CASE REPORT

Comprehensive Case Study of Wolfram Syndrome in a 12-Year-Old: Diagnostic Challenges and Multidisciplinary Care

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Abstract

Wolfram Syndrome (WS) or DIDMOAD is a rare form of inherited disease of the nervous system, which is categorized by diabetes insipidus, diabetes mellitus optic atrophy, and sensorineural deafness. WS is mentioned in the case of a 12-year-old male child diagnosed with diabetes mellitus at two years of age with an additional complication of vision impairment and hearing loss. Further, WS came to a conclusive diagnosis in 2016 and revealed a pathogenic variant within the WFS1 gene. The purpose of this case study paper is to describe the clinical presentation, how he was assessed and diagnosed, and how his care can be best coordinated. While the study focuses on the use of genetic testing in identifying such syndromes, there is a great need for interdisciplinary cooperation with endocrinologists, ophthalmologists, audiologists, and genetic counsellors. Since there is no cure for the disease, early and constant approaches should be implemented to improve the patient's quality of life, and patient-centred care should be encouraged.

Keywords: *Wolfram syndrome, genetic disorder, multidisciplinary care, diabetes mellitus, optic atrophy.*

INTRODUCTION

Wolfram Syndrome (WS) is a rare, genetically inherited neurological disorder. It was first used by Wolfram and Wagener in 1938, and later, they found diabetes mellitus with optic atrophy in four siblings [1, 2]. Wolfram Syndrome is rare, with a birth prevalence of about one in 710,000 [3]. WS's major genetic basis includes mutations in the WFS1 gene that codes for a Wolframin transmembrane protein at chromosome region 4p16.

WS is characterized clinically by IDDM occurring in childhood and leading to optic atrophy in the further course of the disease [2]. Other features like diabetes insipidus and SNHL, typical for WAGR syndrome, usually manifest in the second decade of life [1]. The chronic progressive clinical course of the disease results in severe clinical complications and a marked reduction in life expectancy, with the mean age at death of approximately 30 years [4]. Research shows that more than 200 mutations of the WFS1 gene are linked to WS [5, 6]. These mutations result in the lack of function of Wolframin, which is essential in the functioning of the endoplasmic reticulum and the regulation of calcium balance in neurons and pancreatic beta-cells.

This case study refers to the WS diagnosed in Fatima Hospital, in the Department of Pediatrics, Baqai Medical University, in 2023. The case details, diagnosis, management, and outcomes are discussed herein.

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CASE REPORT

Introduction

A 12-year-old boy with a medical history suggestive of Wolfram Syndrome (WS) underwent evaluation for further diagnosis and management. He was diagnosed with diabetes and began treatment for progressive vision and hearing impairments at the age of two. An ophthalmological consult was taken during the patient's stay in the hospital. Fundoscopic examination revealed bilateral temporal optic disc pallor, which aligns with optic atrophy. Visual acuity could not be assessed as full cooperation could not be gained for assessment. Pure tone Audiometry was advised for hearing assessment but could not be done due to the short stay in the ward.

He also has a history of severe health complications in his family; his mother was recently diagnosed at the age of 60 years with a brain tumour (Meningioma). The WFS1 pathogenic gene mutation was definitively identified only in recent genetic testing (**Table 1**).

Table 1: Case study summary.

Aspect	**Details**
Patient Age	12 years
Date of Birth	June 3, 2008
Diagnosis	Wolfram Syndrome (confirmed *via* genetic testing)
Genetic Mutation	Homozygous for WFS1 nonsense variant NM_006005.3.1433G>A, p.(Trp478Ter)
Gene Location	Chr4.6302955
Diabetes Diagnosis Age	2 years old
Symptoms	Uncontrolled diabetes, decreased vision, decreased hearing, hyperpigmentation
Sample Received Date	August 11, 2023
Laboratory No.	EX2311573

Medical History and First Complaint

Since the time of his early childhood, he has faced numerous health problems. He was diagnosed with diabetes at the age of two years, and he had life-threatening uncontrolled hyperglycemia, which is one of the main symptoms of Wolfram Syndrome. However, comprehensive audiometric and visual assessments were not available to fully quantify the extent of these impairments at the time of case presentation. His family history led to the diagnosis due to his mother's brain tumour, and his brother's symptoms are similar to that of his mother, thus suggesting that there is a tendency to genetic diseases in his family [1, 4].

Genetic Diagnosis and Medical Management

Speaking of the genomic laboratory report, he has been diagnosed as Wolfram Syndrome homozygous for the WFS1 pathogenic variant. This mutation leads to the loss of function of gene WFS1, which is needed for the normal functioning of cells in the pancreas and Brain. He presented with features of this syndrome like diabetes, blindness, deafness, and skin change to dark colour [3]. The care of a patient with Wolfram syndrome should involve an endocrinologist, ophthalmologist, audiologist, genetic counsellor, and others. A multimodal team of caregivers coordinated all the facets of the patient's condition during his management. He was advised to undergo follow-up and be offered targeted management and genetic consultation to make his quality of life better and to help his family receive the needed care and information concerning this type of genetic disorder as advised in [4].

DISCUSSION

The case report on Wolfram Syndrome is valuable as a perspective on this rare hereditary disorder. Wolfram is a disease that affects several organs in the human body: it is characterized by diabetes insipidus, diabetes mellitus, blindness, and deafness. His case is consistent with WS's clinical presentation: He developed diabetes mellitus at two years of age, and his vision and hearing abilities also started deteriorating as the disease progressed further. This case study shows genetic testing in defining the diagnosis and management plan due to the pathogenic mutation in the WFS1 gene.

His case demonstrates the need for a broader approach that implies the involvement of various specialists in the care process. Since he suffers from type 1 uncontrolled diabetes, it will be essential for endocrinologists to ensure that his blood sugar levels are well controlled. Visual field testing and fundoscopy are critical for evaluating optic atrophy and determining potential interventions. Although no definitive cure is currently available, neuroprotective agents such as idebenone, combined with rigorous blood sugar management, may help slow disease progression. Promising advancements in emerging treatments, including gene therapy and stem cell transplantation, offer hope for the future restoration of optic nerve function.

Hearing aid and audiologic assessments are helpful in the management of his hearing loss, which is part of his disability. Genetic advice must be given to the family because it helps the family understand the transmission of the syndrome and possible risks for other family members.

Though there is no remedy for Wolfram Syndrome, appropriate and continuous management from childhood can enhance the quality of life for patients. Given the progressiveness of WS, such complications will require constant vigilance and management approaches to mitigate them. There might be other therapeutic approaches, as participants in the clinical trials for new treatments could experience reduced disease progression and symptoms. Such a holistic, person-centred approach reflects the need to address multiple Wolfram Syndrome symptoms and incorporate medical, psychological, and social interventions to achieve the best patient outcomes [1, 3].

The result of the present case correlates with the previous studies related to Wolfram Syndrome. Like the case presented by Ari *et al.* [1], this case highlights the need for early genetic testing and a collaborative approach to management. But at the same time, this case also has some specifics, for instance, the highly increased risk of severe health problems in the family, including a brain tumour, which makes genetic counselling more complicated. Also, Waschbisch *et al.* [4] pointed out the importance of a coordinated care model, which was reflected in his case, where interventions are supposed to be delivered in a stepped, coordinated, and specific care model across medical specialities.

CONCLUSION

A 12-year-old boy was presented in this case, suffering from Wolfram Syndrome, which is a very rare genetic disorder that is associated with chronic complications such as diabetes mellitus, optic atrophy, and hearing loss. Thus, a confirmed WFS1 gene mutation underlines the significance of genetic analysis for diagnosis. Comparatively, a multifaceted approach that associates endocrinologists, ophthalmologists, audiologists, and genetic counsellors is pivotal for treating such clinical features of the disease and enhancing the patient's quality of life. Thus, continuous monitoring with other

successful attempts at developing adaptive patient care is crucial as Wolfram Syndrome is a progressive condition, therefore demanding patient-centred care.

CONSENT FOR PUBLICATION

This case study report is published after obtaining consent from the patient's parents.

CONFLICT OF INTEREST

There is no conflict of interest among authors.

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AUTHORS' CONTRIBUTION

Writing of manuscript by Dr. Madhia Abid, Case Study findings gathered by Dr. Saba Sohrab and Dr. Areeba Tanveer, and funding arranged by faculty members of the Department of Pediatrics, Fatima Hospital, Baqai Medical University, Karachi.

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