A Case Report of Wolfram Syndrome in a Saudi Child Presenting with an Acute on Top of Chronic Renal Failure

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Abstract

Wolfram syndrome (DIDMOAD syndrome) is an autosomal recessive neurodegenerative disorder characterized by juvenile-onset, non-immune insulin-dependent diabetes mellitus and optic atrophy, often accompanied by other symptoms including diabetes insipidus, neurosensory deafness, urinary tract and neurological abnormalities. We described a child with rapidly progressive renal failure in a region with under reporting of wolfram syndrome.

This case report aims to raise awareness of this rare disease so that individuals with WS are identified and provided with appropriate care.

Keywords: Wolfram Syndrome; DIDMOAD; Renal Failure

Background

Wolfram syndrome (WS) is a rare neurodegenerative disorder. Inherited mainly as autosomal recessive. Also named DIDMOAD syndrome. It was first reported in 1938 by Wolfram and Wagener [1]. There is 2 main identified genes, WFS1 gene, responsible for Wolfram syndrome type 1, it is caused by a mutation in chromosome 4p16.1 with more than 200 mutations [2]. WFS1 encodes the protein Wolframin, which is abundantly expressed in pancreas, brain, heart, and muscle and is thought to be a novel endoplasmic reticulum (ER) calcium channel or a regulator of channel activity [2]. The mutations of the WFS 1 gene founds alternatively in some studies in mitochondrial DNA [3,4]. Hence that, which explains the multi-systemic involvements and WFS 2/CISD2 responsible for Wolfram syndrome type 2, found in chromosome 4q22-q24 [1,4,5,7]. CISD2 has been shown to play a role in ER-mitochondria Ca2+ signaling and regulation of autophagy and CISD2 deficient leads to ER stress and apoptosis [5].

The syndrome is characterized mainly by endocrinological and neurological manifestations which their presence essential for diagnosis (Table 1). Other manifestations of syndrome are variable including gastrointestinal autonomic neuropathy, cardiovascular disorders, hypergonadotrophic hypogonadism, urinary bladder dysfunction, neurologic and psychiatric disorders [1,6].

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
<th>Minimum required</th>
<th>Other variable suggestive evidence</th>
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<tbody>
<tr>
<td>*DM &lt; 16 yrs.</td>
<td>*Diabetes insipidus,</td>
<td>*2 major OR *1 major plus 2 minor criteria</td>
<td>*Hypogonadism (males),</td>
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<td>*OA &lt; 16 yrs.</td>
<td>*Diabetes mellitus &gt; 16 yrs.,</td>
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<td>*Absence of type 1 diabetes auto-anti bodies,</td>
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<td></td>
<td>*Optic atrophy &gt; 16 yrs.,</td>
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<td>*Bilateral cataracts,</td>
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<td></td>
<td>*Sensorineural deafness,</td>
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<td>*Psychiatric disorder,</td>
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<td></td>
<td>*Neurological signs (ataxia, epilepsy, neuropa-thy, cognitive impairment),</td>
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<td>*Gastrointestinal disorders</td>
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<td>*Renal tract abnormalities,</td>
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<td></td>
<td>*1 loss of function mutation in WFS1/CISD2 AND/OR family history of Wolfram syndrome</td>
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Table 1: The diagnostic criteria for Wolfram syndrome.
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Usually the patient start with DM I earlier in 1st decay followed by Optic nerve atrophy, latter on patient will develop the rest of symptoms [7].

The course of the disease is devastating and currently no definitive treatment for it [7]. Patients die young at a median age of 30 years mostly due to respiratory failure caused by brainstem atrophy [12,13]. But clinical trials of drugs like [A Clinical Trial of Dantrolene Sodium in Pediatric and Adult Patients With Wolfram Syndrome (started January 2017) [19] that hope to stop or slow symptom progression are in progress [17].

The prevalence of WS is approximately 1 in 160,000 - 770,000 [7,18]. There is a high prevalence of consanguineous marriages in the Saudi Arabia which increase the incidence of inherited disorder like wolfram syndrome. It seems that wolfram syndrome is under-reported in Saudi Arabia. To our knowledge no single case of Wolfram's syndrome in Saudi child with renal failure have been reported.

In this case report, we are describing a case of wolfram disease with acute kidney injury on top of chronic with presentation in young age.

**Case Presentation**

A 12-year-old Saudi male known case of diabetes mellitus. He presented with 2 days history of fever, vomiting and dysuria. Patient found to have more than 100 pus cells in urine analysis admitted as case of UTI initially. Upon admission patient discovered to have acute renal failure on top of chronic renal failure.

Patient is product of full term with uneventful pregnancy. His parents were consanguineous (first degree cousins). The patient was the first child and had two younger sisters. All are healthy. Neither the parents nor the living siblings had clinical features of Wolfram syndrome.

He was diagnosed with DM at age of 4 years when he presented by polyuria, polydipsia, weight loss and hyperglycemia. Patient was managed with insulin Novo mix BID regimen with suboptimal control but never admitted for diabetic ketoacidosis or hyperglycemia. His anti-GAD antibody and anti-insulin antibody in the serum were negative.

At age of 6 years patient start to developed progressive visual loss, at age of 10 years ataxia, nystagmus and weakness in the left side of the body were noted by the parents, hearing difficulties also noted in same period.

On physical examination; Growth parameters weight = 28.5 kg below the 3rd centile, Height 124 cm below the 3rd centile. blood pressure, 145/85 mmHg (> 95th centile) and heart rate = 140 beats/min., respiratory rate = 26, temp = 37.7°C.

No dysmorphism, the abdomen was mildly distended, by palpation was soft and lax with no organomegaly and there is distended bladder, the urinary catheter inserted and high urine output 11 ml/kg/hour suggestive of obstructive uropathy, with no lower limb edema. He has a hemiparesis with mild ataxia.

Renal function parameters BUN = 26 mmol/L, creatinine = 504 umol/L, sodium 134 mmol/L, potassium = 5 mmol/L, calcium 2.13 mmol/L, phosphorus 2.2 mmol/L, GFR: 9 (GFR < 15 severe).

**Renal US showed:** Diminished corticomedullary differentiation. Bilateral moderate hydronephrosis, hydroureter and urinary bladder showed mucosal thickening suggestive of neurogenic bladder (Figure 1-5).

Figure 1: Lt kidney.
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Figure 4: Rt kidney.

Figure 5: Urinary bladder.

Ophthalmological examination revealed severe decrease in visual acuity, slit-lamp examination revealed primary optic nerve atrophy with no diabetic retinopathy.

Brain and orbit MRI done with unremarkable results (Figure 6-8).
Patient admitted where he received antibiotics for the UTI and hypertension controlled by amlodipine. Upon discharge BUN = 17.85 mmol/L, Cr = 187 umol/L mother trained for Clean intermittent Catheterization and patient started on Oxybutynin for the neurogenic bladder.

**Discussion**

Wolfram syndrome is a rare autosomal recessive known as DIDMOAD which stands for diabetes insipidus, Diabetes mellitus, Optic atrophy and deafness.

A diagnosis of Wolfram syndrome is based on the presence of characteristic signs and symptoms (Table 1). The identification gene mutation in the WFS1 gene or CISD2 gene confirms the diagnosis. However, genotype phenotype correlations in WS are unclear [25].

The minimal criteria for diagnosis are juvenile-onset diabetes and optic atrophy [9]. Our patient also having deafness in addition to some of the neurological and urological manifestation of wolfram but no diabetes insipidus.

The main features are Diabetes mellitus and Optic atrophy, which usually presented in the first decade of life at median ages of 6 years and 11 years, respectively [8].

Insulin-dependent, non-autoimmune DM is often the first manifestation of WS which presents at an average age of 6 years (range from 3 weeks to 16 years) [7]. Patients with wolfram syndrome show smaller glycemic variability than individuals with type 1 diabetes mellitus, and this may be associated with persistent residual insulin secretion [9]. The diabetes mellitus started in our patient at age of 4 years since that time was started on insulin with BID regimen.

Optic atrophy, a consistent finding in all patients, occurs at an average age of 11 years [7]. Manifestations of visual dysfunction, including reduced acuity, dyschromatopsia, afferent pupillary defects, visual field deficits, optic nerve pallor and cupping, thinned retinal nerve
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fiber layer (RNFL), cataracts, nystagmus, and strabismus. RNFL thickness may be the most reliable early marker [14]. Galvez-Ruiz (2017) conducted a study in Saudi Arabia, the authors present a sample of 71 patients with hereditary optic neuropathy [23]. All of these patients later underwent genetic testing to rule out WFS. 18 patients (25.3%) were positive for some type of mutation or variation in the WFS gene. Out of 18,50% had a positive family history, and 100% presented consanguinity between parents [23].

At the age of 6 years our patient started to have progressive visual loss and found to have optic atrophy which is not related to diabetes mellitus because there was no evidence of diabetic retinopathy and progressed till he just hardly see the light.

DI usually started in the second decay of life, due to a loss of vasopressin-producing neurons in the hypothalamus. our patient dose not suffer from it. Hatem., et al. (2000) described a Jordanian families with 16 member diagnosed with wolfram syndrome. There is an absence of diabetes insipidus in all affected family members [4]. On the other hand Kholdon., et al. (2016) report that all of the five patients selected in their study have developed diabetes insipidus early in their life with a median age of 4 years [12].

Urinary tract abnormalities (obstruction of the ureters, an atomic bladder with a large capacity, neurogenic bladder, hydroureteronephrosis, and recurrent infections) are common findings (58%) in WS [15]. Though some studies described up to 90% prevalence among WS patients [10,12,18]. The exact cause of urinary tract dilatation in this syndrome is unclear [16]. But it may be secondary to chronic high urine flow rate or neurodegeneration in different levels of the urinary tract [9]. Also we can it ignore the role of diabetic peripheral neuropathy as causative agent. Our patient having chronic kidney disease mostly secondary to obstructive uropathy from the neurogenic bladder, which usually appears late in the second or third decay of life, but it’s started earlier in our patient. Hüseyin Anıl [6] report a case with wolfram syndrome accompanied by chronic renal failure in 19 year old Turkey male. Another report from Turkish family [3] showed very rapid progression to renal failure before age 12 in three females. also, one Jordanian boy was reported by Hasan., et al. [16] he developed end-stage renal failure and needed hemodialysis at the age of 14 years. Lim MC., et al. [20] describe a Chinese family with three siblings, all females, presenting with the Wolfram Syndrome. All three cases had almost similar clinical presentation of insulin-dependent diabetes mellitus, with rapid development of severe renal and retinal complications. Two siblings died at age thirty and thirty-one years of end-stage renal failure. Salih., et al. (1991) described 3 Sudanese patient with WS. All 3 had severe bilateral hydronephrosis with dilated ureters and distended bladder without vesicoureteral reflux one of them died at age of 20 [27].

Neurological features in wolfram syndrome present commonly with truncal ataxia, startle myoclonus, horizontal nystagmus, dysarthria, central apneas, loss of taste and smell, and hemiparesis [12,26]. Ataxia is the most common neurological symptom affecting almost 60% of patients, onset in early adulthood [18]. Though some believe that Quantifiable gait impairments can be detected in individuals with WFS earlier than previous clinical observations suggested. These impairments are not fully accounted for by the visual or balance deficits associated with WFS and may reflect early cerebellar and/or brainstem abnormalities [11]. In the large cohort series, neurological symptoms were present in 53% of patients by an average age of 15 years [26].

Brain stem atrophy is also a prominent feature that often results in death secondary to central apnea [19] despite of that brain MRI and orbital MRI may normal in almost 46% of the patients with WS [23].

The neurological symptoms in form of ataxia, nystagmus and hemiparesis found in our patient, in the literature it was described later with the disease progression but developed so early in our patient, which put more burden on our patient and his family.

Deafness in WS is commonly a high frequency, symmetric hearing loss, usually detected in the second or third decade with a relatively slow rate of deterioration [9,18].

Short stature and growth hormone deficiency have been reported, either isolated or as part of hypopituitarism, which are believed to be due to Hypothalamo-hypophysial dysfunction. Our patient found to be short and underweight which may explained by CKD but growth hormone deficiency may play a role [25].

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There is no definitive treatment for WS. Diabetes mellitus is managed with insulin, and vasopressin for diabetes insipidus. There is no treatment for loss of vision. Regarding the deafness, hearing aids can help. Neurogenic bladder may be treated by intermittent catheterization and some medications like oxybutynin [9].

Treatments which attempt to reduce ER stress or improve mitochondrial function may improve neurologic and β-cell survival which may improve the neurological and endocrinological outcomes.

A phase 1 clinical trial is currently investigating safety of long term use (A Clinical Trial of Dantrolene Sodium in Pediatric and Adult Patients with Wolfram Syndrome, ClinicalTrials.gov, NCT02829268).

Conclusion

Wolfram syndrome should be considered when the diabetes patients present with optic atrophy. Clinical suspicion at an early stage is important for prompt diagnosis and proper management. Renal failure is one of the important causes of death in WS, a careful assessment for urinary tract abnormalities and urinary infections are recommended [7]. Wolfram syndrome affects different organs and systems in the body. Thus, multidisciplinary care by physicians and healthcare professionals from a range of disciplines is required. Careful clinical monitoring and supportive care can help relieve the suffering of patients and improve their quality of life.

Consent

Written consent from the care giver has been taken.

Bibliography


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