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Two Siblings with 'Diabetes Mellitus and Bilateral Optic Atrophy'

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Abstract: ***Purpose: To report two siblings with diabetes mellitus Type I, bilateral progressive optic atrophy and sensory neural deafness.***

Keywords: Diabetes mellitus, Diabetes insipidus, Optic atrophy, Deafness

1. Introduction

Wolfram syndrome (WS) is a rare autosomal recessive neurodegenerative disorder that minimally requires the presence of two diagnostic criteria, insulin-dependent diabetes mellitus (IDDM) and progressive optic nerve atrophy. [1] WS is variably associated with diabetes insipidus, neurological disorders, urinary tract anomalies, endocrine dysfunctions and many other systemic manifestations. Wolfram and Wagener first described WS in 1938. [2] Patients with WS demonstrate diabetes mellitus followed by optic atrophy in the first decade, diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts early in the third decade, and multiple neurological abnormalities early in the fourth decade. [3] The prognosis of WS is poor, and the death occurs prematurely. Although there are no therapies that can delay or reverse the progression of WS, a careful clinical monitoring can help patients during the rapid progression of the disease, thus relieving the sufferings and improving their quality of life. [4, 5, 6] There should be a high index of clinical suspicion for WS when clinical manifestations of type 1 diabetes and optic atrophy present together. Genetic analysis is often required to confirm the diagnosis. Wolfram syndrome has been demonstrated to result from mutations in two loci: WFS1 and WFS2/CISD2, localized on chromosome 4p166, 7 and 4q24, 8 respectively. [7, 8, 9]

We describe a pair of Indian siblings presenting with IDDM, bilateral optic atrophy and sensori neural hearing loss, at ages 23 and 26 years, respectively.

2. Case Report

Two male siblings, 23 years and 26 years of age, presented with progressive diminution of vision in both eyes for last 8 years. They were known case of diabetes mellitus type I for last 14 years. Both were diagnosed as case of diabetes mellitus Type-I at same time and were on insulin therapy since then. The younger one had best corrected visual acuity (BCVA) of 6/36 in both eyes. He had color vision deficiency in both eyes. The intra-ocular pressure (IOP) was normal in both eyes. On dilated fundoscopic examination he had bilateral partial optic atrophy with mild NPDR in both eyes (Photo-1). Bilateral mild sensori-neural hearing loss was seen on follow-up after 18 months (Photo-2). The central macular thickness (CMT) was 219 µ and 230µ in RE and LE respectively. The average retinal nerve fiber layer (RNFL) thickness was 58µ in both eyes. The elder sibling had BCVA of 2/60 in right eye and hand movements (HM) in left eye. There was bilateral partial optic atrophy with severe non-proliferative diabetic retinopathy (NPDR) in RE and proliferative diabetic retinopathy (PDR) with clinically significant macular edema (CSME) in LE (Photo-3). The color vision deficiency was observed in right eye, but it could not be assessed in left eye due to low vision. The IOP was normal in both eyes. The CMT and average RNFL thickness was 238µ and 59µ respectively in RE and but it could not be assessed in LE due to media haze. The patients were referred to higher center for further investigation and management, where the elder one (26 years old) had undergone vitreo-retinal surgery, after which his visual acuity improved from HM to 6/60. But this elder sibling died after 3 months of surgery due to cardiac arrest.

The parents of these siblings had no history of diabetes mellitus or loss of vision. But their grand mother was a diagnosed case Type II diabetes mellitus and maternal uncle was a diagnosed case of Type I diabetes mellitus (IDDM).

3. Discussion

WS is also referred to as DIDMOAD, an acronym for its most common clinical presentation that includes: diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA) and deafness (D). [9]

The phenotype of the disease has been associated with several mutations in the WFS1 gene, a nuclear gene localized on chromosome 4. Since the discovery of the association between WFS1 gene and Wolfram syndrome, more than 150 mutations have been identified in WS patients. [6]

Earlier diagnosis of this disease is anticipated to improve quality of life for patients with WFS by allowing earlier interventions aimed at managing the clinical features of this syndrome. Physicians and ophthalmologists are likely to have the first opportunity to recognize WFS after the diagnosis of an initial manifestation. School health screening

programs may also provide an opportunity to identify vision defects, hearing impairment, and abnormal urinalysis results. However, a significant delay in the recognition of WFS may occur in some patients, and this would presumably impact their quality of life adversely by prolonging the period of untreated associated symptoms. [5]

WS remains a debilitating and progressive disease with no effective treatment to halt or reverse its progression. The treatment is aimed at treating individual clinical manifestation, slowing disease progression, and improving quality of life. The treatment options include dantrolene, a muscle relaxant drug used for multiple sclerosis and cerebral palsy, targeting ryanodine receptor in the Endoplasmic Reticulum (ER) membrane preventing beta-cell death. The dipeptidyl peptidase-4 inhibitor, a drug to treat diabetes which deactivates glucagon-like-peptide-1 hence providing protection against beta-cell failure and possibly diabetes remission. The valproic acid, an anti-epileptic drug is reported to have neuroprotective function by inhibiting ER stress–induced apoptosis. [7]

Optic nerve atrophy as a result of retinal ganglion axon death is the most common ophthalmic finding in Wolfram syndrome and can lead to the diagnosis of WFS in 39% of the cases. Optic atrophy manifests as constriction of visual fields, color perception deficiencies, especially in the blue-yellow spectrum and loss of visual acuity which, contrary to Leber's hereditary optic neuropathy, may be of variable rate and is usually gradual (1–25 years). Thinning of the RNFL and the macula is the main OCT finding. OCT-angiography shows reduction in the peripapillary microvasculature, most prominent in the temporal area. Electrophysiology tests in Wolfram syndrome are indicative of the optic atrophy. Specifically, electroretinography may vary but is usually normal, while visual evoked potentials show a delayed P100 value with reduced amplitude and abnormal wave morphology. Notably, diabetic retinopathy is rare among patients with Wolfram syndrome, in spite of the early development of diabetes mellitus and poor glycaemic control in general. [10, 11]

But in both the cases which are being reported, diabetic retinopathy was seen on the day of presentation. This may be due to their long duration of IDDM and both were on insulin therapy for last 14 years.

4. Conclusion

Wolfram syndrome should be considered when clinical manifestations of type 1 diabetes and optic atrophy are present together. The availability of facilities for genetic testing should be increased. This will help in identification of more genetic mutations and help in finding interventions to delay the onset of clinical manifestations in these patients. Further genetic counseling may also help in preventing the disease occurrence in families.

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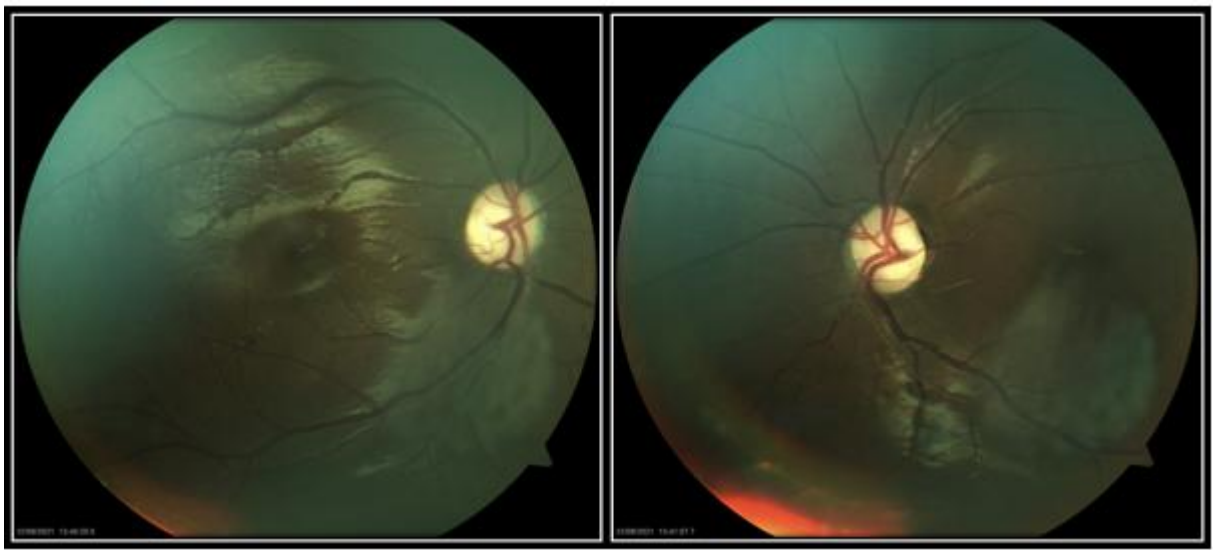

Photo 1: Photograph showing bilateral optic atrophy and mild NPDR in younger sibling.

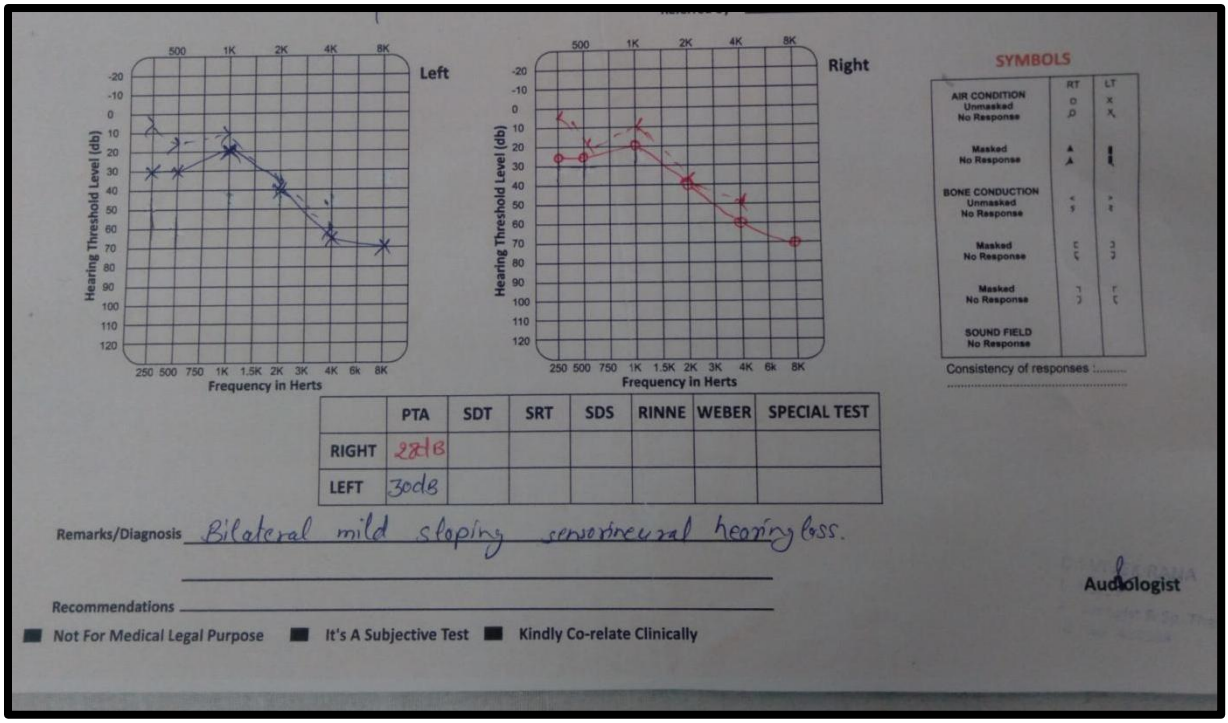

Photo 2: Photograph showing bilateral mild sensory neural hearing loss in younger sibling

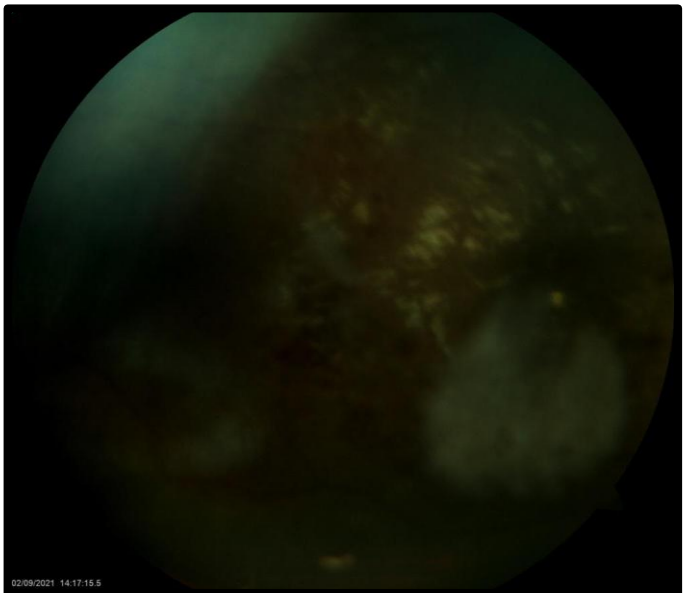

Photo 3: CSME and PDR in left eye of elder sibling