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Case Report
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Wolfram Syndrome: A Case Report

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Introduction

Wolfram Syndrome is autosomal recessive characterized by juvenile diabetes mellitus, optic atrophy and neurodegeneration. It was reported in 1938 by Wolfram and Wagener in four out of eight siblings who has diabetes and optic atrophy [1]. The acronym DIDMOAD comprises of most common findings of the syndrome: Diabetes insipidus, diabetes mellitus, optic atrophy and deafness. The prevalence has been estimated to be 1/770,000 in the UK and 1/100,000 in the North American population [2,3]. In India, the estimated prevalence is 1/805,000 based on the study from North India [4].

Wolfram Syndrome is a neurodegenerative disorder involving the central nervous system, peripheral nerves and neuroendocrine tissue. The major clinical presentation includes Diabetes mellitus, optic atrophy, central diabetes insipidus, sensorineural deafness, urinary tract problems and neurological difficulties. Although a rare disease, it is associated with significant morbidity and mortality due to lack of effective treatment to halt, delay or reverse the progression of disease.

We present a case of Wolfram Syndrome who presented to Medical OPD with polyuria.

Case Presentation

A 22-year-old man presented with history polydipsia and polyuria of 2 years duration. He had juvenile onset diabetes in the last 5 years of age, progressive bilateral visual diminution for five years of age and progressive bilateral hearing impairment for 10 years of age. He had hesitancy, dribbling and straining during micturition in the last 12 years of age. He had younger brother of 8 year of age bronchial, asthma and adenoid hypertrophy. His brother had no visual, auditory or urinary complaints.

He was admitted in our hospital for further work up and evaluation. He had urine output of 8 L/day with water intake 6.5 L/day. After glycemic control was achieved, he underwent water deprivation test which was suggestive of diabetes insipidus (Table 1). Contrast enhanced MRI brain revealed absent of Post-Pituitary Bright Spot. On further evaluation, he had bilateral optic atrophy on fundoscopy. Pure tone audiometry revealed bilateral sensorineural hearing loss. USG KUB revealed dilatation of pelvicalyceal system. He was diagnosed as a case of Wolfram Syndrome-DIDMOAD and started on Tablet Desmopressin for Diabetes Insipidus. He should good response to therapy with reduction in urine output to 1.5 L/day (Figure 1, 2).

Discussion

Wolfram syndrome is rare autosomal recessive disorder with juvenile onset diabetes and neurodegeneration. It is autosomal recessive in inheritance. The diagnosis is based on EURO. WABB diagnostic criteria consisting of major criteria as diabetes mellitus and optic atrophy [5].

Diabetes mellitus in wolfram syndrome is classified as Type 3H diabetes associated with other genetic disorders. It is present in 98% cases of DIDMOAD, however may not be the first presenting feature in 20% cases [6]. It is non-autoimmune, insulin deficient and non-HLA linked [2]. Insulin antibodies are usually negative. However, most patients are misdiagnosed as type 1 diabetes at onset and are started on insulin therapy. The mean age of onset is 6 years of age [2]. It and is not prone to ketoacidosis. In our case it was detected at 5 years of age. Surprising, microvascular complications are not commonly seen even in adulthood [2]. Our case had no evidence diabetic neuropathy, retinopathy or nephropathy. However, glycemic control is achieved by insulin therapy as mentioned in previous case reports.

Optic atrophy is second most common feature of Wolfram syndrome occurring in 82% cases. It presents as painless progressive bilateral diminution of vision. The mean age of onset is 11 years [6]. In our case the onset was at 5 years of age. The treatment usually based on corrective lenses.

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Table 1: Water Deprivation test.

Time/Wt (kg)	Pulse/BP (/min; mmHg)	RBS (mg/dL)	Urine Volume (mL)	Serum Na/K (mEq/L)	Serum Osmolality (mosm/L)	Urine Osmolality (mosm/L)	Urine Specific Gravity	Urine RE/ME (Dipstick)
0800 56.75	76 120/74	102	-	139/4.0	222	114	1.010	Neg
0900 56.3	82 116/80	78	200				1.010	Neg
1000 56.2	80 140/90	102	250	141/4.3	313	120	1.010	Neg
1100 55.25	94 146/102	103	200				1.010	Neg
1200 54.95	92 146/100	80	110	148/3.9	394	121	1.010	Neg
Tab Desmopressin 100 mcg given at 1200 h								
1300 54.7	96 140/98	73	40	143/4.2	-	-	1.015	Neg

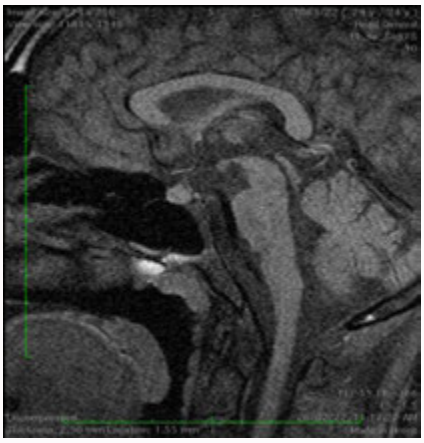

Figure 1: CEMRI brain showing absence of posterior pituitary bright spot.

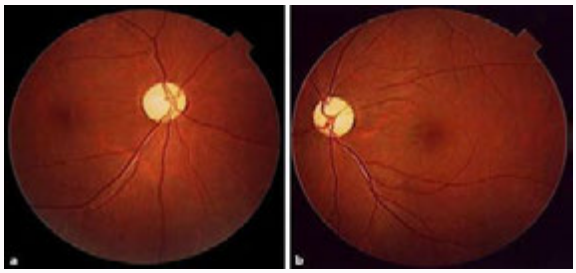

Figure 2: Fundoscopy showing bilateral optic atrophy.

Other ophthalmic features like cataract, pigmentary retinopathy and diabetic retinopathy occur in 66.6%, 30% and 20% cases respectively [7].

Central Diabetes insipidus is seen in 38 % cases of Wolfram syndrome [6]. The mean age of onset 14 years [6]. It our case it was detected at 22 years of age. Water deprivation test is difficult to perform in view of underlying diabetes mellitus. Serum AVP levels and MRI Brain help to confirm diagnosis in cases of polyuria. We did CEMRI brain which revealed absent post pituitary bright spot.

Sensorineural hearing loss is seen in 48% cases [6]. The mean age of onset is 16 years of age [2]. Our patient had sensorineural hearing loss in the past 10 years of age which occurred earlier than previous reported.

Urinary tract anomalies may present at 12 to 20 years of age in about 19% cases [6]. Our patient had neurogenic bladder with dilatation of pelvicalyceal system since 12 years of age.

All four components of DIDMOAD- Diabetes mellitus, Diabetes Insipidus, Optic Atrophy and Sensorineural Hearing Loss is seen 14% to 58% [2,8]. Wolfram syndrome must be suspected in cases of patient diabetes mellitus and optic atrophy occurring in early adolescence.

Neurological manifestations like cerebellar ataxia, central apnea, anosmia, peripheral neuropathy may occur at median age of 30 years. Psychiatric disorder like anxiety, depression, psychosis may be seen in patients with Wolfram Syndrome. Gastrointestinal manifestations like peptic ulcer, diarrhea or constipation may also be present in some cases. Hyponatremia and hypogonadism due to pituitary insufficiency has also been reported [2,9]. The cause of mortality is usually central respiratory failure due to brain stem atrophy and renal failure due to infection [2].

Wolfram syndrome is a manifestation of WFS1 gene located on Chromosome 4p16.1. The WFS 1 protein is located on Endoplasmic Reticulum (ER) and functions to maintain homeostasis by Unfolded Protein Response (UPR) pathways. In cases of deficient WFS1 gene, ER stress leads endocrine dysfunction and neuronal degeneration [10,11]. There is currently no cure for Wolfram syndrome, several studies for drug repurposing, gene therapy and agents targeting ER stress are under investigation [12].

In conclusion, Wolfram syndrome is rare neurodegenerative disorder with multisystem involvement. It should be suspected early in patients with juvenile diabetes and optic atrophy in adolescence. Multidisciplinary approach is required to manage manifestations, complications and for rehabilitation of patients with the disease.

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