

Wolfram syndrome with a rare genetic mutation - Case report

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Wolfram syndrome was first described by Wolfram and Wager in 1938 with an incidence of 1 in 7,70,000 in the United Kingdom.^[1] The clinical features include diabetes insipidus, diabetes mellitus, optic atrophy, and deafness synonymous as the DIDMOAD syndrome. Patients classically present with juvenile-onset diabetes mellitus and optic atrophy before the age of 16 years which is the minimum diagnostic criteria according to European union (EU) Rare Diseases Registry for Wolfram syndrome, Alström syndrome, Bardet-Biedl syndrome and other rare diabetes syndromes (EURO-WABB).^[2] The diagnosis of Wolfram syndrome requires the presence of two major or one major and two minor criteria. The major criteria being diabetes mellitus <16 years, optic atrophy <16 years while the minor criteria include diabetes insipidus, diabetes mellitus >16 years, optic atrophy >16 years, sensorineural deafness, neurological signs, renal tract abnormalities, loss of function mutation in WS1/CISD2, and/or family history of the Wolfram syndrome.

Other clinical manifestations include neuropsychiatric manifestations, reproductive abnormalities, limited joint mobility, cardiovascular and gastrointestinal autonomic neuropathy.^[3]

The Wolfram syndrome is known to be an autosomal recessive condition. Genetic testing plays an important role in distinguishing the optic atrophy associated with the Wolfram syndrome from other causes of juvenile optic atrophy. Genetic studies have revealed that most of the mutations occur in the WFS-1 gene located on chromosome 4p16.1 on Exon 8; a majority being reported as missense, nonsense, and splice-site mutations; followed by deletions and insertions.^[4]

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We describe two cases of the Wolfram syndrome presenting with progressive loss of vision and uncontrolled diabetes previously undiagnosed and under the care of pediatricians and endocrinologists for individual systemic manifestations. Genetic analysis showed a rare nonsense, homozygous mutation, reported only once in the literature before. The diagnosis confirmed by genetic analysis helped in establishing the diagnosis and planning a coordinated multidisciplinary treatment with appropriate rehabilitation and explaining of prognosis.

Case 1

A fifteen-year-old boy presented with progressive diminution of vision in both eyes for 10 years and deafness for a year. He was on treatment for juvenile diabetes from the age of 3 years. The best-corrected visual acuity (BCVA) OD: -0.50 DC × 130 (3/60), N36 and OS: -0.25 dioptres sphere (DSPH) (6/24), N36. The pupils were mid-dilated and sluggishly reactive to direct and consensual light in both eyes. The fundus examination showed bilateral disk pallor [Fig. 1]. Lister's perimetry was done in view of poor vision which showed generalized constriction of fields.

In the presence of two major criteria viz., juvenile diabetes and optic disk pallor, the possibility of the Wolfram syndrome was considered, and a pediatric endocrinologist's opinion and Brainstem Evoked Response Audiometry (BERA) were advised. The results of the BERA were awaited as the patient was yet to come for follow-up. The MRI of the brain and serum vitamin B12 were advised in view of the optic atrophy, which were normal.

The pediatric endocrinologist concurred with our diagnosis and genetic testing was done by targeted sequencing of genes in clinical exome on Illumina sequencing platform and it revealed autosomal-dominant WFS-1 gene, chr4:6302670 c.1148G>A p.R383H Exon 8, heterozygous, confirming the diagnosis. Low-vision aid (X4) Dome magnifier for near and 2.1ATTV for distance was prescribed.

Case 2

An 11-year-old girl child, born out of a consanguineous marriage, presented to us with gradually progressive visual deterioration for 7 years. She was a known case of juvenile diabetes mellitus and neurogenic bladder on treatment since the age of 4 years. No history of deafness was noted. The BCVA was OD 6/60, N36, and OS 5/60, <N36. Hirschberg's test showed left exotropia with latent nystagmus in both eyes. The anterior segment examination showed (OU) mid-dilated pupils with sluggish reaction to direct and consensual light and blue-dot cataract. The fundus evaluation showed the presence of gross pallor of the optic disk [Fig. 2]. In view of suspected Wolfram syndrome genetic testing (clinical exome) was done which revealed the presence of homozygous, nonsense variation in

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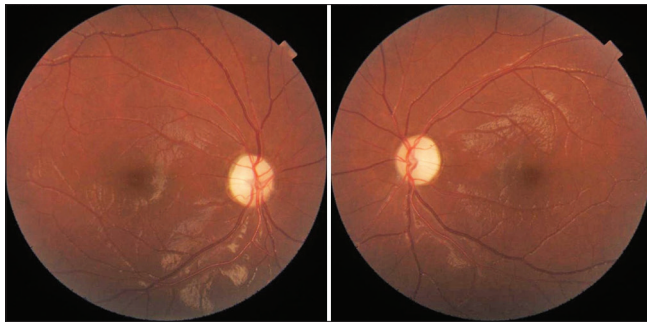


Figure 1: Fundus photos of case 1 showing pallor of the disc in both eyes

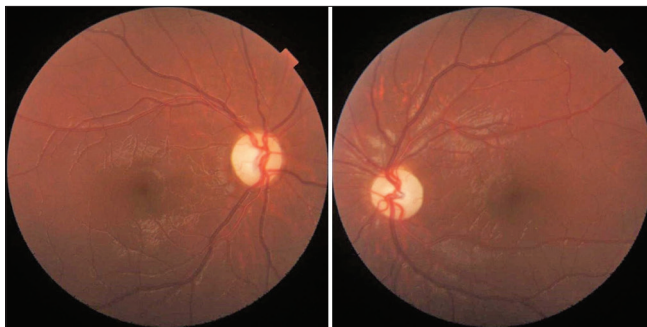


Figure 2: Fundus photos of case 2 showing pallor of the disc in both eyes

Exon 8 of the WFS1 gene (stop codon and premature truncation of the protein at codon 678), autosomal recessive, c2034G>A. A pediatric endocrinologist's opinion was sought who advised for serum electrolytes and osmolarity and diabetes insipidus was diagnosed based on the reports. A low-vision aid trial was given. The child was advised to stay under the care of a pediatric endocrinologist.

Discussion

Wolfram syndrome is a rare genetic disease occurring in approximately 1 out of 150 cases of juvenile onset insulin dependent diabetes mellitus presenting with optic atrophy simultaneously or after; rarely precedes the onset of the endocrine disturbances.^[5] Primary optic atrophy is the major component of the syndrome which is bilateral and presents within the first decade, progressing eventually to blindness.^[5] A deterioration of visual acuity and defective color vision with peripheral constriction of visual fields are also observed.^[6] Both our patients presented with primary optic atrophy in their first decade with gradual progressive diminution of visual acuity. Other ocular findings included blue-dot cataract and latent nystagmus in case 2.

Other systemic manifestations reported include neuropsychiatric abnormalities, neurological abnormalities, renal abnormalities like neurogenic bladder, dilation of the urinary tract, and hearing abnormalities. The hearing loss was noted in case 1 while case 2 had a neurogenic bladder.

Both cases fulfilled two major criteria of EURO-WABB for the diagnosis of Wolfram syndrome. In both cases, though the children were under the care of a pediatrician and endocrinologist, the diagnosis of Wolfram syndrome was

not considered until we suggested the possibility. Both cases fulfilled the diagnostic criteria according to the EURO-WABB criteria.^[2]

So, it is important for the ophthalmologist to have a high index of suspicion in cases of juvenile optic atrophy and diabetes with poor vision. Other differential diagnoses in a juvenile diabetic presenting with optic atrophy include Leber's hereditary optic neuropathy, maternally inherited diabetes mellitus and deafness, autosomal-dominant optic atrophy, Friedreich's ataxia, and thiamine-responsive megaloblastic anemia with diabetes and deafness.^[7] All of them need genetic analysis for diagnosis except thiamine-responsive anemia with diabetes and deafness which needs blood investigations.^[8] The last being juvenile diabetic papillopathy which is a diagnosis of exclusion.

The inheritance of the Wolfram syndrome can be (a) mitochondrial (b) autosomal recessive-classical WS affecting WFS-1 gene (c) autosomal-dominant WS-like disease.^[9] The history of consanguinity was present in the female patient who tested positive for homozygous, an autosomal recessive gene having a nonsense mutation which is a new and rare mutation described only once in the literature before^[10] while the male patient tested positive for autosomal-dominant type (WS-like disease). The Wolfram syndrome owing to the clinical heterogeneity, and lack of phenotype-genotype correlation, clinical findings may be missed by the physician, and thus, the ophthalmologist plays a central role in correctly identifying and diagnosing the syndrome. This enables timely rehabilitation of treatable systemic manifestations and allows the detection of carrier state via pre-conceptual counseling and sibling genetic analysis.

The varied clinical presentation in both cases and different genetic mutations highlight the importance of having high index of clinical suspicion in cases of optic atrophy in young children with diabetes and the need for genetic analysis in them. It is, therefore, necessary that all juvenile diabetics should be screened for vision problems regularly by an ophthalmologist.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Toppings NB, McMillan JM, Au PYB, Suchowersky O, Donovan LE. Wolfram syndrome: A case report and review of clinical manifestations, genetics pathophysiology, and potential therapies. *Case Rep Endocrinol* 2018;2018:1-8.
2. Farmer A, Aymé S, de Heredia ML, Maffei P, McCafferty S, Mlynarski W, *et al.* EURO-WABB: An EU rare diseases registry for Wolfram syndrome, Alström syndrome and Bardet-Biedl syndrome. *BMC Pediatr* 2013;13:1-7.

3. Soares A, Mota Á, Fonseca S, Faria O, Brandaõ E, Falcaõ Dos Reis F, *et al.* Ophthalmologic manifestations of wolfram syndrome: Report of 14 cases. *Ophthalmologica* 2019;241:116-9.
4. Çelmeli G, Türkkahraman D, Çürek Y, Houghton J, Akçurin S, Bircan İ. Clinical and molecular genetic analysis in three children with wolfram syndrome: A novel WFS1 mutation (c.2534T>A). *J Clin Res Pediatr Endocrinol* 2017;9:80-4.
5. Ganie MA, Laway BA, Nisar S, Wani MM, Khurana ML, Ahmad F, *et al.* Presentation and clinical course of Wolfram (DIDMOAD) syndrome from North India. *Diabet Med* 2011;28:1337-42.
6. Ari Ş, Keklíkçi U, Çaça I, Ünlü K, Kayabaşı H. Wolfram syndrome: Case report and review of the literature. *Compr Ther* 2007;33:18-20.
7. Zaarour KG, Traboulsi EI. Wolfram Disease/DIDMOAD Syndrome (WFS) 2021;2:1-7.
8. Syndrome SR. Thiamine-responsive megaloblastic anemia syndrome. Summary Suggestive Findings 2020;1-14.
9. Tranebjærg L, Barrett T, Dahl ND. WFS1 wolfram syndrome spectrum disorder. Summary Genetic counseling Suggestive Findings 2020;1-27.
10. Galvez-Ruiz A, Galindo-Ferreiro A, Schatz P. Genetic testing for Wolfram syndrome mutations in a sample of 71 patients with hereditary optic neuropathy and negative genetic test results for OPA1/OPA3/LHON. *Neuroophthalmology* 2018;42:73-82.