CASE REPORT

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Early Diagnosis of Wolfram Syndrome by Ophthalmologic Screening in a Patient with Type 1B Diabetes Mellitus: A Case Report

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What is already known on this topic?

Wolfram syndrome (WS) is typically associated with childhood-onset insulin dependent diabetes mellitus (DM) as a first manifestation and progressive optic atrophy. Recently, the *WFS1* variants have been reported to be a major cause of autoantibody-negative type 1 DM (type 1B DM; T1BDM), but there are no clinical screening methods for WS without symptoms other than those of DM. Therefore, patients with WS remains misdiagnosed as T1BDM.

What this study adds?

We report a case of WS diagnosed by ophthalmologic screening before the appearance of visual impairment. The male patient developed T1BDM at the age of 3 years. At the age of 6 years, his endogenous insulin secretion was impaired but was still preserved. Fundus examinaton at that time revealed optic nerve head pallor, and *WFS1* gene analysis confirmed the diagnosis of WS. We propose that patients with T1BDM who have preserved endogenous insulin secretion may be eligible for ophthalmologic screening to detect WS, even if they are younger than suggested for current ophthalmologic screening for detection of diabetic retinopathy.

Abstract

Wolfram syndrome (WS) is a monogenic diabetes caused by variants of the *WFS1* gene. It is characterized by diabetes mellitus (DM) and optic atrophy. Individuals with WS initially present with autoantibody-negative type 1 DM (type 1B DM; T1BDM). The diagnosis is often delayed or misdiagnosed, even after visual impairment becomes apparent. We report a case of WS diagnosed by ophthalmologic screening before the appearance of visual impairment. A 7-year-old male patient developed T1BDM at the age of 3 years. At 6 years of age, his endogenous insulin secretion decreased but was not completely absent, and glycemic control was good with insulin treatment. Fundus examination at that time revealed optic nerve head pallor, and *WFS1* gene analysis confirmed a compound heterozygous variant (c.2483delinsGGA/c.1247T > A). Ophthalmological screening can help in early diagnosis of WS in T1BDM, especially when endogenous insulin secretion is preserved, which would facilitate effective treatment.

Keywords: Wolfram syndrome, type 1B diabetes mellitus, ophthalmologic screening

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Introduction

Wolfram syndrome (WS) is a rare, autosomal recessive genetic, disorder characterized by juvenile-onset diabetes mellitus (DM), optic atrophy (OA), diabetes insipidus (DI), deafness, and neurological complications. Typically, in most cases of WS, OA is detected by subjective symptoms, such as decreased vision, and is diagnosed later in the course of the disease (1). Recently, variants in the *WS* gene, *WFS1*, have been reported to be a major cause of autoantibody-negative type 1 DM (type 1B DM; T1BDM) (2,3). However, it is difficult to clinically diagnose WS unless the patient presents with symptoms other than those of diabetes. Here, we report a case of WS in which the diagnosis was made by ophthalmologic screening and subsequent genetic analysis, before the patient presented with obvious vision loss.

Case Report

The patient was a 7-year-old Japanese boy. He was the third child of healthy, non-consanguineous Japanese parents. His sister, brother, and parents had no signs or symptoms of diabetes or visual impairment. At the age of 3 years, he was diagnosed with DM following presentation with symptoms of polyuria and polydipsia. His laboratory test results at the time of diagnosis were: blood glucose level, 682 mg/dL; hemoglobin A1c (HbA1c) level, 12.2%; serum fasting C-peptide level, 0.30 ng/mL; serum immunoreactive insulin concentration, 0.8 μU/mL. Notably; all four anti-autoantibodies directed against pancreatic islets, including anti-glutamic acid decarboxylase (GAD) antibody, anti-insulin antibody, anti-insulinoma-associated protein-2 (IA-2) antibody and anti-zinc transporter 8 antibody, were negative. These findings led to the diagnosis of T1BDM, for which he was treated with subcutaneous insulin injection therapy. Insulin therapy twice daily was initiated, and at 5 years, his insulin therapy was transitioned to basal-bolus therapy.

At the age of 6 years, the patient was referred to Asahikawa Medical University Hospital for initiation of insulin-pump therapy. On a total daily dose of insulin of 0.46 units/kg/day, his HbA1c level was 6.9% and his serum fasting C-peptide level was 0.24 ng/mL, indicating that endogenous insulin secretion was impaired but still preserved. The islet-specific autoantibodies, anti-GAD antibody, anti-insulin antibody, and anti-IA-2 antibody were all rechecked and all remained negative.

Thus, ophthalmologic screening was performed to determine the cause of his T1BDM. His uncorrected visual acuity was 0.15 in the right eye and 0.2 in the left eye. Ophthalmoscopy revealed OA in both eyes, manifesting as optic disc pallor (Figure 1). Critical flicker frequency, which can detect optic nerve disease (normal, >35 Hz; abnormal, <25 Hz), was abnormal in both eyes; 23.1 Hz in the right eye and 20.8 Hz in the left eye. Magnetic resonance imaging revealed no obvious optic nerve atrophy. No abnormalities were detected on screening for other complications associated with WS, including hearing loss, urinary tract malformations, DI, and psychiatric symptoms.

Mutation Analysis for *WFS1*, *INS*, *KCNJ11* and *ABCC8*

Based on the above clinical findings, WS was suspected and *WFS1* gene analysis was performed. In addition, the *INS*, *KCNJ11*, and *ABCC8* genes were also investigated to exclude early onset monogenic diabetes (4). Blood samples were collected from the patient and his mother, from which genomic DNA was obtained. His father refused to undergo genetic analysis. This study was approved by the Asahikawa Medical University Research Ethics Committee, and informed consent was obtained from the parents. Direct sequencing was undertaken to analyze all exon and exon-intron boundary regions of the *WFS1*, *INS*, *KCNJ11*, and *ABCC8* genes. No variants were identified in the INS, *KCNJ11*, and *ABCC8* genes. We identified two heterozygous variants in exon 8 of the *WFS1* gene. The first variant was NM_006005.3: c.2483delinsGGA, resulting in a frameshift and premature stop codon (p.Ile828Arg fs*35) (Figure 2A). This variant has been reported to cause WS in Japanese patients (5). The second variant was NM_006005.3: c.1247T>A (p.Ile416Asn) (Figure 2B). The allele frequency of this variant is 6.98×10^{-6} in gnomAD and 7.96×10^{-5} in TOPmed, a comprehensive Japanese genetic variation database. *In silico* analysis predicted that this variant was probably damaging (Polyphen-2) or deleterious (PROVEAN). These two variants were confirmed to be in different alleles using the TA cloning method and showed compound heterozygous variants. Based on the American College of Medical Genetics and Genomic standards and guidelines, the

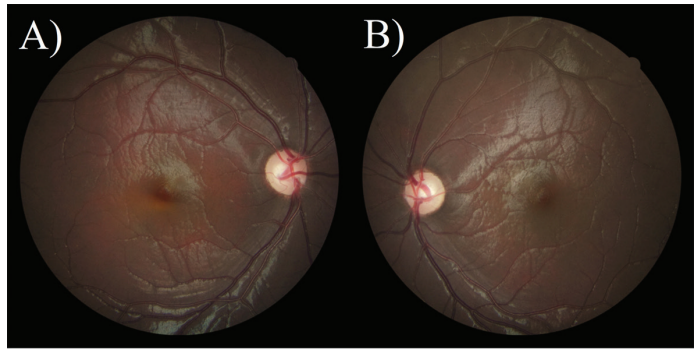

Figure 1. Fundus images of the right (A) and the left (B) eye, revealing optic disc pallor

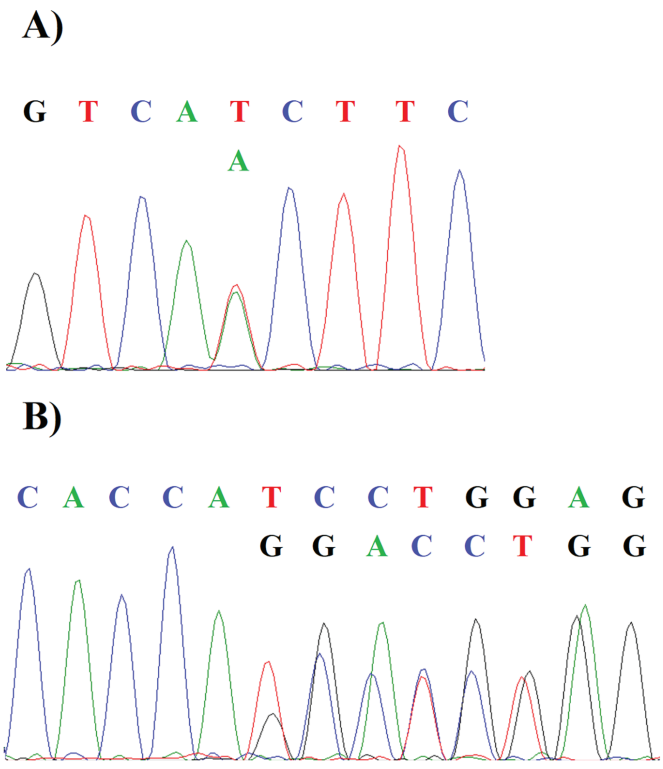

Figure 2. Sequence of the patient's *WFS1* gene. A) Forward sequences of position from 1243 to 1251. T to A single nucleotide change at position 1247 for heterozygosity. B) Forward sequences of position from 2478 to 2490. Single deletion of T and insertion of GGA at position 2483 for heterozygosity

c.2483delinsGGA and c.1247T>A variants were classified as pathogenic and likely pathogenic, respectively. Analysis of the mother, for these *WFS1* variants, showed that she had only the c.2483delinsGGA variant.

Discussion

Herein, we report a case of WS diagnosed with T1BDM at the age of 3 years. The patient was suspected of having WS based on optic nerve head pallor during ophthalmologic screening at the age of 6 years and this was subsequently confirmed by *WFS1* gene analysis.

WS usually presents with DM at a median age of 6 to 8 years, and subsequently manifests with OA at a median age of 11 to 15 years (1,5). In a previous report from Japan, 80% of cases (32 out of 40) followed the typical course (5). Therefore, WS usually remains misdiagnosed as autoantibody-negative DM for a long time (6). These authors, Zmyslowska et al. (6) reported that, although OA was identified based on progressive vision loss over an average period of 4 years after the diagnosis of DM, it took an additional average of 7 years for the patients to be diagnosed with WS. In addition to DM and OA, patients with WS may manifest with a variety of symptoms, such as hearing loss, urinary tract malformations, DI, and psychiatric symptoms (1). Therefore, early diagnosis is important for early management of these complications. Recently, off-label use of a GLP-1 receptor analog for WS showed promising results in preventing disease progression; patients receiving this treatment showed no deterioration of insulin secretion and no significant changes in ophthalmological, neuroradiological, and neurophysiological parameters during follow-up (7). Thus, early detection of WS in patients with DM is important, considering the availability of this promising therapy.

Recently, a comprehensive genetic analysis of T1BDM suggested that *WFS1* may be the major causative gene in T1BDM (2,3). There are no reports of whether patients with *WFS1* variants, detected by comprehensive genetic analysis, showed OA or other complications, except for one who had DM alone (2,3). Therefore, the presented patient may be one of the few cases in which early ophthalmologic screening was indicative of WS, which was confirmed by gene analysis of *WFS1*, before the appearance of visual symptoms, instead of a comprehensive genetic analysis.

The ISPAD Clinical Practice Consensus Guidelines recommend that ophthalmologic screening for pediatric T1DM should begin at puberty when there is a possibility of developing diabetic retinopathy (8). In these guidelines, as the purpose of ophthalmologic screening is to detect the early stage of diabetic retinopathy, there is no mention of screening for OA associated with WS. In the present patient, the optic nerve head pallor enabled the diagnosis of WS. This abnormality can be detected on fundus examination. As a fundus examination is a minimally invasive test, ophthalmologic screening for younger patients with T1BDM may be useful for early diagnosis of WS. As in the present case, we propose that patients with T1BDM who have preserved endogenous insulin secretion may be eligible for ophthalmologic screening to investigate for WS. In patients with WS, the decline in endogenous insulin secretion is gradual and often maintained for a long time after diagnosis (9), whereas insulin secretion is usually depleted within a few years in patients with T1DM, especially in early childhood-onset cases (10).

Conclusion

Ophthalmologic screening can help in the early diagnosis of WS in patients with T1BDM and can facilitate effective treatment. The usefulness of this strategy for diagnosing WS should be validated in the future.

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Ethics

Informed Consent: Consent form was filled out by the parents.

Authorship Contributions

Surgical and Medical Practices: Takahide Kokumai, Shigeru Suzuki, Noriko Nishikawa, Hinako Yamamura, Tokuo Mukai, Yusuke Tanahashi, Concept: Takahide Kokumai, Shigeru Suzuki, Design: Takahide Kokumai, Shigeru Suzuki, Data Collection or Processing: Takahide Kokumai, Shigeru Suzuki, Noriko Nishikawa, Hinako Yamamura, Tokuo Mukai, Yusuke Tanahashi, Analysis or Interpretation: Takahide Kokumai, Shigeru Suzuki, Literature Search: Takahide Kokumai, Shigeru Suzuki, Satoru Takahashi, Writing: Takahide Kokumai, Shigeru Suzuki, Satoru Takahashi.

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