EDITORIAL

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Research Article

MOLECULAR GENETIC DIAGNOSIS AND TREATMENT OF CONGENITAL HYPERINSULINISM: RESULTS OF OBSERVATION OF PATIENTS WITH VARIANTS IN THE GENES *ABCC8* AND *KCNJ11*

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ABSTRACT

Congenital hyperinsulinism is a rare hereditary disease characterized by inadequate hypersecretion of insulin by pancreatic β-cells, clinically manifested by persistent hypoglycemia, which poses a great threat to patient survival and a high risk of developing severe neurological complications.

The article presents the results of clinical, hormonal and molecular genetic examination and treatment of 10 patients with congenital hyperinsulinism caused by mutations in the genes of ATP-dependent potassium channels (*KCNJ11*, *ABCC8*), hospitalized in Saint Petersburg State Pediatric Medical University clinic in 2010–2023. In all the studied patients, the disease manifested from the 1st to the 3rd day of life, and the median age of diagnosis of congenital hyperinsulinism in the study group was 1 month (min 14 days; max 3 years 9 months). In 8 out of 10 patients, a severe course of hypoglycemic syndrome was noted at the onset of the disease. According to the molecular genetic investigation results, 8 different mutations were identified: in the *KCNJ11* (2/8) and *ABCC8* (6/8) genes. Identical variants were found in two pairs of related patients. In children with mutations in the *ABCC8* gene (n = 8), 2 variants with unknown clinical significance were identified, which were not previously described in allelic databases and scientific literature. According to the analysis of anamnestic and clinical and laboratory data, 80.0% of children, including patients with new, previously not described in the scientific literature, variants in the *ABCC8* gene have a severe progressive course of congenital hyperinsulinism, requiring the appointment of insulinostatic therapy.

Keywords: congenital hyperinsulinism; persistent hypoglycemia; ABCC8 and KCNJ11 genes; ATP-dependent potassium channels.

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МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКАЯ ДИАГНОСТИКА И ЛЕЧЕНИЕ ВРОЖДЕННОГО ГИПЕРИНСУЛИНИЗМА: ОПИСАНИЕ РЕЗУЛЬТАТОВ НАБЛЮДЕНИЯ ЗА ПАЦИЕНТАМИ С ВАРИАНТАМИ В ГЕНАХ *ABCC8* И *KCNJ11*

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АННОТАЦИЯ

Врожденный гиперинсулинизм относится к редким орфанным заболеваниям, представляющим большую угрозу в отношении выживаемости пациентов и высокого риска развития тяжелых неврологических осложнений. Нами обобщены данные, полученные при наблюдении за 10 пациентами с врожденным гиперинсулинизмом, обусловленным дефектами в генах *ABCC8* и *KCNJ11*, накоплен уникальный опыт диагностики и лечения пациентов с орфанными заболеваниями, в том числе с врожденным гиперинсулинизмом, позволяющий усовершенствовать алгоритмы дифференциальной диагностики и лечения, прогнозировать течение заболевания. В статье представлены результаты клинического, гормонального и молекулярно-генетического обследования и лечения 10 пациентов с врожденным гиперинсулинизмом, обусловленным мутациями генов АТФ-зависимых калиевых каналов (*KCNJ11*, *ABCC8*), наблюдавшихся в Клинике Санкт-Петербургского государственного педиатрического медицинского университета за период с 2010 г. по настоящее время. У всех пациентов заболевание манифестировало с 1-го по 3-й день жизни, медиана возраста диагностики врожденного гиперинсулинизма в исследуемой группе составила 1 мес. (min 14 дней; max 3 г. 9 мес.). У 8 из 10 пациентов отмечалось тяжелое течение гипогликемического синдрома в дебюте заболевания. По результатам молекулярно-генетического исследования выявлено 8 различных мутаций: в генах *KCNJ11* (2/8) и *ABCC8* (6/8). Одинаковые варианты обнаружены у двух пар родственных пациентов. У детей с мутациями в гене *ABCC8* ($n = 8$) выявлено два варианта с неизвестным клиническим значением, ранее не описанных в аллельных базах и научной литературе. У пациентов с врожденным гиперинсулинизмом наблюдалась высокая вариабельность клинических проявлений и лабораторных показателей, обусловленная гетерогенностью гистологических форм врожденного гиперинсулинизма и полиморфностью молекулярно-генетических вариантов. Дальнейшее изучение особенностей пациентов с врожденным гиперинсулинизмом, проведение молекулярно-генетического анализа с внесением новых вариантов в таргетную панель генов позволит усовершенствовать алгоритмы дифференциальной диагностики и лечения.

Ключевые слова: врожденный гиперинсулинизм; персистирующая гипогликемия; мутация; гены *ABCC8* и *KCNJ11*; АТФ-зависимые К-каналы.

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BACKGROUND

Congenital hyperinsulinism (CHI) is becoming the most common cause of persistent hypoglycemia in ≤1-year-old children. It poses a significant threat to patient survival and a high risk of severe neurological complications [1, 2, 3, 5, 10]. Its prevalence is approximately 1:30,000–50,000, reaching 1:2,500 in countries with common consanguineous marriages [11, 13]. In Russia, according to 2015–2017 data, the primary incidence of CHI was 1:50,638 live newborns [7].

Due to the development of molecular genetic analysis and active introduction of new diagnostic methods into practical medicine, it is possible to determine the genetic basis of the disease and early verification of the diagnosis. In literature, gene mutations induce the development of various forms of CHI, isolated and syndromic (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *UCP2*, *HNF4A*, *HNF1A*, *HK1*, *KCNQ1*, *CACNA1D*, *FOXA2*, *EIF2S3*, *PGM1*, *PMM2*, etc.) [4, 14, 16, 18, 25]. In most cases (40%–60%), the disease is associated with *KCNJ11* and *ABCC8* gene mutations, which encode proteins responsible for ATP-dependent potassium channels in pancreatic β-cells [5]. Defects in *ABCC8* and *KCNJ11* result in decreased expression of ATP-dependent K-channels on the membrane, decreased receptor sensitivity, and closure of these channels. This situation creates conditions in which, regardless of the glycemia level, β-cell membrane remains depolarized, leading to excessive entry of Ca^{2+} into the cell and hypersecretion of insulin. Recessive and dominant autosomal mutations of these genes have been described [7]. As a rule, the disease manifests in the initial days of life, but a later onset is also possible [5]. The clinical presentation of hypoglycemic syndrome in CHI is varies [5]; the disease can be asymptomatic with mild hypoglycemia and respond well to conservative therapy with diazoxide and/or somatostatin analogs [7, 11, 21]; however, in most cases, a severe course of hypoglycemic syndrome is noted, often requiring urgent surgical treatment [9]. CHI is characterized by the absence of suppression of insulin secretion in response to declining glucose levels, resulting in hypoketotic hypoglycemia and a high degree of its utilization (>8 mg/[kg·min]), provided that other causes of hypoglycemia are ruled out (glycogenosis, defects in β-oxidation of fatty acids, aminoaciopathy, deficiency of counterinsular hormones, etc.) [6, 11]. Morphologically, two forms of CHI are distinguished: focal and diffuse, while atypical (a combination of diffuse and focal forms) is rare [6, 11]. The focal form is characterized by damage to a separate area of pancreatic tissue (40%–50% of cases). Focal formation occurs when inheriting a paternal mutation in *KCNJ11* and *ABCC8* with somatic loss of homozygosity [5, 21]. The affected area is well visualized using 18-F-Dopa positron emission tomography (18-F-Dopa PET) [8]. In the diffuse form, changes occur in the entire pancreatic islets (50%–60% of all CHI cases). The diffuse form is inherited in an autosomal recessive manner, less often in an autosomal dominant manner [5]. Identifying the genetic causes of CHI enables the verification of diagnosis and improves the understanding of pathophysiological aspects; however its treatment remains complex and requires the generalization of clinical, biochemical, and hormonal data, along with the results of molecular genetic studies (MGS) and 18-F-Dopa PET, to select the appropriate conservative therapy or surgical treatment. Cases of CHI caused by mutations in *KCNJ11* and *ABCC8* are more often severe and difficult to respond to drug therapy [5, 18].

We are presenting the anamnestic, clinical, laboratory, and molecular genetic aspects of 10 CHI patients followed up at the St. Petersburg State Pediatric Medical University clinic of the Ministry of Health of the Russian Federation (SP SPMU MHRF) from 2010 to the present, including 4 boys and 6 girls. The follow-up period ranged from 10 months to 13 years. The disease manifested itself in all subjects during the initial days of life (1–3 days). The median age of patients during MGS was 5.5 months (minimum 2 months; maximum 3 years 9 months). In addition, four siblings and nine parents took part in the study.

All pediatric patients underwent a comprehensive examination, including anamnestic data analysis (age of manifestation and range of disease symptoms, anthropometry at birth, while the nutritional status of premature newborns was assessed using Fenton's gender nomograms, hereditary history); biochemical and hormonal blood tests (insulin, C-peptide, cortisol, thyroid-stimulating hormone, free T4, insulin-like growth factor 1), glycemic monitoring with 24-h monitoring systems and portable glucometers, and 18-F-Dopa PET was performed in 5 patients. The diagnosis of CHI was established according to the following criteria: at the time of hypoglycemia (blood glucose <2.8 mmol/l), the plasma insulin level in one of the samples was >2.0 U/l; the presence of an elevated or normal level of C-peptide; the absence of ketonuria and signs of a pancreatic tumor according to ultrasound and/or multislice computed tomography

of the abdominal cavity. An additional criterion for diagnosing CHI was a high glucose requirement, >8 mg/(kg·day), to maintain normoglycemia (>3.5 mmol/l). Conservative therapy (diazoxide, somatostatin analog) was selected in stages, taking into account the patients' age and their efficiency assessment. Children with drug-resistant forms underwent surgical treatment in the form of partial resection of the pancreas.

MGS was performed in the medical genetic laboratory of SP SPMU MHRF, in the Department of Hereditary Endocrinopathies of the National Medical Research Center of Endocrinology, and the Laboratory of Prenatal Diagnostics of Hereditary and Congenital Human Diseases of the D.O. Ott Scientific Research Institute of Obstetrics, Gynecology, and Reproductology as part of the Alpha-Endo program.

Two patients underwent molecular genetic research using direct Sanger sequencing of individual genes (*ABCC8*, *KCNJ11*), while remaining patients, a massive parallel sequencing for the presence of variants in a targeted panel of CHI candidate genes was used [*KCNJ11*, *ABCC8*, *GLUD1*, *HADH (SCHAD)*, *GCK*, *SLC16A1*, *HNF4A*, *HNF1A*, *UCP2*, *INSR*, *AKT2*, *GCG*, *GCGR*, *PPARG*, and *PTF1A*]. In addition, MGS was performed in four siblings and nine parents to confirm or refute the pathogenicity of the variant identified [*ABCC8*, *KCNJ11*, *GLUD1*, *HADH (SCHAD)*, *GCK*, *SLC16A1*, *HNF4A*, *HNF1A*, *CP2*, *HK1*, *KCNQ1*, *CACNA1D*, *FOXA2*, *EIF2S3*, *PGM1*, and *PMM2*].

Exome DNA libraries were prepared using TruSeq Exome Library Prep Kit (Illumina, Inc., USA) or its analogs. Library concentrations were determined fluorometrically. The finished libraries were sequenced on Illumina HiSeq 2500 high-throughput sequencing system in paired-end sequencing mode 2 × 100 [TruSeq SBS Kit v3-HS (200 cycles)], or 2 × 125 [HiSeq® SBS Kit v4 (250 cycles)]; further, there were 100 or 125 nucleotides from each end of the fragment. After demultiplexing and converting the sequencing results into FASTQ format, separate file groups in FASTQ format were obtained for each sample using bcl2fastq program. These files were transferred for further bioinformatics analysis. Bioinformation processing of data was performed using the software bwa v. 0.7.12-r1044 aligner, Picard tools v. 2.0.1, and Genome Analysis Toolkit (GATK) v. 3.5. To rank the variants, a metric considering several factors was used: the type of substitution (synonymous, nonsynonymous, nonsense, etc.), the effect of this substitution (using the pathogenicity prediction programs PROVEAN, SIFT, and Polyphen2), incidence of this substitution in "1,000 Genomes," Exome Aggregation Consortium, ESP6500 databases, and incidence of this substitution in the study cohort.

Variant pathogenicity was assessed according to international recommendations using ClinVar database of genetic variants. Based on this assessment, pathogenic and likely pathogenic changes, and those of unknown clinical significance, were identified. Verification of WES results for DNA samples from the probands, followed by families' subsequent DNA analysis, was performed using direct sequencing of PCR products. Special primers were designed to test each case.

PCR products were purified using 5-mol NH_4Ac and 96% ethanol, followed by 70% ethanol, dried at 60 °C, and dissolved in 10-mL distilled water. After purification, PCR products were prepared using ABI PRISM® BigDye™ Terminator 3.1 kit reagent (Applied Biosystems, USA). The next stage was Sanger sequencing using GA3130xl Genetic Analyzer (Applied Biosystems, USA). Sequence products were analyzed using Sequence Scanner software (Applied Biosystems, USA). Gen-bank reference numbers NM_000525 and NM_000352 were used as reference cDNA sequences for *KCNJ11* and *ABCC8* [27]. Statistical processing of the research data was performed in StatTech v.2.8.2 program. The results are presented as average values, *Me* [Q_1; Q_3], where *Me* is the median, and Q_1 and Q_3 are the lower and upper quartiles, the minimum and maximum values (min–max).

HISTORICAL, CLINICAL, AND LABORATORY CHARACTERISTICS OF PATIENTS WITH CONGENITAL HYPERINSULINISM

Early onset of the disease was observed among the group studied. In all children, the disease manifested from day 1 to day 3 of life, with a median CHI diagnosis age of 1 month (minimum 14 days; maximum 3 years 9 months). Eight out of 10 patients experienced a severe hypoglycemic syndrome during the onset. In literature, the age of manifestation of a hypoglycemic syndrome in CHI, in most cases, occurs in the first week of life, and the age of diagnosis establishment is, on average, 1 month [7].

When analyzing anamnestic data, it was revealed that all patients had an aggravated perinatal history. Unfavorable pregnancy factors in their mothers were anemia (5 cases), exacerbation of chronic pyelonephritis (4 cases), polyhydramnios (2 cases), threatened miscarriage (2 cases), preeclampsia (1 case), and autoimmune thyroiditis with hypo-

thyroidism (1 case). Gestational diabetes mellitus was diagnosed in mothers of 2 related patients with heterozygous missense mutations in *ABCC8*. In two women, pregnancy was accompanied by uterine fibroids. In one case, complete didelphia was detected, which, in all cases, led to premature delivery by cesarean section. Surgical delivery was performed for two women due to poor uterine contraction strength and the failure of the uterine scar. Three out of 10 babies were born prematurely at weeks 26, 29, and 34 of gestation. Two full-term newborns had high birth weight (>4,000 g), 1 boy had "giant" weight (>5,000 g), and another premature girl was overweight (>97th percentile) according to Fenton's gender nomograms, while in the remaining children, birth weight corresponded to gestational age. According to most authors, prematurity, which causes immaturity of enzyme systems involved in gluconeogenesis and glycogenolysis, lack of endogenous glucose substrate, namely, glycogen, asphyxia, and polycythemia, aspects of the course of pregnancy, and associated changes in metabolism in mothers (gestational diabetes mellitus, preeclampsia, anemia) can cause the development of transient hypoglycemia in newborns, which complicates early CHI diagnostics [7].

Patients' genealogical data analysis with variants in *ABCC8* and *KCNJ11* showed that 7 of them had aggravated heredity, while 5 had first-degree relatives with persistent hypoglycemia, and in another two cases, CHI was diagnosed in the first- and second-degree relatives. In majority of cases, CHI was inherited autosomal recessively and is sporadic. In addition, *de novo* mutations occur [17]. CHI cases with a dominant type of inheritance are registered less frequently and are described by other researchers, primarily in the form of individual clinical cases [18, 26]. CHI patients' genealogical data are presented in Table 1.

Concerning international recommendations, the gold standard for diagnosing CHI is the determination of insulin and C-peptide levels against laboratory hypoglycemia to assess the presence or absence of its suppression [12].

In our study, the average insulin level in patients during the onset and at the time of hypoglycemia was 17.7 μIU/ml (2.0–56.6). In 8 pediatric patients, the insulin level had a diagnostic value and was borderline (2.0 μIU/ml) in 2 children with a mild phenotype of CHI. The mean C-peptide level was 4.7 ng/ml (0.7–13.48). The cortisol level was <500 nmol/l in all subjects; in 4 cases, there was a significant decrease in this indicator, which complicated diagnostics and required additional examination, including to rule out adrenal insufficiency.

According to federal clinical guidelines for the diagnostics, treatment, and monitoring of children and adolescents with CHI [6], the insulin level in the blood can have detectable values against hypoglycemia (>2μU/ml). It does not necessarily have to be high and may not exceed the reference limits. C-peptide level, basally and during hypoglycemia, may be normal or high. Similarly, the cortisol level during hypoglycemia may be >500 nmol/l, which does not indicate the presence of adrenal insufficiency in the pediatric patient.

According to most authors, a characteristic in pediatric patients with CHI is the absence of a hyperergic adrenal response to hypoglycemia. This absence indicates insufficiency in adrenocorticotropic hormone and cortisol secretions in the presence of rapidly developing hypoglycemia in newborns, as well as depletion of the counterinsular activity of the pituitary gland in case of chronic hypoglycemia [20].

18-F-Dopa PET was performed in 5 patients with severe CHI. A focal form of the disease was diagnosed in 2 cases, and a diffuse form was registered in 3 patients. The main clinical and laboratory parameters of CHI patients are presented in Table 2.

MOLECULAR GENETIC CHARACTERISTICS OF PATIENTS WITH CONGENITAL HYPERINSULINISM

According to MGS results, performed on all pediatric patients, the median time from diagnosis to study completion in our patients was 3 months (minimum 0.5 months; maximum 1 year 10 months), and the median of final diagnosis verification was 5.5 months.

In our study, eight different mutations were identified in *KCNJ11* (2/8) and *ABCC8* (6/8). The same variants were detected in two pairs of related patients in *ABCC8*, namely, c.4432G>A (patient no. 1 and 2) and c.3754–2A>G (patient no. 5 and 6). Two heterozygous missense mutations were identified in pediatric patients with variants in *KCNJ11* ($n = 2$); one was found to have a combination of a variant in the gene encoding ATP-dependent potassium channel proteins (*KCNJ11*) and a mutation in the hepatocyte nuclear factor 1 alpha gene (*HNF1A*), causing a defect in insulin secretion.

Six variants were identified in patients with mutations in *ABCC8* ($n = 8$). These included two variants classified as likely pathogenic, one as pathogenic, one with a controversial interpretation of pathogenicity, and two variants of unknown clinical

Table 1 / Таблица 1

Genealogical data of patients with congenital hyperinsulinism
Генеалогические данные пациентов с врожденным гиперинсулинизмом

Patient No. / № пациента	Gene / Ген	Variant in a gene / Вариант в гене	Family history in first-degree relatives / Отягощенная наследственность у родственников 1-й линии	Family history in second-degree relatives / Отягощенная наследственность у родственников 2-й линии	Inheritance type / Тип наследования
1	*ABCC8*	c.4432G>A (p.Gly1478Arg)	Mother, brother / Мать, брат	Maternal grandmother / Бабушка по линии матери	Autosomal dominant / Аутосомно-доминантный
2		c.4432G>A (p.Gly1478Arg)	Mother, sister / Мать, сестра	Maternal grandmother / Бабушка по линии матери	Autosomal dominant / Аутосомно-доминантный
3		c.259T>C (p.Cys87Arg)	Sister / Сестра	–	Autosomal recessive / Аутосомно-рецессивный
4		c.2696T>C (p.Ile899Thr)	–	–	Autosomal recessive / Аутосомно-рецессивный
5		c.3754-2A>G	Sister / Сестра	–	Autosomal recessive / Аутосомно-рецессивный
6		c.3754-2A>G	Sister / Сестра	–	Autosomal recessive / Аутосомно-рецессивный
7		*c.2866* del. (p.S956Lfs*86)	–	–	Autosomal recessive / Аутосомно-рецессивный
8		c.1332G>T (p.Q444H)	–	–	Autosomal recessive / Аутосомно-рецессивный
9	*KCNJ11*	c.356G>A (p.R119H)	–	–	Autosomal recessive / Аутосомно-рецессивный
10	*KCNJ11* + *HNF1A*	c.406G>T (p.Arg136Cys) + c.257T>A	–	–	Autosomal recessive / Аутосомно-рецессивный

significance. Most defects in *ABCC8* 66.7% ($n = 4$) are represented by missense mutations. However, splice acceptor mutations were also identified in two related probands in one (16.7%) case and one deletion causing a reading frame shift. Single variants in *ABCC8* were localized in exons 2, 8, 23, and 24, and paired variants were located in exons 31 and 37.

Table 2 / Таблица 2

Main clinical and laboratory parameters of patients with congenital hyperinsulinism
Основные клинические и лабораторные показатели пациентов с врожденным гиперинсулинизмом

Patient No. / № пациента	1	2	3	4	5	6	7	8	9	10
Sex / Пол	f / ж	m / м	f / ж	m / м	f / ж	f / ж	m / м	f / ж	f / ж	m / м
Gene / Ген	*ABCC8*								*KCNJ11*	*KCNJ11 + HNF1A*
Variant in a gene / Вариант в гене	c.4432G>A (p.Gly1478Arg)	c.4432G>A (p.Gly1478Arg)	c.259T>C (p.Cys87Arg)	c.2696T>C (p.Ile899Thr)	c.3754–2A>G	c.3754–2A>G	c.2866 del. (p.S956Lfs*86)	c.1332G>T (p.Q444H)	c.356G>A (p.R119H)	c.406G>T (p.Arg136Cys) + c.257T>A
Gestational age, weeks / Гестационный возраст, нед.	40	40	41/2	34	39	39	39	40	29	26
Weight at birth, g / Масса при рождении, г	4660	5020	4000	2550	3920	3290	3430	3430	2100	–
Length at birth, cm / Длина при рождении, см	55	58	54	45	53	50	53	51	44	–
Age of manifestation, days / Возраст манифестации, дни	2	1	2	1	1	2	1	3	1	1
Glycemia at debut, mmol/l / Гликемия в дебюте, ммоль/л	1.2	1.2	0.9	0.8	0.98	1.4	2.2	0	1.7	2.8
Min indicator of glucose, mmol/l / Min показатель глюкозы, ммоль/л	1.2	1.2	0.8	0.8	0.98	1.4	0.9	0	1.1	1.4
Insulin level at the time of hypoglycemia, μIU/ml / Уровень инсулина в момент гипогликемии, мкМЕ/мл	25.9	2.0	9.1	7.1	2.0	3.13	56.58	10.2	47.5	13.9
C-peptide level at the time of hypoglycemia, ng/ml / Уровень С-пептида в момент гипогликемии, нг/мл	8.08	0.7	2.6	9.4	0.83	0.981	9.08	–	13.48	4.7
Cortisol level, nmol/l / Уровень кортизола, нмоль/л	22.9	109	23.4	224	276	141.6	4.35	16.6	75.8	76
TSH, μIU/ml / ТТГ, мкМЕ/мл	5.63	3.13	1.2	3.87	1.5	2.13	–	0.99	3.14	7.5
T-4-svob, pmol/l / Т 4св, пмоль/л	20.8	20.1	11.6	11.8	17.1	14.97	–	20.2	15.1	12.4
IGF-1, ng/ml / ИФР-1, нг/мл	–	67.9	67.1	–	62.0	–	–	–	–	–
PET/CT-results / Результаты ПЭТ КТ /	Diffuse / Диффузная			Study was not carried out / Исследование не проводили			Focal / Фокальная		Study was not carried out / Исследование не проводили	

Note. TSH — thyroid-stimulating hormone, IGF-1 — insulin-like growth factor 1, PET/CT — positron emission tomography/computed tomography. *Примечание.* ТТГ — тиреотропный гормон; ИФР-1 — инсулиноподобный фактор роста 1; ПЭТ КТ — позитронно-эмиссионная томография, совмещенная с компьютерной томографией.

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In patients with mutations in the *ABCC8* gene, in most cases, variants were found in a heterozygous state. Two pediatric patients with focal forms were inherited from the father (patients No. 7 and 8), while two more cases were inherited from the mother (patients No. 1 and 2). Parallelly, a similar heterozygous variant in the causative gene and a mild course of CHI was revealed in the patient's mother and grandmother, indicating an autosomal dominant type of inheritance of the disease in this family.

Some authors emphasize a milder course of CHI with heterozygous variants in *ABCC8*. In addition, such patients may develop diabetes mellitus over time due to β-cells apoptosis as a result of excessive Ca^{2+} ion intakes [19, 24]. Among our patients with the heterozygous missense mutation c.4432G>A (p.Gly1478Arg) in *ABCC8*, there were 2 pediatric patients (siblings) with a diffuse form (according to 18-F-Dopa PET) and a relatively mild, controlled CHI course. The boy achieved a stable compensation of the disease during diet therapy, while his sister required drug therapy with diazoxide. In literature [23], patients with inactivating mutations in *ABCC8*, with an autosomal dominant type of inheritance, have a mild phenotype of the disease course and high sensitivity to diazoxide due to preserved expression of channels on the cell membrane [15, 19, 22], which was noted in our patients. Similar variants in *ABCC8* were described in a child from Norway, who displayed a mild course of the disease [11, 13], and in a patient from USA. The disease manifested at the age of 3 years, and normoglycemia was achieved during treatment with diazoxide [26].

In our study, severe CHI cases were associated with compound variants. Specifically, this included a combination of a pathogenic variant in *KCNJ11* and a mutation in *HNF1A* (patient no. 10) and heterozygous variants in *ABCC8* and *KCNJ11* (patients No. 4 and 9). The compound heterozygous mutation detected in our patient with severe CHI had unknown clinical significance according to ClinVar, and it has not been described in CHI patients' scientific literature, although it is present in the Maturity Onset Diabetes of the Young database. Patient no. 4 had a variant revealed in *ABCC8* c.2696T>C. (p.Ile899Thr) had unknown clinical significance according to ClinVar and not described in the scientific literature.

Homozygous mutations in *ABCC8* were revealed in 3 patients; two of them were sisters (a detailed description of patients with homozygous mutations will be presented in clinical cases in the next article).

The molecular genetic characteristics of CHI patients are presented in Table 3.

TREATMENT OF PATIENTS WITH CONGENITAL HYPERINSULINISM

Upon disease manifestation, all pediatric patients received infusion therapy with a glucose solution to relieve persistent hypoglycemia. Eight (80%) out of 10 patients required long-term infusion of glucose solution. The average glucose requirement in the studied patients was 12 (10–13) mg/(kg·min), while the maximum need was in a patient with pharmacoresistant CHI, namely, 13 mg/(kg·min), caused by a nucleotide deletion in *ABCC8*. The median duration of glucose solution infusion was 21 days (7–84).

According to our data, in most cases, stabilization of glucose levels was achieved with an intravenous glucose supplement of >10 mg/(kg·min), and the concentration of the administered solution reached 20%. A high rate of glucose utilization, specifically exceeding 8 mg/(kg·day), is considered one of the additional criteria for CHI diagnosis [6]. Most authors noted the need for long-term continuous infusion of highly concentrated glucose solutions to achieve normoglycemia (>3.5 mmol/l) in pediatric patients with CHI [6].

Conservative treatment was initiated in all patients with somatostatin analog (octreotide). In 7 pediatric patients, an attempt was made to transfer to a drug with ATP-dependent K-channel agonists (diazoxide). Two of them demonstrated high sensitivity to the drug, achieving an euglycemic profile. Two (20%) patients with focal CHI who were subsequently operated on were resistant to conservative treatment with diazoxide and octreotide.

Currently, 6 out of 10 patients receive insulinostatic therapy, namely, 33.3% of patients ($n = 2$) with ATP-dependent K-channel agonists (diazoxide) and 66.7% ($n = 4$) with a somatostatin analog (octreotide), while two cases are compensated for diet therapy. In two pediatric patients who underwent surgical treatment, glycemic indicators are within the reference values.

CONCLUSION

Most patients (80.0%) with variants in *ABCC8* and *KCNJ11* had an early onset and severe progradient course of the disease, which required insulinostatic therapy and, in some cases, surgical treatment. In CHI patients, high variability of clinical manifestations and laboratory parameters was noted

Table 3 / Таблица 3

Molecular genetic characteristics of patients with congenital hyperinsulinism
Молекулярно-генетическая характеристика пациентов с врожденным гиперинсулинизмом

Patient No. / № пациента	Gene / Ген	Variant location / Локализация варианта	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 (according to gnomAD) / Частота аллеля (по gnomAD)	Pathogenicity (according to ClinVar) / Клиническая значимость (по ClinVar)
1	*ABCC8*	37	c.4432G>A	p.Gly1478Arg	Heterozygote / Гетерозигота	Missense / Миссенс	+	0,00001	Pathogenic/likely pathogenic / Патогенный/вероятно патогенный
2	*ABCC8*	37	c.4432G>A	p.Gly1478Arg	Heterozygote / Гетерозигота	Missense / Миссенс	+	0.00001	
3	*ABCC8*	2	c.259T>C	p.Cys87Arg	Homozygous / Гомозигота	Missense / Миссенс	–	–	Unknown clinical significance / Неизвестного клинического значения
4	*ABCC8*	23	c.2696T>C	p.Ile899Thr	Heterozygote / Гетерозигота	Missense / Миссенс	–	–	
5	*ABCC8*	31	c.3754–2A>G	–	Homozygous / Гомозигота	Splicing defect / Дефект сплайсинга	+	–	Conflicting interpretations of pathogenicity: likely pathogenic (1) / uncertain significance (2) / Противоречивые интерпретации патогенности: вероятно патогенный (1) / неопределенная значимость (2)
6	*ABCC8*	31	c.3754–2A>G	–	Homozygous / Гомозигота	Splicing defect / Дефект сплайсинга	+	–	
7	*ABCC8*	24	*c.2866*del	p.Ser956Leufs*86	–	Frameshift deletion / Делеция, приводящая к сдвигу рамки считывания	+	–	Pathogenic / Патогенный
8	*ABCC8*	8	c.1332G>T	p.Gln444His	Heterozygote / Гетерозигота	Missense / Миссенс	+	–	Pathogenic/likely pathogenic / Патогенный/вероятно патогенный
9	*KCNJ11*	2	c.356G>A	p.Arg119His	Heterozygote / Гетерозигота	Missense / Миссенс	+	–	
10	KCNJ11 + HNF1A	1	c.406G > T c.257T>A	p.Arg136Cys	Heterozygote / Гетерозигота Heterozygote / Гетерозигота	Missense / Миссенс Missense / Миссенс	+ –	0,00006 –	Pathogenic/likely pathogenic / Патогенный/вероятно патогенный Unknown clinical significance / Неизвестного клинического значения

due to the heterogeneity of histological forms of CHI and polymorphism of molecular genetic variants. Heterozygous mutations identified in CHI patients demonstrated the heterogeneity of clinical presentation, whereas homozygous ones were associated only with severe CHI. Two homozygous variants (c.2696T>C, p.Ile899Thr and c.259T>C, p.Cys87Arg) in *ABCC8* were described for the first time and are absent in allelic databases.

Further study of CHI patients' characteristics and introduction of new variants into the target gene panel will improve the algorithms for differential diagnostics and treatment.

ADDITIONAL INFORMATION

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