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Case Series
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Wolfram Syndrome: A Series of 4 Cases

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Introduction

Wolfram Syndrome (WS), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness), is a rare neurodegenerative disorder [1, 2]. This condition features symptoms that typically appear progressively from childhood through adulthood [3, 4, 5]. Diagnosis is based on specific clinical criteria and confirmed by genetic testing for mutations in the *WFS1* gene [6, 7]. Insulin therapy remains the mainstay treatment for diabetes mellitus, but incretin analogs may provide benefit if initiated early [8, 9]. Prognosis is generally poor, with a mean life expectancy of 39 years, often due to central respiratory complications [3, 10]. Gene therapyiscurrentlyexperimental but promising [11].

Clinical Cases

See Table 1.

Case Descriptions

Case 1

A 20-year-old male born of first-degree consanguineous parents with a diabetic father. Diagnosed with insulin-dependent diabetes mellitus at 8 years old with low insulin requirements and frequent hypoglycemia episodes. Presents with bilateral vision loss and recent bilateral sensorineural hearing loss and bilateral hydronephrosi. Diabetes insipidus was diagnosed at 17 years.

Case 2

A 17-year-old male from a consanguineous marriage. Insulin-dependent diabetes diagnosed at 7 years. Hospitalized for diabetic ketoacidosis, during which bilateral optic atrophy, asymmetric sensorineural hearing loss, neurogenic bladder, and bilateral hydroureteronephrosis were found. He also had low insulin needs and frequent hypoglycemic episodes.

Case 3

A 16-year-old female, second child of non-consanguineous parents; father is diabetic with pre-lingual deafness and blindness. Diagnosed with insulin-dependent diabetes at 4 years after a ketoacidotic coma. Presents with pre-lingual sensorineural deafness and optic atrophy. Insulin requirements are low with frequent hypoglycemia. Abdominal ultrasound was normal.

Case 4

The father of Case 3, aged 50, with pre-lingual deafness and insulin-dependent diabetes

Table 1:

Parameters	Case 1	Case 2	Case 3	Case 4
Age at Diagnosis	20 years	17 years	16 years	50 years
Family History	First-degree consanguineous marriage, diabetic father	Consanguineous marriage	Non-consanguineous parents, diabetic father	Father of Case 3
Insulin-dependent Diabetes	Since 8 years, low insulin requirements, frequent hypoglycemia	Since 7 years, low insulin requirements, frequent hypoglycemia	Since 4 years, low insulin requirements, frequent hypoglycemia	Since 30 years, severe DKA at diagnosis
Optic Atrophy	Bilateral	Bilateral	Present	Blindness at 40 years
Sensorineural Deafness	Recent bilateral	Asymmetric	Pre-lingual	Pre-lingual
Diabetes Insipidus	Present (diagnosed at 17 years)	Absent	Absent	Absent
Urinary manifestations	bilateral hydronephrosi	Neurogenic bladder, bilateral hydroureteronephrosis	Normal abdominal ultrasound	normal

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diagnosed at 30 years during a severe diabetic ketoacidosis episode requiring intensive care. Progressed to blindness at 40 years.

Discussion

Wolfram Syndrome is a rare autosomal recessive disorder affecting the nervous system, pancreatic beta cells, and sensory organs [1, 3]. Symptoms usually appear progressively between childhood and adulthood [3, 6]. Diabetes mellitus is typically the first clinical sign, preceding optic atrophy and hearing loss [3, 7].

It is important to note that although all our patients have insulin-dependent diabetes, **only one case exhibited diabetes insipidus**, while literature reports diabetes insipidus in about 70% of Wolfram patients [8, 9]. This variability highlights the phenotypic heterogeneity of the disease [10, 11].

Cases 1, 2 and 3 exhibited relatively low insulin requirements and frequent hypoglycemia, consistent with the literature describing complex beta-cell dysfunction due to endoplasmic reticulum stress [12, 13].

Diagnosis is based on clinical criteria combined with genetic confirmation via *WFS1* mutation analysis [6, 14]. Family history and consanguinity are important risk factors [10].

Treatment remains mainly symptomatic. Insulin therapy is essential, with careful monitoring to avoid hypoglycemia [12]. Early introduction of incretin analogs may be beneficial [9, 15]. Management of other complications is palliative, while gene therapy represents a promising future approach [11, 16].

Overall prognosis remains poor, with an average life expectancy of 39 years, mainly due to central espiratory failure [3, 17].

Conclusion

Wolfram Syndrome is a rare neurodegenerative disorder requiring multidisciplinary management. Close monitoring of diabetes, sensory deficits, and neurological complications is critical. Early diagnosis and tailored treatment can improve quality of life while awaiting major therapeutic advances such as gene therapy.

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