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Case Report

Two Cases of Wolfram Syndrome Who Were Initially Diagnosed With Type 1 Diabetes

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ABSTRACT

Objective: Early diagnosis of syndromic monogenic diabetes allows for proper management and can lead to improved quality of life in the long term. This report aimed to describe 2 genetically confirmed cases of Wolfram syndrome, a rare endoplasmic reticulum disorder characterized by insulin-dependent diabetes mellitus, optic nerve atrophy, and progressive neurodegeneration.
Case Report: A 16-year-old Caucasian male patient and a 25-year-old Caucasian female patient with a history of diabetes mellitus and optic nerve atrophy presented at our medical center. Both patients were initially diagnosed with type 1 diabetes but negative for islet autoantibodies. Their body mass indexes were under 25 at the diagnosis. Their history and presentation were highly suspicious for Wolfram syndrome.
Discussion: The genetic tests revealed a known Wolfram syndrome 1 (WFS1) pathogenic variant (homozygous) in the 16-year-old male patient and 2 known WFS1 pathogenic variants (compound heterozygous) in the 25-year-old female patient with diabetes mellitus and optic nerve atrophy, confirming the diagnosis of Wolfram syndrome. The first patient had a moderate form, and the second patient had a milder form of Wolfram syndrome.
Conclusion: Providers should consider monogenic diabetes genetic testing, including WFS1 gene, for patients with early-onset diabetes who are negative for islet autoantibodies and lean. Two patients described in this article could have been diagnosed with Wolfram syndrome before they developed optic nerve atrophy. Genetic testing is a valuable tool for the early detection of Wolfram syndrome, which leads to proper management and improved quality of life in patients with this rare medical condition.

Introduction

Recent genetic and clinical findings indicate that monogenic diabetes is often misdiagnosed and treated as type 1 or 2 diabetes.[1,2] Patients with monogenic diabetes may have syndromic diabetes, which requires management by a multidisciplinary clinical team. These considerations raise the importance of early diagnosis of monogenic and syndromic diabetes.[3] Wolfram syndrome is a rare monogenic syndromic diabetes characterized by juvenile-onset diabetes mellitus, optic nerve atrophy, and progressive neurodegeneration.[4] There are other clinical manifestations commonly seen in patients with this syndrome. These include diabetes insipidus, sensorineural hearing loss, neurogenic bladder, and ataxia. Severe neurologic disabilities caused by brainstem and cerebellar atrophy are associated with a shortened lifespan in patients with Wolfram syndrome.[5] Because there is currently no treatment that has been proven to provide a cure or halt the progression of this disease, proper management and care for each aspect of the disease are crucial for

Abbreviation: WFS1, Wolfram syndrome 1.

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improving the quality of life and prognosis of patients with Wolfram syndrome.

Most patients with Wolfram syndrome carry pathogenic variants in the Wolfram syndrome 1 (*WFS1*) gene. In a small fraction of patients, pathogenic variants in the CDGSH iron sulfur domain protein 2 (*CISD2*) gene have been reported.[6-8] The prevalence is estimated at 1:200 000 to 1:700 000. Recent clinical and genetic findings have revealed that Wolfram syndrome is best characterized as a spectrum disorder and ranges from mild-to-severe clinical manifestations.[9] Typical patients with Wolfram syndrome carry 2 recessive pathogenic variants in the *WFS1* gene.[4,6,10-12] Due to the rarity of this disorder, only a few cases are reported for each WFS1 pathogenic variant, which makes it challenging for medical geneticists to classify WFS1 variants into pathogenic or likely pathogenic. Here we report 2 cases of Wolfram syndrome to contribute to the ongoing efforts in understanding the pathogenicity of each WFS1 variant and study the genotype-phenotype correlation in Wolfram syndrome.

Case Report

Case 1

A 16-year-old Caucasian male patient born to consanguineous parents (second-degree cousins) was evaluated in the clinic for uncontrolled diabetes mellitus. Family history revealed 2 paternal family members with type 1 and 2 diabetes. He was diagnosed with type 1 diabetes at the age of 5 years. When he was 15 years old, he switched from multiple daily injections to continuous subcutaneous insulin therapy for his glycemic control. At the age of 14 years, he was diagnosed with optic nerve atrophy during the sports eligibility examination. Subsequent examination by the neuro-ophthalmologist confirmed his diagnosis of bilateral optic nerve atrophy. His visual acuity has been reduced from 8/10 bilateral to 4/10 bilateral since then. Around the same time, he experienced dyspnea, heat intolerance, excessive sweating, and agitation, which forced him to wake up at night. He was also diagnosed with sensorineural hearing loss then. He was negative for islet autoantibodies, including anti-glutamic acid decarboxylase antibody and insulin autoantibody, and his body mass index was 21, which was atypical in a patient with type 1 or 2 diabetes. Based on these symptoms, we suspected that he had syndromic and monogenic diabetes, especially Wolfram syndrome, and conducted a genetic test, which identified the pathogenic variant WFS1 c.1525_1539del (p.Val509_Tyr513del). He was homozygous for this variant. We confirmed that both of his father and mother are carriers of this variant. Brain magnetic resonance imaging revealed optic nerve atrophy, optic chiasm thinning, and brainstem atrophy. The retinal nerve fiber layer thickness measured by optical coherence tomography was thinner than normal. Neurologic examination revealed upward nystagmus and diffuse weakness of osteotendinous reflexes. An electroencephalogram was normal, and the electrophysiologic study showed mild motor polyneuropathy of the lower limbs. The patient reported a feeling of incomplete bladder emptying. His postvoid residual volume was estimated to be 30 mL based on the bladder scan. He was negative for respiratory and cardiovascular symptoms. He was also negative for obstructive sleep apnea but complained of difficulty swallowing. He was taking α-lipoic acid in addition to the continuous subcutaneous infusion of insulin.

Case 2

A 25-year-old Caucasian female patient was evaluated for glycemic control. She was diagnosed with type 1 diabetes at the age of 6 years. She was initially treated with multiple daily injections of insulin but after 2 years switched to continuous subcutaneous insulin therapy, which improved her glycemic control. When she was 19 years old, she was diagnosed with sensorineural hearing loss and needed hearing aids. At the age of 24 years, her visual acuity declined. She had an enlarged blind spot and central vision loss.[13,14] She was negative for anti-glutamic acid decarboxylase and insulin autoantibody, and her body mass index was 22.6, which was atypical in a patient with type 1 or 2 diabetes. Her history and presentation were strongly suggestive of Wolfram syndrome. Therefore, we conducted a genetic test. The test identified 2 heterozygous pathogenic WFS1 variants, WFS1 c.2099G>A (p.Trp700*) and WFS1 c.1381A>C (p.Thr461Pro), which was consistent with the diagnosis of Wolfram syndrome. She was negative for bladder dysfunction or respiratory or cardiovascular symptoms. Electroneurography showed no signs of peripheral nerve damage. Her diabetes was well-controlled by continuous subcutaneous insulin therapy. She was taking idebenone (540 mg/day) and α-lipoic acid.

Discussion

Wolfram syndrome is a rare monogenic disorder characterized by juvenile-onset insulin-dependent diabetes and optic nerve atrophy. Other common manifestations are sensorineural deafness, diabetes insipidus, neurogenic bladder, anxiety, depression, ataxia, sharp headaches, dysphagia, obstructive sleep apnea, and central apnea. Most patients with Wolfram syndrome carry 2 autosomal recessive pathogenic *WFS1* alleles. Typically, patients who carry 2 recessive pathogenic alleles develop diabetes mellitus at the age of approximately 6 years and optic nerve atrophy at the age of approximately 11 years. Some pathogenic variants of *WFS1*, particularly dominant variants, cause deafness or diabetes alone.[15-17] Other dominant *WFS1* variants are associated with deafness and optic nerve atrophy.[18] Autosomal dominant congenital cataract is also associated with dominant variants of *WFS1*. Recently, we have identified several dominant de novo *WFS1* variants associated with a genetic syndrome of neonatal/infancy-onset diabetes, congenital sensorineural deafness, and congenital cataracts.[9] Generally, recessive *WFS1* variants can vary in clinical severity. For example, *WFS1* c.1672C>T (p.Arg558Cys) variant is associated with mild syndromic manifestations but poses a greater risk to the Ashkenazi Jewish population due to its higher allele frequency in this ethnic group.[19] More than 200 *WFS1* pathogenic/likely pathogenic variants associated with Wolfram syndrome have been identified. Based on the previous case reports and genetic studies, Wolfram syndrome is recognized as a spectrum of disorder because the manifestations can be diversified and the disease severity can range from mild to severe.

The patients reported in this article have 2 pathogenic *WFS1* alleles. The first patient in this report developed diabetes mellitus at the age of 5 years and optic nerve atrophy at the age of 14 years. He also had sensorineural hearing loss and brainstem atrophy. These are cardinal features of Wolfram syndrome. Two homozygous deletion alleles of WFS1 were identified in this patient. Thus, this patient has a typical and moderate form of Wolfram syndrome. The second patient developed diabetes mellitus at the age of 6 years, but her optic nerve atrophy was diagnosed the age of approximately 24 years, which is later than usual. One deletion allele and 1 missense allele of WFS1 were identified in this patient. It has been suggested that patients who carry missense alleles tend to have mild manifestations. Therefore, the second patient may have a milder form of Wolfram syndrome. The pathogenicity of autosomal recessive alleles of WFS1 should be further evaluated in the future.

The second patient was taking idebenone for her optic nerve atrophy. Idebenone was originally developed for the treatment of Alzheimer disease and then authorized for the treatment of Leber hereditary optic neuropathy, a mitochondrial disorder, by the European Medicines Agency in 2015. The primary cause of Wolfram syndrome is endoplasmic reticulum dysfunction, but it has been shown that endoplasmic reticulum dysfunction and stress can lead to a secondary mitochondrial dysfunction. Thus, medications targeting mitochondria, such as idebenone, could be beneficial for patients with Wolfram syndrome.[20]

Conclusion

One of the commonalities of rare diseases is the extensive timeline to reach an accurate diagnosis. Although there is currently no treatment that can delay, halt, or reverse the progression of Wolfram syndrome, early diagnosis of this syndrome with genetic testing is essential to offer therapies aimed at treating each aspect of the disease and ensure the best possible quality of life for these patients. Early detection of symptoms commonly observed in patients with Wolfram syndrome, such as diabetes insipidus, ataxia, neurogenic bladder, central dyspnea, and dysphagia, will help physicians and caretakers to improve the quality of life of patients and prevent premature death due to complications of Wolfram syndrome. Thus, monogenic diabetes genetic testing should be considered for patients with early-onset diabetes who are negative for islet autoantibodies and lean. An accurate and swift diagnosis of Wolfram syndrome by genetic testing will facilitate the coordinated care of patients and the networking of physicians to further improve the clinical care of this rare disease.[21]

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Disclosure

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