Int. j. adv. multidisc. res. stud. 2026; 6(4):1719-1724

Received: 07-07-2026
Accepted: 17-08-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

Diagnostic Delays in Hereditary Nephropathies: Wolfram Syndrome Revealed by Diabetic Nephropathy in a Consanguineous Algerian Family

[1] G Khellaf, [2] M Benabadji

[1, 2] Faculty of Medicine, University of Health Sciences, Dr. Youcef El Khatib, Algiers, Algeria

[1] Department of Nephrology, Dialysis and Renal Transplantation, CHU Bab El Oued, Mohamed Lamine Debaghine Hospital, Algiers, Algeria

[2] Department of Nephrology, Dialysis and Renal Transplantation, CHU Beni Messous, Issad Hassani Hospital, Algiers, Algeria

DOI: https://doi.org/10.62225/2583049X.2026.6.4.6801

Corresponding Author: **G Khellaf**

Abstract

Background: Wolfram syndrome is a rare autosomal recessive neurodegenerative disorder characterized by juvenile-onset diabetes mellitus, optic atrophy, diabetes insipidus, sensorineural deafness, and progressive neurological deterioration. The diagnosis is often delayed due to the sequential appearance of clinical manifestations and the lack of multidisciplinary awareness.

Case Presentation: A 24-year-old Algerian man, born to first-degree consanguineous parents, with type 1 diabetes since age 4, was referred for chronic kidney disease (eGFR 24 mL/min). He presented with a permanent urinary catheter, polyuropolydipsia (4.5 L/day), visual impairment, bilateral hearing loss, and cerebellar syndrome. Ophthalmological examination revealed bilateral optic atrophy without diabetic retinopathy. Audiometry confirmed bilateral sensorineural deafness. Renal ultrasound showed severe hydronephrosis with significant post-void residual volume. His 18-year-old brother had similar symptoms but had never been investigated. The association of juvenile diabetes, optic atrophy, deafness, and familial presentation suggested Wolfram syndrome.

Conclusions: This case illustrates a 20-year diagnostic delay due to the progressive onset of manifestations and insufficient multidisciplinary coordination. Wolfram syndrome should be systematically suspected in young patients with diabetes and unexplained renal failure, optic atrophy, or deafness. Nephrologists must be vigilant for syndromic associations when evaluating diabetic nephropathy, particularly in consanguineous populations.

Keywords: Wolfram Syndrome, Diabetic Nephropathy, Diagnostic Delay, Consanguinity, Algeria, Case Report

1. Introduction

Wolfram syndrome (WFS), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness), is a rare autosomal recessive neurodegenerative disorder caused by mutations in the *WFS1* gene on chromosome 4p16.1 [1, 2]. The classical triad includes juvenile-onset diabetes mellitus, progressive bilateral optic atrophy, and sensorineural deafness [3]. Diabetes insipidus, urological abnormalities (neurogenic bladder, hydronephrosis), cerebellar ataxia, peripheral neuropathy, and psychiatric disorders may also occur [4, 5]. The prevalence of Wolfram syndrome is estimated at 1 in 770,000 in the UK and 1 in 500,000 in North America [6, 7]. However, it is likely underdiagnosed, particularly in populations with high consanguinity, where recessive disorders are more frequent [8]. In Algeria, no epidemiological data exist regarding the prevalence of this condition, and it is probably underrecognized [9].

Type 1 diabetes is usually the first manifestation, occurring before age 16 in 90% of cases [3]. Optic atrophy typically appears between ages 6 and 14, followed by deafness in the second decade [10]. Urinary tract abnormalities, including neurogenic bladder and hydronephrosis, are frequent and can lead to end-stage renal disease if not managed early [11]. The diagnosis is often delayed because the manifestations appear sequentially and are initially attributed to common conditions such as diabetic complications [12]. Renal involvement in Wolfram syndrome is frequently misdiagnosed as diabetic nephropathy, leading to inappropriate management and delayed diagnosis. The recent Italian Society of Diabetes (SID) and Italian Society for Pediatric Endocrinology and Diabetology (SIEDP) expert consensus emphasizes that initial management often focuses on treating a

single disease, commonly diabetes mellitus, with other associated conditions emerging gradually and subtly over time, leading to significant diagnostic delays [13].

We report a consanguineous Algerian family where the proband was referred for diabetic nephropathy, revealing a 20-year diagnostic odyssey of Wolfram syndrome. His 18-year-old brother presented with similar symptoms but had never been investigated, illustrating the importance of family screening and multidisciplinary awareness [13, 14].

2. Case Presentation

2.1 Family History

The family originates from a rural region of northern Algeria. The parents are first-degree cousins (coefficient of inbreeding F = 1/16). The proband is the second child of five siblings. His 18-year-old brother (II3) presented with similar symptoms but had never been investigated. There is no known family history of diabetes, deafness, or visual impairment (Fig 1).

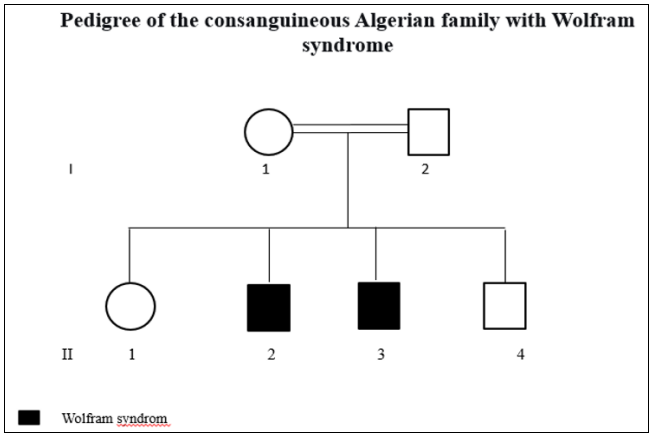

Fig 1: Pedigree of the consanguineous Algerian family with Wolfram syndrome. Squares represent males; circles represent females. The double line between parents (I1 and I2) indicates first-degree consanguinity (cousin marriage). Filled symbols indicate affected individuals: the proband (II2, arrow) and his affected brother (II3). The proband is a 24-year-old man with type 1 diabetes, optic atrophy, sensorineural deafness, neurogenic bladder, and cerebellar syndrome. His 18-year-old brother (II3) presents similar symptoms but had never been investigated. Other siblings (II1, II4) are asymptomatic. The arrow indicates the proband. This pedigree is consistent with an autosomal recessive inheritance pattern, characteristic of Wolfram syndrome. Deceased individuals are marked with a diagonal line

2.2 Proband (II2): A 24-Year-Old Man

A 24-year-old Algerian man was referred to our nephrology outpatient clinic for management of chronic kidney disease. He had been diagnosed with type 1 diabetes at the age of 4 years and had been treated with insulin since then. His diabetes was managed in general medicine, without specialized endocrinological or ophthalmological follow-up. He had a permanent urinary catheter in place for 2 years due to chronic urinary retention. He reported polyuropolydipsia of approximately 4.5 L/day, progressive visual impairment, bilateral hearing loss, and unsteady gait.

Clinical examination revealed blood pressure at 130/85 mmHg, weight 62 kg, height 172 cm (BMI 21 kg/m²). Neurological examination showed cerebellar syndrome with ataxia, dysmetria, and dysdiadochokinesia. Urological examination revealed a permanent urinary catheter in place. Ophthalmological examination demonstrated decreased visual acuity and pale optic discs bilaterally. Auditory examination revealed reduced hearing bilaterally.

Laboratory investigations showed fasting blood glucose at 5.0 g/L (27.8 mmol/L), glycated hemoglobin at 12.5%, serum creatinine at 3.2 mg/dL, eGFR (Cockcroft-Gault) at 24 mL/min, and proteinuria at 0.5 g/24h. Urine culture revealed *Escherichia coli* infection. Serum electrolytes were normal. Urine osmolality was 180 mOsm/kg, suggestive of diabetes insipidus. Morning paired urine and fasting plasma osmolarity testing confirmed impaired urine concentration ability [14].

Fundoscopy revealed bilateral optic disc pallor (optic atrophy) without diabetic retinopathy (Fig 2). Audiometry confirmed bilateral sensorineural hearing loss. Renal ultrasound showed severe bilateral hydronephrosis with significant post-void residual volume. Brain MRI was not performed due to unavailability. The association of juvenile diabetes, optic atrophy, bilateral deafness, familial presentation, and urological abnormalities strongly suggested Wolfram syndrome (DIDMOAD) [3, 14].

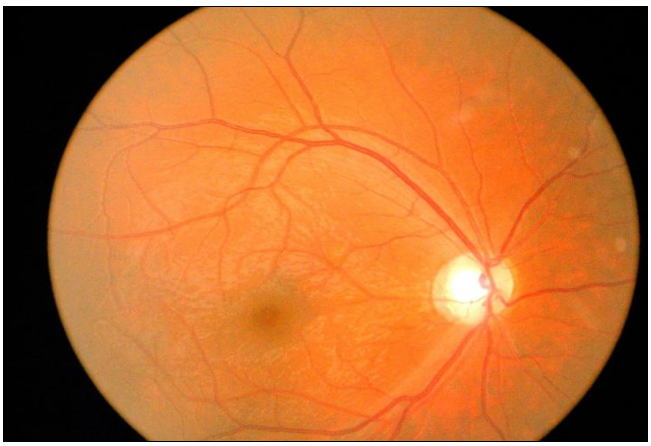

Fig 2: Fundoscopy of the proband (II2) showing bilateral optic atrophy. The optic disc appears pale, reflecting loss of nerve fibers. No signs of diabetic retinopathy (hemorrhages, exudates, or microaneurysms) are present. This finding, associated with juvenile diabetes mellitus and sensorineural deafness, guided the diagnosis toward Wolfram syndrome

2.3 Brother (II3): An 18-Year-Old Man with Similar Symptoms

The proband's 18-year-old brother had a similar history. He had been diagnosed with type 1 diabetes at age 5, with progressive visual impairment, hearing loss, and urinary dysfunction. He had never been investigated for these complications and was not receiving specialized care. This further supported the diagnosis of an autosomal recessive familial disorder.

2.4 Multidisciplinary Management and Treatment Initiation

Following the clinical diagnosis of Wolfram syndrome, the patient was referred to a multidisciplinary team for comprehensive management [13, 14]. The management plan included:

a) Diabetes Mellitus Management

Optimization of glycemic control was initiated using a continuous glucose monitoring system coupled with an insulin pump [13, 14]. Given the patient's preserved C-peptide levels and absence of diabetic ketoacidosis, a trial of combination therapy was initiated with metformin

(biguanide) and an SGLT2 inhibitor (empagliflozin) to improve insulin sensitivity and glycemic control, in addition to insulin [13]. The recent SID/SIEDP consensus recommends considering these agents in patients with residual C-peptide secretion [13].

b) Diabetes Insipidus Management

Desmopressin (DDAVP) was prescribed for the management of central diabetes insipidus, administered intranasally [14]. Prior to dose escalation, bladder dysfunction was carefully evaluated to avoid the risk of hyponatremia, as recommended by current guidelines [14]. The patient's polyuria and polydipsia improved significantly following desmopressin initiation.

c) Ophthalmological Management

The patient was referred to ophthalmology for visual rehabilitation and monitoring of optic atrophy progression [14]. An annual eye examination including visual acuity, fundoscopy, visual fields, and OCT scan was planned as per international recommendations [13, 14]. Considering the progressive optic atrophy, neuroprotective treatments were discussed, including idebenone (300 mg three times daily), although this product is not currently commercialized in Algeria [13]. CoQ10/Ubiquinol (200 mg per day) was prescribed as an alternative neuroprotective agent [14].

d) Audiological Management

The patient was referred to otolaryngology for hearing aids fitting [14]. A cochlear implant was discussed as a potential option depending on the evolution of hearing loss, as recommended for severe to profound sensorineural deafness [14].

e) Urological and Nephrological Management

The patient was referred to urology for management of neurogenic bladder and hydronephrosis [14]. Management included medications to improve bladder emptying and intermittent catheterization to reduce post-void residual volume. Regular renal function monitoring was planned, with particular attention to the risk of recurrent urinary tract infections [14].

f) Neurological and Endocrine Management

Referral to neurology was arranged for assessment of cerebellar syndrome and evaluation for other neurological manifestations [14]. Given the patient's symptoms of delayed puberty and signs of hypogonadism, endocrine evaluation was performed, including testosterone, FSH, LH, and inhibin B levels [14]. Hormonal replacement therapy with testosterone was considered. Thyroid function testing (free T3, free T4, TSH) was also performed, with substitution therapy by L-thyroxine (25 µg/day starting dose) if hypothyroidism was confirmed [14].

g) Genetic Counseling

Genetic counseling was offered to the family to discuss the autosomal recessive inheritance pattern and the 25% recurrence risk for future offspring [14]. In Algeria, *WFS1* gene sequencing is not currently available, limiting genetic confirmation. However, the clinical diagnosis remains valid based on the presence of juvenile diabetes, optic atrophy, and at least one other typical manifestation in a consanguineous family context [13, 14].

3. Discussion

3.1 Diagnostic Delay: A 20-Year Odyssey

Our patient was diagnosed with type 1 diabetes at age 4 and developed progressive complications over the following 20 years. He was referred to nephrology only at age 24, when his renal function had already declined to stage IV CKD (eGFR 24 mL/min). This diagnostic delay is consistent with the literature. In a series of 45 patients, the mean time from diabetes onset to the diagnosis of Wolfram syndrome was 17.2 years [15]. The Italian SID/SIEDP consensus highlights that "initial management often focuses on treating a single disease, commonly diabetes mellitus, with other associated conditions emerging gradually and subtly over time, leading to significant delays in obtaining a comprehensive diagnosis and appropriate care for individuals with WFS" [13].

Several factors contributed to this diagnostic delay. The first factor was the sequential onset of manifestations. Diabetes appeared at age 4, optic atrophy between ages 10 and 14 (undiagnosed), deafness between ages 14 and 18, urinary symptoms between ages 18 and 22, and renal failure between ages 22 and 24. Each manifestation was attributed to diabetic complications rather than a syndromic cause, a phenomenon well described in the literature where symptoms like polyuria, polydipsia, and vision loss are easily attributed to poorly controlled diabetes [12].

The second factor was the lack of multidisciplinary coordination. The patient was followed exclusively in general medicine for his diabetes. No systematic screening for extra-pancreatic manifestations was performed. The PNDS (Protocole National de Diagnostic et de Soins) for Wolfram syndrome emphasizes that the diagnosis is often difficult and delayed due to the rarity of the condition, and requires coordinated multidisciplinary care involving diabetologists, endocrinologists, ophthalmologists, ENT specialists, nephrologists, and neurologists [14].

The third factor was insufficient awareness among clinicians. The association of diabetes with optic atrophy and deafness was not recognized as Wolfram syndrome. Diabetic nephropathy was considered the primary cause of renal failure, delaying the diagnosis of neurogenic bladder. The French PNDS recommends that the general practitioner should suspect Wolfram syndrome in any child who develops insulin-dependent diabetes and bilateral optic neuropathy without identifiable cause [14].

3.2 Treatment Initiation in Algeria

Following the diagnosis, the patient was initiated on a comprehensive multidisciplinary treatment plan as detailed above. The management of Wolfram syndrome in Algeria faces challenges including limited access to genetic testing (*WFS1* sequencing is not currently available in the country) and restricted availability of certain medications such as idebenone. However, essential treatments including insulin, metformin, SGLT2 inhibitors, desmopressin, thyroid hormone replacement, and hearing aids are available in Algeria [9]. A case report from Algeria published in 2025 confirms that multidisciplinary management involving pediatricians, endocrinologists, ophthalmologists, and psychiatrists is feasible in the Algerian context [9].

3.3 Clinical Diagnosis in the Absence of Genetic Testing

In Algeria, genetic testing for *WFS1* mutations is not currently available. This is a common challenge in many resource-limited settings where rare diseases are often

underdiagnosed [8, 9]. The clinical diagnosis of Wolfram syndrome is based on the association of two major criteria (insulin-dependent diabetes before age 16 and bilateral optic neuropathy progressing to optic atrophy before age 16) or one major criterion and two minor criteria (diabetes insipidus, sensorineural deafness, neurological manifestations, urinary tract abnormalities, family history of Wolfram syndrome) [14]. In such contexts, the clinical diagnosis is considered valid and allows appropriate multidisciplinary management [13, 14].

3.4 How to Avoid Diagnostic Delays?

Based on this case and current guidelines, we propose the following recommendations to avoid diagnostic delays in Wolfram syndrome.

For general practitioners and endocrinologists, in any young patient with type 1 diabetes, systematically question about visual impairment, hearing loss, and urinary symptoms [13]. Refer to ophthalmology for fundoscopic examination, as optic atrophy is often missed on routine examination [14]. Consider Wolfram syndrome when diabetes is associated with optic atrophy, regardless of glycemic control [13].

For nephrologists, do not attribute all renal failure in diabetic patients to diabetic nephropathy. In young patients with diabetes and renal failure, investigate for neurogenic bladder using ultrasound and post-void residual volume measurement [14]. Look for other syndromic manifestations such as optic atrophy and deafness when renal failure is unexplained. Urinary tract anomalies may present at 12 to 20 years of age in approximately 19% of cases [11].

For ophthalmologists, in young patients with optic atrophy, question about diabetes and deafness [14]. Consider Wolfram syndrome before diagnosing "isolated" optic atrophy. Annual eye examination including visual acuity, fundoscopy, visual fields, and OCT is mandatory [13, 14].

For families, in consanguineous populations, genetic counseling is essential. Siblings of index cases should be systematically screened for early detection and management [14].

3.5 Wolfram Syndrome: Key Features and Diagnostic Criteria

Wolfram syndrome is characterized by several key features. Diabetes mellitus occurs in 100% of patients, with onset before age 16. Optic atrophy occurs in 98% of patients, with onset between ages 6 and 14. Deafness occurs in 60 to 70% of patients, with onset in adolescence. Diabetes insipidus occurs in 40 to 70% of patients, with onset in adolescence. Neurogenic bladder occurs in 50% of patients, with onset in adolescence or adulthood. Neurological signs occur in 60% of patients, with onset in adulthood. Psychiatric disorders occur in 50% of patients, with onset in adulthood [3].

The SID/SIEDP expert consensus recommends the revision of diagnostic protocols to include genetic testing and comprehensive multidisciplinary evaluations to ensure accurate diagnosis of Wolfram syndrome, and advocates for personalized management plans tailored to the unique needs of each patient [13].

3.6 Renal Involvement in Wolfram Syndrome

Renal disease in Wolfram syndrome is frequently misdiagnosed as diabetic nephropathy. However, the etiology is often urological. Neurogenic bladder results from detrusor-sphincter dyssynergia leading to chronic urinary retention. Hydronephrosis results from neurogenic bladder. Urinary tract infections are recurrent due to stasis. Renal failure may be post-renal (obstructive) or mixed (post-renal plus diabetic nephropathy). Between 60 and 90% of individuals with Wolfram syndrome develop urinary tract problems [11]. In our patient, the presence of a permanent urinary catheter, severe hydronephrosis, and recurrent urinary tract infections suggested predominantly post-renal causes of renal failure, rather than pure diabetic nephropathy.

3.7 Genetic Basis

Wolfram syndrome is caused by mutations in the *WFS1* gene, which encodes wolframin, a protein involved in endoplasmic reticulum calcium homeostasis and β-cell survival [16, 17]. Over 200 *WFS1* mutations have been identified [18]. The disorder is inherited in an autosomal recessive manner, explaining its frequent occurrence in consanguineous populations. Heterozygous *WFS1* mutations may also lead to early development of diabetes, sometimes presenting as MODY [10]. The SID/SIEDP consensus notes that the WFS1 gene encodes wolframin, which plays a critical role in the regulation of the endoplasmic reticulum's stability within pancreatic β cells and other tissues [13].

3.8 Comparison with Published Literature

Our case is similar to previously reported cases of diagnostic delay in Wolfram syndrome. In a series of 45 patients, the mean time from diabetes onset to the diagnosis was 17.2 years [15]. The most common reason for delay was the lack of recognition of optic atrophy and deafness as part of a syndromic diagnosis [11]. Renal involvement is a frequent and life-threatening complication in Wolfram syndrome. End-stage renal disease is reported as one of the most common causes of death among Wolfram syndrome patients, and urinary tract dysfunction affects up to 90% of affected individuals [11]. Many of these patients were initially diagnosed with diabetic nephropathy before the correct diagnosis was made. A case report from Algeria published in 2025 described a 17-year-old patient with Wolfram syndrome, confirming that this condition exists in the Algerian population and is likely underdiagnosed [9]. Our case is original for several reasons. It illustrates a 20-year diagnostic delay. It highlights the importance of systematic family screening, as the affected brother was identified. It demonstrates the need for multidisciplinary evaluation. It emphasizes the role of the nephrologist in recognizing syndromic causes of renal failure.

3.9 Strengths

Our case report has several strengths. We provide a comprehensive clinical description of a rare syndromic disorder. We illustrate the diagnostic delay and its contributing factors. We emphasize family screening in consanguineous populations. We provide practical recommendations for clinicians. We adopt a multidisciplinary approach. We highlight the challenges of diagnosis and management in resource-limited settings.

3.10 Limitations

This case report has several limitations. Genetic confirmation of *WFS1* gene mutations is not available in Algeria, and the diagnosis remains clinical. Brain MRI was not performed. There was no systematic evaluation of

diabetes insipidus prior to treatment initiation.

3.11 Implications for Clinical Practice

When evaluating a young patient with diabetes and renal failure, consider the following red flags: optic atrophy (look for pale optic discs on fundoscopy), deafness (ask about hearing loss), neurological signs (ataxia, cerebellar syndrome), urological symptoms (urinary retention, hydronephrosis), family history of similar symptoms, and consanguinity.

The SID/SIEDP expert consensus recommends a holistic care model that addresses the medical, psychological, and social challenges faced by patients with Wolfram syndrome and their families, and emphasizes the importance of educating healthcare professionals about WFS to enhance early diagnosis and intervention [13].

We propose a screening protocol for Wolfram syndrome. All patients with juvenile diabetes should undergo annual ophthalmological examination with fundoscopy. If optic atrophy is detected, screen for hearing loss, urological symptoms, and neurological signs. If syndromic association is suspected, a clinical diagnosis of Wolfram syndrome can be made in the absence of genetic testing, particularly in consanguineous families. In settings where genetic testing is not available, clinical diagnosis should guide multidisciplinary management.

4. Conclusion

We report a consanguineous Algerian family where the proband was clinically diagnosed with Wolfram syndrome 20 years after the onset of type 1 diabetes, following referral for diabetic nephropathy. The diagnosis was revealed by the association of juvenile diabetes, optic atrophy, deafness, neurogenic bladder, and familial presentation. His 18-year-old brother had similar symptoms but had never been investigated, illustrating the importance of systematic family screening. Following diagnosis, the patient was initiated on multidisciplinary care including insulin optimization with metformin and SGLT2 inhibitor, desmopressin for diabetes insipidus, neuroprotective agents (CoQ10) for optic atrophy, hearing aids, and management of neurogenic bladder.

The essential message for clinicians is that Wolfram syndrome is a rare but important cause of renal failure in young diabetic patients. Diagnostic delay is common due to the sequential onset of manifestations and insufficient multidisciplinary coordination. Nephrologists must be vigilant for syndromic associations when evaluating diabetic nephropathy, particularly in consanguineous populations. The recent SID/SIEDP expert consensus emphasizes that a holistic care model addressing medical, psychological, and social challenges is essential for optimal management [13]. A systematic approach to family screening can prevent diagnostic delays and enable early management of renal and extra-renal complications. In resource-limited settings where genetic testing is unavailable, clinical diagnosis remains essential to guide appropriate multidisciplinary care.

5. Declarations

Ethics Approval and Consent to Participate: This study was approved by the Ethics Committee of the University of Algiers 1 Benyoucef Benkhedda. Written informed consent was obtained from the patient and his brother for publication of this case report.

Consent for Publication: Written informed consent was obtained from the patient and his brother for publication of this case report and accompanying images.

Availability of Data and Material: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare no competing interests.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' Contributions: GK conceived the study, collected and interpreted the data, and wrote the manuscript. AB collected and interpreted the data and revised the manuscript critically. All authors read and approved the final manuscript.

Acknowledgements: The authors thank the patient and his family for their participation and consent to publish. We acknowledge the technical staff of the Nephrology Department at CHU Mohamed Lamine Debaghine for their assistance with patient management and sample collection.

6. References

1. Barrett TG, Bundey SE. Wolfram (DIDMOAD) syndrome. J Med Genet. 1997; 34(10):838-841.
2. Inoue H, *et al*. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat Genet. 1998; 20(2):143-148.
3. Barrett TG, BS. Wolfram (DIDMOAD) syndrome., In GeneReviews, 1997, 838-841.
4. Swift RG, Sadler DB, Swift M. Psychiatric findings in Wolfram syndrome homozygotes. Lancet. 1990; 336(8716):667-669.
5. Urano F. Wolfram Syndrome: Diagnosis, Management, and Treatment. Curr Diab Rep. 2016; 16(1):p. 6.
6. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet. 1995; 346(8988):1458-1463.
7. Rigoli L, Di Bella C. Wolfram syndrome 1 and Wolfram syndrome 2. Curr Opin Pediatr. 2012; 24(4):512-517.
8. Bittles AH, Black ML. Evolution in health and medicine Sackler colloquium: Consanguinity, human evolution, and complex diseases. Proc Natl Acad Sci U S A. 2010; 107(Suppl 1):1779-1786.
9. Ameur A, *et al*. Wolfram syndrome in early adulthood: A Case Report. The Middle East Journal. 2025; 8:p. 6.
10. Chaussenot A, *et al*. Neurologic features and genotype-phenotype correlation in Wolfram syndrome. Ann Neurol. 2011; 69(3):501-508.
11. La Valle A, *et al*. Urinary Tract Involvement in Wolfram Syndrome: A Narrative Review. Int J Environ Res Public Health. 2021; 18(22).
12. Echcharii N, *et al*. A Hidden Diagnosis: Neurogenic Bladder Leading to Acute Kidney Failure in Wolfram Syndrome. Cureus. 2025; 17(5):p. e83594.
13. Frontino G, *et al*. SID/SIEDP expert consensus on optimizing clinical strategies for early detection and management of wolfram syndrome. J Endocrinol Invest. 2025; 48(3):507-525.
14. Christian Hamel DAC, *et al*. Protocole National de Diagnostic et de Soins (PNDS) - Syndrome de Wolfram. Centre de référence des maladies rares en

ophtalmologie – OPHTARA, 2019.
15. Zmyslowska A, *et al*. Delayed recognition of Wolfram syndrome frequently misdiagnosed as type 1 diabetes with early chronic complications. Exp Clin Endocrinol Diabetes. 2014; 122(1):35-38.
16. Fonseca SG, *et al*. WFS1 is a novel component of the unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic beta-cells. J Biol Chem. 2005; 280(47):39609-39615.
17. Matsunaga K, *et al*. Wolfram syndrome in the Japanese population; Molecular analysis of WFS1 gene and characterization of clinical features. PLoS One. 2014; 9(9):p. e106906.
18. De Heredia ML, Clèries R, Nunes V. Genotypic classification of patients with Wolfram syndrome: Insights into the natural history of the disease and correlation with phenotype. Genet Med. 2013; 15(7):497-506.