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WOLFRAM (DIDMOAD) SYNDROME: A FAMILIAL CLINICAL CASE WITH LITERATURE REVIEW

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Abstract: This article presents an extended familial clinical case of Wolfram (DIDMOAD) syndrome with an in-depth literature review, discussion of genetic mechanisms, and therapeutic perspectives. Wolfram syndrome is a rare hereditary disorder characterized by the combination of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, along with neurological and endocrine complications. Despite its rarity, the disease has significant clinical relevance due to its diagnostic complexity and poor prognosis. This paper emphasizes the importance of timely diagnosis, interdisciplinary management, and future therapeutic approaches.

Introduction

Wolfram syndrome, also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness), is a rare autosomal recessive or, in rare cases, autosomal dominant disorder. The prevalence is estimated at approximately 1 in 100,000 to 1 in 500,000 live births. The syndrome is typically associated with mutations in the WFS1 gene, which encodes the protein wolframin, or CISD2 mutations linked to type 2 Wolfram syndrome. The clinical presentation is highly variable, often beginning with non-autoimmune diabetes mellitus in childhood followed by progressive optic atrophy, diabetes insipidus, sensorineural hearing loss, and neurodegeneration. Due to the heterogeneity of clinical manifestations, the diagnosis is often delayed, leading to increased morbidity.

Literature Review

Recent studies have expanded understanding of the molecular mechanisms underlying Wolfram syndrome. Mutations in WFS1 disrupt calcium homeostasis, endoplasmic reticulum stress response, and insulin secretion, leading to β-cell death and neurodegeneration. According to Mishra et al. (2021), therapeutic approaches targeting ER stress pathways and mitochondrial function are under investigation. Iafusco et al. (2022) described metabolic management strategies to improve glycemic control and delay complications. Serbis et al. (2023) highlighted the importance of early recognition in pediatric practice, while Du et al. (2023) presented diverse case series indicating significant clinical variability. Rosanio et al. (2022) reviewed type 2 Wolfram syndrome caused by CISD2 mutations, emphasizing distinct features such as gastrointestinal ulceration and bleeding.

Pathogenesis and Genetics

The pathogenesis of Wolfram syndrome centers around dysfunction of the endoplasmic reticulum (ER). Wolframin, the protein encoded by WFS1, regulates ER calcium levels and stress response. Mutations lead to chronic ER stress, triggering apoptosis of pancreatic β-cells and neuronal cells. This explains the combination of diabetes mellitus and progressive neurodegeneration. Additionally, WFS1 mutations affect auditory pathways, optic nerve survival, and renal tubular function, contributing to the DIDMOAD clinical spectrum. CISD2 mutations in type 2 Wolfram syndrome involve mitochondrial dysfunction and impaired redox signaling.

Case Description and Clinical Findings

Patient 1

Patient H.N., born on 20.07.2009. Height 148 cm, weight 38 kg, BMI 17.3. Normal pregnancy and delivery, second pregnancy, second child. Birth weight 3200 g, breastfed, vaccinated according to schedule. Psychomotor development was on time. Past infections: ARVI, chickenpox, measles. Type 1 diabetes mellitus diagnosed in February 2014.

Laboratory findings: complete blood count and biochemical blood test showed no significant changes. Blood glucose fluctuations: 5.3 – 12.7 mmol/L, HbA1c 10.9%. Zimnitsky test: average urine volume 425 ml, specific gravity 1000–1004.

Diagnosis: Type 1 diabetes mellitus, subcompensated stage (E10.7) (DIDMOAD syndrome). Comorbidities: diffuse goiter grade 1 (E01.0). Complications: diabetic polyneuropathy grade 1 (G63.2), central diabetes insipidus (E25.1). Associated conditions: partial optic nerve atrophy OU (H47.2), bilateral sensorineural hearing loss grade 3, vitamin D deficiency (E55.9).

Treatment and recommendations: diet No.15; insulin therapy: bolus (Novorapid) 4/4/4 IU before meals, basal (Levemir) 18 IU morning, 8 IU evening; blood glucose monitoring six times daily; desmopressin 1 drop intranasally twice daily; potassium iodide 200 mcg after breakfast continuously; cholecalciferol 500 IU, 10 drops once daily for 3 months; follow-up with endocrinologist, nephrologist, ENT, ophthalmologist.

Patient 2

Patient H.M., born on 17.06.2011. Height 134 cm, weight 28 kg, BMI 15.6. Normal pregnancy and delivery, third pregnancy, third child. Birth weight 3200 g, breastfed, vaccinated according to schedule. Psychomotor development was on time. Past infections: ARVI, chickenpox, measles. Type 1 diabetes mellitus diagnosed in February 2014.

Laboratory findings: complete blood count showed no significant abnormalities. Biochemical tests: urea 14.8 mmol/L, creatinine 233 µmol/L. Blood glucose fluctuations: 8.5 – 18.4 mmol/L, HbA1c 10.4%. Zimnitsky test: average urine volume 300 ml, specific gravity 1002–1005.

Diagnosis: Type 1 diabetes mellitus, subcompensated stage (E10.7) (DIDMOAD syndrome). Comorbidities: diffuse goiter grade 1 (E01.0). Complications: diabetic polyneuropathy grade 1 (G63.2), central diabetes insipidus (E25.1). Associated conditions: partial optic nerve atrophy OU (H47.2), bilateral sensorineural hearing loss grade 3, vitamin D deficiency (E55.9), short stature syndrome (E34.3).

Treatment and recommendations: diet No.15; insulin therapy: bolus (Novorapid) 4/4/4 IU before meals, basal (Levemir) 14 IU morning, 12 IU evening; blood glucose monitoring six times daily; desmopressin 1 drop intranasally twice daily; potassium iodide 200 mcg after breakfast continuously; cholecalciferol 500 IU, 10 drops once daily for 3 months; follow-up with endocrinologist, nephrologist, ENT, ophthalmologist.

Patient 3

Patient H.S., born on 17.06.2016. Height 122 cm, weight 21 kg, BMI 14.1. Normal pregnancy and delivery, fifth pregnancy, fifth child. Birth weight 3200 g, breastfed, vaccinated according to schedule. Psychomotor development was on time. Past infections: ARVI, chickenpox, measles. Type 1 diabetes mellitus diagnosed in March 2020.

Laboratory findings: complete blood count and biochemical tests showed no significant abnormalities. Blood glucose fluctuations: 7.2 – 13.9 mmol/L, HbA1c 9.2%. Zimnitsky test: average urine volume 450 ml, specific gravity 1003–1010.

Diagnosis: Type 1 diabetes mellitus, labile course (E10.7). Comorbidities: diffuse goiter grade 1 (E01.0). Associated conditions: vitamin D deficiency (E55.9).

Treatment and recommendations: diet No.15; insulin therapy: bolus (Novorapid) 3/3/3 IU before meals, basal (Levemir) 7 IU morning, 3 IU evening; blood glucose monitoring six times daily;

potassium iodide 200 mcg after breakfast continuously; cholecalciferol 500 IU, 10 drops once daily for 3 months; follow-up with endocrinologist, nephrologist, ENT, ophthalmologist.

Discussion

This familial case demonstrates the clinical variability of Wolfram syndrome, even among siblings with the same genetic background. Early-onset diabetes is a common first manifestation, but progression to optic atrophy, hearing loss, and neurodegeneration differs significantly. Compared with international case series, our findings are consistent with the reported heterogeneity. The diagnosis remains challenging due to overlapping features with type 1 diabetes and other neurodegenerative disorders. Genetic testing is essential for confirmation.

Management and Future Perspectives

Currently, there is no curative treatment for Wolfram syndrome. Management focuses on symptomatic relief and prevention of complications. Insulin therapy, desmopressin for diabetes insipidus, vitamin D supplementation, and auditory support are key interventions. Experimental approaches under investigation include chemical chaperones, GLP-1 receptor agonists, and gene therapy aimed at restoring WFS1 function. Clinical trials are ongoing, offering hope for disease-modifying strategies.

Clinical Significance

This case report underscores the importance of considering Wolfram syndrome in young patients with non-autoimmune diabetes mellitus and additional neurological or endocrine symptoms. Early recognition is critical for appropriate management and family counseling. In Uzbekistan, reporting such cases contributes to raising awareness of rare genetic disorders and may facilitate earlier diagnosis in future patients.

Conclusion

Wolfram syndrome is a devastating rare disease with highly variable clinical presentation. Our familial case illustrates the spectrum of manifestations within a single family, emphasizing the diagnostic challenges. While current therapies remain supportive, advances in molecular medicine provide new hope for targeted treatment. Early detection and multidisciplinary care are crucial to improve quality of life and prognosis.

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