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Multifaceted diabetes: a clinical case

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DIDMOAD syndrome (Wolfram syndrome type 1 is an orphan multisystem mitochondrial dysfunction, the name of which is an acronym for the combination of the following nosologies: Diabetes Insipidus (DI), Diabetes Mellitus (DM), Optic Atrophy (OA), Deafness (D), which is associated with a biallelic mutation in the wolframin gene (*Wolframin ER transmembrane glycoprotein 1 — WFS1*) and is inherited in an autosomal recessive manner.

Objective — to study in detail and present a specific clinical case of DIDMOAD syndrome, including its manifestations, diagnosis, treatment and prognosis, in order to expand medical knowledge, improve clinical practice and education.

Materials and methods. A systematic analysis of 29 modern literature sources on the topic was conducted, with an emphasis on clinical manifestations, genetics and differential diagnosis. A patient with a clinical case of classic DIDMOAD syndrome (Wolfram syndrome type 1) was under observation, which was verified by whole exome sequencing in a certified laboratory of the University of Exeter (UK, Exeter).

Results and discussion. About 200 cases of DIDMOAD syndrome are described in the scientific literature in the world, and in Ukraine, including this one, only two. Unlike the results of other researchers, in our patient, hypoinsulinemic hyperglycemia was combined with a congenital anomaly of the urinary system (duplication of the right kidney) without early manifestation of visual and hearing impairment, which led to the differential diagnosis of his pathological condition with other types of nonautoimmune diabetes mellitus accompanied by impairment of the urinary system.

Conclusions. DIDMOAD syndrome is an extremely rare disease, in which genetic testing helps to select precision treatment. The clinical case described by us will serve as a guide for clinicians to increase awareness of the detection of this orphan disease and intensify its management.

Keywords: *Wolframin ER transmembrane glycoprotein 1*, DIDMOAD syndrome, whole exome sequencing, clinical case.

DIDMOAD syndrome (Wolfram syndrome — WS; OMIM 222300) was first described in 1938 by Don J. Wolfram, MD and Wagner in 4 siblings [26], combining Diabetes Insipidus (DI), Diabetes Mellitus (DM), Optic Atrophy (OA) and Deafness (D), and was also characterized by a high risk of premature death. DIDMOAD syndrome is a progressive multisystem autosomal recessive disease [14, 21, 28], additional clinical features include other symptoms such as urinary tract abnormalities, psychiatric and neurological manifestations (headaches similar to trigeminal neuralgia, dysphagia, neurogenic bladder, anxiety and depressive disorders). Given that urinary tract dysfunction (UD) occurs more frequently than expected, this has prompted some researchers to suggest that the acronym DIDMOADUD is more appropriate. At the same time, gonadal dysfunction, described mainly in adults, was classified as a secondary clinical feature [11].

DIDMOAD syndrome is a very rare disease, the prevalence of which in the world is 1 case per 160,000—

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770,000 people. In the USA it is estimated as 1 : 100,000, while in the UK it is 1 : 770,000, in North India 1 : 805,000 and in Italy 0.74 : 1,000,000 [21]. In the scientific literature, about 200 cases are described in the world, and in Ukraine, including this one, only two [12].

Classic Wolfram syndrome type 1 (WS1, OMIM #222300) is caused by a homozygous mutation in the wolframin gene (*Wolframin ER transmembrane glycoprotein 1 — WFS1*), located on chromosome 4 (locus 4p16.1) [15, 23], which leads to the formation of an aberrant transmembrane protein wolframin [19].

Wolframin consists of 890 amino acids and is physiologically involved in several crucial cellular signaling pathways, including protein folding, insulin signaling, dynamic interaction with mitochondria at mitochondrial-associated membranes (MAMs), calcium homeostasis, regulation of apoptosis, and endoplasmic reticulum (ER) stress responses [15]. Cellular dysfunction due to loss of WFS1 protein in the islets of Langerhans is characterized by increased β-cell death and decreased insulin secretion [7]. Impaired Ca^{2+} flux leads to hyperactivation of calpains, which are cysteine proteases. This results in increased caspase-3 activity and cell apoptosis [4, 6, 8].

Wolframin levels are significantly increased in neuronal cells, pancreatic islets of Langerhans, and other organs (heart, parathyroid gland, testicular vas deferens cells, placental trophoblastic cells, renal tubule cells, inner ear, including the middle stele, spiral ganglion, and hair cells) [18, 20].

The different phenotypes of WS are explained by multitissue expression of wolframin [14, 16] and require an improved clinical and diagnostic search algorithm.

Objective — to study in detail and present a specific clinical case of DIDMOAD syndrome, including its manifestations, diagnosis, treatment and prognosis, in order to expand medical knowledge, improve clinical practice and education.

Materials and methods

Presented according to the CAse REport (CARE) standards [22] and with the informed consent of the child's legal representatives, the clinical case is a case of Wolfram syndrome type 1 associated with a homozygous mutation in the WFS1 gene, confirmed by molecular genetic whole exome sequencing in a certified laboratory at the University of Exeter (UK, Exeter). Clinical examination of the patient during inpatient treatment at the pediatric endocrinology department of the Municipal Non-Profit Enterprise «Dnipro City Clinical Hospital No. 6» of the Dnipro City Council» with analysis and interpretation of the obtained clinical, anamnestic, laboratory and instrumental data was the main method of research. The list of additional paraclinical examination methods was compiled in accordance with the Order of the Ministry of Health of Ukraine No. 413 dated April 27, 2006 «Protocol for providing medical care to children with diabetes mellitus», No. 864 dated October 7, 2013 «On amendments to the protocol for providing medical care to children with diabetes mellitus», No. 413 dated February 28, 2023 «Diabetes mellitus in children», as well as in accordance with the SID/SIEDP expert consensus on optimizing clinical strategies for early detection and management of Wolfram syndrome [11].

Description of a clinical case

We observed a *boy K.*, 9 years old, of Caucasian appearance, who first came to the hospital with complaints of: thirst, weight loss, frequent copious urination, hyperemia of the mucous membranes of the external genitalia.

Medical anamnesis: the listed complaints were noted in the boy for about 6 months.

Medical history: the listed complaints were noted in the boy for about 6 months.

Life anamnesis: born from the 3rd pregnancy, which took place against the background of the threat of abortion, chronic fetoplacental insufficiency, second birth (the first child born in a previous marriage is healthy), body weight at birth 3200 g, body length 49 cm, Apgar score 8/8 points. Up to 1 year, he was observed by a neurologist for perinatal damage to the central nervous system: hypertensive-hydrocephalic syndrome, muscle hypotension, delayed motor development.

Objective condition: moderate severity due to the underlying disease. Consciousness: preserved. Active position in bed. Skin of normal moisture, clean, normal color. Subcutaneous fat layer is sufficiently developed, uniform. Body structure is normosthenic. Body length 134 cm (+1.3 SDS), body weight 27.5 kg, BMI 15.36 kg/m^2, body temperature 36.5 °C. Respiratory organs: frequency 18 per min., breathing above the lungs is vesicular, no wheezing. Percussion: clear lung sound. Cardiovascular system: pulse 84 per min, rhythmic. Blood pressure lying 90/60 mm Hg. Heart limits are age-appropriate. Heart sounds are loud. Digestive organs: tongue is moist, clean. Abdomen is soft, painless on palpation. The liver is 1.5 cm below the costal arch along the lateral edge of the rectus abdominis muscle, not painful on palpation. Genitourinary system: urination is not impaired. Pasternacki's symptom is negative. Sexual development: F1P1Ax1G1, corresponds to sex and age. External genitalia are formed according to the male type. The thyroid gland is not enlarged, soft, elastic, not painful on palpation. Peripheral lymph nodes are not enlarged. Musculoskeletal system: without features. There are no edemas or pastiness (Table 1).

Consultations of related specialists. Neurologist's conclusion: Volumetric brain process? Neurosurgeon consultation: MRI of the brain recommended. Otolaryngologist: Bilateral sensorineural hearing loss. Ophthalmologist's conclusion: Optic nerve atrophy? Genetics conclusion of the Kryvyi Rih Medical Center: No amino acid metabolism disorders were detected.

Table 1
Results of laboratory examination methods at initial presentation

Research method	Parameter studied, units of measurement	Result of patient examination	Reference values
Enzyme (hexokinase) method	Postprandial serum glucose, mmol/L	12.5	4.11—5.89
Immunoturbidimetric method of blood serum research	Glycosylated hemoglobin (HbA1c), %	8.4	4.8—5.9
Immunochemical method of blood serum research with chemiluminescent detection	C-peptide, ng/mL	0.87	0.9—7.1
Immunoenzyme analysis of blood serum research	Markers of autoimmune destruction of the pancreas (IgG autoantibodies), U/l:		
	• Glutamate decarboxylase (GAD)	<10	<10
	• Insulinoma-antigen (IA-2α)	<10	<10
	• Zinc transporters (ZnT8)	4,63	<10
	• C-terminus of zinc transporters (C-terminus of ZnT8)	4,22	<10
Urine analysis according to Zimnytsky	Determination of daily diuresis, mL	1650	1000—1500
	Determination of the concentrating ability of the kidneys, g/mL	1.004—1.026	1.003—1.030

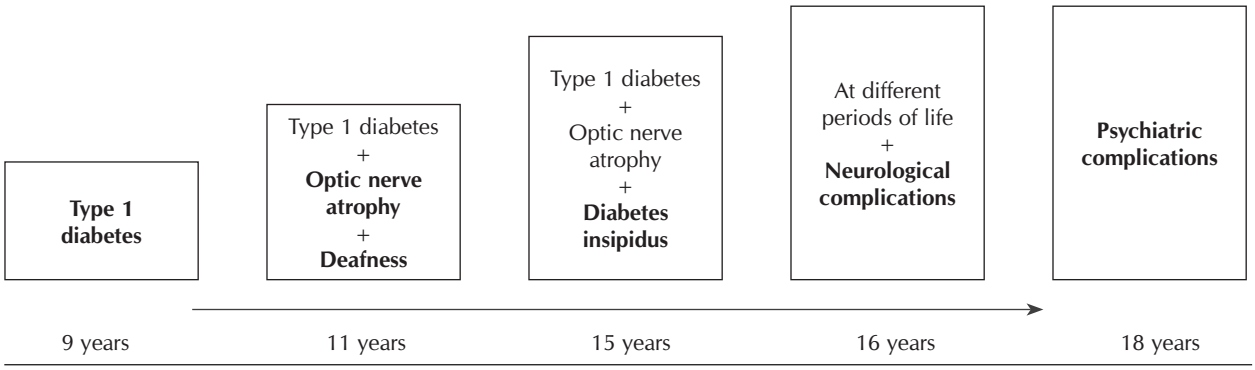

Fig. 1. **Results of dynamic observation of a boy K. from 9 to 18 years old with type 1 diabetes**

Instrumental examination methods. Rheoencephalography: Moderately obstructed venous outflow. Echoencephaloscopy: Signs of impaired cerebrospinal fluid dynamics. Ultrasound examination of the abdominal organs: Hepatomegaly. Ultrasound examination of the kidneys: Developmental anomaly — doubling of the right kidney. Magnetic resonance imaging of the brain: No organic pathology was detected. Electroencephalography: No epiactivity patterns were detected, the basic rhythm is age-related, not modulated. Electromyography: Moderately pronounced sensory neuropathy of the deep branch of the peroneal nerve on both sides.

A chronological description of further observation is presented in Fig. 1.

Radioimmunoassay of blood serum with determination of antidiuretic hormone in a 15-year-old child demonstrated its low level, which did not correlate with plasma osmolarity, which confirmed the presence of diabetes insipidus in the patient.

Diagnosis verification

Classic WS1 is a progressive neurodegenerative disorder characterized by the onset of diabetes mellitus and optic atrophy before the age of 16 years. Additional complications may include one or more of the following: variable hearing loss/deafness, diabetes insipidus, neurological disorders, neurogenic bladder, and psychiatric disorders. The diagnosis is made in a proband with suggestive findings and biallelic pathogenic variants (likely pathogenic) of the *WFS1* gene identified by molecular genetic testing.

Exome sequencing in our patient revealed a pathogenic variant of the *WFS1* gene as a biallelic mutation inherited from heterozygous parents who had no clinical signs of WS1, Fig. 2.

The set of complaints, history, clinical manifestations, results of laboratory and instrumental research methods and identification of the *WFS1* gene mutation made it possible to establish a clinical diagnosis according to the International Classification of Diseases (ICD)-10: E34.8 Other specified endocrine disorders (DIDMOAD syndrom), or according to ICD-11 to include it in subcategory 5A16.1.

Disease management

After the diagnosis was confirmed, the patient's disease management was based on: (1) Insulin therapy (actrapid, protaphane) and monitoring of insulin-

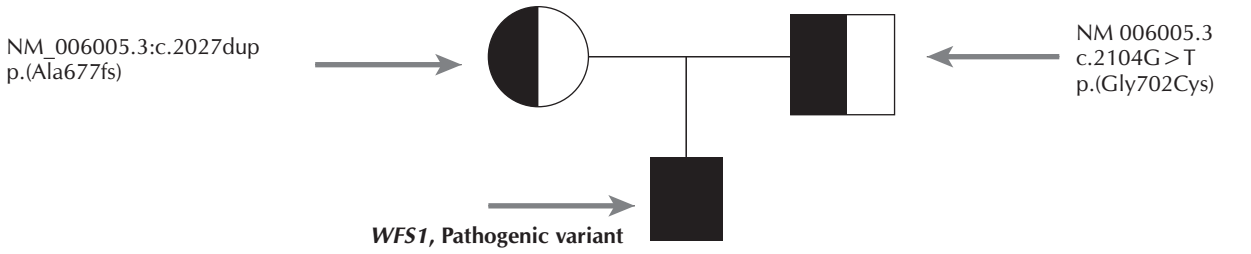

Fig. 2. **Pedigree of a patient with DIDMOAD syndrome**

dependent diabetes (blood sugar level, search for complications); (2) Monitoring for the detection of kidney function disorders; (3) Monitoring and compensation for vision disorders (visual aids, rehabilitation of low vision, etc.); (4). Monitoring and compensation for hearing disorders; (5) Treatment of diabetes insipidus; (6) Regular search for other diseases associated with WS, and their specific treatment or compensation; (7) Genetic counseling; (8) Recognition of the pathological condition in the patient as an orphan disease, which leads to a reduction in the patient's life expectancy and disability.

Prognostic characteristics, promising therapeutic approaches to the treatment of patients with DIDMOAD syndrom

DIDMOAD syndrome leads to premature death in the fourth decade (25—49 years) in affected people from acute respiratory failure due to brain atrophy, bulbar dysfunction [20, 24].

In order to improve the patient's quality of life, optimal educational integration and professional orientation of the patient, the general practitioner should ensure the optimization of the management of DIDMOAD syndrome in collaboration with various relevant specialists (diabetologist, endocrinologist, ophthalmologist, pediatrician, otolaryngologist, nephrologist, neurologist); inform the family about any benefits and social assistance to which they may be entitled in connection with WS [17].

Currently, there is no effective treatment for *WFS1* that would increase the life expectancy of patients [20]. Post-syndromic therapy is recommended [9, 13]. At the same time, new treatment strategies for patients with Wolfram syndrome type 1 are being developed:

1. Chemical chaperones (4-phenylbutyric acid and tauroursodeoxycholic acid), which provide: improvement of β-cell functions due to action on ER in «stressed cells»; stabilization of the native conformation during folding of mutant *WFS1* proteins; slowing down neurodegeneration in WS1 [21].
2. Calcium stabilizers in the ER:

2.1. Calpain XI inhibitor (SNJ-1945) — normalization of cytosolic calcium;
2.2. Ibudilast (blocking the cleavage of cAMP, which interacts with the calcium pathway. Normalization of calcium levels when interacting with *NCS1*);
2.3. Dantrolene (blockade of ryanodine receptors in the ER membrane and subsequent inhibition of calcium outflow from the ER into the cytosol);
2.4. Drugs that activate the SERCA ATPase (maintenance of high calcium levels in the ER);
2.5. Pioglitation effect (inhibition of IPR3-mediated calcium release from the ER);
2.6. Rapamycin (reduction of cytoplasmic calcium levels);
2.7. Carbachol (mobilization of intracellular calcium, enhancement of glucose-stimulated insulin secretion).

3. Drugs aimed at eliminating ER stress:

3.1. Valproic acid (protection against apoptosis, induction of *WFS1* expression, modulation of the ER stress response);
3.2. GLP-1R agonists (liraglutide, exenatide, semaglutide): prevention and inhibition of ER stress-mediated cell death [13];
3.3. Dipeptidyl peptidase-4 inhibitors (hemigliptin, sitagliptin, vildagliptin): increase in GLP-1 levels.

4. Mitochondrial modulators (restoration of mitochondrial function).
5. Gene therapy:

5.1. Transfection of wild-type *WFS1* into retinal ganglion cells of WS1 patients to obtain physiologically native protein;
5.2. CRISPR/Cas9 editing of the *WFS1* gene;
5.3. Replacement of the mutant *WFS1* gene with alleles of the «wild-type» *WFS1* gene.

6. Regenerative medicine:

6.1. Cell replacement therapy: replacement of damaged tissues in WS1, such as β-cells of the pancreas, retina;
6.2. Regenerative gene delivery: activation of pancreatic β-cell proliferation, protection against ER stress-mediated apoptosis, and inhibition of neurodegeneration.

Discussion and analysis of literary sources

The main symptoms and signs of DIDMOAD syndrome: diabetes, diabetes mellitus, optic atrophy, neurosensory hearing loss, ataxia, urinary tract problems, neurogenic bladder, urinary tract infections, peripheral neuropathy [7, 19], which take place in our patient, enabled us, based on the results of a paraclinical examination to suspect the presence of a DIDMOAD syndrome.

Table 2
Genetic Syndromes of Diabetes ([25], modification)

Denomination/Syndrome	Acronym	OMIM	Protein	Inheritance	Gene
Maturity-Onset Diabetes of the Young type 5	MODY5	137920	HNF1B	AD	*HNF1B*
Permanent Neonatal Diabetes Mellitus	PNDM	606176	Insulin	AD	*INS*
Walcott-Rallison Syndrome (Neonatal diabetes, multiple epiphyseal dysphasia and liver disease)	WRS	226980	PERK/ EIF2AK3	AR	*EIF2AK3*
Mental retardation, Epileptic seizures, Hypogonadism, and Hypogenitalism, Microcephaly, and Obesity syndrome	MEHMO	300148	eIF2γ	XLR	*EIF2S*
Microcephaly, Short Stature, and impaired Glucose Metabolism-2	MSSGM2	616817	CReP	AR	*PPP1R15B*
Ataxia, combined Cerebellar and Peripheral, with Hearing loss, and Diabetes Mellitus	ACPHD	616192	p58IPK	AR	*DNAJC3*
Microcephaly with simplified gyral pattern, Epilepsy, and Permanent Neonatal Diabetes syndrome-1	MEDS1	614231	IER3IP1	AR	*IER3IP1*
Wolfram syndrome 1	WS1	222300	Wolframin	AR*	*WFS1*
Wolfram syndrome 2	WS2	604928	CISD2	AR	*CISD2*

Note. PERK/EIF2AK3 — Protein kinase R-like ER kinase or eukaryotic translation initiation factor 2 alpha kinase 3; EIF2S — eukaryotic translation initiation factor 2 subunit alpha; XLR — X-linked recessive; CReP — constitutive repressor of eIF2α phosphorylation, the product of the *PPP1R15B* p58IPK — 58-kDa inhibitor of the interferon-induced double-stranded RNA-activated protein kinase, the product of the *DNAJC3* gene; *IER3IP1* — Immediate early response-3 interacting protein 14; *CISD2* — CDGSH iron-sulfur domain 2.
*The majority of Wolfram syndrome 1 cases are autosomal recessive, however a small subset of patients carry only one mutant *WFS1* allele.

The clinical course of the DIDMOAD syndrome is usually characterized by an accurate chronological order of various symptoms, starting with non-autoimmune type 1 diabetes (in 98 % of patients) over 6 years [20], which coincided with such a characteristic debut of the disease in our patient.

Atrophy of the optic nerve, which is observed in 82 % of patients, manifests as a defect in peripheral vision, followed by a loss of color perception, which occurs, on average, at the age of 11 years. The bilateral pallor of the optic disc is the most pronounced in the temporal areas. The development of diabetes and bilateral atrophy of the optic nerve under the age of 16 is a determining clinical feature and «minimal criteria» for clinical diagnosis of DIDMOAD. Hearing loss caused by progressive sensorineural hearing loss is observed in 48.21 %, diabetes insipidus in 37.76 %, and neurological complications in 17.09 % of cases. Diabetes insipidus, which affects about 75 % of patients with DIDMOAD syndrome, usually occurs by the age of 14. Diabetes insipidus is a known clinical component in DIDMOAD syndrome and is characterized by satisfactory control, with adherence to usual treatment recommendations. Patients may also have a balance disorder, but they are more often associated with neurological rather than vestibular damage.

Since non-autoimmune type 1 diabetes is the first clinical manifestation, DIDMOAD syndrome should be recognized earlier, with concomitant vision and/or hearing loss [1]. It is established that the prevalence of DIDMOAD syndrome in patients with diabetes ranges from 0.57 to 4.8 % [21].

Unlike patients with type 1 diabetes, ketoacidosis is a rare complication of DIDMOAD [2, 3]. In addition, DIDMOAD syndrome is characterized by a reduced need for insulin, lower HbA1c and a lower frequency of microvascular complications. Patients with DIDMOAD syndrome show less glycemic variability than persons with type 1 diabetes, and this may be associated with stable insulin residual secretion. In patients with WS, the C-peptide level is much higher (0.31 ± 0.2 ng/ml) than in patients with T1D (0.04 ± 0.04 ng/ml; p = 0.006) [29].

Unlike the data of other researchers, in our patient, hypoinsulinemic hyperglycemia was combined with a congenital anomaly of the urinary system (duplication of the right kidney) without early manifestation of visual and auditory impairment, which led, first of all, to the exclusion of maturity onset diabetes of the young 5 (MODY5). MODY5 occurs due to a mutation of the hepatic transcription factor-1 gene (*HNF1B*) on chromosome 17cen-q21.3 with autosomal dominant inheritance and has an insulin-independent course [25], Table 2.

Some syndromic forms of genetic diseases can also phenotypically mimic DIDMOAD syndrome, combining several disorders, including at least two of the following anomalies: optic neuropathy, deafness, or insulin-dependent diabetes. Faced with these syndromic forms of dominant inheritance, the question of differential diagnosis with dominant optic atrophy and deafness types with heterozygous mutation in the protein optic atrophy 1 (*OPA1*) gene (or the *OPA1* form + *OPA3* gene mutation) arises.

However, the course of the above forms is associated with primary bilateral vision loss that occurs around age 50, followed by the development of neurological disorders associated with mutations in the *OPA1* gene, called Leber syndrome. Postural tremor, peripheral neuropathy, nonspecific myopathy, and movement disorders are more common in people with

Table 3
WFS1-related disorders [11]

Denomination/Syndrome	Acronym	OMIM	Inheritance	Gene
Wolfram-like syndrome	WFSL	614296	AD	*WFS1*
Genetic syndrome with neonatal or childhood onset diabetes, congenital sensorineural deafness, and congenital cataract (Hattersley-Urano subtype)	ND	ND	AD	*WFS1*
Congenital Cataract 41	CTRCT41	116400	AD	*WFS1*
Autosomal-Dominant Deafness 6/14/38	DFNA6/14/38	600965	AD	*WFS1*
Non-insulin-dependent diabetes mellitus	WFS1-related diabetes	125853	AD	*WFS1*

Leber syndrome than in the general population. Some patients with Leber syndrome may also develop deprivation, multiple sclerosis [27].

A rarer variant of Wolfram syndrome type 2 (WS2, OMIM #604928) is caused by mutations c.310T>C, c.103+1G>A, c.215A>G, c.272_273del in the CDGSH *iron-sulfur domain 2* (*CISD2*) gene located at locus q24 of chromosome 4. The protein produced by *CISD2*, known as ERIS (small intermembrane protein of ER), is also associated with ER, although it does not directly interact with wolframin. The function of *CISD2* is still unclear, but it has been shown to play a role in the regulation of the pro-apoptotic molecule, calpain 2, the aging process and autophagy. The WS2 variant predominantly affects populations of Jordanian descent. The clinical manifestations of WS2 syndrome are similar to the symptomatic spectrum of WS1 syndrome. The distinctive feature of WS2 is considered to be the absence of diabetes insipidus, hypogonadism, neurological and psychiatric disorders. This may include platelet dysfunction, gastric disorders, and gastrointestinal bleeding [21].

Pathogenic variants of *WFS1* gene in patients with autosomal dominant inheritance type cause a wide range of disorders and have been included in the classifier, such as non-classical (non-classical) Wolfram Syndrome 1 Spectrum Disorder (WFS1-SD). Phenotypes at WFS1-SD are characterized by a lighter course than the classic WS1 and include: (1) optic atrophy with hearing impairment; (2) neonatal diabetes, deep congenital deafness and cataract; (3) isolated congenital cataract; (4) isolated diabetes; (5) isolated congenital, slowly progressive/low-frequency (< 2000 Hz) sensorneural hearing loss. Currently, the diagnosis of WFS1-SD is established in a proband with suggestive signs and heterozygous pathogenic (or probably pathogenic) variant identified by molecular genetic testing [9].

The disorders of the spectrum associated with WFS1 are presented in Table 3.

In general, *WFS1*-related disorders represent a milder spectrum of conditions associated with pathogenic *WFS1* variants, with the exception of Hattersley-Urano syndrome, which is characterized by early-onset diabetes mellitus, optic atrophy, cataracts, hypotonia, intellectual disability, and developmental delay. This syndrome is associated with three different variants of the *WFS1* gene (c.2425G>A (p.Glu809Lys), c.2489A>C (p.Glu830Ala), and c.937C>T (p.His313Tyr)). The *WFS1* gene mutation in this syndrome occurs de novo in the egg or sperm of one parent or in the fertilized egg itself [5].

Conclusions

Integration of early diagnosis, molecular stratification and personalized therapy is a promising basis for the treatment of DIDMOAD syndrome in the coming decade. An important approach to the management of patients with DIDMOAD syndrome, in which endoplasmic reticulum stress is a universal pathological mechanism of degenerative processes, is to understand the pathogenesis of cell degeneration after *WFS1* gene deletion and to identify differences in these mechanisms for different types of tissues involved. Although the Wolfram syndrome phenotype is complex (diabetes mellitus, diabetes insipidus, sensorineural hearing loss, and optic atrophy), the use of genome sequencing can provide a comprehensive description of the involved genetic networks that have been altered by the mutation [24].

Genetic syndromes associated with endoplasmic reticulum stress represent an important group of diseases that continue to expand our understanding of the biological basis of ER stress and diabetes mellitus [25]. However, most of them, including Wolfram Syndrome 1 Spectrum Disorder, unlike the classic DIDMOAD syndrome, are characterized by an autosomal dominant type of inheritance.

The absence of counterinsular immunogenesis, ketoacidosis, microvascular complications, reduced daily insulin requirements, and multiorgan involvement at the onset of juvenile diabetes require the exclusion of monogenic forms of diabetes and other genetic syndromes that coexist with diabetes, including DIDMOAD syndrome.

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Багатогранний діабет: клінічний випадок

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DIDMOAD синдром (синдром Вольфраму 1 типу) — орфанна мультисистемна мітохондріальна дисфункція, назва якої є акронімом таких нозологій: Diabetes Insipidus (DI), Diabetes Mellitus (DM), Optic Atrophy (OA), Deafness (D), що асоціюється з біалельною мутацією в гені вольфраміну (*Wolframin ER transmembrane glycoprotein 1* (*WFS1*)) та успадковується за автосомнорецесивним типом.

Мета роботи — детально вивчити та представити клінічний випадок синдрому DIDMOAD, зокрема його вияви, діагностику, лікування та прогноз, для розширення медичних знань, поліпшення клінічної практики та освіти.

Матеріали та методи. Проведено системний аналіз 29 сучасних літературних джерел за темою, з акцентом на клінічні прояви, генетику та диференціальну діагностику. Під спостереженням перебував пацієнт з клінічним випадком класичного DIDMOAD синдрому (синдрому Вольфраму 1 типу), що верифікований повним секвенуванням екзому в сертифікованій лабораторії University of Exeter (UK, Exeter).

Результати та обговорення. У науковій літературі описано близько 200 випадків DIDMOAD синдрому у світі, а в Україні, включно з даним, — лише два. На відміну від результатів інших дослідників, у нашого пацієнта гіпоінсулінемічна гіперглікемія поєднувалась з вродженою аномалією розвитку сечової системи (подвоєнням правої нирки) без ранньої маніфестації враження органів зору та слуху, що і призвело до диференціальної діагностики його патологічного стану з іншими видами неавтоімунних цукрових діабетів, що супроводжуються враженням сечовидільної системи.

Висновки. DIDMOAD синдром — надзвичайно рідкісне захворювання, при якому генетичне тестування допомагає підібрати прецизійне лікування. Описаний клінічний випадок слугуватиме настановою для клініцистів щодо виявлення цього орфанного захворювання та інтенсифікації його менеджменту.

Ключові слова: *Wolframin ER transmembrane glycoprotein 1*, DIDMOAD синдром, повне екзомне секвенування, клінічний випадок.

ДЛЯ ЦИТУВАННЯ • *FOR CITATION*

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