chances to require psychiatric hospitalization, 26-fold (23).
Alongside gene mutation, epigenetic factors that change the contribution of genes may play a role in suicide. For instance, McGowan et al. showed significant hypermethylation in the brain of suicide subjects led to rRNA expression reduction observed in the hippocampus, but not the cerebellum (24).

The genetic study, in this case, revealed a new unreported stop-codon mutation on WFS1 gene. Although the previous documents affirm the role of WFS1 gene contribution in suicide, the high amount of suicidal attempts in our case is unusual. He had at least 16 suicidal attempts. This high tendency for suicide may be due to the new detected mutation which was found in our patient. The variability in a tendency for suicide and genotype variations of WS was suggested by by Sequeira et al. They found that there was a significantly higher frequency of suicide in carriers of H611R, R456H, and I333V which are three major locus variations of WFS1 at the locus of H611R (8). Furthermore, the patient had an incidental finding of a small cavernoma in neuroimaging. It is not clear that if this structural lesion located in the left frontal cortex may have a role in the high tendency for suicidal behavior or impulsivity observed in the patient.

Furthermore, twin and family studies revealed that suicidal behavior could be heritable (25, 26). As of now, besides genetic and epigenetic factors discussed above, some studies demonstrated some other candidate genes to play a role in the etiology of suicidal behaviors (26). For example, the effect of various serotonergic and dopaminergic genes, dysregulation of fibroblast growth factor genes, glial cells, and oxytocin –related genes have all been proposed for the possible connection of the role of genes in suicidal behavior (26, 27).

**Conclusion:**

We report a novel gene mutation in a young man who suffered from WS with repetitive suicidal attempts. We suppose that this new mutation might be responsible for the high tendency to suicide in our patient. Also, it is recommended that psychological support should be a routine practice in patients with WS.
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Conflict of Interest:

None of the authors have no Conflict of Interest related to this manuscript to disclose.

Authors' contributions:

Five authors were contributed in this manuscript. Dr Fatemeh Sadat Mirfazeli is the first author and Dr Mostafa Almasi-Dooghaee is the corresponding author.

Fatemeh Sadat Mirfazeli: writing the draft, design, Diagnosis of the case, Psychiatry consultant

Fatemeh Mohebi: final conclusion

Amin Jahanbakhshi: writing the draft, design

Omid Aryani: providing Genetic study, design

Mostafa Almasi-Dooghaee: writing the draft, final conclusion, Neurology consultant

All of the authors are agree with authorship rules.
References:


Figure 1 legend: Brain MRI; axial plane, Fluid-attenuated inversion recovery (FLAIR) (A1 and A2), T2-weighted (B1 and B2) and T1-weighted (C1 and C2) sequences showed global atrophy and a 2-cm “target-like” appendance of cavernous malformation in left frontal lobe.

Figure 2 legend: Clinical features and Genetic study. The patient had 16 consecutive suicidal attacks within 10 years. DNA sequencing result showing a homozygous c.493C> T mutation in WFS1 gene on chromosome 4p16.
Supplementary Table 1. Primer sequences for PCR-Sequencing of WFS1 gene.

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<th>Primer name</th>
<th>5’ Forward 3’</th>
<th>5’ Reverse 3’</th>
<th>PCR Product (bp)</th>
<th>Anneling temperature (°C)</th>
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