DOI: https://doi.org/10.17816/PED1445-12
Research Article

Congenital organic hyperinsulinism. Phenotype spectrum predetermined by *ABCC8* gene variants

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ABSTRACT

Congenital hyperinsulinism is a hereditary disease belonging to the orphan group, clinically manifested by the development of persistent hypoglycemia in the neonatal period. Neurological disorders resulting from persistent hypoglycemia, in most cases, are accompanied by dysfunction of the central nervous system, regression and delayed psychomotor and speech development. Congenital hyperinsulinism is characterized by heterogeneity of disease phenotypes, manifested by different severity of hypoglycemic syndrome, metabolic and neurological manifestations, which makes it difficult to verify the diagnosis, dictates the need for a comprehensive examination, including molecular genetic analysis in patients and their families. This allows timely appointment of insulinostatic therapy, thereby reducing the risk of severe neurological and metabolic complications. The article presents a description of three clinical cases of congenital hyperinsulinism associated with homozygous variants in the *ABCC8* gene and an autosomal recessive type of inheritance, which were included in the number of patients previously studied by us with variants in the *ABCC8* and *KCNJ11* genes. The results of this study were partially published by the authors earlier. The experience of monitoring these patients reflects the importance of early diagnosis of congenital hyperinsulinism, including the use of molecular genetic testing, the timely administration of insulinostatic therapy, allows an objective assessment of the effectiveness of the treatment, and reduces the risk of developing severe metabolic and neurological complications.

Keywords: congenital hyperinsulinism; persisten hypoglycemia; *ABCC8*; ATP-dependent potassium channels.

To cite this article:
Ivanov DO, Ditkovskaya LV, Maryina OI, Turkunova ME, Suspitsin EN, Prokhorovich TI. Congenital organic hyperinsulinism. Phenotype spectrum predetermined by *ABCC8* gene variants. *Pediatrician (St. Petersburg).* 2023;14(4):5–12. DOI: https://doi.org/10.17816/PED1445-12

Received: 14.07.2023 **Accepted:** 21.07.2023 **Published:** 31.08.2023

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DOI: https://doi.org/10.17816/PED1445-12
Научная статья

Врожденный органический гиперинсулинизм. Спектр фенотипов, обусловленных вариантами в гене *ABCC8*

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АННОТАЦИЯ

Врожденный гиперинсулинизм — наследственное заболевание, относящееся к группе орфанных, клинически проявляющееся развитием персистирующих гипогликемий в неонатальном периоде. Неврологические расстройства, возникающие вследствие персистирующих гипогликемий, в большинстве случаев сопровождаются нарушением функции центральной нервной системы, регрессией и задержкой психомоторного и речевого развития. Для врожденного гиперинсулинизма характерна гетерогенность фенотипов заболевания, проявляющаяся различной выраженностью гипогликемического синдрома, метаболических и неврологических симптомов, что затрудняет верификацию диагноза, диктует необходимость комплексного обследования, в том числе проведения молекулярно-генетического анализа у пациентов и членов их семей. Это позволяет своевременно назначить инсулиностатическую терапию, тем самым снизить риск развития тяжелых неврологических и метаболических осложнений. В статье представлено описание трех клинических случаев врожденного гиперинсулинизма, сопряженных с гомозиготными вариантами в гене *ABCC8* и аутосомно-рецессивным типом наследования, вошедших в число ранее исследованных нами пациентов с вариантами в генах *ABCC8* и *KCNJ11*. Результаты данного исследования частично опубликованы авторами ранее. Опыт наблюдения за данными пациентами отражает важность ранней диагностики врожденного гиперинсулинизма, в том числе с использованием молекулярно-генетического исследования, своевременного назначения инсулиностатической терапии, позволяет объективно оценить эффективность проводимого лечения, снизить риск развития тяжелых метаболических и неврологических осложнений.

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

Как цитировать:
Иванов Д.О., Дитковская Л.В., Марьина О.И., Туркунова М.Е., Суспицын Е.Н., Прохорович Т.И. Врожденный органический гиперинсулинизм. Спектр фенотипов, обусловленных вариантами в гене *ABCC8* // Педиатр. 2023. Т. 14. № 4. С. 5–12. DOI: https://doi.org/10.17816/PED1445-12

Рукопись получена: 14.07.2023 **Рукопись одобрена:** 21.07.2023 **Опубликована:** 31.08.2023

INTRODUCTION

Congenital hyperinsulinism (CHI) is an inherited disorder characterized by persistent hypoglycemia in the neonatal period [3, 8]. CHI is classified as an orphan disease and has a prevalence of 1:30,000–50,000, which increases to 1:2,500 in countries with high rates of consanguinity [11, 12]. In the Russian Federation, the latest data show that the primary prevalence of CHI was 1:50,638 live newborns between 2015 and 2017 [7].

CHI exhibits high clinical variability resulting from the heterogeneity of histological forms and polymorphism of molecular genetic defects [1, 4, 7, 14, 17].

In most cases (40%–60%), CHI is caused by pathogenic variants of genes that encode proteins associated with ATP-dependent K-potassium channels in pancreatic β-cells (*ABCC8* and *KCNJ11*) [6]. Currently, autosomal dominant and autosomal recessive mutations of *ABCC8* and *KCNJ11* have been reported. According to several studies, autosomal recessive inheritance results in the development of severe diffuse forms of diazoxide-resistant disease [13, 16, 19]. These variants can be passed down from the parents or occur spontaneously [15]. Homozygous cases are the most severe, which lead to neurological and metabolic complications. Furthermore, the same variant in the causative gene exhibits high penetrance, resulting in various phenotypes in CHI [7, 14, 17, 20]. This necessitates a thorough assessment, involving molecular genetic testing (MGT) in the proband and their relatives, to confirm the diagnosis and promptly initiate insulinostatic therapy, thereby mitigating the likelihood of severe neurological and metabolic complications.

This paper describes three clinical CHI cases associated with homozygous *ABCC8* variants and autosomal recessive inheritance. These cases were part of the *ABCC8* and *KCNJ11* variant patient cohort previously studied by the authors [5].

CASE REPORT 1

Patient C, a female from the fourth pregnancy, has a family history of CHI (in her sister) and a complicated antenatal history. Her mother suffered from toxicosis during the first trimester and was subsequently diagnosed with anemia, cytomegalovirus infection, ureaplasmosis, candidal colpitis during the second and third trimesters, and edema during pregnancy. During labor, patient C experienced early amniotic fluid shedding. She was born at 41 weeks, weighing 4,000 g with a length of 54 cm and an Apgar score of 8/9 points. On the second day of life, her condition worsened as her saturation levels dropped to 70%–75%, and she experienced hypoglycemia, with a plasma glucose level of 0.9 mmol/L. In addition, she had convulsions, eye rolling, and muscle hypotonia. After glucose administration, seizures stopped, and blood glucose normalized. However, upon attempting to discontinue the intravenous administration of glucose solution, she suffered repeated hypoglycemic attacks with convulsions and apnea, ultimately requiring artificial ventilation. Based on the hormonal study, the following values were obtained: insulin, 9.1–16.1 (normal range, 2.0–25.0) μED/mL; C-peptide, 2.76–7.9 (normal range, 0.5–3.2) ng/mL; insulin-like growth factor 1 (IGF-1), 67.1 (normal range, 31.0–43.0) ng/mL; cortisol, 23.4–109.8 (normal range, 55.0–304.0) nmol/L; thyroid hormone (thyroid-stimulating hormones [TSH]), 1.2 (normal range, 0.34–5.6) μIU/mL; and free thyroxine (T4sv), 11.6 (normal range, 7.9–14.4) μmol/L. Blood and urine tests for ketones and ammonium were negative. During the dynamic observation, physicians noted frequent episodes of severe hypoglycemia, which required high glucose supplementation at a dosage of 12 mg/(kg/day). The patient was diagnosed with congenital hyperinsulinism, and an attempt to treat it using diazoxide, an ATP-dependent K-channel agonist, at a dosage of 20 mg/(kg/day) was ineffective. Glucose levels were stabilized after administering octreotide, a somatostatin analog, at a subcutaneous dose of 5–10 mcg/kg/day. At 7 months of age, the patient developed recurrent seizures with epileptiform activity, which was confirmed by electroencephalography (EEG) in a normoglycemic state. Anticonvulsant therapy was subsequently prescribed.

MGT was performed to confirm the diagnosis and determine a personalized treatment approach. In exon 2 of *ABCC8* (NM_000352.6), a homozygous single nucleotide substitution was identified, resulting in the substitution of amino acid c.259T>C, p. Cys87Arg. This *ABCC8* mutation was detected in her father, mother, and older sister who suffered from organic lesions of the central nervous system (CNS) and persistent hypoglycemia. At the age of 12, the diagnosis of the older sister was confirmed following the acquisition of MGT results from all family members. Genealogical information of the patient is shown in Fig. 1.

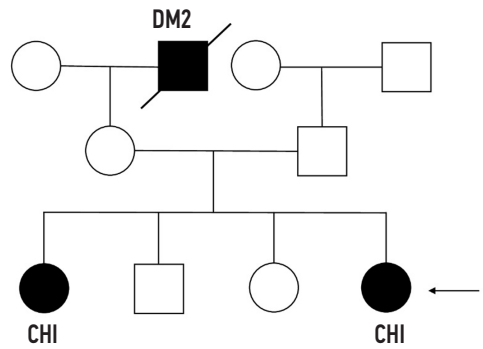

Fig. 1. The genealogy of the patient C. with congenital hyperinsulinism
Рис. 1. Генеалогические данные пациентки С. с врожденным гиперинсулинизмом

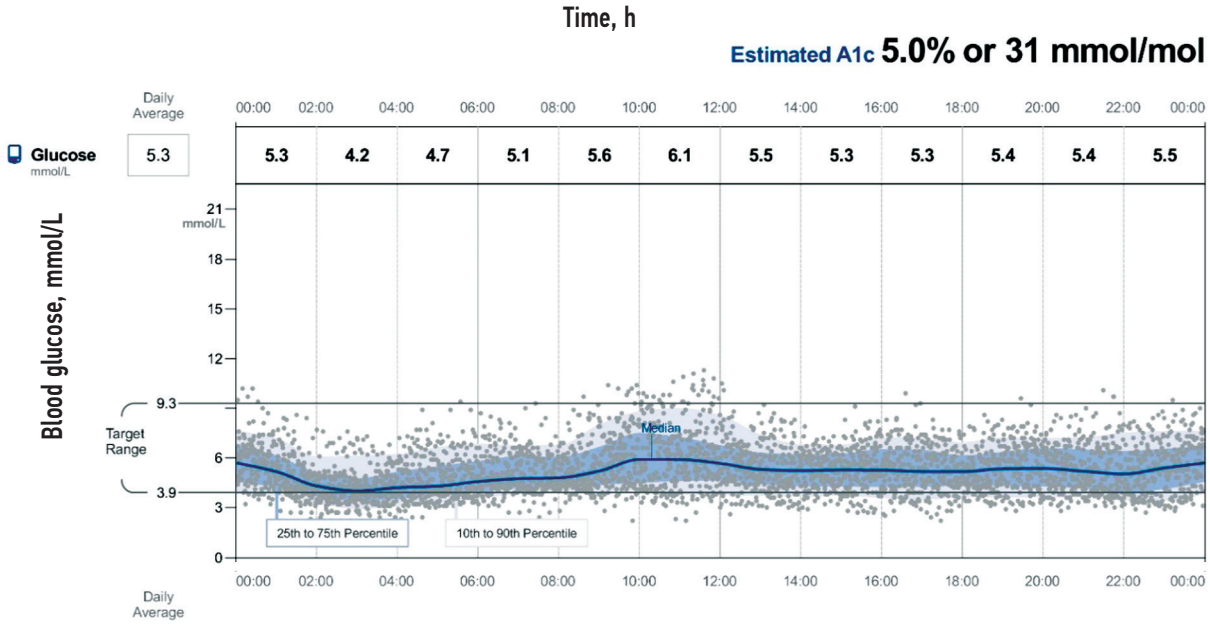

Fig. 2. Daily sensory monitoring of glycemia in a patient C. with congenital hyperinsulinism
Рис. 2. График суточного мониторирования гликемии у пациентки С. с врожденным гиперинсулинизмом

At age of 18 months, the patient was reevaluated at the endocrinology department. Her physical examination revealed an overweight status; she weighed 11 kg, with a body mass index (BMI) of 17.63 kg/m^2 (SDS_{BMI} +1.42) and an average height of 79 cm (–1.50 SDS). An analysis of the daily diet revealed an imbalance among the primary nutritional components (carbohydrates, proteins, and fats), with an overabundance of carbohydrates caused by a high consumption of foods with a high glycemic index. During neurological evaluation, a delay in age-related psychomotor development was observed, including inability to stand independently, relying on support for walking, inability to drink from a cup, inability to assemble a pyramid, and difficulty guessing objects in pictures. No convulsive seizures have occurred within the past 6 months. Her speech was predominated by syllabic babbling. EEG data showed polymorphic activity in the background pattern with no registered focal or epileptiform activity.

The child is still undergoing treatment with a subcutaneous pump method of somatostatin analog (octreotide) at a dose of 6.2 mcg/kg/day and antiepileptic monotherapy (valproic acid) at a dose of 180 mg/day.

Blood glucose control was performed 24/7 using a flash monitoring system (Fig. 2). The disease was in remission, as confirmed by laboratory examinations, which showed glycated hemoglobin (HbA1c) at 4.7% (normal range, 4.0%–6.0%), insulin level of 2.0 (normal range, 2.0–25.0) μED/mL, and C-peptide level of 2.24 (normal range, 0.50–3.20) ng/mL. Episodes of hypoglycemia infrequently occur during intercurrent illnesses (minimum blood glucose, 2.9 mmol/L).

CASE REPORT 2

Patient Z (older sister) was born following anemic pregnancy, exacerbation of chronic pyelonephritis, and premature amniotic fluid retention during labor. She was born at term with a weight of 3,920 g, length of 53 cm, and an Apgar score of 7/8 points. From birth, she experienced regular (fasciculations) or spasmodic muscle contractions in the right arm and leg and hyporeflexia and lethargic feeding. On day 3, hypoglycemia (blood glucose 0.98 mmol/L) occurred for the first time, accompanied by tonic–clonic seizures and respiratory issues, including apnea. On that day, she required artificial ventilation. Intravenous glucose solution effectively controlled the hypoglycemia, which was categorized as transient because of normal glucose values during the 1-month long-term observation. Recurring hypoglycemic episodes accompanied by convulsions, with acute respiratory viral infection, were observed at 1.5 and 4 months of age. The patient was examined in the endocrinology department to determine the causes of persistent hypoglycemia. The hormonal study revealed the following levels: insulin, 2. (normal range, 2.0–5.0) 0 μED/mL; C-peptide, 0.83 (normal range, 0.5–3.2) ng/mL; cortisol, 276.0 (normal range, 55.0–304.0) nmol/L; and IGF-1, 62.0 (normal range, 31.0–43.0) ng/mL. Ketones and ammonium were not detected in the blood sample. The results of the glucagon test were as follows: at baseline, the glucose level was 1.69 mmol/L, and insulin was 2.0 μED/mL. After 15 min, glucose levels rose to 5.42 mmol/L, accompanied by an insulin spike to 11.1 μED/mL. At the 90-min mark, glucose levels decreased to 2.16 mmol/L, with insulin

returning to baseline levels at 2.0 μED/mL. The examination by the neurologist did not register any epileptiform activity based on a series of EEGs. The patient did not undergo anticonvulsant therapy. In an outpatient observation, the endocrinologist incorporated corn starch into the patient's diet at an early age to prevent hypoglycemia. The child underwent regular glycaemia control but did not receive insulinostatic therapy. The patient was compensated for a prolonged period along with dietary measures. Nonsevere hypoglycemia rarely occurs during intercurrent diseases. The patient was registered with a neurologist because of delayed psychospeech development.

At the age of 9 years, she underwent examination at the endocrinology department. Her anthropometric parameters were assessed, and the diagnosis revealed grade III obesity with a weight of 53 kg (BMI 27.7 kg/m^2, SDS_{BMI} +3.02) and an average height of 139 cm (SDS_{height} +0.49). During daily monitoring of blood glucose levels, episodes of asymptomatic hypoglycemia were observed, characterized by a decrease in blood glucose to 2.7 mmol/L. At the time of hypoglycemia, the insulin level was 39.85 (normal range, 2.9–28.8) μED/mL, and the C-peptide level was 3.89 (normal range, 0.78–5.19) ng/mL.

CASE REPORT 3

Patient M (younger sister) was born from a pregnancy with threatened termination and gestosis, where premature amniotic fluid shedding occurred during delivery. She was delivered at term with a weight of 3,290 g, length of 50 cm, and an Apgar score of 8/9 points. Recurrent hypoglycemia was observed starting from the second day of life with a minimum blood glucose level of 1.4 mmol/L. To maintain normal glucose levels, long-term intravenous administration of glucose solutions [10–12 mg/(kg/day)] and prednisolone injections were administered. Daily episodes of hypoglycemia, which included postprandial hypoglycemia (a decrease in blood glucose levels to 2.5 mmol/L), were detected during dynamic observation and were accompanied by symptoms of weakness, eye rolling, and tachycardia. According to the laboratory findings, the insulin level was 3.13 (normal range, 2.0–10.0) μED/mL; C-peptide, 0.98 (normal range, 0.5–3.2 ng/mL); IGF-1, 46.1 (normal range, 31.0–43.0) ng/mL; cortisol, 141.0 (normal range, 55.0–304.0) nmol/L; TSH, 2.13 (normal range, 0.34–5.6) μIU/mL; and T4sv, 14.97 (normal range, 7.9–14.4) μmol/L. Based on the hormonal examination data and persistent nature of severe hypoglycemia, the patient was suspected to have CHI. Therapy was initiated with a subcutaneous injection of the somatostatin analog octreotide at a dosage of 25 mcg/kg/day. However, switching to ATP-dependent K-channel agonists (diazoxide, max 15 mg/kg/day) was ineffective. As a result, conservative therapy with octreotide was continued, which eventually resulted in stable normoglycemia.

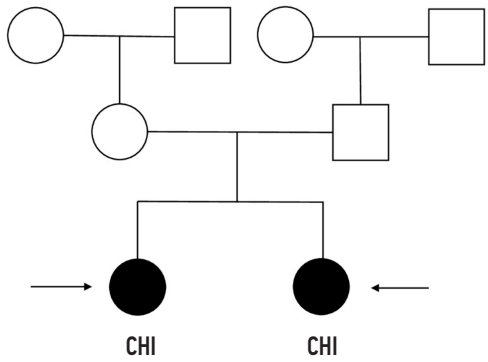

Fig. 3. Genealogical data of siblings Z. and M. with congenital hyperinsulinism
Рис. 3. Генеалогические данные сибсов З. и М. с врожденным гиперинсулинизмом

Owing to the family history (the older sister's extensive history of persistent hypoglycemia), molecular genetic analysis was conducted on both girls to fully confirm the diagnosis. A homozygous variant in *ABCC8* (NM_000352) c.3754–2A>G was detected in the patients. In addition, the family and patient underwent medical and genetic counseling. The father was identified to possess a similar *ABCC8* mutation in a heterozygous state, whereas the mother declined to participate in the study (Fig. 3). The sisters were 3.5 years and 3 months old during the MGT. Family history information for the siblings is presented in Fig. 3.

During a routine checkup at the age of 7, Patient M was diagnosed with grade II obesity, with a weight of 34 kg, BMI of 22.84 kg/m^2, and SDS_{BMT} of +2.69. She had an average height of 122 cm and an SDS_{height} of 0.46. Patient M exhibited delays in psychospeech development and was observed by a neurologist for dysarthria. According to the most recent laboratory examination, Patient M's insulin level was 8.9 (normal range, 2.9–28.8) pmol/L, and her C-peptide level was 0.97 (normal range, 0.78–5.19) ng/mL.

As part of her insulinostatic treatment, she was administered 4.7 mcg/kg/day octreotide through subcutaneous injections. Throughout her treatment and continuous monitoring of her blood glucose levels, instances of hypoglycemia were observed, including severe hypoglycemia (minimum blood glucose level of 1.9 mmol/L). These episodes are characterized by neuroglycopenic symptoms such as headache, dizziness, and syncope.

DISCUSSION

All three patients had homozygous *ABCC8* mutations and exacerbated heredity. Patient S had the most common missense mutation typical of CHI. A splicing mutation was identified in related probands with a different

course of phenotype. During the investigation of the family members, the same variations in the causative gene were identified in siblings who also experienced persistent hypoglycemia. These variations were detected in the homozygous state. Moreover, the heterozygous state of these variations was uncovered in the healthy parents of the affected siblings.

The literature depicts comparable cases of CHI among populations with a high incidence of consanguineous marriages [12,16]. The genealogical history indicated that no closely related marriages occurred within the families under study.

The cases of CHI described herein demonstrated significant variability in both clinical manifestations and laboratory parameters. Patient S exhibited early onset and a severe and progressive disease course characterized by persistent hypoglycemia, seizures, and a high requirement for prolonged glucose solution infusion up to 14 mg/kg/day. Her sister (patient M) experienced a severe disease course, whereas the other sister (patient Z) had a mild CHI course that did not necessitate insulinostatic therapy. Although many researchers have documented a severe CHI course in homozygous *ABCC8* variants, cases with a mild phenotype and delayed manifestation have also been reported [4, 18].

Based on the findings of international researchers, the variations in the CHI proband's phenotypic course are risks for gene modification, influence of epigenetic factors, and peculiarities of the splicing mechanism [20]. Patients with homozygous splice mutations from Japan exhibited analogous clinical heterogeneity [20]. When evaluating laboratory parameters in patients with severe CHI, we observed high levels of insulin and C-peptide during hypoglycemia. However, in a girl with mild disease (patient Z), the insulin level had a nondiagnostic value, posing difficulties in diagnosing the condition. Moreover, patient S, who had severe CHI, exhibited reduced cortisol levels, leading to a possible diagnosis of adrenal insufficiency. Patients with CHI often experience persistent hypoglycemia, which can reduce the glycemic threshold and ultimately suppress cortisol secretion, further complicating the diagnosis [10, 18].

The assessment of psychomotor development and neurological status parameters in all three patients indicated a delay in both mental and speech development. Patients Z and M are currently being treated by a neurologist for delayed psychospeech development. Moreover, in addition to delayed psychospeech development, patient S was diagnosed with encephalopathy of mixed etiology (metabolic–ischemic), which caused cystic–gliosis lesions in the occipital lobes of both hemispheres, along with structural epilepsy.

CNS damage, including metabolic impairment caused by hypoglycemia, could lead to functional impairment and developmental regression, as confirmed by EEG data [2, 9].

CONCLUSIONS

The significant variation observed in the metabolic and neurological symptoms among the three CHI clinical cases presented indicates a high level of genetic penetrance and expressivity that governs the diversity of phenotypes, complicating the diagnosis and necessitating molecular genetic analysis in both patients and their relatives.

A thorough genetic examination of probands and their relatives enables the clarification of inheritance patterns, verification of diagnosis, and prediction of the likelihood of CHI in the offspring of families with a history of the condition.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, 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.

Acknowledgement. The authors are grateful to all employees and specialists who conducted molecular genetic study at the National Research Center for Endocrinenology (Moscow) and D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology (St. Petersburg), patients and their relatives.

Conflict of interests. The authors declare that there is no conflict of interest.

Funding source. This study was funded by the Foundation for the Support and Development of Philanthropy (CAF).

Consent for publication. Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

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