

# Wolfram Syndrome with Non-Symptomatic Neurodegenerative Changes- A Rare Case Presentation

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## Abstract

Wolfram syndrome (WFS) (MIM22230, chromosome 4; MIM 598500, mitochondrial) referred to as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness), firstly described in 1938 by Wolfram and Wagener, is a rare neurodegenerative autosomal-recessive disorder mainly characterized by juvenile-onset Diabetes Mellitus (DM) by the age of 7 year and Optic Atrophy(OA) by 11 years of age. Other features include diabetes insipidus, sensorineural hearing loss, peripheral-neuropathy, ataxia, psychiatric problems, renal-tract abnormalities, and bladder-atonny. Clinical diagnosis of WFS was confirmed by existence of DM and OA at an early age in the affected patients. WFS can be of; Type 1- mutations in *WFS1* gene located at 4p16.1.116 chromosome and Type 2- mutation in *WFS2* (*CISD2*) gene located at chromosome 4Q22-Q24, of Mitochondrial DNA. Disruption of the function of Wolframin, a transmembrane protein encoded by *WFS1*, has been found to cause early apoptosis, accounting for progressive beta-cell loss and neuronal degeneration associated with disease.

**Keywords:** Wolfram syndrome; *WFS1* gene; Diabetes Mellitus (DM); Neurodegenerative disorders; DIDMOAD

## Introduction

Wolfram Syndrome (WFS) is a rare autosomal recessive disease with a prevalence estimate of 1 in 100,000 to 1 in 700,008 based on an observation of the prevalence of optic atrophy and diabetes mellitus.<sup>[1]</sup> Parental consanguinity has been noted and estimated 1 in 350 people carry the genes of WFS.<sup>[2]</sup> Approximately 200 cases have been described in the scientific literature. Only a few families from Jordan have been found to have WFS Type 2.<sup>[3]</sup> *WFS1* gene mutations is most common cause found 85-90% cases worldwide. *WFS2* incidence is found very low as in 3 large consanguineous Jordanian families characterized by juvenile-onset diabetes mellitus, optic atrophy, deafness, urinary tract dilatation, impaired renal function, hypogonadism, and severe gastrointestinal ulcer and bleeding, but not diabetes insipidus.<sup>[4]</sup>

## Case History

Patient X, a 17-year-old female born to a non-consanguineous marriage with full term normal delivery, diagnosed with Diabetes Mellitus (DM) at the age of 5 and has been on split-insulin regimen since then. Patient presented with progressive diminution of vision since 6 months, hearing loss since 4 months and polyuria and polydipsia since 4 months when presented to us.

Her brother, father and grandmother has diabetes. She achieved menarche at age of 15 years with normal menstrual cycle. She is 151 cm tall weighing 46.3 kg and BMI of 20.3. Her growth is adequate with no any psychological and growth abnormalities. She was an average student in school with normal intelligence having friends and happy go lucky in nature. Her Systemic Examination was normal except fundus showing temporal disc pallor, margins well defined suggestive of partial Optic Atrophy (OA) bilaterally in Ophthalmological examination and absolute

conduction test reduced bilaterally with Pure tone audiometry suggestive of Bilateral Ear Moderately Severe SNHL.

All blood parameters were within normal range except HbA1c which was markedly high 13% and BSL(R) 283.4 mg/dl, 24 hour Urine is 6-7 litres. Urine Specific-gravity 1.005, Urine Micro Albumin 18.98 mg/dl. Serum Osmolality normal 294.2 mosmo/kg but Urine osmolality 216.7 mosm/kg

Water deprivation test concluded Diabetes Insipidus (DI) with Urine Output of 6 litre/24 hours.

MRI brain [Figure 1].

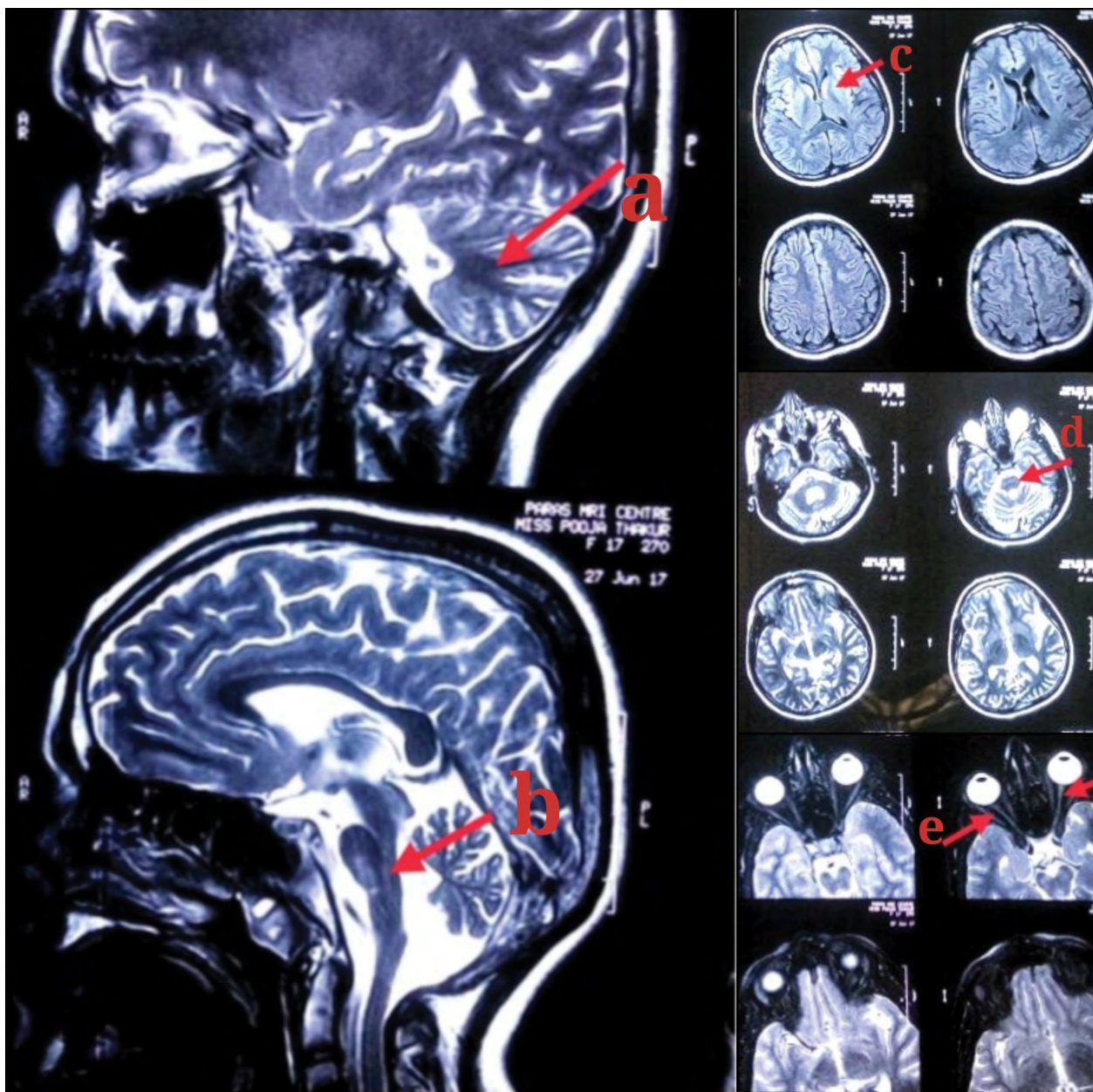
- S/O Mild cerebellar atrophy with reduced bulk of brain stem.
- Small T2W bright signal was seen in Pons anterior s/o chronic ischemia / demyelinating plaque.
- Calcification seen in Globus pallidum (Bright signals are seen apart from normal).
- Reduced Caliber of Optic nerve complex on both the sides (app. 2 mm), more on Right side.

USG-abdomen revealed significant post void urine volume of 514.09 ml with bilateral hydronephrosis due to retention of urine.

Her Mutation and Bioinformatics Analysis Confirmed

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**Figure 1:** (a) Mild cerebellar atrophy; (b) Reduced bulk of brain stem; (c) Calcification in globus pallidum; (d) Small T2W bright signal in Pons; (e) Reduced caliber of optic nerve.

the Diagnosis Of Wolfram Syndrome by Revealing a Variant of Unknown Significance on *WFS1* gene, exon 8 NM\_006005.3:c.1399\_1401delCTG NP\_005996.2:p.Leu468del Homozygous.

### Discussion

Patient had all the 4 cardinal features which is required for the clinical diagnosis of the Wolfram Syndrome (WFS) Type 1. Patient developed Diabetes Mellitus (DM) at the age of 5 years, mean age to develop DM in WFS reported in Barrett study is 6 years. DM may result from hypothalamic degeneration, although loss of pancreatic  $\beta$ -islet cells as part of a specific defect in neuroectodermal amine precursor uptake and decarboxylation-derived cells in the pancreas and in the supraoptic and paraventricular nuclei has also been postulated.<sup>[5]</sup>

Patient developed Optic Atrophy at the age of 17 years, mean

age in Barrett study is 11 years. Patient had progressive painless diminution of vision which didn't improve on pin hole. Colour vision was normal. No evidence of diabetic retinopathy. The cause for blindness can be due to severe axonal loss and demyelination of optic nerves, chiasma and tracks.

Patient developed Diabetes Insipidus (DI) at the age of 17 years; mean age onset according to Kinsley studies is 15.5 years (range 4-41). DI are present in approximately 38%. 9 Points that favour diagnosis of central DI in this patient is polyuria, positive water deprivation test and low urine osmolality. A loss of vasopressin-producing neurons in the hypothalamus has been well documented in this disease and is thought to be the cause of WFS-associated DI.<sup>[6]</sup>

Patient developed SNHL at the age of 17 years, median age according to Kinsley study is 14.6 years (range 1-29). Deafness

in these patients is neurological affecting auditory nerve and its central pathways, degenerative atrophy of the vestibulocochlear nuclei and inferior colliculi leading to decreased perception of sounds rather than deficit in transmitting the sound to the nerve.

Dilation of the urinary tract is observed in 45% of cases which may be secondary to chronic high urine flow rates (DI) or neuronal degeneration at various levels of the urinary tract or atony of the bladder.<sup>7</sup> Our patient had polyuria and Post-void residual volume by ultrasound imaging is 514.09 ml with bilateral hydronephrosis.

According to the largest cohort series to date, neurological symptoms were present in 53% of patients by an average age of 15 years. The majority of symptoms were related to the brainstem and cerebellum, specifically, cerebellar ataxia (45%), peripheral neuropathy (39%), cognitive impairment (32%), epilepsy (26%), and lastly dysarthria, dysphagia, and nystagmus in 10%. Brain MRI was abnormal in 54%, including atrophy of the cerebrum, cerebellum, and brainstem.<sup>[7]</sup>

Our patient had no neurological complaint though her MRI report showed neurodegenerative changes in form of mild cerebellar atrophy with reduced bulk of brain stem(a), small T2W bright signal was seen in Pons anterior s/o chronic ischemia/demyelinating plaque. Calcification is seen in Globus pallidum. Similarly, there was a case reported by S. Ito, R. Sakakibara and T. Hattori in which patient had marked brain MR imaging abnormalities affecting the pontocerebellar tract, though there were no neurologic abnormalities suggesting cerebellar dysfunction showing discrepancies between neurologic and radiologic findings.

## Conclusion

Patients with juvenile onset DM and vision loss in early decade of life can be clinically diagnosed as WFS to be confirmed with Genetic study and other siblings to be screened. One should keep track of patient and regular follow up for tight sugar controls and to detect serious complications which are known to manifest later in life like hyperglycemic hyperosmolar hypernatremic coma to avoid poor quality of life and increase survival. Later in their life, they are known to suffer from neuro-psychiatric illness such as depression, schizophrenia and suicidal tendency, therefore yearly psychiatric evaluation is necessary. Females

with Wolfram Syndrome can give birth to healthy babies provided the DM, DI and associated disorders are intensively monitored and aggressively managed.

## Recommendations

Since examination anxiety can often adversely interfere with the performance of the students, it is recommended that the students identify such factors through mindfulness. Recognizing the problems is the first step in managing it effectively. It is also recommended that students consult with a psychologist or a counselor for expert management.

## Competing Interests

The authors declare that they have no competing interests.

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