Late recognition of wolfram syndrome type 1 in adulthood: multisystemic presentation with a founder WFS1 variant - a case report

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ABSTRACT

Background: Wolfram syndrome type 1 is a rare, autosomal recessive neurodegenerative disorder caused by pathogenic variants in the WFS1 gene. It is classically characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, but its clinical spectrum is highly heterogeneous. Delayed recognition is common, especially when features are misattributed to diabetes complications.

Case Report: We present a 39-year-old man with insulin-dependent diabetes mellitus since adolescence, who developed progressive multisystem involvement, including optic atrophy, neurogenic bladder with end-stage renal disease, psychiatric manifestations, and neurological complications. Despite early diabetes onset, Wolfram syndrome (WS) was not suspected until late in the disease course. Genetic analysis revealed a homozygous missense variant in WFS1 (c.1672C>T; p.Arg558Cys), previously described as a founder mutation and classified as pathogenic according to the criteria of the American College of Medical Genetics and Genomics. The patient exhibited an incomplete phenotype, with optic atrophy and suspected central diabetes insipidus, but without documented sensorineural hearing loss. Despite multidisciplinary supportive care, the disease followed a relentlessly progressive course, and the patient died due to multisystem failure.

Conclusion: This case highlights the diagnostic challenges of WS in adulthood, where overlapping features with diabetic complications may obscure recognition. Early genetic testing in patients with juvenile-onset diabetes and optic atrophy is critical for timely diagnosis, comprehensive surveillance, and appropriate counseling. Reporting adult-onset cases with founder variants contributes to expanding the clinical spectrum and emphasizes the importance of multidisciplinary management in this rare but devastating disorder.

Keywords: Wolfram syndrome type 1, WFS1 mutation, founder variant, adult-onset, optic atrophy.

Type of Article: CASE REPORT **Specialty:** Internal Medicine

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Introduction

Wolfram syndrome (WS) is a rare, autosomal recessive neurodegenerative disorder, first described in 1938 by Wolfram and Wagener in siblings with juvenile-onset diabetes mellitus (DM) and optic atrophy (OA). The condition is classically defined by the acronym DIDMOAD - diabetes insipidus (DI), DM, OA, and sensorineural deafness - yet its clinical spectrum extends well beyond these features, frequently encompassing endocrinological, psychiatric, neurological, and urological abnormalities [1].

The majority of patients are affected by Wolfram syndrome type 1 (WS1; OMIM 222300), caused by biallelic pathogenic variants in the *WFS1* gene on chromosome 4p16.1, encoding wolframin, a transmembrane protein localized in the endoplasmic reticulum (ER). Wolframin is essential for Ca^{2+} homeostasis, ER stress regulation, and ER - mitochondrial communication. Pathogenic variants lead to chronic Endoplasmic Reticulum stress, β-cell apoptosis, and widespread neurodegeneration [1]. Recent genomic studies have further expanded our understanding of *WFS1*, highlighting mutational hotspots (particularly in exon 8) and demonstrating that phenotype cannot be explained by mutation position alone. Instead, gene regulation, expression patterns, and tissue vulnerability contribute significantly to the marked interindividual variability in clinical presentation [2].

A smaller subset of patients presents with Wolfram syndrome type 2 (WS2; OMIM 604928) due to mutations in the *CISD2* gene. WS2 shares a partial overlap with WS1 but typically lacks DI and deafness while being characterized by upper gastrointestinal ulceration, bleeding, and platelet aggregation defects [3]. This distinction underscores the genetic and phenotypic heterogeneity across Wolfram spectrum disorders.

Epidemiological studies estimate a prevalence of approximately 1:770,000 in the United Kingdom and 1:100,000 in North America, with higher incidence in populations with high rates of consanguinity. Population-specific founder mutations in *WFS1* have also been described, further underscoring the genetic heterogeneity of WS1 [4].

Clinically, WS1 is relentlessly progressive, with an average life expectancy of approximately 30 years, most often shortened by central respiratory failure due to brainstem atrophy [5]. In addition to the core DIDMOAD features, up to 60% of patients develop neurological manifestations such as cerebellar ataxia, dysarthria, epilepsy, and psychiatric disorders, including anxiety and depression [5]. Urological involvement - particularly neurogenic bladder and upper urinary tract dilatation - is highly prevalent, occurring in up to 90% of patients, and represents a major risk factor for renal failure and mortality [6]. Case series have further highlighted the heterogeneity in age at onset, systemic involvement, and disease progression, emphasizing the need for early genetic confirmation [7].

Metabolic management remains central to patient care. Poor glycemic control can accelerate the onset of extrapancreatic complications, while strict metabolic monitoring may delay progression. Insulin therapy is the cornerstone, but incretin-based therapies and novel agents targeting ER stress and mitochondrial function are under investigation [1,8].

Here, we report a genetically confirmed adult-onset WS1 case with extensive multisystem involvement, contributing to the expanding clinical spectrum and underscoring the diagnostic and therapeutic challenges of delayed recognition.

Case Presentation

A 39-year-old man with a history of insulin-dependent diabetes mellitus since adolescence was admitted with progressive multisystem complications. Despite long-standing diabetes, WS had not been suspected until late in the disease course.

The patient had brittle diabetes with recurrent episodes of decompensation, including several admissions for diabetic ketoacidosis. He also developed chronic kidney disease secondary to neurogenic bladder, requiring intermittent catheterization for over 10 years, and had been on maintenance hemodialysis for the past 5 years. A right below-knee amputation had been performed due to diabetic foot infection.

Ophthalmological assessment revealed bilateral pseudophakia, microhemorrhages, exudates, optic disc pallor, and retinal thinning with laser scars in the left eye. Visual acuity was reduced in the left eye (0.5), while the right eye maintained full vision; binocular visual acuity was 97 points. The patient also exhibited left exotropia. These findings were initially attributed to diabetic retinopathy, which contributed to a delayed diagnosis of syndromic optic atrophy.

Neurological and psychiatric complications emerged in adulthood. The patient experienced hypoxic myoclonus, polyneuropathy, and recurrent psychotic episodes. Brain Magnetic Resonance Imaging demonstrated microcephaly, thinning and partial agenesis of the corpus callosum, and nonspecific periventricular gliotic foci, while cerebellar and brainstem structures appeared preserved.

During a hospitalization in early 2025, the patient was found unconscious at home and admitted with diabetic ketoacidosis and pneumonia. He required intubation, chest drainage for pleural effusion, and intensive supportive care. Despite treatment, he remained clinically fragile with hypoalbuminemia, secondary immunological alterations, and recurrent infections.

Given the combination of early-onset diabetes, optic atrophy, neurogenic bladder, renal failure, neurological and psychiatric involvement, and craniofacial features such as microcephaly and left exotropia, the possibility of an underlying syndromic disorder was considered. The multisystemic phenotype strongly suggested WS, and genetic analysis was therefore performed.

Genetic testing confirmed a homozygous missense variant in *WFS1* (c.1672C>T; p.Arg 558Cys), classified as pathogenic according to American College of Medical Genetics and Genomics criteria. This mutation has been previously described as a founder variant in certain populations and is well established as causative for WS1. The genetic finding was consistent with the patient's clinical manifestations, thereby confirming the diagnosis.

There was no documented hearing loss during follow-up. Although formal testing for diabetes insipidus could not be performed, retrospective history revealed marked polydipsia, raising suspicion of central DI.

Despite supportive management across endocrinology, nephrology, neurology, ophthalmology, psychiatry, and genetics, the disease followed a relentlessly progressive course, and the patient ultimately died due to multisystem involvement.

Timeline of clinical events

Age / Time	Clinical event
Adolescence	Onset of insulin-dependent diabetes mellitus
20 second-30 second	Progressive visual impairment → optic atrophy
Early 30 seconds	Neurogenic bladder → intermittent catheterization
Mid-30 seconds	Recurrent DKA; psychiatric manifestations
~34–35	End-stage renal disease → hemodialysis
Late 30 seconds	Hypoxic myoclonus and polyneuropathy
Early 2025 (age 39)	DKA + pneumonia →intubation
2025	Genetic testing confirms *WFS1 c.1672C>T*
2025	Death due to multisystem failure

Discussion

Wolfram syndrome is typically diagnosed in childhood or adolescence, when the hallmark manifestations of insulin-dependent diabetes mellitus and optic atrophy become evident [1]. However, in our case, although diabetes was present since adolescence, the diagnosis of WS1 was only established decades later, after the development of multiple systemic complications. This delay illustrates a well-recognized challenge: features such as optic atrophy or neurogenic bladder may initially be attributed to diabetes-related complications rather than being recognized as part of a syndromic presentation. Similar diagnostic delays have been highlighted in recent reviews and case series, where patients often experienced years of fragmented management before the correct diagnosis was made [3,7].

Genetically, our patient carried a homozygous *WFS1* missense variant, c.1672C>T (p.R558C). This variant has been reported as a founder mutation in specific populations, such as the Druze community, contributing to increased local prevalence [4]. The clinical heterogeneity associated with *WFS1* mutations means that even the same variant may lead to variable severity and different ages at diagnosis. As Kõks highlighted, while exon 8 is a mutational hotspot in *WFS1*, phenotypic expression is influenced by additional regulatory and tissue-specific factors beyond the mutation site itself [2]. Such genomic complexity, together with the overlapping clinical features of diabetes-related complications, may explain why our patient's syndrome remained unrecognized for so long despite the early onset of symptoms.

Multisystem involvement is a hallmark of WS1, and our patient displayed several of the most frequent and debilitating complications. Optic atrophy (OA) is one of the cardinal features of WS1, typically developing in the first decade of life [1]. In our case, progressive bilateral vision loss was documented early but was initially attributed to diabetic complications, contributing to the diagnostic delay. Jurca et al. [3] emphasized that the coexistence of juvenile-onset diabetes and OA should prompt evaluation for WS, even in the absence of other classical features [3]. Du et al. [7] further highlighted the variability in age of onset and progression of OA, which may account for differences in recognition. Beyond its diagnostic relevance, OA profoundly impacts quality of life, with Caruso et al. [5] noting that visual impairment, when combined with neurological and psychiatric manifestations, substantially increases functional disability.

Urological dysfunction is another frequent and severe complication. Occurring in up to 90% of patients, it often manifests as neurogenic bladder, urinary retention, and recurrent infections [6]. In our case, neurogenic bladder required clean intermittent catheterization for several years and ultimately progressed to end-stage renal disease necessitating hemodialysis. This course is consistent with the review by La Valle et al. [6] which emphasized that urinary tract involvement in WS is primarily a neurodegenerative manifestation rather than a secondary diabetic complication, and represents a major determinant of morbidity and mortality.

Neurological and psychiatric manifestations further contributed to the disease burden in our patient. Caruso et al. [5] reported that up to 60% of patients develop neurological complications such as cerebellar ataxia, dysarthria, seizures, and psychiatric symptoms, including anxiety and depression. Our patient exhibited hypoxic myoclonus requiring antiepileptic therapy and experienced recurrent psychotic episodes, reflecting the broad spectrum of neuropsychiatric involvement. Brain MRI in our patient did not reveal cerebellar or brainstem atrophy, which are frequently reported in advanced cases of WS1 [5]. Instead, the imaging demonstrated microcephaly, thinning, and partial agenesis of the corpus callosum, and nonspecific periventricular gliotic foci, supporting the concept of heterogeneous neurodegenerative patterns in WS1.

In addition, our patient lacked documented hearing loss, and diabetes insipidus could only be suspected retrospectively based on a history of excessive water intake. This incomplete DIDMOAD phenotype has been described in previous reports and contributes to the diagnostic challenge in adult patients. *GeneReviews* describes such cases as "nonclassic WFS1-spectrum disorder," where some DIDMOAD components are absent or appear later, including patients with optic atrophy but without hearing impairment [9]. Similarly, Sultanova et al. reported a case series in which several genetically confirmed patients did not present with sensorineural hearing loss, underscoring the variability in phenotypic expression [10].

Currently, no curative treatment exists for WS1, and management is primarily supportive. Insulin therapy remains the cornerstone for diabetes, while multidisciplinary care is essential for addressing ophthalmological, neurological, psychiatric, and urological complications [1]. Beyond symptomatic management, metabolic control may influence the overall disease trajectory. Iafusco et al. [8] reported that strict glucose monitoring may delay the onset of extrapancreatic features, underscoring the importance of optimized diabetes management. Emerging therapeutic approaches, such as Glucagon-Like Peptide-1 receptor agonists and ER stress modulators, have shown potential in preclinical and early clinical studies [1]. Advances in genomics may also provide the basis for targeted molecular therapies in the future.

Conclusion

This case illustrates that WS1 may remain undiagnosed for decades despite early manifestations, with the correct diagnosis only established after the development of multisystem complications. The findings emphasize the importance of early genetic testing in patients with

juvenile-onset diabetes and optic atrophy, as well as the need for comprehensive long-term surveillance. As research into novel therapies evolves, timely recognition and coordinated multidisciplinary management remain the key to improving quality of life and outcomes in WS1.

What is new?

Wolfram syndrome can hide for decades behind presumed diabetes complications. Earlier recognition and coordinated multidisciplinary care are crucial to prevent irreversible damage and preserve quality of life.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for Publication

Written informed consent for publication was obtained from the patient's next of kin.

Ethics approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	Patient (gender, age)	39 years, male
2	Final diagnosis	Wolfram syndrome type 1 (WFS1-related disorder)
3	Symptoms	Insulin-dependent diabetes mellitus, optic atrophy, neurogenic bladder, renal failure, neurological and psychiatric manifestations
4	Medications	Insulin therapy, antiepileptic drugs, hemodialysis, supportive treatment
5	Clinical procedure	Genetic testing confirming WFS1 mutation (c.1672C>T; p.Arg558Cys); long-term multidisciplinary management
6	Specialty	Internal medicine