



# Wolfram syndrome: Are we aware of the severe hypoglycemic unawareness?

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## Abstract

**Background:** Wolfram syndrome is a genetic condition, which is typically inherited in autosomal recessive fashion, characterized by the combination of diabetes mellitus and optic atrophy. It is along a spectrum which encompasses DIDMOAD (Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Profound hypoglycemic unawareness can be seen in this condition but is not commonly described as an associated feature in the literature.

**Case report:** A 16 year old female with history of presumed type 1 diabetes presented to urology clinic with urinary incontinence. She was found to have profound dilation of the bladder and was admitted for bladder decompression. During the course of admission she was found to also have diabetes insipidus and optic atrophy. She had several severe hypoglycemic episodes with profound hypoglycemia unawareness during this admission. Genetic testing for Wolfram syndrome was positive. As an outpatient she was placed on a continuous glucose monitor to help manage her hypoglycemia. Additionally, psychiatric support to manage her associated depression was an important aspect of her therapy. As her depression improved so did her ability to comply with the necessary therapies.

**Conclusions:** Wolfram syndrome is a rare syndrome that has been well described. However, patients with this syndrome have frequent hypoglycemia unawareness and severe hypoglycemia likely related to the neurologic deterioration that occurs at the molecular level in the pathogenesis of Wolfram syndrome. Strategies must be put in to place to help prevent and quickly treat these hypoglycemic events.

**Key words:** Wolfram syndrome, diabetes mellitus, neurogenic bladder, hypoglycemia, optic atrophy, diabetes insipidus, DIDMOAD, endoplasmic reticulum stress, *WFS1*

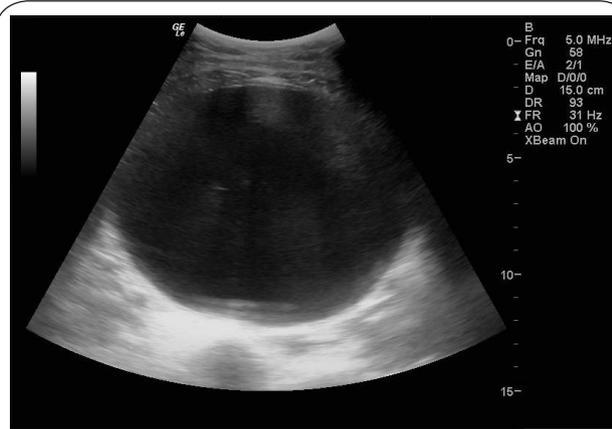
## Background

Wolfram syndrome is a genetic condition, which is typically inherited in autosomal recessive fashion, characterized by the combination of diabetes mellitus and optic atrophy. It is along a spectrum which encompasses DIDMOAD (Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). The syndrome occurs in 1:770,000 individuals with a characteristic timeline for its clinical manifestations [1]. There are some key features that distinguish the diabetes associated with Wolfram syndrome from Type 1 autoimmune diabetes mellitus. This syndrome is important to recognize as there are prognostic implications for those affected.

The genetic defect is a mutation in the *WFS1* gene, located on chromosome 4p16.1 [2,3,4], which encodes the protein wolframin [5]. Recently, Wolfram syndrome 2 has been described and is caused by mutation in the *CISD2* gene on chromosome 4q22-q24 [6] which encodes the protein ERIS. This protein also localizes to the endoplasmic reticulum but does not interact directly with WOLFRAMIN [7]. *WS2* will not be discussed further in this article. Wolframin is a transmembrane glycoprotein that localized in the endoplasmic reticulum (ER). This protein has been characterized as part of the

unfolded protein response, which is a cellular stress response induced by the accumulations of unfolded proteins within the ER lumen. This response is key to maintaining cellular homeostasis. Loss of this function by alteration of the *WFS1* gene is thought to result in chronic ER stress leading to apoptosis in pancreatic beta cells, neuroendocrine cells, and neuronal cells. Together, these processes result in a progressive decline of endocrine and neuroendocrine function [8]. The *WFS1* gene also plays a key role in intracellular calcium homeostasis and cAMP mediated signaling. Recent studies have suggested that *WFS1* deficiency may also lead to impaired acidification of insulin secretory granules [9,10]. This *WFS1* mutation and subsequent downstream effects are hypothesized to be the central defect in the constellation of symptoms described in the Wolfram syndrome [5].

The progressive loss of neuronal cell function has been implicated in the loss of ability to recognize insulin induced hypoglycemia. Severe hypoglycemia with hypoglycemic unawareness can lead to significant morbidity and mortality in diabetic patients including seizure, coma, and even death. Recognition that a particular patient is at increased risk for poor hypoglycemia recognition can result in changes in management of that patient to



**Figure 1.** Bladder ultrasound demonstrating massive dilatation. Images extending beyond edges of imaging field making measurements impossible.

prevent further morbidity.

We report the case of a 16 year old female with presumed type 1 diabetes, who presented with daytime enuresis and was ultimately diagnosed with Wolfram syndrome. In the course of her evaluation she was noted to have significant hypoglycemic unawareness resulting in repeated low blood glucoses <40mg/dL and one episode of unresponsiveness related to hypoglycemia during her hospital stay. We aim to review the presenting signs and symptoms of Wolfram syndrome and to highlight the significant hypoglycemia unawareness that can occur as part of this syndrome, but is not commonly considered in the evaluation of patients with such a condition.

### Clinical presentation

A 16 year old Caucasian female with a history of presumed type 1 diabetes of 10 years duration presented to the urology clinic with symptoms of progressive daytime and nighttime enuresis. A bladder ultrasound performed in clinic demonstrated a profoundly enlarged bladder consistent with the size of a 20 week gravid uterus. (Figure 1) The patient had a current HbA1c of 15.3% and therefore her symptoms were presumed to be secondary to neurogenic bladder of poorly controlled diabetes mellitus. She was admitted to the general pediatrics service for bladder decompression with indwelling catheter and monitored for post-obstructive diuresis [11].

During the course of bladder decompression she continued to have up to 10 liters per day of urine output for one week. A spinal MRI was performed to evaluate for other causes of bladder distention and was normal. Orthostatic blood pressures, ECG, and gastric emptying study were performed to assess for signs of autonomic neuropathy associated with diabetes and these were also normal.

On review of her history, her diabetes had only become

poorly controlled over the previous 1-2 years. She had maintained an HbA1c in the 5-6% range despite a minimal insulin requirement of 0.3 units per kilogram per day for several years following diabetes diagnosis at 6 years of age. During this time period GAD-65 and IA2 antibody titers were obtained and were negative. Testing for monogenic diabetes (MODY) was considered but was not performed, in consideration of the negative family history of diabetes.

After one week of no improvement in urine output, she was given a test dose of oral desmopressin acetate (DDAVP) to which she responded well with a decrease in urine output from 800mL/hr to 150mL/hr with stable serum sodium and urine osmolarity increase from 152 to 502 Osm per liter.

During the course of her hospitalization she was also noted to have repeated episodes of hypoglycemia requiring frequent decreases in her insulin doses. She had marked hypoglycemia unawareness. At one point she had a blood glucose of 34mg/dL associated with loss of consciousness. She required a bolus of IV dextrose in order to raise her blood glucose and return to normal mental status. Despite the decrease in insulin doses she continued to have wide variation in her glycemic control. Hypoglycemic events were noted incidentally on routine blood glucoses checks, and were consistently asymptomatic. An ophthalmologic exam performed during this admission showed optic disc pallor which was more pronounced in the temporal quadrants. At this time she was also suffering from severe depression that predated the admission for indwelling catheter, and was transferred to an inpatient psychiatric hospital for further treatment.

Subsequent testing for Wolfram syndrome was positive for a homozygous genetic mutation in the WFS1 gene at the coding region (c.1838G>A, p.Trp613Stop) (Reference Laboratory: University of Iowa Diagnostic Laboratories, 5270CBRB, Iowa City, Iowa 52242-1078). This is a known deleterious mutation consistent with DIDMOAD [12].

Audiologic exam subsequent to this diagnosis demonstrated bilateral high frequency sensorineural hearing loss. She continues to struggle with depression and is followed by psychiatry. Her diabetes self care has waxed and waned. She now wears a continuous glucose monitor due to her profound hypoglycemic unawareness with severe hypoglycemia. An insulin pump was also prescribed, however the patient self-discontinued the pump after a short period of time due to difficulty with use. She performs intermittent self-catheterization every 4 hours due to bladder atony. She continues to take DDAVP 0.2mg orally in the morning and 0.3mg at night for her diabetes insipidus. She and her family received genetic counseling on this condition. Although genetic testing of the parents is recommended for determination of inheritance, her parents, who had been divorced for several years, declined testing in this case.

### Discussion

Wolfram syndrome is a disease with phenotypic variability. However, nearly all patients will have DM and this is typically the presenting feature with a peak incidence of onset at 5

years of age [13]. The average age of onset of diabetes in Wolfram syndrome has been reported to be younger than the average age of onset in Type 1 diabetes (T1DM) [15]. There are multiple differences between the presentation and course of autoimmune Type 1 diabetes and diabetes of Wolfram syndrome. Namely, patients affected with Wolfram have a low incidence of diabetic ketoacidosis at diagnosis (only 3% compared to 30% in T1DM), a much lower insulin requirement in the first several years after diagnosis, rare microvascular complications, and rare presence of diabetes antibodies [14]. The other ubiquitous finding in Wolfram syndrome is optic atrophy, which can progress to blindness, and typically presents at an age of 10 years. This finding is required to make the diagnosis [15]. Additional features include diabetes insipidus with peak onset at 14 years of age and present in 73% of patients, hearing impairment progressing to deafness (onset at 15 years, prevalence of 62%), renal and GU tract abnormalities (onset at 20 years, prevalence of 58%; a large, atonic bladder is a characteristic finding), and neurologic abnormalities, most commonly progressive ataxia (peak onset at 30 years of age with prevalence of 62-70%) [15]. Endocrine disorders that have been described in this condition include hypogonadotropic hypogonadism, hypothyroidism, and growth failure. Another common finding is depression pre-existing the diagnosis of Wolfram syndrome. Patients with this syndrome typically have early death from brain stem atrophy leading to central apnea, at a median age of 30 years. Diagnosis is made by genetic testing.

An increased frequency of hypoglycemic unawareness or severe hypoglycemia has been described in patients with Wolfram syndrome, although is not frequently reported as a common manifestation. It is thought that the neurologic damage associated with the impaired unfolded protein response underlying the pathogenesis of Wolfram syndrome causes impairment in the body's ability to properly recognize the low blood glucoses associated with insulin treatment. One study showed a prevalence of severe hypoglycemia of approximately 37% in patients with Wolfram syndrome compared to only 8% in a cohort with type 1 autoimmune diabetes [13]. While few studies comment on this potentially fatal complication of Wolfram syndrome, there is a reported case of death from hypoglycemic coma in a Wolfram patient [15].

Glucotoxicity from uncontrolled diabetic hyperglycemia has been linked to exacerbation of the unfolded protein response described above, leading to worsening of neurologic symptoms. This was hypothesized in a retrospective review of patients with Wolfram syndrome who experienced acute worsening of neurologic symptoms when their diabetes became uncontrolled [13]. Our patient had very low insulin requirements and a near normal HbA1c for many years despite reported suboptimal compliance with insulin therapy. Once her reserve beta cell function and endogenous insulin production decreased below a critical threshold, as part of the natural history of her disease,

her diabetes became uncontrolled. In keeping with the above theory, the manifestations of neurogenic bladder and severe hypoglycemia with unawareness emerged after less than 2 years of poor diabetes control, in contrast with the appearance of autonomic symptoms after much longer periods of poor control in young subjects with type 1 diabetes. Thus, this rapid and substantial deterioration in glucose control was likely an important factor in the development and quick progression of her hypoglycemia unawareness [8].

## Conclusions

We report a patient with classic features of a rare disease. This case reviews many important points regarding the time course and recently discovered mechanisms of disease progression, and emphasizes the need for a high index of suspicion when dealing with unusual features of presumed type 1 diabetes in a pediatric patient.

This case also emphasizes the importance of multi-disciplinary care of patients with Wolfram which should include behavioral health or psychiatric care. The underlying depression begets worsened glycemic control, leading to decreased beta cell function and even worse hyperglycemia. The latter then causes ER stress and hypoglycemia unawareness all leading to worsening of depression, in a vicious cycle. It is important to put mechanisms in place early to prevent the ongoing cell damage and ultimately decrease morbidity in these delicate patients. These patients require intensive diabetes care through a diabetes specialist, diabetes educator, behavioral health provider, and open lines of communication with their diabetes team in addition to other specialists that may be involved. Additional support from ophthalmology, nephrology, audiology and urology is also necessary. Continuous glucose monitoring should be strongly considered in these patients, preferably in association with continuous subcutaneous insulin infusion, and the importance of the monitoring system and good glycemic control should be discussed at length to ensure compliance with its use. Genetic counseling should be offered to family members, and genetic testing should be recommended to putative carriers of the mutation.

Hypoglycemia unawareness is an important aspect of the morbidity and mortality associated with Wolfram syndrome and should be considered in the routine care of these patients.

## Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

All authors have made substantive intellectual contributions to this paper. All authors Have contributed to the concept and design of the case report.

MB: Primary drafting of the manuscript and literature

review as well as clinical care of patient.

KBK: Clinical care of patient, literature review and manuscript review.

MV: Clinical care of patient, literature review and manuscript review.

LG: Clinical care of patient. Revisions and oversight of manuscript preparation.

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