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CASE REPORT

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A p.Val412Serfs pathogenic variant associated with Wolfram-like syndrome and leukodystrophy

Ayca Kocaaga[1*], Sevgi Yimenicioglu[2] and Murat Bayav[3]

Abstract

Background Wolfram syndrome is due to a mutation of the *WFS1* gene that codes for the transmembrane protein wolframin. This protein is located in the endoplasmic reticulum and is expressed at higher concentrations in the beta cells of pancreatic islets and the brain. The term "Wolfram syndrome spectrum" is often used because of its genetic and clinical heterogeneity. Disorders associated with the *WFS1* gene include Wolfram syndrome following an autosomal recessive inheritance pattern and Wolfram-like syndrome following an autosomal dominant inheritance pattern, and congenital cataract. Here, we report a case with Wolfram-like syndrome presented with bilateral congenital cataract, optic atrophy, nystagmus, ataxia, mild intellectual disability, epilepsy and leukodystrophy.

Case report Magnetic resonance imaging (MRI) showed bilateral cerebral T2 and flair hyperintensities that causes diffusion restriction in some areas with hypoperfusion. Bilateral T2 cerebellar central white matter hyperintensities and atrophy of brain stem were revealed by the brain MRI. There was also found evidence of a proximal cervical cord lesion and syrinx cavity in the vertebral MRI. The heterozygous frame-shift (c.1230_1233delCTCT; p.Val412Serfs) mutation in the *WFS1* gene. This heterozygous pathogenic variant in the *WFS1* gene was identified in both the father and grandmother.

Conclusions To our knowledge, this is a novel Wolfram-like syndrome-related phenotype. This case report broadens the currently known phenotypic presentations of Wolfram-like syndrome and suggests that the p.Val412Serfs variant in the *WFS1* gene may be associated with syrinx cavity and leukodystrophy.

Keywords Dominant inheritance, Leukodystrophy, Optic atrophy, *WFS1* (*Wolframin*) gene, Wolfram-like syndrome

Introduction

Wolfram syndrome is an autosomal recessive progressive neurodegenerative disorder characterized by homozygous mutations in the *WFS1* (*Wolframin*) gene. It can occur onset with diabetes mellitus, optic atrophy, sensorineural hearing loss, and progressive neurologic abnormalities (cerebellar ataxia, peripheral neuropathy, dementia, intellectual disability) [1]. A dominant mutation in the *WFS1* gene may result in Wolfram-like syndrome which is characterized by congenital progressive hearing impairment, optic atrophy, impaired glucose regulation [2]. Eiberg et al. described a Danish family with autosomal dominant optic neuropathy and deafness caused by a mutation in the *WFS1* gene. They also demonstrated that the patients also had impaired glucose tolerance [3]. The present report describes a case with autosomal dominant optic atrophy, congenital cataract, nystagmus, ataxia, mild intellectual disability, epilepsy

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and leukodystrophy with a frame-shift mutation in *WFS1*.

Case report

A 16-year-old boy was admitted to Department of Pediatric Neurology with an ataxic gait and epilepsy. He was born with spontaneous vaginal delivery at 38 weeks of gestational age as the second child of healthy and non-consanguineous parents (Fig. 1). He had bilateral cataract and nystagmus. The patient was also diagnosed with bilateral optic atrophy (OA) by brain magnetic resonance image (MRI) (Fig. 2d). His grandmother (paternal) had congenital deafness, cataract and non-insulin-dependent diabetes mellitus (Table 1), and his aunt (paternal) had non-insulin-dependent diabetes mellitus. His laboratory tests results were as follows: arylsulfatase A gene mutation was negative, very long chain fatty acids were normal, lysosomal enzyme panel was within standard limits, lactate 11 (N:0.5–1 mmol/L), ammonia 49 (N:15 to 45 µ/dL), pyruvate 0.8 (N:0.08–0.16 mmol/L), insulin 14.8 (< 25 mIU/L), glucose 77 (N:72–99 mg/dL). The HbA1c was 5.8% (N:4–5.6%) and the HOMA (Homeostatic model assessment) index was 2.81 (N:2.07–2.83). His auditory brainstem response test was normal. The visual evoked potentials (VEP) and electromyography (EMG) were found normal before but these tests were not be repeated. Brain MRI showed bilateral cerebral T2 and flair hyperintensities that causes diffusion restriction in some areas with hypoperfusion in perfusion images (Fig. 2a, b, c, g, h). Bilateral T2 cerebellar central white matter hyperintensities and atrophy of brain stem (Fig. 2f). Bilateral optic nerve was thinner than normal.

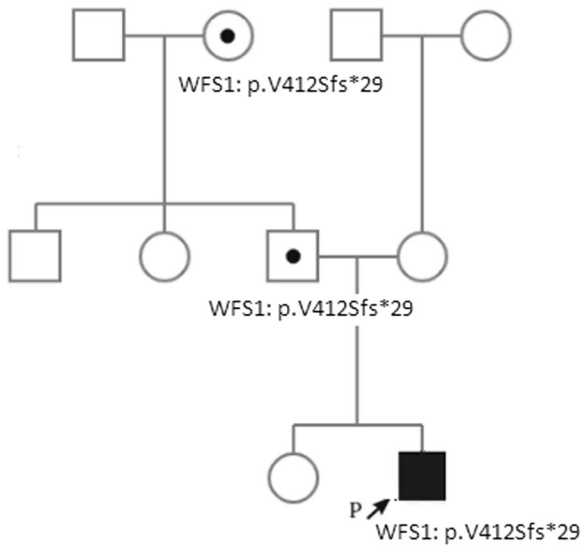

Fig. 1 Three-generation family pedigree of the patient

Bulbus oculi was slightly microphtalmic (Fig. 2d, e). The magnetic resonance spectroscopy (MRS) of brain did not show any metabolic abnormality (Fig. 3c–e). The cervical and thoracolumbar MRI results were revealed a proximal cervical cord lesion and syrinx cavity with a diameter of 3×3.5 mm beginning from the lower cervical segment toward the upper lumbar segment (Fig. 3a, b). The patient was diagnosed as Wolfram-like syndrome due to having clinical manifestations as bilateral congenital cataract, optic atrophy, ataxia, nystagmus, seizures and having a heterozygous mutation in the *WFS1* gene. Karyotype analysis of G-banding indicated an ordinary 46,XY karyotype. Agilent Oligonucleotide microarray to investigate for copy number variants was done using the 8X60K probe. When the Agilent cytogenomic 5.0.0.38 (GRCh 37/hg 19) analysis program was used, there was no deletion or duplication in the patient. Whole-genome sequencing of a DNA sample from our patient performed by MGI (DNBSEQ-G400). Genemaster analysis programme revealed a heterozygous mutation (c.1230_1233delCTCT; NM_006005.3) in the *WFS1* gene resulting in a stop codon (p.V412Sfs*29). Segregation analysis revealed that the clinical unaffected father had the same variant of *WFS1* in a heterozygous state. His father had the same p.V412Sfs*29 mutation; but he did not have any signs of this syndrome. The grandmother (father's mother) of the proband, who had a history of type 2 diabetes, cataract and hearing loss, also carried this mutation heterozygously (Table 1). The mother and the grandfather (father's dad) did not carry c.1230_1233delCTCT mutation in the *WFS1* gene. His aunt had no history of any other disease other than type 2 diabetes. This mutation localized in the exon 8 of *WFS1* was reported before and it was described as a pathogenic mutation (https://www.ncbi.nlm.nih.gov/clinvar/variation/429753/). In silico analysis of this mutation using prediction programs did not give data. In the mutation tester prediction tool, it is estimated that this variant has a disease-causing effect by changing the amino acid sequence and affecting the protein feature. The family of the patient provided informed consent for publication of this case report.

Discussion

Here we report a case with a rare heterozygous variant (c.1230_1233delCTCT; p.V412Sfs*29) in exon 8 of the *WFS1* gene and extensive leukodystrophy change in the central nervous system with syrinx cavity. This variant has been reported in Clinvar (SCV000582399) in 2017. This mutation was described as homozygous (c.1230 1233 deteCT) in a female patient who had showed all the clinical features of Wolfram syndrome [4]. We diagnosed Wolfram-like syndrome in our patient who had optic

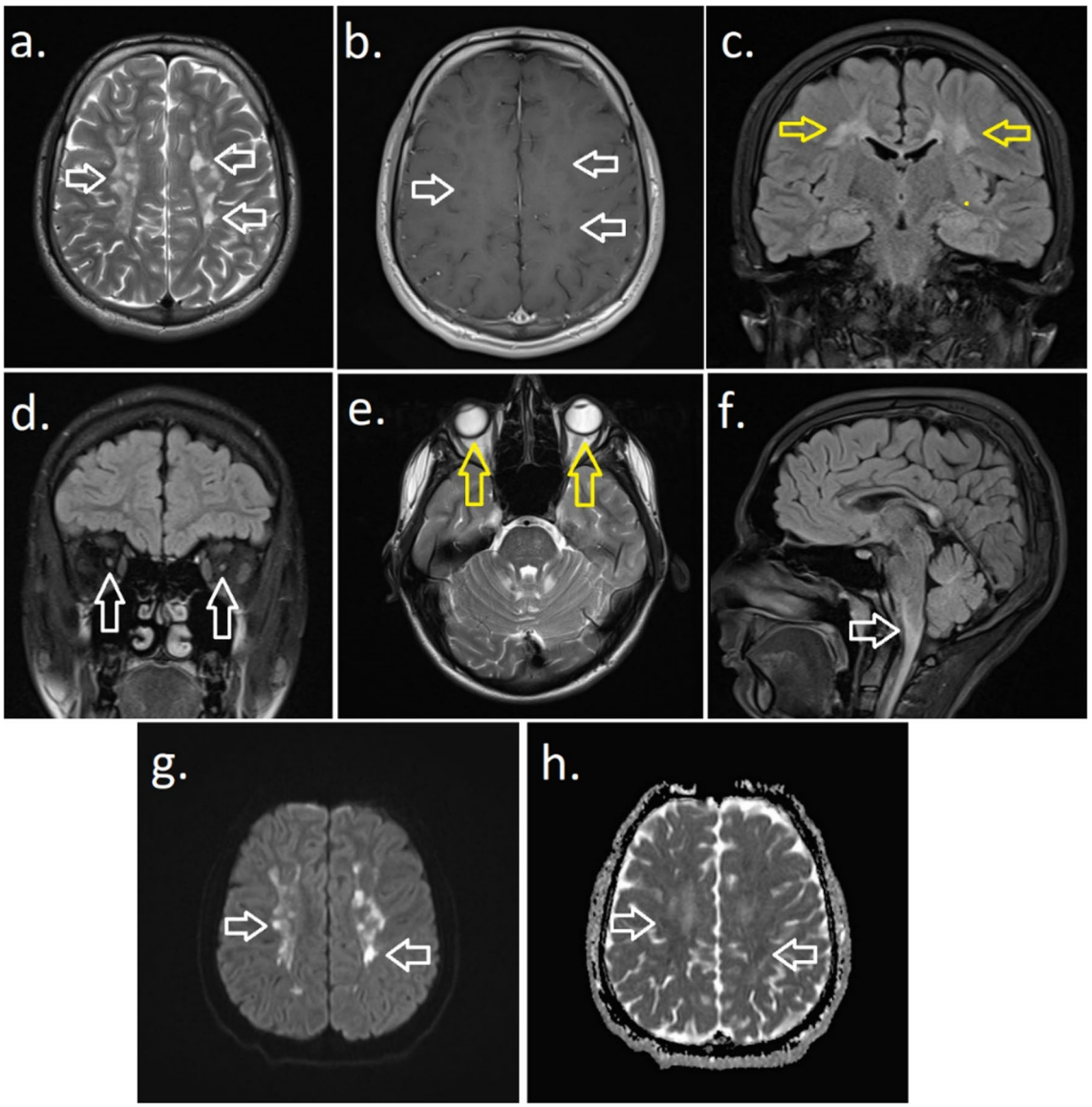

Fig. 2 **a** T2 axial MR image: hyperintensity at periventricular white matter (white arrows), **b** contrast-enhanced T1 axial MR image: no contrast enhancement is seen at the same white matter lesions (white arrows), **c** coronal FLAIR (Fluid-Attenuated Inversion Recovery) MR image: same lesions on periventricular white matter (yellow arrows), **d** bilateral atrophic optic nerves (white arrows), **e** bilateral micro-ophthalmia (yellow arrows), **f** sagittal FLAIR image: atrophy and hyper-intensity on brainstem (white arrow), **g** diffusion restriction on diffusion-weighted image and **h** on ADC (apparent diffusion coefficient) map (arrows)

Table 1 Clinical characteristics of the proband's family

	The proband	Father	Mother	Grandmother
Age	12	46	44	65
Type 2 DM	−	−	−	+
Hearing loss	None	None	None	+(congenital)
Optic atrophy	+	−	−	−
Bilateral Cataract	+(congenital)	−	−	+(onset at 6 years)
WFS1 gene mutation	c.1230_1233delCTCT	c.1230_1233delCTCT	−	c.1230_1233delCTCT

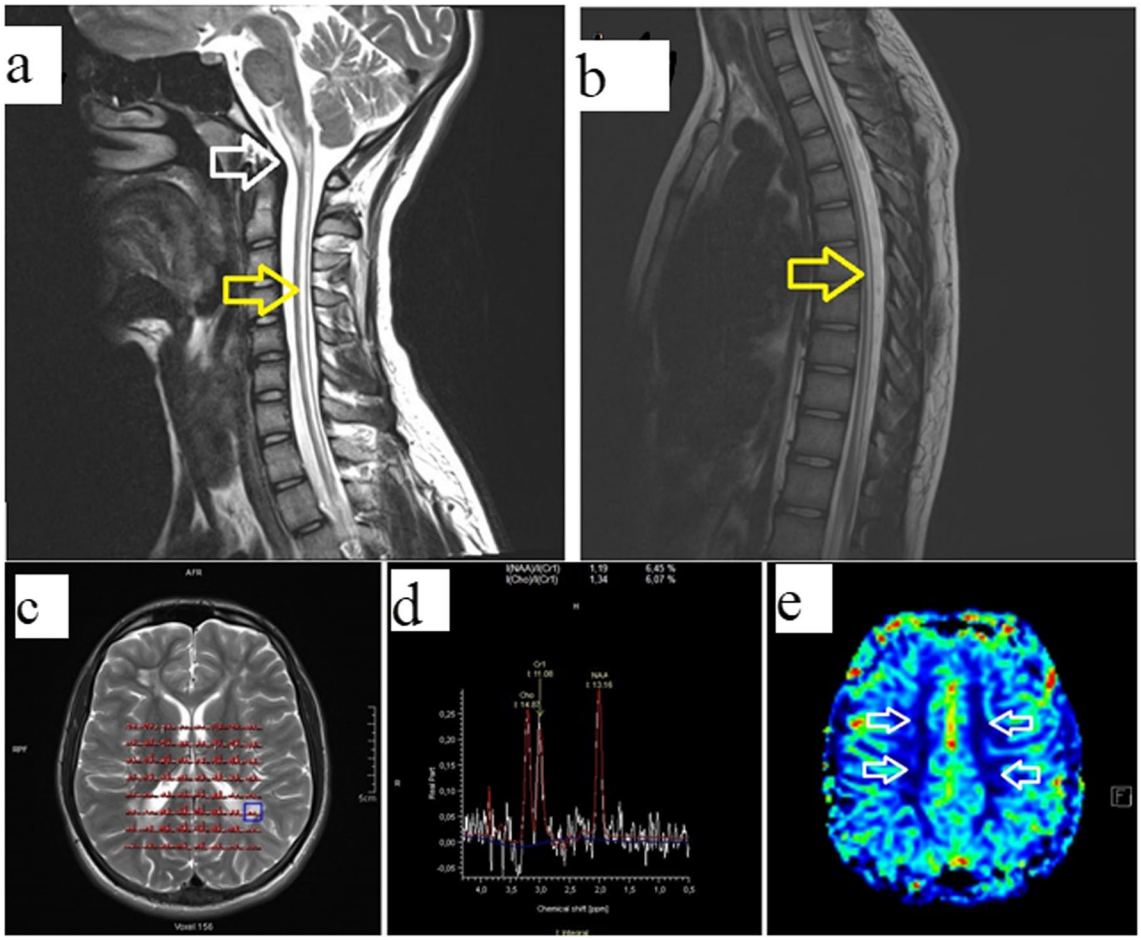

Fig. 3 Spinal MRI. **a** Sagittal T2 image of the cervical spinal cord: syrinx cavity (yellow arrow) and brain stem lesions are also seen (white arrow), **b** sagittal T2 image of the thoracic spinal cord: syrinx cavity (yellow arrow). Brain Spectroscopy imaging: **c** sample on white matter lesion (blue square), **d** Choline(Cho), Cretininine (cr1) and N-acetyl aspartate (NAA) metabolites with nearly normal values, **e** cerebral blood volume map of brain perfusion imaging showing decreased white matter perfusion

atrophy, congenital cataract, nystagmus, ataxia, mild mental disability, epilepsy, leukodystrophy and a heterozygous (frame-shift) mutation in the *WFS1*. To date, more than 400 different mutations have been identified in *WFS1* (https://www.ncbi.nlm.nih.gov/clinvar/?term=WFS1%5Bgene%5D).

They are often located in exon 8 and are inactivating (nonsense or frameshift) mutations. *WFS1* mutations can be dominantly or recessively inherited and both the onset of the disorder and degree of severity are highly variable [5]. According to the genetic test results, our patient and his grandmother are likely to have a mild form of this syndrome. Although the patient's father had the same mutation, he did not have diabetes mellitus (DM), visual loss, or hearing problems. The HbA1c value was 5.8% at the last follow-up of the patient, who maintained drug-free glucose control with diet and exercise for the last 3 months. The genotype–phenotype correlation is difficult to establish due to the molecular complexity of *WFS1*. Bonnycastle et al. have found heterozygous nonsynonymous variant (p.Trp314Arg) in the *WFS1* gene with dominantly inherited nonsyndromic adult-onset diabetes mellitus in a large four-generations family [6]. Morikawa et al. have shown a de novo heterozygous mutation (p.N325_I328del) in a patient with Wolfram-like syndrome with insulin-dependent DM, congenital cataract, and severe bilateral hearing loss. In general, cataract is not a typical sign of the syndrome, but most patients associated with *WFS1* heterozygous mutations had congenital cataract [7]. Neuro-radiological manifestations of Wolfram syndrome include atrophy of the brainstem, diffuse cerebellar gray and white matter atrophy, thinning of the middle cerebellar peduncle and optic nerve and optic tract atrophy [8]. Leukodystrophies are a group of disorders that involve the myelin tracts in the central nervous system, where myelin involvement is the primary feature

and not secondary to any underlying neuronal pathology [9]. Leukodystrophy is classified into peroxisomal disorders, lysosomal storage diseases, diseases caused by mitochondrial dysfunction. Each group of leukodystrophy has distinct clinical, biochemical, pathological, and radiologic features. According to Abdelsalam and colleagues MRS revealed abnormal NAA/Cr (The N-acetylaspartate to creatine), Cho/Cr (Colin to creatine), and Cho/NAA (Colin to N-acetylaspartate) ratios which were highly characteristic in the majority of cases, elevated Cho/Cr, decreased NAA/Cr and elevated Cho/NAA ratios were the dominant finding with leukodystrophies. One-way analysis of variance for the spectroscopic metabolite ratios revealed statistical significance in leukodystrophies. Our patient had no abnormality in MRS [10]. Leukodystrophies have never been reported in Wolfram syndrome before. The application of the next-generation sequencing technology allowed for rapid diagnosis and appropriate evaluations of our patient. Identification of a heterozygous variant (p.V412Sfs*29) found in the patient supports the diagnosis of the Wolfram-like syndrome with dominant inheritance in the patient. The present case also described a new neuroradiologic sign observed on MR imaging in Wolfram-like syndrome. The most common findings of neuroradiologic features in the patients with Wolfram syndrome have involved the posterior pituitary gland, optic nerve and optic chiasm, cerebral white matter, brain stem, and cerebellum [11, 12]. Neuroradiologists should be aware of leukodystrophies and other findings when reading MRI studies of patients with genetically confirmed Wolfram-like syndrome. Variable inheritance pattern together with the progressive character of clinical symptoms complicate the diagnosis and family genetic counseling in Wolfram syndrome.

Conclusions

Patients should be examined with the solidarity of each department in a multidisciplinary way. Practitioners should keep in mind Wolfram-like syndrome with a static leukodystrophy without devastating outcome and the clinical findings as nystagmus, cataract, insulin resistance.

Abbreviations

Cho/Cr	Colin to creatine
Cho/NAA	Colin to N-acetylaspartate
DM	Diabetes mellitus
EMG	Electromyography
GRCh	Genome Reference Consortium human genome
HOMA	Homeostatic model assessment
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAA/Cr	The N-acetylaspartate to creatine
WFS1	Wolframin gene

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Author contributions
AK and SY made substantial contribution to the conception of the patient's diagnostic process, conducted the diagnostic procedures, and collected and interpreted clinical data concerning the patient. AK, SY and MB were major contributors in drafting the initial version of the manuscript. AK reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data can be found in the archives of the Department of Medical Genetics, Eskişehir City Hospital.

Declarations

Ethics approval and consent to participate
The authors' institution does not require ethical approval for publication of a single case report.

Consent for publication
Written informed consent was obtained from patient's parents for publication of this case report and accompanying images.

Competing interests
The authors declare no conflicts of interest.

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