

A Rare Genetic Disorder in Juvenile Diabetes: Wolfram Syndrome – Case Report

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Abstract

Wolfram syndrome is a hereditary autosomal recessive disease with an estimated prevalence of 1/550,000 in children. The mutations of the Wolfram syndrome 1 gene, which encodes Wolframin are responsible for the majority of cases of Wolfram syndrome. In this case report, a 16-year-old young man with a medical history of diabetes mellitus and bilateral blindness secondary to optic atrophy presented with severe hyperglycaemia without ketoacidosis. Polyuria secondary to partial neurologic diabetes insipidus, primary hypogonadism and bilateral sensorineural hearing loss were also identified. The genetic diagnosis of Wolfram syndrome was ultimately confirmed through genetic studies of patient and his mother. With the knowledge of Wolfram syndrome being a rare genetic disorder causing juvenile non-autoimmune diabetes, the early diagnosis is imperative to provide proper early managements. With genetic analysis of patient with suspected features, the early diagnosis becomes an achievable reality.

Key words Juvenile diabetes; Optic atrophy; Wolfram syndrome

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Introduction

Wolfram syndrome, a rare hereditary autosomal recessive disease, also called DIDMOAD because of its clinical features of diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy and deafness.¹ The prevalence of the syndrome in the UK is estimated to be 1/770,000.¹ The estimated prevalence in children has been reported to be around 1/500,000.² The median age at death of Wolfram syndrome patients was 30 years (range 25-49) and these patients usually die as a result of central respiratory failure.¹ The mutations of the Wolfram syndrome 1 (WFS1) gene, mapped on chromosome 4p16.1³ are responsible for the majority of Wolfram syndrome. Another new locus, Wolfram syndrome 2 (WFS2) gene, mapped on chromosome 4q22-q24 was identified by El-Shanti et al in 2000.⁴

Case Presentation

A juvenile male patient was diagnosed with type 1 DM at age of 10 years and was treated with human regular

insulin and human isophane insulin. He had progressive visual impairment since age of 8 years and optic atrophy was diagnosed at age of 11 years. He had total blindness since age of 14 years. He presented to a local hospital at age of 16 years with hyperglycaemia (Glucose 959 mg/dl 53.23 mmol/L) without ketoacidosis. His BMI was 18.8 kg/m² (height 158 cm, weight 47 kg). The HbA1c was 14.5%. His fasting C-Peptide was 0.49 ng/ml indicating an insulin deficiency. After his blood glucose had been under control, he still suffered from polyuria (urine volume over 5000 ml/day). The water deprivation test revealed

partial neurologic DI (urine osmolality increased from 481 to 589 mOsm/kg after subcutaneous injection of 2 microgram desmopressin). The MRI of the pituitary fossa revealed unremarkable change in the pituitary gland (Figure 1A). The sex hormone levels at age of 17 years disclosed primary hypogonadism (FSH 59 mIU/mL, LH 39.93 mIU/mL, Testosterone 171.96 ng/dL 5.96 nmol/L). An image of ocular fundus examination showed bilateral optic disc pallor, indicating optic atrophy (Figure 1B). An audiogram at age of 18 years revealed bilateral sensorineural hearing loss (Figure 1C).

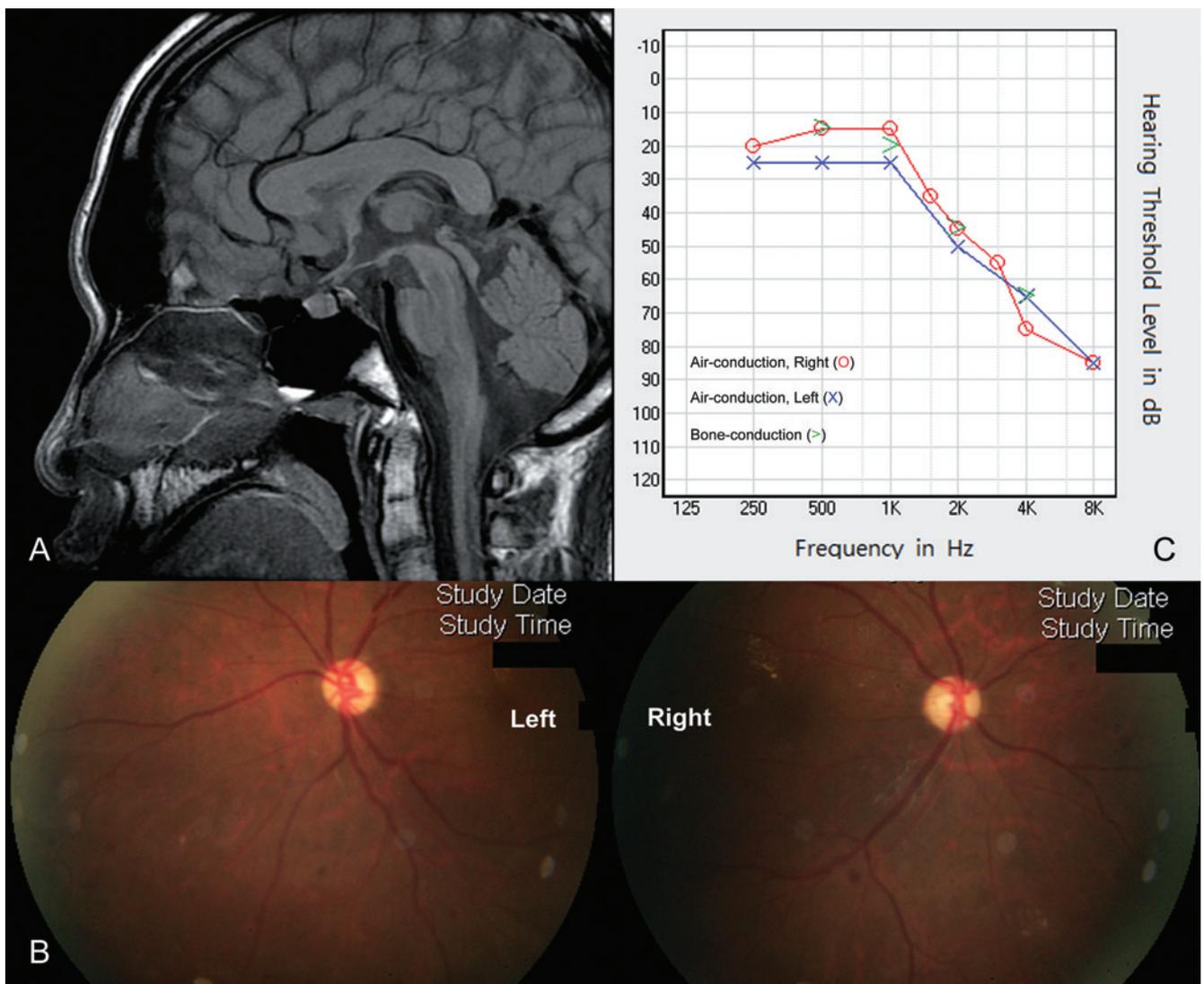


Figure 1 Clinical presentation. (A) Sagittal T1 weighted unenhanced magnetic resonance imaging of the pituitary fossa showing unremarkable change in the pituitary gland; (B) Fundus photograph showing bilateral optic disc pallor, indicating optic atrophy; (C) Results of audiometric testing conforming to ANSI 1969 standards. Pure tone average: Right: 38 dB, Left: 41 dB. (ANSI = American National Standards Institute; dB = decibel; Hz = hertz).

His severe hyperglycaemia without the presence of ketoacidosis and blindness secondary to optic atrophy raise a query regarding his previous diagnosis of type 1 DM. His clinical features, including DI, DM, optic atrophy and hearing impairment, suggested the possibility of Wolfram syndrome.

The genetic studies for WFS1 gene of patient and his mother showed that patient had a mutation Q667X⁵ in one allele and a novel mutation A370fsX445 inherited from his mother in another allele (Figure 2). The mutation (Gln→X) at amino acid residue 667 in exon 8 predicted a protein product with the majority of the carboxy tail deleted. The insertion mutation, inherited from his mother, came from

11 base pairs (CGGACAGCAAG) insertion in exon 8, which caused a frameshift at codon 370 and lead to premature termination at codon 445, resulting in a complete absence of the carboxy tail of the WFS1 protein. The result of molecular study confirmed the diagnosis of Wolfram syndrome.

Discussion

Wolfram syndrome is a hereditary neurodegenerative disease. Non-autoimmune DM usually presents at average age of 6 years (range 3 weeks to 16 years). Optic atrophy presents at a median age of 10 years (range 6 weeks to 19

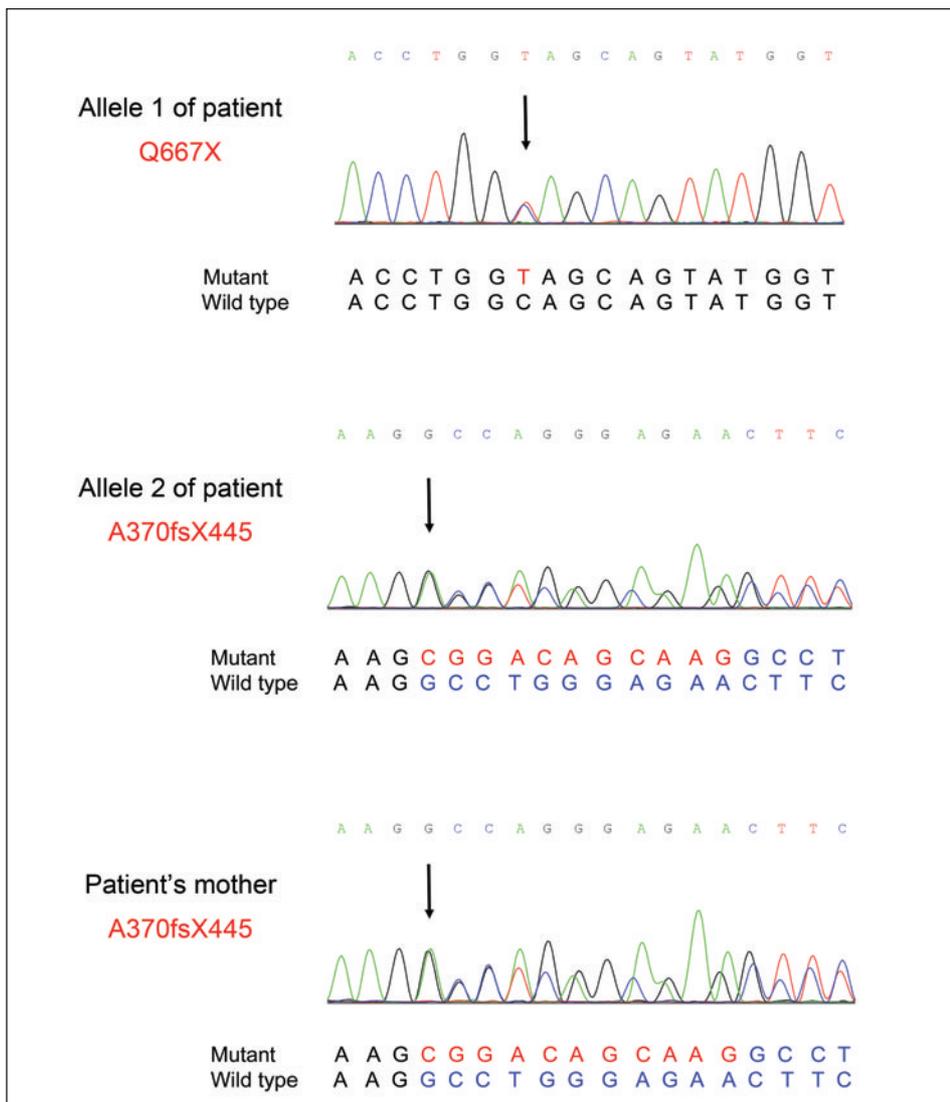


Figure 2 Patient having a mutation Q667X in one allele and a mutation A370fsX445 inherited from his mother in another allele.

years) with reduced visual acuity leading to blindness in most of the patients. Neurologic DI occurred at average age of 15.5 years and sensorineural deafness develops in the second decade (average age of 16 years).¹

This patient was previously diagnosed with type 1 DM. His low fasting C-Peptide indicated an insulin deficiency. His HbA1c (14.5%) revealed a poorly controlled DM. It is well known that patients with poorly controlled autoimmune type 1 diabetes are prone to ketoacidosis. This patient's presentation of severe hyperglycaemia without the presence of ketoacidosis and the molecular evidence of Wolfram syndrome led to revision of the patient's diagnosis of DM. In the UK nationwide study, C-peptide assays showed insulin deficiency and all of the patients assessed for antibodies to glutamic acid decarboxylase were negative.¹ This patient's clinical course and the evidence from the UK study alert clinicians on the possible diagnosis of Wolfram syndrome in juvenile patients with features of non-autoimmune insulin-deficient DM.

Poorly controlled diabetes are complicated with multiorgan disorders, such as nephropathy, retinopathy, neuropathy and vasculopathy. However, some monogenetic diseases, such as maternally inherited diabetes and deafness (MIDD), Alstrom syndrome and Wolfram syndrome, always associate with diabetes and also present with multiorgan involvement. It is important to distinguish these monogenetic diabetes from type 1 and type 2 diabetes because the optimal treatment and risk for complications varies with the underlying genetic defect. The molecular diagnosis of Wolfram syndrome reminds us the spectrum of this disorder. For earlier detection of central respiratory failure to prevent the early death of this syndrome, the respiratory condition of patients with Wolfram syndrome should be closely monitored.

The WFS1 gene is expressed in a variety of tissues, including heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas⁶ and encodes Wolframin, a transmembrane protein with 890-aminoacid long.⁷ Wolframin is a membrane protein localised in the endoplasmic reticulum⁸ and plays a role in the regulation of the ionised Ca concentration in the endoplasmic reticulum.⁹ Other research findings showed that the WFS1 gene regulates endoplasmic reticulum stress signaling.¹⁰ Mutations in WFS1 gene and dysfunction of Wolframin contribute to the clinical features of Wolfram syndrome.

Genetic analysis for patient's father was not performed because we cannot obtain sample from his father. The mutation Q667X in one allele could be inherited from his father or get from sporadic mutation.

Conclusion

Wolfram syndrome is a rare genetic disorder in juvenile non-autoimmune diabetes. Its clinical features (the acronym DIDMOAD) are clues for early suspicion of this diagnosis. The screening for features of Wolfram syndrome is imperative, especially when patient has juvenile diabetes associated with optic atrophy. With the universal availability of molecular analysis, the early genetic diagnosis of Wolfram syndrome becomes an achievable reality.

Declaration of Interest

The authors declare that there are no conflicts of interest.

References

1. Barrett TG, Bunday SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. *Lancet* 1995;346:1458-63.
2. Kumar S. Wolfram syndrome: important implications for pediatricians and pediatric endocrinologists. *Pediatr Diabetes* 2010;11:28-37.
3. Inoue H, Tanizawa Y, Wasson J, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet* 1998; 20:143-8.
4. El-Shanti H, Lidral AC, Jarrah N, Druhan L, Ajlouni K. Homozygosity mapping identifies an additional locus for Wolfram syndrome on chromosome 4q. *Am J Hum Genet* 2000; 66:1229-36.
5. Hardy C, Khanim F, Torres R, et al. Clinical and molecular genetic analysis of 19 Wolfram syndrome kindreds demonstrating a wide spectrum of mutations in WFS1. *Am J Hum Genet* 1999;65:1279-90.
6. Strom TM, Hortnagel K, Hofmann S, et al. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. *Hum Mol Genet* 1998;7:2021-8.
7. Hofmann S, Philbrook C, Gerbitz KD, Bauer MF. Wolfram syndrome: structural and functional analyses of mutant and wild-type wolframin, the WFS1 gene product. *Hum Mol Genet* 2003; 12:2003-12.
8. Takeda K, Inoue H, Tanizawa Y, et al. WFS1 (Wolfram syndrome 1) gene product: predominant subcellular localization to endoplasmic reticulum in cultured cells and neuronal expression in rat brain. *Hum Mol Genet* 2001;10:477-84.
9. Takei D, Ishihara H, Yamaguchi S, et al. WFS1 protein modulates the free Ca(2+) concentration in the endoplasmic reticulum. *FEBS Lett*. 2006;580:5635-40.
10. Fonseca SG, Ishigaki S, Oslowski CM, et al. Wolfram syndrome 1 gene negatively regulates ER stress signaling in rodent and human cells. *J Clin Invest* 2010;120:744-55.