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Case Report

Wolfram syndrome: a case report with severe polyuria and secondary urological abnormalities

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ABSTRACT

Wolfram syndrome is the condition characterized by juvenile onset diabetes mellitus and optic atrophy, which is also known as DIDMOAD. Classical Wolfram syndrome is a rare autosomal recessive disorder caused by mutations in WFS1, a gene involved in endoplasmic reticulum and mitochondrial function. Patients present with type 1 diabetes mellitus followed by optic atrophy in the first decade, diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts as early as in the third decade, and various neurological abnormalities in the early fourth decade. We describe a case report of 14-year-old male child diagnosed as wolfram syndrome with type 1 diabetes mellitus, diabetes insipidus, deafness, optic atrophy and severe urological abnormalities. Patients who present with early onset insulin-dependent diabetes mellitus and optic atrophy together should be evaluated with respect to Wolfram Syndrome. If a patient, who is a known case of diabetes mellitus, presents with persistent polyuria or neurogenic bladder despite good glycemic control, suspicion of wolfram syndrome and further evaluation regarding the same must be made. Recognizing and timely management of this condition will help to improve the quality of life in the patient.

Keywords: Wolfram syndrome, Secondary urological abnormalities, Polyuria

INTRODUCTION

In the year 1938, Wolfram syndrome (WS) was described in four siblings who had features of diabetes mellitus and optic atrophy.[1] The hallmark characteristics of wolfram syndrome are type 1 diabetes mellitus, diabetes insipidus, sensorineural deafness and optic atrophy.[2,3] Hence it is also known by the acronym DIDMOAD syndrome (diabetes mellitus, diabetes insipidus, optic atrophy and deafness). It is a progressive neurodegenerative disorder, in which patients present with nonautoimmune and non-HLA linked diabetes mellitus associated with optic atrophy in the first decade; followed by diabetes insipidus and sensorineural deafness in the second decade; thereafter renal tract abnormalities early in the third decade; and various neurological abnormalities, like cerebellar ataxia, myoclonus early in the fourth decade.[4]

Previously it was hypothesized to be a mitochondrial disorder. However now it is known that classical Wolfram syndrome (WS) is the result of autosomal recessive mutations affecting the WFS1 gene, which is involved in endoplasmic reticulum (ER) function. Autosomal dominant mutations in WFS2 have also been noted to cause WS like disease characterised by diabetes,

sensorineural hearing loss, psychiatric disorders and variable optic atrophy.[5,6]

Associated morbidities include hypogonadism, infertility, hypopituitarism, peripheral neuropathy, dementia, psychiatric illness and urinary tract problems.[7] The prognosis of this syndrome is poor at present as most patients succumb prematurely to severe neurological disabilities like bulbar dysfunction and organic brain syndrome, with the median mortality age being 30 years (ranging 25 to 49 years), usually from respiratory failure as a result of brain stem atrophy. In current case report, we are describing a case of wolfram syndrome with neurogenic bladder with grade 3 hydroureteronephrosis.

CASE REPORT

A 14 year old male child, who was diagnosed with insulin dependent diabetes mellitus four years ago, presented to the pediatric department with the chief complaints of lower abdominal distension and difficulty in voiding urine since one month. There was also history of polyuria and polydipsia over the last 6 years. On examination, anthropometry revealed short stature with an SMR stage of 2. Urine culture showed urinary tract infection (UTI) with *E. coli* growth sensitive to ciprofloxacin. Renal sonography showed bilateral moderate to gross hydroureteronephrosis and increased cortical echopattern with blunting of corticomedullary junction suggestive of grade 3 hydronephrosis.

Antibiotic therapy and strict glycemic control was advised. After resolution of UTI, micturating cystourethrogram (MCU) was done which showed bilateral moderate hydroureteronephrosis and bladder appears distended with mucosal irregularities, features suggestive of neurogenic bladder. Adequate insulin therapy was given for glycemic control. However, polyuria and polydipsia persisted despite good glycemic control. Child had polyuria (11 ml/kg/hour) and polydipsia (water intake of >3 litres/m^2/day).

Further workup for polyuria was done. Early morning baseline value of plasma osmolarity and urine osmolarity was found to be 282 mOsm/kgH2O and 84 mOsm/kgH2O respectively. Since urine osmolarity was less than 300 mOsm/kgH2O and plasma osmolarity was between 270-300 mOsm/kgH2O, water deprivation test was done to confirm the diagnosis of diabetes insipidus. Baseline vitals along with the weight of the child (18.3 kg) were recorded and water deprivation test was started at 9:00 in morning. Post 6 hours of water deprivation test, plasma sodium was 149 mmol/l, corresponding plasma osmolarity and urine osmolarity was found to be 313 mOsm/kgH2O and 129 mOsm/kgH2O respectively. Urine output was 10 ml/kg/hr. Diagnosis of diabetes insipidus was confirmed. Desmopressin challenge test was done with nasal desmopressin of 0.01 mg. Post one hour of desmopressin challenge test, plasma sodium was 143 mmol/l, corresponding plasma osmolarity and urine osmolarity was found to be 312 mOsm/KgH2O and 316 mOsm/kgH2O respectively. Urine output was 3 ml/kg/hr. Post two hour of desmopressin challenge test, plasma sodium was 139 mmol/l, corresponding plasma and urine osmolarity was 308 mOsm/kgH2O and 352 mOsm/kgH2O respectively. Urine output was 0.6 ml/kg/hr. This confirmed the diagnosis of central diabetes insipidus (DI). In suspicion of Wolfram syndrome, hearing evaluation and ophthalmic evaluation was done, which showed left sided sensorineural hearing loss and bilateral optic atrophy with non-proliferative diabetic retinopathy with posterior subcapsular cataract respectively (Figure 1-2). Child was discharged successfully with nasal desmopressin (for central diabetes insipidus), 0.01 mg (nasal puff) once a day at 10:00 in night along with suprapubic catheterization in view of neurogenic bladder. With the above management, his urine output varied in the range of 1.5-2 ml/kg/hour in contrast to the baseline output of 10 ml/kg/hour prior to admission. His oral intake was 0.8 liters/day. MRI Brain and thyroid function test was done ans was with in normal limits.

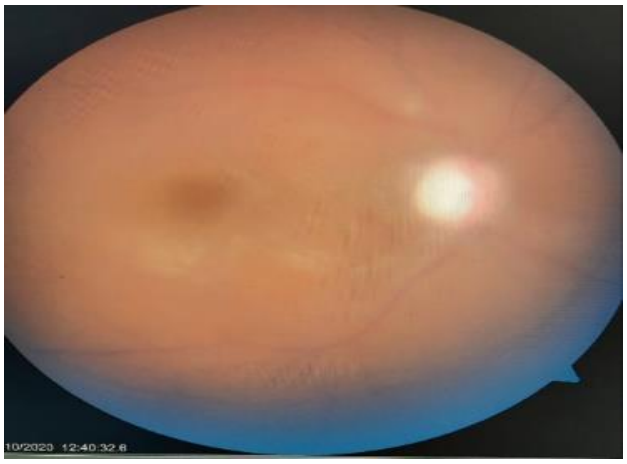

Figure 1: Mild optic atrophy of right eye.

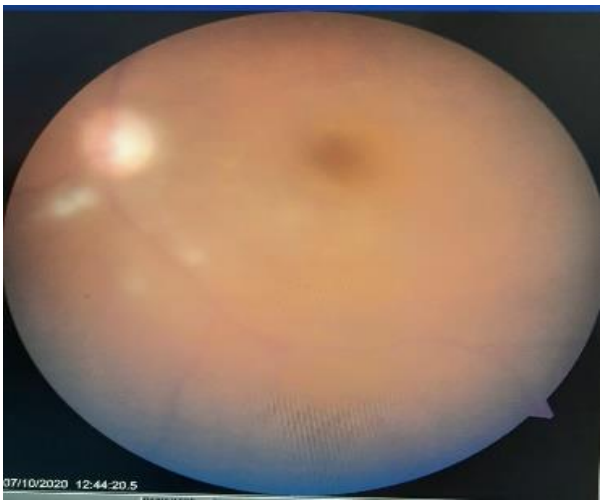

Figure 2: Mild optic atrophy of left eye.

DISCUSSION

Wolfram syndrome is a neurodegenerative disease, whose incidence is estimated to be one in every 770,000 live births. Early onset IDDM and optic atrophy are the initial and basic features of this syndrome. Patients present with diabetes mellitus associated by optic atrophy in the first decade, sensorineural deafness and diabetes insipidus in the second decade, dilated renal outflow tracts in the early third decade, and multiple neurological abnormalities early in the fourth decade.[8]

Table 1: Classical features of wolfram syndrome.

Features	% Frequency	Findings in current case report
Type 1 diabetes mellitus	95-98	Present diagnosed 4 years back
Optic atrophy	82	Bilateral optic atrophy with mild non proliferative diabetic retinopathy with bilateral subcapsular cataract
Sensorineural deafness	48	Left sided mild sensorineural hearing loss
Central Diabetes insipidus	70	Present
Urinary tract abnormalities	60-70	Grade 3 hydroureteronephrosis with neurogenic bladder
Neurological manifestation (cerebellar ataxia, peripheral neuropathy, dementia	53	Absent
Psychiatric illness	39	Absent
Endocrine abnormalities	-	Absent
Autonomic disturbance	-	Absent

In current case diabetes insipidus, optic atrophy and dilated renal outflow tracts have appeared in second decade. Patients with WS can be initially misdiagnosed as type 1 diabetes mellitus. However, patients with WS are less likely to experience diabetic ketoacidosis. Most common cause of morbidity and mortality in patients with WS are neurological complications, such as central respiratory failure, ataxia, and neurogenic bladder.[9] Glycemic control seems to be better in those with WS than individuals with type 1 diabetes. The lower daily insulin requirements per kg of body weight in WS patients suggest better insulin sensitivity when compared to individuals with type 1 diabetes. Severe hypoglycemia was more commonly reported in WS patient with coexist neurological symptoms.

In addition to diabetes, other endocrinological abnormalities such as diabetes insipidus are present in approximately 38%. Other abnormalities include primary gonadal atrophy in males and menstrual irregularities and delayed menarche in females. Short stature and growth hormone deficiency have also been reported. Neurological symptoms were seen in 53% of patients by an average age of 15 years. The majority of these symptoms were related to the brainstem and cerebellum, specifically, cerebellar ataxia (45%), peripheral neuropathy (39%), cognitive impairment (32%), epilepsy (26%), and dysarthria, dysphagia, and nystagmus in 10%.[10]

Classical WS is due to autosomal recessive mutations affecting the WFS1 gene, which is involved in endoplasmic reticulum (ER) function. Autosomal dominant mutations in WFS1 have been known to cause WS-like diseases attributed by diabetes, sensorineural hearing loss, psychiatric illness, variable degree optic atrophy, and WSF1-related low frequency sensorineural hearing loss.

Pathophysiology

WSF1 gene maps on chromosome 4p, whose gene product is a transmembrane glycoprotein Wolframin located on the endoplasmic reticulum. The WFS1 gene is expressed in a variety of tissues, including heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas. Function of wolframin is to maintain homeostasis in endoplasmic reticulum responsible for folding of secretory proteins including insulin. Mutation in WSF1 gene causes disruption in homeostasis of endoplasmic reticulum with increase in misfolded and unfolded proteins with is responsible for endoplasmic reticulum stress which results in cellular apoptosis.[11] In WS functional WFS1 protein deficiency alter inositol triphosphate receptor (IP3R) mediated endoplasmic reticulum calcium release disrupting cytoplasmic calcium homeostasis. Calpain-2 a calcium dependent pro-apoptotic cellular protease gets activated and cause apoptosis of β-cells of pancreas.[12] Disruption of cytoplasmic calcium homeostasis in neurons also dysregulates mitochondrial dynamics and ATP levels which hinders the neuronal development and survival.[13] Endoplasmic reticulum (ER) transmembrane proteins sense the stress and activate the unfolded protein response (UPR). The UPR may culminate in either an adaptive response which decreases the workload on the ER or a maladaptive response (as occurs in chronic hyperglycemia or WS) which culminates in cellular apoptosis.[14] ER calcium channels, such as the ryanodine receptor (RyR) and inositol triphosphate receptor (IP3R),

permit efflux of calcium from the ER to the cytosol. It is believed that increased cytoplasmic calcium levels activate the calcium-dependent protease, calpain-2, which promotes cellular apoptosis.[15]

Therapeutic considerations for Wolfram syndrome

WS mutations lead to increased ER stress, altered cytoplasmic calcium, and dysregulation of mitochondria, which inhibits cellular growth and survival.[16] Dantrolene inhibits ryanodine receptors in the ER and functions to suppress efflux of calcium from the ER to the cytosol and thereby inhibits calpain-2 mediated apoptosis.[16] Exenatide a glucagon-like peptide-1 receptor (GLP-1R) agonist decreases the apoptotic signaling by interfering with ER unfolded protein response and hence increases cell survival.[17]

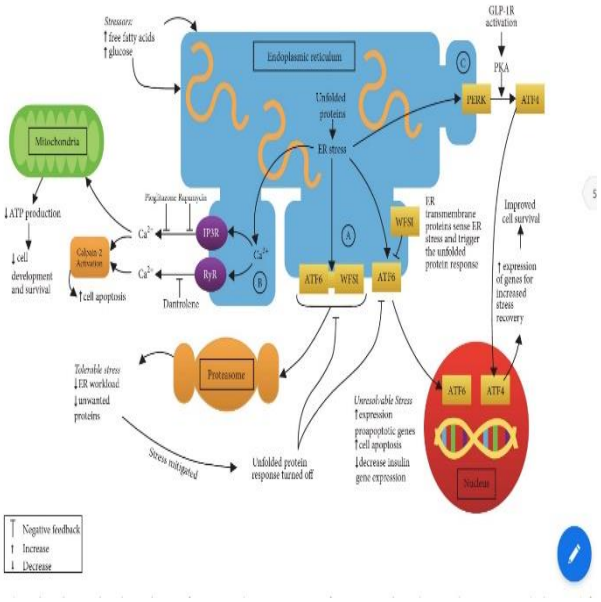

Figure 3: Molecular pathophysiology of WS.

Pioglitazone, a thiazolidinedione inhibits inositol triphosphate receptor (IP3R) release of calcium from the endoplasmic reticulum. This can have a therapeutic role in the management of patients with WS.[18] In addition to the targeted drug approaches described above, gene-based therapies which include adeno-associated virus and clustered regularly interspaced short palindromic repeats (CRISPR) technology are also being pursued. Mesencephalic astrocyte-derived neurotrophic factor (MANF) is also being tested as a method of preserving and proliferating existing β-cells and neurons.[19]

CONCLUSION

If a patient, who is a known case of diabetes mellitus, presents with persistent polyuria or neurogenic bladder despite good glycemic control, suspicion of wolfram syndrome and further evaluation regarding the same must be made. Recognizing and timely management of this condition will help to improve the quality of life in the patient.

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