



# Wolfram Syndrome

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## Abstract

Wolfram syndrome is a rare neurodegenerative and genetic disorder, which should be suspected in patients with young onset non-immune insulin dependent diabetes mellitus and optic atrophy. Patients are most likely to develop diabetes insipidus, deafness, urinary tract, and neurological abnormalities. 60% of the people with Wolfram syndrome die at age 35, usually due to central respiratory center failure following brain stem atrophy. Though there is no treatment to reverse the underlying mechanism of neurodegeneration, early diagnosis and adequate hormonal replacement could improve quality of life and survival. ©

## INTRODUCTION

First described in 1938 by Wolfram and Wagener, Wolfram syndrome (WFS) is a rare, complex, hereditary, neurodegenerative and genetic disorder. It manifests as a combination of young onset non-immune insulin dependent diabetes mellitus and progressive optic atrophy<sup>1</sup> in all patients with added diabetes insipidus and sensory neural deafness in 70% of the patients, where it is referred to as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness)

Wolfram syndrome may also include urinary tract,<sup>2</sup> neurological,<sup>3</sup> reproductive and psychiatric<sup>4</sup> abnormalities, limited joint mobility,<sup>5</sup> cardiovascular<sup>6</sup> and gastrointestinal autonomic neuropathy, as well as some types of endocrine dysfunction.<sup>7</sup> Cases of upper gastro intestinal bleeds and heart malformations have also been reported in Wolfram syndrome.

The prevalence estimate is 1 in 100,000 to 1 in 700,000 based on an observation of the prevalence of optic atrophy and diabetes mellitus. Parental consanguinity has been noted and an estimated 1 in 350 people carry the genes of WFS.

### Genetics and Mechanism of disease

There are two documented genetic routes of inheritance of Wolfram syndrome, either autosomal recessive (A.R.) or mitochondrial (Mt). The mutant genes responsible for Wolfram syndrome include WFS1 gene in chromosome 4P16.1 (A.R.), WFS2 gene in chromosome 4Q22-Q24 (A.R.), and mitochondrial genes.

WFS1 gene mutations is the most common cause of Wolfram syndrome. It is inherited as an autosomal recessive trait, which means, for a patient to manifest a disease he has to receive the defective genes from both his parents. Carriers do not develop WFS, but are at increased risk of developing serious psychiatric illness or adult onset diabetes mellitus.

Usually the mutant gene is on the short arm of 4<sup>th</sup> chromosome 4P16.1 (WFS1gene)<sup>9</sup> that normally encode for the structural properties and function of mitochondria, and also provide instruction for making an endoglycoside H sensitive protein called Wolframin.

Wolframin is a transmembrane protein (also found in endoplasmic reticulum) located throughout the body and has strong activity in heart, brain, pancreas, liver, kidney, skeletal muscle and inner ear.

There are more than 100 mutations identified so far, that could cause Wolfram syndrome. Some mutations delete or insert DNA from WFS gene. As a result no or little Wolframin is present in cells. Other mutations replace amino acids that make Wolframin, with incorrect amino acid. As a result the Wolframin activity is reduced dramatically. Alterations of 3 dimensional shape of the protein due to mutations could be the probable cause of decreased activity.

Researchers suggest that the loss of Wolframin that is essential for neuron survival leads to neurodegeneration and its features in CNS. Apart from neurodegeneration it also disrupts production of insulin from proinsulin and there by leads to poor glucose control and diabetes mellitus. It is also evidenced that altered Wolframin disturbs the balance of calcium ions in the inner ear, which interferes with hearing process.

WFS2 gene mutations are seen in Jordanian consanguineous families. These patients differ from classical WFS by absent or decreased incidence of

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diabetes insipidus and increased incidence of peptic ulcer disease. In mitochondrial variant of WFS the mitochondrial genes themselves are defective<sup>10</sup> and features of DIDMOAD are comparatively late in onset. Inheritance is exclusively from mother to child.

### CASE DETAILS

Patient 'S' is a 14-year-old male child born to a 2<sup>nd</sup> degree consanguineous marriage and was a product of an uncomplicated pregnancy. He was diagnosed with diabetes mellitus at the age of 7 years for which he has been receiving insulin, but his glycemic control has rather been poor.

He has presented with polyuria, polydipsia, bedwetting, visual impairment, hearing loss, and quick emotional upset/agitation. His height was 139 cm and weight was 30.4 kg. He is currently showing normal development of secondary sexual characteristics denoting onset of puberty. No limited joint mobility, no obvious cardiovascular, gastrointestinal, endocrine dysfunction. No regular physical activity, intermittently consumes pastries and sweets. His scholastic performance was average.

#### Work Up

Patient underwent detailed laboratory evaluation that included complete blood count, urea/creatinine, lipid profile, liver function tests, serum electrolytes, serum osmolality, urine osmolality, C-peptide, and GAD anti bodies. We measured the volume of a 24 hr collection of urine and performed a water deprivation test for about 6 hrs. Spot urine studies (spot sodium ISE) were also done.

The radiological evaluation included MRI axial study of brain, which was done in flair and T2W sequence. T2W coronal images and T1W sagittal images were also obtained. Additional T2W sagittal screening of the entire spinal cord was done. Echocardiogram, chest X-ray, ultrasonography of the abdomen, Doppler studies of lower limb vessels, nerve conduction velocity tests, complete ophthalmic and ENT evaluation was done.

### RESULTS

The biochemical and hematological results were within normal limits except raised HbA1C (14.8%), increased serum osmolality (301 mosm/kg) and decreased urine osmolality (177 mosm/kg) values by osmometer. Spot sodium ISE =39 meq/l. There has been decrease in fasting and stimulated C-peptide levels. GAD antibodies were negative. Serum Na<sup>+</sup> was 145. His calcium and renal function test was normal. Water deprivation test was in favor of central DI.

On ophthalmic examination his best-corrected visual acuity was 6/24 in both eyes. IOP was 16mmhg in both eyes. Fundus examination with indirect ophthalmoscopy showed pale disc in both eyes indicative of optic atrophy.



Fig. 1 : Fundoscopy picture showing pale disc

Audiogram revealed moderate to severe sloping showing sensory neural loss in both ears. Psychosocial consultation unveiled components of anxiety as well as depression.

Radiologically MRI brain/spinal cord showed no significant abnormalities except for absent posterior pituitary signal. USG abdomen revealed thickened bladder wall. Post-voidal residual volume was 85 ml and features are suggestive of diabetic cystopathy.

### DISCUSSION

Patient reported here have, at the age of 13yrs, all the four cardinal features of Wolfram syndrome. Patient developed DM at age 7yrs, before any other symptom of Wolfram syndrome is identified. The mean age of DM diagnosis reported earlier in kinsley studies is 8.2yrs (range 1-26). He had negative GAD anti bodies and decreased fasting and stimulated C-peptide levels which show its non-immune insulin dependent nature. Non-immune IDDM in these patients could result from hypothalamic degeneration although pancreatic beta islet cell loss is part of a specific defect of neuroectodermal amine precursor uptake decarboxylation derived cells in the pancreas and in the supraoptic and paraventricular nuclei.<sup>11</sup>

Optic atrophy, which is a hallmark trait of Wolfram syndrome, was diagnosed at the age of 9 years. Mean age in Kinsley's study being 13.1yrs (range 6-30). Patient here was only able to differentiate between light & darkness and he is legally blind. There has been no evidence of diabetic retinopathy. Total blindness is unusual in Wolfram syndrome and it takes 7yrs for the significant deterioration in vision to be categorized as legally blind. The cause for blindness is severe axonal loss and demyelination of optic nerves, chiasm and tracks.

Polys, nocturia, enuresis, very dilute clear odorless urine with biochemically raised serum osmolality,

decreased urine osmolality and water deprivation test all confirmed the presence of diabetes insipidus at the age 13yrs. The mean age onset according to Kinsley studies is 15.5yrs (range 4-41). Diabetes insipidus of Wolfram syndrome is caused by degeneration and atrophy of hypothalamus with loss of vasopressin secreting neurons in the supraoptic and paraventricular nuclei<sup>12</sup> leading to the deficiency in vasopressin that is responsible for concentration of urine. Hence patients pass very dilute clear odorless excessive amounts of urine. However in our patient the symptom due to Diabetes insipidus are not very severe and hence been advised to monitor serum sodium every 2 months and a desmopressin spray has to be considered if sodium increases or symptoms worsen.

Symptomatic sensory neural hearing loss to both high frequency followed by low frequency sounds developed at the age 13 yrs and is confirmed with audiogram. Mean age of onset in Kinsley studies being 14.6 yrs (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<sup>13</sup> leading to decreased perception of sounds rather than deficit in transmitting the sound to the nerve.

Urinary tract abnormalities are expected in about 66% of persons with Wolfram syndrome and are as well present in our patient with symptoms of frequent urination, incontinence and recurrent infection of the bladder. Post-voidal residual volume by ultrasound imaging is 85 ml and there is thickened bladder wall. The symptoms are caused by bladder nerve dysfunction and a loss of nerve tissue in the bladder and the ureters. The nervous centers in the brain that control urination may also play a role.

As age advances impaired sexual development, central nervous system complication such as nystagmus, ataxia, startle myoclonus, seizure disorders, mental health disorders and digestive problems are likely to appear and are not identified till now in our patient and hence to be screened periodically.

The median age of death in these patients according to Kinsley is 28 yrs and 60% of the people with Wolfram syndrome die at age 35. Death can be caused by central respiratory center failure following brain stem atrophy, complications related to urinary tract atony, bulbar dysfunction (aspirations) and in some cases suicide secondary to depression.

There has been no treatment to reverse the underlying mechanism of neuro degeneration in persons with WFS and all cases reported till now have progressed to one or more of the above discussed life-threatening complications and premature death.

## CONCLUSION

Though a rare disorder Wolfram syndrome is to be suspected in any individual presenting with IDDM and OA within first 3 decades of life. Genetic studies offer the best opportunity to confirm diagnosis and multidisciplinary assessment is vital to manage many facets of this condition. Early adequate treatment avoids serious complications such as hyperglycemic, hyperosmolar, hypernatremic coma, and can improve the quality of life and survival.

In addition, these patients have wide variety of social, emotional and psychological needs. Blind school, computers with software for blind, listening to books on tape could accommodate the visually disabled and help build self-esteem, confidence as well as maximizing school performance. Skills and attitudes that build self-confidence, autonomy and self-control should be focused upon and parents and relatives should help them to reach their goals. No matter how short and challenging life should be worthwhile.

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