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Research Article

Anamnestic, clinical, laboratory and molecular genetic characteristics of patients with neonatal diabetes mellitus

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ABSTRACT

BACKGROUND: Currently, there is an increase in the incidence of diabetes mellitus throughout the world, including the steadily increasing number of rare, genetically determined forms of diabetes. Of particular interest are monogenic forms, including neonatal diabetes mellitus, which is a rare heterogeneous disease that manifests, as a rule, in the first 6 months of a child's life, characterized by a severe labile course and a high risk of complications. Neonatal diabetes mellitus is a rare heterogeneous disease that usually manifests itself in the first 6 months of a child's life, characterized by a severe, labile course and a high risk of complications. Currently, more than 25 genes are known, mutations in which cause both permanent and transient neonatal diabetes mellitus, as well as syndromic variants of this disease, which are of particular interest due to their severity and polymorphic clinical picture. In this regard, timely verification of the diagnosis is of particular importance.

AIM: The aim of this study is to increase the efficiency of diagnosis of neonatal diabetes mellitus based on the analysis of anamnestic, clinical, laboratory and molecular genetic characteristics of patients.

MATERIALS AND METHODS: 14 patients with transient and permanent neonatal diabetes mellitus were examined.

RESULTS: 11 (78.6%) patients had isolated neonatal diabetes, in three of them the disease was verified in the structure of hereditary syndromes (Wolcott–Rallison syndrome, IPEX syndrome and Donohue syndrome). According to molecular genetic analysis, 14 variants were found in the genes *ABCC8*, *KCNJ11*, *GCK*, *GATA6*, *WFS1*, *CACNA1D*, *EIF2AK3*, *FOXP3*, *PAX4*, *INSR*, *IGF1R*, three of which were not previously described in the literature.

CONCLUSIONS: The clinical heterogeneity identified in patients is determined primarily by the diversity of verified variants in causative genes. New variants in the *CACNA1D* and *IGF1R* genes that may be associated with the development of NDM, remain poorly understood and require further research.

Keywords: neonatal diabetes mellitus; monogenic diabetes; gene *IGF1R*; gene *CACNA1D*; Walcott–Rallison syndrome; IPEX syndrome; Donohue syndrome.

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Оригинальное исследование

Анамнестические, клинико-лабораторные и молекулярно-генетические особенности пациентов с неонатальным сахарным диабетом

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АННОТАЦИЯ

Актуальность. В настоящее время отмечается рост заболеваемости сахарным диабетом во всем мире, в том числе неуклонно увеличивается число редких, генетически обусловленных форм диабета. Особый интерес представляют моногенные формы, в том числе неонатальный сахарный диабет, представляющий собой редкое гетерогенное заболевание, манифестирующее, как правило, в первые 6 мес. жизни ребенка, характеризующееся тяжелым лабильным течением и высоким риском развития осложнений. В настоящее время известно более 25 генов, мутации в которых вызывают как перманентный, так и транзиторный неонатальный сахарный диабет, а также синдромальные варианты этого заболевания, представляющие особый интерес ввиду их тяжести и полиморфности клинической картины. В связи с этим особую важность представляет своевременная верификация диагноза.

Цель — повысить эффективность диагностики неонатального сахарного диабета на основе анализа анамнестических, клинико-лабораторных и молекулярно-генетических особенностей пациентов.

Материалы и методы. Обследовано 14 пациентов с транзиторным и перманентным неонатальным сахарным диабетом.

Результаты. Изолированный неонатальный диабет имели 11 (78,6 %) пациентов, у троих заболевание верифицировано в структуре наследственных синдромов (синдром Уолкотта – Раллисона, IPEX-синдром и синдром Донохью). По данным молекулярно-генетического анализа обнаружено 14 вариантов в генах *ABCC8*, *KCNJ11*, *GCK*, *GATA6*, *WFS1*, *CACNA1D*, *EIF2AK3*, *FOXP3*, *PAX4*, *INSR*, *IGF1R*, три из которых ранее не описаны в литературе.

Выводы. Выявленная у пациентов клиническая гетерогенность определяется преимущественно разнообразием верифицированных вариантов в каузативных генах. Новые варианты в генах *CACNA1D* и *IGF1R*, которые могут быть ассоциированы с развитием диабета, остаются малоизученными и требуют дальнейшего исследования.

Ключевые слова: неонатальный сахарный диабет; моногенный диабет; ген *IGF1R*; ген *CACNA1D*; синдром Уолкотта – Раллисона; IPEX-синдром; синдром Донохью.

Как цитировать
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BACKGROUND

Neonatal diabetes mellitus (NDM) is a rare and heterogeneous group of diseases characterized by chronic hyperglycemia in the first six months of a child's life. In some children, the presence of mutations in the causative gene aids in the diagnosis of NDM between the ages of 6 and 12 months [8, 20, 32]. The incidence of NDM reportedly ranges between 1:90,000 to 1:500,000 live newborns, with a higher prevalence in isolated populations, such as in Middle Eastern countries (1:21,000–1:29,000), due to the persistence of inbreeding.

Currently, two principal forms of NDM are recognized, transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM), in addition to syndromal variations of this condition. TNDM is characterized by clinical and laboratory remission after manifestation of the condition. It is also associated with a high risk of readmission in adolescence. In PNDM, remission of the disease does not occur [2, 5, 20, 24].

NDM is a monogenic form of diabetes mellitus (DM). Currently, more than 25 genes are associated with its development (*ABCC8*, *KCNJ11*, *GCK*, *GATA4*, *GATA6*, *PDX1*, *EIF2AK3*, *FOXP3*, *GLIS3*, *INS*, insulin receptor (*INSR*), *HNF1B*, *IER3IP1*, *PTF1A*, *NEUROD1*, *NEUROG3*, *RFX6*, *SLC2A2*, *SLC19A2*, *WFS1*, *ZFP5*, *KCNMA1*, and *CACNA1D*) [20, 33]. Furthermore, chromosomal aberrations of the imprinted locus in 6q24 (uniparental disomy of chromosome 6, duplication of the paternal copy of chromosome 6, and hypomethylation of the ICR copy of the maternal chromosome 6q24) have been identified as a cause of TNDM [5, 20, 32].

A substantial proportion of NDM cases are attributed to genetic alterations in the *KCNJ11* and *ABCC8* genes. These genes encode proteins involved in the ATP-dependent K^+ channels in pancreatic β-cells and regulate insulin secretion in response to glucose levels [20].

The glucose transporter GLUT2 facilitates the entry of glucose into β-cell, where it is metabolized. This metabolic process results in the accumulation of ATP, which inhibits ATP-dependent K^+ channels and causes their closure. The depolarization of the cell membrane and subsequent increase in the concentration of Ca^{++} ions within the cell induce insulin secretion. The activation of mutations in the *KCNJ11* gene, which encodes the Kir6.2 subunit, and in the *ABCC8* gene, which encodes sulfonylurea receptor-1 (SUR1), distorts the closure of the ATP-dependent K^+ channel. Consequently, the K^+ channels remain open, resulting in the insufficient stimulation of insulin release into the bloodstream in response to hyperglycemia [13, 25, 32].

Heterozygous inactivating mutations in the *INS* gene, which decrease proinsulin function and cause premature apoptosis of the pancreatic β-cells, are less prevalent in NDM [20, 32]. Furthermore, inactivating mutations in the *GCK* gene, which encode a key β-cell enzyme in the insulin secretion pathway, may cause NDM. These mutations are either homozygous or compound heterozygous. A reduction in enzyme activity results in an elevated threshold for β-cell sensitivity to glucose and a concomitant decrease in insulin secretion. The synthesis of the altered *GCK* disrupts glycogen accumulation in the liver and accelerates gluconeogenesis, which increases glucose production at physiological insulin concentrations and elevates fasting hyperglycemia [1, 4].

The development of NDM due to mutations in the *EIF2AK, FOXP3, IER3IP1*, and *WFS1* genes is a consequence of β-cell death [5, 20]. Some NDM forms are caused by mutations in the *GATA* family of genes. The *GATA6* gene is expressed in tissues of endodermal and mesodermal origin, including the intestine, lung, heart, and pancreas. This explains the formation of defects in these organs and systems. Moreover, the *GATA6* and *GATA4* genes play a role in the regulation of postembryonic function of the pancreatic acinar cells. In such instances, NDM may be associated with congenital hypothyroidism and cardiovascular malformations [33].

NDM is distinguished in the structure of rare inherited syndromes associated with mutations in the genes: *EIF2AK3*, Wolcott–Rallison syndrome; *FOXP3*, immunodeficiency, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome; *SLC2A2*, Fanconi–Bickel syndrome; *SLC19A2*, Rogers syndrome; *KCNJ11*, DEND syndrome; *GLIS3*, NDH syndrome; *KCNMA1*, Liang–Wang syndrome; and *INSR*, Donohue syndrome [5, 10, 23, 33].

NDM in Walcott–Rallison syndrome may manifest with concomitant growth retardation, skeletal epiphyseal dysplasia, and severe liver pathology, including hepatitis and liver failure. Other components, such as exocrine pancreatic insufficiency, hypothyroidism, recurrent infections, developmental delay, and renal failure, including acute kidney injury, which significantly worsens the patient's prognosis, are less common [5, 31].

(IPEX) syndrome is an autoimmune polyglandular syndrome that is characterized by a triad of autoimmune enteropathy, polyendocrinopathy, and skin and mucous membrane lesions. In addition to PNDM, the syndrome is associated with marked developmental delay, primary immunodeficiency, autoimmune thyroid disease, and less frequently autoimmune cytopenia, pneumonitis, nephritis, hepatitis, arthritis, myositis, and alopecia [5, 11].

Donohue syndrome, also known as leprechaunism, is a severe form of insulin resistance due to biallelic mutations in the *INSR* gene. This syndrome is characterized by a severe course of illness with pronounced clinical symptoms and an unfavorable prognosis. The primary clinical and laboratory characteristics of insulin resistance syndromes include the presence of acanthosis nigricans, a marked elevation in plasma insulin levels in the absence of obesity, androgen excess, and, in most cases, the emergence of NDM [3].

The heterogeneity of genetic mutations in NDM, the polymorphism of its clinical manifestations, and the wide spectrum of organ and system damage observed in syndromal forms necessitate the timely verification of the diagnosis using molecular genetic testing (MGT). This allows for the identification of the mechanism of cellular damage and personalization of the patient's treatment.

In our study, we have presented the results of the clinical, laboratory, instrumental, and molecular genetic examinations as well as treatment results of 14 patients with NDM associated with mutations in the *ABCC8*, *KCNJ11*, *GCK*, *GATA6*, *WFS1*, *CACNA1D*, *EIF2AK3*, *FOXP3*, *PAX4*, *INSR*, and *IGF1R* genes.

In this study, *we aimed* to improve the efficiency of NDM diagnosis by analyzing the anamnestic, clinical, laboratory, and molecular genetic characteristics of the patients.

MATERIALS AND METHODS

A total of 14 patients with NDM were followed up at St. Petersburg's State Pediatric Medical University, which belongs to the Ministry of Health of Russia. Of the 14 patients, 5 (35.7%) were boys and 9 (64.3%) were girls. The age of the patients at the time of the study ranged from 2 months to 21 years, which corresponded to the follow-up period (mean age, 6 years).

A comprehensive examination of all the children was performed, and it encompassed an analysis of the anamnestic data (including age of manifestation and hereditary history), anthropometric measurements, and nutritional status of the newborns (using Fenton and INTERGROWTH 21 sex-based nomograms). Additionally, biochemical and hormonal blood analyses were performed (including estimation of insulin and c-peptide levels). The glucose levels were monitored using continuous flash monitoring systems.

MGT was conducted in 12 patients (85.7%) at the medical genetic laboratory of St. Petersburg State Pediatric Medical University, Department of Hereditary Endocrinopathies of the National Medical Center of Endocrinology, and Laboratory of prenatal diagnostics of hereditary and congenital human diseases of the D.O. Ott Research Institute of Obstetrics, Gynecology, and Reproductology, Russian Federation. The remaining two patients are currently undergoing MGT.

In a majority of the patients, MGT was performed via next generation sequencing (NGS) for mutations from the DM–hyperinsulinism targeting panel of 46 genes (*ABCC8*, *AKT2*, *ALMS1*, *ARMC5*, *BLK*, *CACNA1D*, *DIS3L2*, *EIF2AK3*, *FOXA2*, *GATA6*, *GCG*, *GCGR*, *GCK*, *GLIS3*, *GLUD1*, *GPC3*, *HADH*, *HNF1A*, *HNF1B*, *HNF4A*, *IGF1*, *IGF1R*, *INS*, *INSR*, *KCNJ11*, *KDM6A*, *LIPE*, *MC3R*, *MC4R*, *NEUROD1*, *NSD1*, *PAX4*, *PDX1*, *PGM1*, *PIK3CA*, *PPARG*, *PPP1R3A*, *PTF1A*, *RFX6*, *SH2B1*, *SIM1*, *SLC16A1*, *TUB*, *UCP2*, *WFS1*, and *ZFP57*). In two children, MGT was performed via direct Sanger sequencing of individual genes (*GCK* and *KCNJ11*). In one patient with IPEX syndrome, targeted sequencing was performed using the primary immunodeficiency and hereditary anemias genetic panel, which encompasses 368 genes associated with persistent immune dysfunction. Furthermore, MGT was conducted in five parents from three families. The pathogenicity of mutations was assessed using international recommendations of the American College of Medical Genetics and Genomics and the Russian guidelines for NGS data interpretation [6].

All data were statistically analyzed using Statistica (version 10; StatSoft, USA). The data are presented as medians and lower and upper quartiles (*Me* [Q_1, Q_3]) or means and minimum (min) and maximum (max) values.

RESULTS AND DISCUSSION

Anamnestic, clinical, and laboratory characteristics of the patients with NDM

In the study, four patients (28.6%) were diagnosed with TNDM, eight (57.1%) were diagnosed with PNDM, and two (aged 2 and 4 months) required insulin therapy. In three patients (21.4%), DM was associated with rare hereditary syndromes. The genealogical data of the patients with NDM are presented in Table 1.

Three patients (21.4%) exhibited aggravated heredity in the first and second line of descent (Table 1). The mother of patient 4 was diagnosed with gestational DM, and her cousin had type 1 DM. In patient 5, a homozygous mutation in the *GCK* gene was observed, and the monogenic DM form was verified in the father, mother, grandfather, and uncle on the father's side, as well as in the maternal grandmother. The parents of patient 7, who had previously been diagnosed with type 1 DM, possessed a heterozygous mutation in the *WFS1* gene, which was identical to that observed in the proband. Additionally, other relatives of the proband exhibited a history of DM as follows: maternal grandmother, type 2 DM without obesity; paternal aunt, type 2 DM being treated with oral antidiabetics; paternal cousin, type 1 DM.

In four families, DM was exclusively identified in second line relatives. Marriage between close relatives was noted in three families. Data on the hereditary nature of NDM in our study were similar to those of previous studies [14, 20].

The analysis of anamnestic data revealed an aggravated perinatal anamnesis of the following conditions: threat of pregnancy termination (*n* = 5, 35.7%), anemia (n = 1, 7.1%), exacerbation of chronic pyelonephritis (*n* = 1, 7.1%), and multiple pregnancy (*n* = 2, 14.3%). Two mothers had already been diagnosed with DM before the pregnancy, while one mother was diagnosed with gestational DM. Six (42.9%) children were born prematurely. The presence of adverse antenatal factors

Table 1. Genealogical data of patients with neonatal diabetes mellitus

Таблица 1. Генеалогические данные пациентов с неонатальным сахарным диабетом

Patient No. / № пациента	Gene / Ген	Family history of diabetes in first-degree relatives / Отягощенная наследственность по сахарному диабету у родственников 1-й линии	Family history of diabetes in second-degree relatives / Отягощенная наследственность по сахарному диабету у родственников 2-й линии	Consanguineous marriage / Кровнородственный брак
1	*ABCC8*	–	+	–
2	*KCNJ11*	–	–	–
3	*KCNJ11*	–	–	–
4	*ABCC8* + *GCK*	+	+	–
5	*GCK*	+	+	+
6	*GATA6*	–	–	–
7	*WFS1*	+	+	–
8	*EIF2AK3*	–	–	+
9	*CACNA1D* + *PAX4*	–	+	–
10	*FOXP3*	–	–	–
11	*INSR*	–	–	–
12	–	–	–	–
13	*IGF1R*	–	+	+
14	–	–	+	–

made it challenging to confirm the diagnosis due to the high prevalence of transient disorders of carbohydrate metabolism in the neonatal period.

Anthropometric data analyses revealed that four patients were born with a weight lower than the normal weight for their gestational ages. Two patients were born with a very low birth weight, and three were born with an extremely low birth weight. A weight deficit (below the 3rd percentile) was observed in seven newborns (50%), four of whom were born prematurely. Three patients exhibited signs of intrauterine growth retardation, which may be attributable to an intrauterine insulin deficiency [14, 20].

In 11 children (78.6%), the disease manifested during the first month of life. In the remaining three children (21.4%), a later onset was observed. The median age of NDM manifestation was 9 days of life (range, 1–52.5 days), with a minimum age of 1 day and a maximum age of 4 months. In 13 children, elevated glucose levels (mean, 31.4 ± 8.1 mmol/L) were observed. The insulin and/or C-peptide levels were low in six patients (42.9%). The principal clinical and laboratory parameters of the patients are presented in Table 2.

Neonatal diabetes mellitus

A total of 12 children (85.7%) exhibited a severe and unstable course of DM at the time of onset. Ultimately, 11 patients (78.6%) had to be transferred to the intensive care unit (ICU). The primary indication for admission to the ICU was the need for intensive metabolic support. A majority of the children exhibited multiorgan damage, with involvement of the respiratory and central nervous systems, during the pathological process. One patient with NDM remained in the ICU for an extended period following surgical treatment for congenital heart disease.

The development of classic diabetic ketoacidosis was observed in only one patient with PNDM that was caused by a mutation in the *KCNJ11* gene. However, periodic appearance of ketones in the urine was noted in four children at the time of disease onset and during its course, while the acid-base status remained normal.

The development of diabetic ketoacidosis in children with NDM is not a typical occurrence due to antiketogenic effect as a result of excessive hyperglycemia and severe dehydration, as well as the distinctive metabolic processes in newborns [5]. Therefore, diabetic ketoacidosis should be differentiated from a hyperosmolar hyperglycemic state, which is characterized by the absence of ketosis and acidosis [19].

There have been a few reports \ ketoacidosis, including severe ketoacidosis in patients with NDM. In one patient from India with a homozygous variant in the *EIF2AK3* gene and a diagnosis of Walcott–Rallison syndrome, the onset of NDM was complicated by the development of diabetic ketoacidosis [30].

This demonstrates the need for a more comprehensive analysis of the underlying pathogenic mechanisms and the anti-ketogenic effect in this specific age group.

Table 2. Basic clinical and laboratory parameters of patients with neonatal diabetes mellitus

Таблица 2. Основные клинические и лабораторные показатели пациентов с неонатальным сахарным диабетом

Parameter / Показатель	Patient No. / № пациента													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age / Возраст	21 years / год	5 years / лет	12 years / лет	2 years / год	10 years / лет	9 years / лет	9 years / лет	6 years / лет	3 years / год	1 year / год	1 year / год	5 years / лет	2 months / мес.	2 months / мес.
Sex / Пол	Ж / F	M	Ж / F	Ж / F	Ж / F	Ж / F	Ж / F	Ж / F	M	M	Ж / F	M	Ж / F	Ж / F
Gene / Ген	ABCC8	KCNJ11	KCNJ11	ABCC8 + GCK	GCK	GATA6	WFS1	EIF2AK3	CACNA1D + PAX4	FOXP3	INSR	–	IGF1R	–
Variant in a gene / Вариант в гене	c.4139G>A p.Arg1379His	c.133_135del p.Ala45del	c.988T>C p.Tyr330His	c.756G>C p.Lys252Asn + c.483+26C>A	c.1039C>T p.Gln347	c.1477C>T p. Arg493*	c.2327A>T p.Glu776Val	c.1912C>T p.Arg638*	c.1189G>A p.Val397Ile + c. 467A>G p.His156Arg	c.1190G>T p.Arg397Leu	c.G839A p.Cys280Tyr	–	c.3904A>T p.Ser1302Cys	– –
Form of NDM / Форма НСД	TNDM / ТНСД	PNDM / ПНСД	PNDM / ПНСД	TNDM / ТНСД	PNDM / ПНСД	PNDM / ПНСД	TNDM / ТНСД	PNDM (Wallcott–Rallison syndrome) / ПНСД (синдром Уолкотта – Раллисона)	TNDM / ТНСД	PNDM (IPEX syndrome) / ПНСД (IPEX-синдром)	PNDM (Donohue syndrome) / ПНСД (синдром Донохью)	TNDM / ТНСД	PNDM / ПНСД	PNDM / ПНСД
Gestational age, weeks / Гестационный возраст, нед.	38	–	39	29	37	36	24	38	36	38	40	25	41	36
Weight at birth, g / Масса при рождении, г	3000	–	2400	990	1800	1440	550	3100	1860	2840	1760	830	3610	1420
Length at birth, cm / Длина при рождении, см	51	-	50	38	43	44	28	49	45	51	45	31	53	38
Congenital defects and developmental anomalies / Врожденные пороки и аномалии развития	Yes / Да	No / Нет	No / Нет	No / Нет	No / Нет	Yes / Да	No / Нет	Yes / Да	Yes / Да	Yes / Да	Yes / Да	No / Нет	Yes / Да	Yes / Да
Age of manifestation / Возраст манифестации	3 months / 3 мес.	4 months / 4 мес.	2 months / 2 мес.	1 day / 1 сут	1 day / 1 сут	2 days / 2 сут	5 days / 5 сут	3 months / 3 мес.	13 days / 13 сут	1 day / 1 сут	1 month / 1 мес.	1 day / 1 сут	1 month / 1 мес.	1 day / 1 сут
Max indicator of glucose, mmol/l / Максимальный показатель глюкозы, ммоль/л	29.0	26.3	27.0	31.0	35.7	27.0	37.5	30.0	52.0	35.0	30.0	15.4	35.5	27.9
Insulin, μIU/ml / Инсулин, мкМЕ/мл (N 1,9–10,0)	–	–	2.0	3.5	–	6.08	1.55	–	–	–	>302.0	–	–	0.12
C-peptide ng/ml С-пептид, нг/мл / (N 0,5–3,2)	0.8	0.1	0.2	2.6	1.2	2.18–4.64	0.3	0.2	0.6–3.53	0.1–3.53	>16.0	–	0.90–0.85	1.90

Note. TNDM — transient neonatal diabetes mellitus; PNDM — permanent neonatal diabetes mellitus.
Примечание. ТНСД — транзиторный неонатальный сахарный диабет; ПНСД — перманентный неонатальный сахарный диабет.

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Molecular genetic characteristics of the patients with NDM

The MGT of the 12 patients (85.7%) revealed 14 different mutations in the following causative genes: *ABCC8*, *KCNJ11*, *GCK*, *GATA6*, *WFS1*, *CACNA1D*, *EIF2AK3*, *FOXP3*, *PAX4*, *INSR*, and *IGF1R*. Two patients exhibited paired mutations in two distinct genes in the DM-hyperinsulinism target panel. In three pediatric patients (patients 8, 10, 11) with mutations in the *EIF2AK3, FOXP3*, and *INSR* genes, syndromal forms of NDM were identified. Two additional patients (patients 12 and 14) are currently undergoing molecular genetic confirmation. The molecular and genetic characteristics of the patients with NDM are presented in Table 3.

Activation of mutations in the genes that encode ATP-dependent K^+ channels (*KCNJ11* and *ABCC8*) were identified in four patients. Two children (patients 2 and 3) with permanent forms of NDM exhibited mutations in the *KCNJ11* gene. One deletion and one missense mutation were identified as the possible pathology. Two additional probands with the transient form of NDM exhibited missense mutations in the *ABCC8* gene. A child with TNDM, which was caused by a pathogenic mutation in the causative gene (patient 1), experienced a relapse in DM at the age of 12 years after a prolonged clinical and laboratory remission. However, another child (patient 4), who had a previously undescribed missense mutation of uncertain clinical significance and a *GCK* gene mutation, exhibited clinical and laboratory remission.

The observed diversity of phenotypes, including the occurrence of TNDM and transient forms, is likely attributable to the varying degrees of gene expression. Most authors have suggested that there is a high risk of relapse in TNDM after prolonged clinical and laboratory remission, a phenomenon that was observed in our patient [5, 9].

In our study, there was one familial case of DM associated with a *GCK* gene mutation (patient 5). A homozygous inactivating mutation, p.Q347X (p.1039C>T), was identified in the proband, which resulted in the development of PNDM. A similar heterozygous mutation was identified in the proband's mother, father, and maternal grandmother, indicating an autosomal dominant mode of inheritance. The child's mother and father are closely related. The proband's mother, father, and maternal grandmother were diagnosed with diabetes mellitus at an older age of 17, 32, and 26 years, respectively. The proband's mother and grandmother are being treated with an insulin regimen comprising basal and bolus doses, whereas the diabetes in the father and his relatives is being managed through dietary adjustments.

The have been numerous reports of heterozygous mutations in the *GCK* gene that can cause MODY2-type diabetes. Large cohort studies conducted in different countries have demonstrated that MODY2-type is the most prevalent monogenic form of DM (incidence, 32%–77.5%), with a ranking of first or second [7, 26].

Homozygous and compound heterozygous inactivating mutations in the *GCK* gene are relatively uncommon. However, analogous cases of NDM associated with gene mutations have been documented. In one study in Oman, seven children with PNDM that was caused by the c.292C>T and c.781G>A mutations in the *GCK* gene were identified. The c.292C>T mutation was identified in five related probands [12].

A rare heterozygous pathogenic mutation, c.1477C>T (p. Arg493*), was identified in patient 6 with PNDM, congenital heart disease (aortic stenosis at the isthmus, patent ductus arteriosus, and patent foramen ovale), inguinal hernia, and congenital hypothyroidism. This mutation leads to the formation of a stop codon. MGT of the proband's parents revealed the absence of analogous mutations in the *GATA6* gene, indicating the occurrence of a de novo mutation. The anamnesis revealed that the girl was born prematurely with a low birth weight and exhibited intrauterine growth retardation. Previous studies have also demonstrated low body weight and stunting, including at birth, in patients with *GATA6* gene mutations [21, 33]. In addition to NDM, the child exhibited signs of exocrine insufficiency. A multispiral computed tomography of the abdominal cavity revealed gallbladder aplasia and pancreatic hypoplasia. The child is currently being treated with an insulin pump and enzymes.

In addition to DM, mutations in the *GATA* family genes are associated with the formation of congenital heart defects, pancreatic malformations, hepatobiliary abnormalities, and other pathologies, including endocrine pathologies (e.g., stunting, and hypothyroidism). *De novo* mutations are more frequently observed in patients with NDM and pancreatic agenesis than in patients with mutations inherited from parents [33]. In general, extrapancreatic manifestations in patients with *GATA6* gene mutations account for approximately 3% of NDM cases and > 50% of pancreatic aplasia cases [17].

A heterozygous missense mutation, c.2327A>T (p.Glu776Val), in the WFS1 gene was found in patient 7 who had TNDM. Given the aggravated heredity, MGT was performed in the other family members. The proband's mother exhibited a similar *WFS1* gene mutation. It was not observed in any other family member. During the study, no additional characteristic symptoms of Wolfram syndrome were identified in the patient. However, given the stage of manifestation of the syndrome components, the child requires careful, dynamic observation.

Several authors have documented instances of isolated diabetes in members of multiple families with *WFS1* gene mutations. In a study of 408 patients with childhood-onset DM who required insulin therapy, *WFS1* gene mutations were identified in 22 probands (4.2%), with a higher prevalence observed in patients from

Table 3. Molecular genetic characteristics of patients with neonatal diabetes mellitus

Таблица 3. Молекулярно-генетическая характеристика пациентов с неонатальным сахарным диабетом

Patient No. / № пациента	Gene / Ген	Nucleotide / Нуклеотид (положение в кДНК)	Amino acid replacement / Замена аминокислоты	Genotype / Генотип	Type of variant / Тип варианта	Description in the literature "+"/"–" / Описание в литературе «+»/«–»	Allele frequency (by gnomAD*) / Частота аллеля (по gnomAD*)	Clinical significance of ACMG variants / Клиническая значимость вариантов по ACMG
1	*ABCC8*	c.4136G>A	p. Arg1379His	Heterozygote / Гетерозигота	Missense / Миссенс	+	0.00001	Pathogenic / Патогенный
2	*KCNJ11*	c.133_135del	p.Ala45del	Heterozygote / Гетерозигота	Deletion, no frameshift / Делеция, без сдвига рамки	–	–	–
3	*KCNJ11*	c.988T>C	p.Tyr330His	Heterozygote / Гетерозигота	Missense / Миссенс	+	–	Likely pathogenic / Вероятно патогенный
4	*GCK* + *ABCC8*	c.483+26C>A	p.Lys252Asn	Heterozygote / Гетерозигота	Intron / Интрон	+ –	0.00048	Likely benign / Вероятно доброкачественный
		c.756G>C		Heterozygote / Гетерозигота	Missense / Миссенс		–	Uncertain significance / Неопределенная значимость
5	*GCK*	c.1039C>T	p.Gln347	Homozygous / Гомозигота	Нонсенс / Nonsense	+	0.00019	Pathogenic / Патогенный
6	*GATA6*	c.1477C>T	p. Arg493*	Heterozygote / Гетерозигота	Nonsense / Нонсенс	+	–	Pathogenic / Патогенный
7	*WFS1*	c.2327A>T	p.Glu776Val	Heterozygote / Гетерозигота	Missense / Миссенс	+	–	Benign / Доброкачественный
8	*EIF2AK3*	c.1912C>T	p.Arg638*	Homozygous / Гомозигота	Nonsense / Нонсенс	+	–	Likely pathogenic / Вероятно патогенный
9	*CACNA1D* + *PAX4*	c.1189G>A	p.Val397Ile	Heterozygote / Гетерозигота	Missense / Миссенс	+	0.00003	Uncertain significance / Неопределенная значимость
		c. 467A>G:	.His156Arg	Heterozygote / Гетерозигота	Missense / Миссенс	+	–	Uncertain significance / Неопределенная значимость
10	*FOXP3*	c.1190G>T	p.Arg397Leu	Homozygous / Гомозигота	Missense / Миссенс	+	–	Likely pathogenic / Вероятно патогенный
11	*INSR*	c.G839A	p.Cys280Tyr	Homozygous / Гомозигота	Missense / Миссенс	+	–	Likely pathogenic / Вероятно патогенный
13	*IGF1R*	c.3904A>T	p.Ser1302Cys	Heterozygote / Гетерозигота	Missense / Миссенс	–	–	Uncertain significance / Неопределенная значимость

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consanguineous marriages [34]. A previous study has also demonstrated the presence of a *WFS1* gene mutation in patients with classic Wolfram syndrome [16]. Mutations in the *WFS1* gene can manifest in numerous ways, from isolated forms with a single component to Wolfram syndrome, a severe and progressive disease with autosomal recessive inheritance. Wolfram syndrome is characterized by diabetes insipidus, non-sugar diabetes, optic atrophy, and sensorineural hearing loss. It can lead to severe degenerative disorders that result in respiratory failure of central genesis, brainstem atrophy, and renal failure [16].

A biallelic (homozygous) mutation, c.1912C>T (p.Arg638*), in the *EIFAK3* gene was identified in patient 8. This mutation is responsible for the development of PNDM in a patient with Walcott–Rallison syndrome, a rare genetic disease. The parents, who are closely related, also underwent an MGT, which revealed a similar heterozygous *EIFAK3* mutation in both parents. In such patients, the substitution of p.Arg638* in the gene's coding region results in the formation of a stop codon at the 638th position. Although the female infant (patient 8) in our study was born at term with a normal weight (3100 g) and body length (49 cm), she exhibited a disproportionate physique that was characterized by a moderate shortening of the upper and lower extremities. In this patient, the DM and respiratory viral infection manifested acutely, at the age of three months. The clinical manifestations of the Walcott–Rallison syndrome, including skeletal dysplasia, stunting, and growth SDS (–3.1), became apparent at approximately two years of age. A delay in psycho-verbal development and chronic hepatitis with marked hyperfermentemia (ALT, 4164.4 mU/L and LDH, 2275 U/L) were also observed in the patient. Furthermore, the DM course was unstable, with episodes of severe hypoglycemia.

There have been several single reports of the disease, which differ in terms of components and the age of their manifestation. In addition to DM, chronic hepatitis, including acute liver failure, renal failure, exocrine pancreatic dysfunction, anemia, and neutropenia are frequently observed in this disease. Furthermore, there have been reports of stunting, severe delay in psychomotor development, and cerebellar ataxia. Biallelic mutations in the *EIF2AK3* gene are the underlying cause of this rare autosomal recessive syndrome [31].

A rare combination of two missense mutations of uncertain significance, c. 467A>G (p.His156Arg) in the *PAX4* gene and c.1189G>A (p.Val397Ile) in the *CACNA1D* gene, was identified in a patient with PNDM and congenital neurosensory hearing loss. This male infant (patient 9) was born at 36 weeks of gestation with a low for gestational age birth weight. The NDM manifested on day 13 of life. It was labile and required prolonged intravenous insulin injections. Subsequently, he was transitioned to a subcutaneous insulin injection regimen via an insulin pump. Presently, the need for insulin is discernible in instances of concurrent illnesses or dietary irregularities.

Since the early 2000s, there have been numerous studies on the function of the *PAX4* and *CACNA1D* genes, including their association with carbohydrate metabolism disorders. In 2007, the initial findings of a study examining the correlation between pathogenic *PAX4* gene mutations and onset of MODY-type DM, subsequently named as MODY, were published [27]. Individual cases of MODY9 in children and young adults have been documented. The youngest reported case of MODY9 in China is a 19-month-old male with a heterozygous missense mutation (c.487>T) in exon 7 of the *PAX4* gene [35]. The precise role of the *CACNA1D* gene in the pathogenesis of carbohydrate metabolism disorders remains to be elucidated. This gene reportedly encodes L-type calcium channels, which are essential for the functioning of pancreatic β-cells. Thus, the potential association between *CACNA1D* gene mutations and the development of type-2 DM is currently being investigated. Numerous studies have already evaluated the association between *CACNA1D* gene mutations and the development of congenital hyperinsulinism, degenerative diseases of the nervous system, epilepsy, autism spectrum disorders, and hearing impairment [29]. However, there have been no reports of NDM associated with c.467A>G (p.His156Arg) mutation in the *PAX4* gene and/or c.1189G>A (p.Val397Ile) mutation in the *CACNA1D* gene.

A hemizygous missense mutation, c.1190G>T (p.Arg397Leu), was identified in a patient's *FOXP3* gene, which is located in the DNA-binding C-terminal forkhead domain. This mutation was observed in patient 10 and was determined to be pathogenic by the primary predictive programs. A similar mutation in the causative gene was identified in the proband's mother. From the first day of life, the child exhibited hyperglycemia, with blood glucose levels reaching a peak of 33.6 mmol/L. Additionally, metabolic acidosis was observed. The hyperglycemia was accompanied by glucosuria (up to 2000 mg/dL) and moderate ketonuria (1.5 mmol/L). The patient was diagnosed with NDM. Further examination revealed a severe autoimmune enteropathy with autoimmune thyroiditis, specific skin lesions, anemia, and eosinophilia. The child was also diagnosed with congenital primary immunodeficiency. The autoimmune nature of DM and autoimmune thyroiditis were corroborated by the findings of the immunologic study. The concentration of antibodies against TPO and GAD were 243.9 Med/mL (normal range, 0–30) and 1.29 U/mL (normal range, 0.0–1.0), respectively. Antibodies against ICA were also present (normal range, 0.0–1.0). Considering the presence of autoimmune thyroiditis, severe enteropathy, primary immunodeficiency, and pronounced eosinophilia in a child with NDM, IPEX syndrome was considered. The MGT findings confirmed the diagnosis [11].

Till date, over 70 pathogenic mutations of the *FOXP3* gene have been identified. *FOXP3* is a transcription factor that affects the activity of regulatory T cells, which are responsible for maintaining autotolerance. Consequently, mutations in this gene can lead to the development of multiple autoimmune diseases and severe primary immunodeficiency. In severe cases, this can cause septic complications and even death [5, 15, 22]. This was observed in our patient.

A pathogenic homozygous variant of the *INSR* gene, c.G839A: p.c280y (HGMD: CH010893), which has been previously described in insulin resistance type A [3], was located in exon 3 of the β-subunit of the insulin receptor. This variant was identified in patient 11, who had been diagnosed with Donohue syndrome. From birth, the child exhibited multiple developmental microanomalies, including macrocephaly, disproportionate physique, limb shortening, muscular hypotrophy, acanthosis nigricans, hypertrichosis (pubic and axillary hair), telarche, macrogenitalism, and hypertrophied clitoris. Furthermore, an umbilical hernia and a permanent repositionable rectal prolapse were also observed. Pronounced signs of facial dysmorphism, which have been described as "elfin-like facies" (high forehead, large protruding eyes, wide back of the nose, wide nostrils, and gingival hyperplasia), were also noted. A multispiral computed tomography revealed a congenital heart defect (pulmonary artery valve stenosis) and multifollicular ovaries.

From the first month of life, the patient exhibited hyperglycemia, necessitating the initiation of insulin therapy. Subsequent data from a blood hormonal study revealed prohibitively high levels of insulin and C-peptide. The insulin levels exceeded 302.0 μIU/mL (normal range, 2.0–25.0) and the C-peptide levels exceeded 16.0 ng/mL (normal range, 0.5–3.2). Glycemic monitoring demonstrated considerable variability in the blood glucose levels with a proclivity for hypoglycemia (range, 1.7–22.0 mmol/L). Subsequently, the child was transitioned to biguanides, which resulted in the stabilization of blood glucose levels within the target range.

Our study results confirm those of previous studies, which have demonstrated that biallelic mutations in the α- and/or β-subunits of the *INSR* gene are associated with a severe polymorbid course and poor prognosis [3, 10].

Another rare, previously undescribed, heterozygous mutation [HG38, chr15:98957242A>T, c.3904A>T (p.Ser1302Cys); NM_000875.5] in the *IGF1R* gene was identified in patient 13 who was diagnosed with NDM and congenital hypothyroidism. This mutation's clinical significance is considered to be uncertain according to the major genetic prediction databases. Currently, there is evidence indicating a correlation between *IGF1R* gene mutations and both intrauterine and postnatal growth retardation, as well as an increased risk of developing cancer. Reports on carbohydrate metabolism disorders associated with *IGF1R* gene mutations are predominantly in the form of single clinical observations [18]. A review of the literature revealed no data on the development of NDM in patients with *IGF1R* gene mutations.

CONCLUSIONS

A majority of the study participants exhibited isolated NDM (78.6%). In three children, the disease was associated with a hereditary syndrome. We found that the clinical heterogeneity of NDM is determined by several factors. Among these, genetics is the most significant factor, and it determines the diversity of phenotypes. In our study, MGT identified 14 distinct variants in the causative genes. However, the role of novel *CACNA1D* and *IGF1R* gene mutations in the development of NDM remains poorly understood and requires further investigation. Our study findings indicate that early verification of the NDM form via molecular genetic analysis allows for the determination of the pathogenetic mechanisms of the disease that induce carbohydrate metabolism disruption. This, in turn, will enable the development of a personalized treatment plan, prediction of the disease course, and prevention of severe complications.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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