DIABETES MELLITUS ASSOCIATED WITH THE MUTATION OF THE ABCC8 GENE (MODY 12): FEATURES OF CLINICAL COURSE AND THERAPY

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Maturity-Onset Diabetes of the Young (MODY) is a heterogeneous group of diseases associated with genes mutations leading to dysfunction of pancreatic β-cells. Among the 14 identified MODY variants, MODY 1–5 are the most studied. The article reports a MODY 12 clinical case, with mutation in ABCC8, encoding the sulphonylurea receptor. Diabetes mellitus manifested in a 27-year-old man with hyperglycaemia up to 24 mmol/L, without ketosis. Non-proliferative diabetic retinopathy, microalbuminuria, dyslipidaemia and carotid atherosclerosis were revealed upon initial examination. The levels of pancreatic islet cell antibodies and glutamate decarboxylase antibodies were negative, while the level of C-peptide was within the normal range. Insulin therapy in the basal-bolus regimen was provided with a gradual dose reduction due to frequent hypoglycaemia. The preproliferative retinopathy with macular oedema was revealed after 4 months of therapy, and panretinal photocoagulation of both eyes was performed. A molecular genetics study revealed a mutation in the gene ABCC8, the same mutation was found in patient's mother and uncle. Insulin therapy was cancelled, and the treatment of gliclazide MR 60 mg/day was initiated, which resulted in extreme glycaemic excursions. Thereby, sodium–glucose cotranporter-2 (SGLT2) inhibitor dapagliflozin 10 mg/day was added. A reduction in glucose variability parameters were observed on combination therapy. After 6 months till 1.5 years of treatment, glycaemic control was optimal, no hypoglycaemic episodes were observed. This case study demonstrates clinical features of MODY 12, and the potential of combination of sulfonylurea and SGLT2 inhibitor in the treatment of this disease.

KEYWORDS: MODY diabetes; mutations; clinical case; ABCC8; molecular-genetic investigation; SGLT2 inhibitors

САХАРНЫЙ ДИАБЕТ, СВЯЗАННЫЙ С МУТАЦИЕЙ ГЕНА ABCC8 (MODY 12): ОСОБЕННОСТИ КЛИНИЧЕСКОГО ТЕЧЕНИЯ И ТЕРАПИИ

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Сахарный диабет взрослого типа у молодых (MODY) представляет собой группу заболеваний, связанных с мутацией генов, приводящих к дисфункции β-клеток поджелудочной железы. Известно 14 вариантов MODY, наиболее изученными являются MODY 1–5. В статье приводится клинический случай MODY 12, в основе которого лежит мутация гена *ABCC8*, кодирующего рецептор сульфонилмочевины. Диабет дебютировал у мужчины в возрасте 28 лет с гипергликемией до 24 ммоль/л без кетоза. При верификации диагноза выявлены непролиферативная диабетическая ретинопатия, микроальбуминурия, дислипидемия, атеросклероз сонных артерий. Антитела к островковым клеткам и глутаматдекарбоксилазе не выявлены, С-пептид был в норме. Назначена инсулинотерапия в базис-болюсном режиме, доза инсулина постепенно снижалась в связи с гипогликемиями. Препролиферативная диабетическая ретинопатия и макулярный отек выявлены через 4 мес после начала терапии, выполнена панретинальная лазерная фотокоагуляция сетчатки. При проведении молекулярно-генетического исследования верифицирована мутация в гене *ABCC8*. Идентичная мутация выявлена у матери и дяди пробанда. Инсулин отменен, назначен гликлазид МВ 60 мг/сут, на фоне приема которого сохранялись значительные колебания гликемии. В лечение был присоединен ингибитор глюкозо-натриевого транспортера 2 (SGLT2) дапаглифлозин в дозе 10 мг/сут. На фоне комбинированной терапии отмечено уменьшение вариабельности гликемии. Через 6 мес и 1,5 года сохранялся оптимальный гликемический контроль, эпизодов гипогликемии не зафиксировано. Описание данного случая демонстрирует особенности клинического течения MODY 12 и возможности его лечения комбинацией препарата сульфонилмочевины и ингибитора SGLT2.

КЛЮЧЕВЫЕ СЛОВА: MODY диабет; мутации; клинический случай; ABCC 8 ген; молекулярно-генетическое исследование; ингибиторы SGLT2

Received: 13.03.2018. Accepted: 10.11.2018.

Maturity-onset diabetes of the young (MODY) is a heterogeneous group of diseases that occur as a result of gene mutations that cause pancreatic ⊠-cell dysfunction. Diagnostic criteria of MODY include hyperglycaemia that is usually diagnosed under the age of 35 years, an autosomal dominant inheritance with vertical transfer for at least three generations, a similar disease phenotype in all members of the family and C-peptide levels persisting for a long time within reference values [1–3]. MODY verification is quite complicated, but it enables proper management of the disease, ensures adequate pregnancy follow-up and provides an opportunity to perform medical and genetic counselling of families [4–6].

Currently, mutations in 14 genes are known, which lead to the development of different MODY subtypes, all which differ in prevalence, clinical presentation and patient management [1, 7, 8]. Despite the significant variability in the frequency of individual forms of the disease, mutations in the genes of the nuclear factor of hepatocytes 1α (*HNF1A*) and glucokinase, leading to the development of the MODY 3 and MODY 2 subtypes, respectively, are prevalent in different populations [9]. These subtypes account for up to 90% of all MODY cases [10]. MODY 1 to 5 are the most studied and described in the literature. The remaining subtypes are very rare, and data on their prevalence and clinical course are limited.

In this report, we describe a clinical case of MODY 12 associated with a mutation in the sulphonylurea receptor 1 gene (*ABCC8*).

CASE DESCRIPTION

The patient A is a 28-year-old male. During the routine medical examination in September 2015, he complained of burning sensation, intense pain in the legs during the day, numbness of the toes, headaches and blurred vision.

The patient's case history revealed that in February 2014, he experienced severe dry mouth, thirst, frequent urination and weight loss (approximately 5 kg over 4 months), as well as intense headaches, the emergence of which were not associated with anything by the patient. Examination at his primary health care facility revealed fasting hyperglycaemia up to 24 mmol/L without ketosis, nonproliferative diabetic retinopathy (DR) and microalbuminuria. Tests for pancreatic islet cell antibodies and glutamate decarboxylase antibodies were negative. The patient's C-peptide level was 338 pmol/L (normal for patient was 298–2350 pmol/L), and glycated haemoglobin (HbA_{1c}) was 7.1%. Type 1 diabetes mellitus (DM) was diagnosed, and insulin therapy was prescribed, namely, glargine 100 U/mL 16 U before bedtime and lispro 4 to 6 U before the main meals (i.e. lunch and dinner). Ramipril 2.5 mg/day was also initiated.

In October 2014, the patient complained of visual deterioration; ophthalmoscopy revealed preproliferative DR and diabetic macular oedema of both eyes. At that time, panretinal photocoagulation of the retina of the right eye was performed, and in February 2015, the procedure was performed on the left eye.

As a result of the insulin therapy, the patient's body weight increased by 10 kg. Frequent mild hypoglycaemia was noted throughout the day; therefore, the insulin dose was gradually decreased. In June 2015, the patient's HbA_{1c} level was 5.1%. In July 2015, he had severe hypoglycaemia and was admitted to hospital, where the insulin therapy was cancelled. After the insulin was withdrawn, an increase in glycaemia to 15 mmol/L was noted, and it was recommended to resume the injections. Upon admission to the clinic of the Research Institute of Clinical and Experimental Lymphology, the patient received insulin glargine 13 U before bedtime and insulin lispro 4 U before lunch and dinner (insulin was not administered before breakfast because of low glycaemic levels). The daily insulin dose was 0.3 U/kg.

The case history indicated that the patient was the firstborn at 35 to 36 weeks gestation and with birth weight of 2500 g. Hydrocephaly was observed. At the age of 5 years, convulsive seizures lasting 1 to 2 min appeared, which were accompanied by short-term loss of consciousness. The seizures arose spontaneously once every 1 to 2 months and were self-limiting. The patient was examined by a neurologist, and electroencephalography and MRI of the brain were performed; no evidence of organic pathology or epilepsy was detected. The seizures stopped at the age of 9 years, and later, only the impairment of fine motor skills was observed.

Among the relatives of the proband, on his mother's side, DM was diagnosed in six people across three generations: the patient himself, his mother, her full sister and brother, and two sisters of the mother's mother (Fig. 1). The age of onset was approximately 40 years, and they all took oral antihyperglycaemics. The patient's mother had DM from the age of 43 years. At the time of the examination, she complained of dry mouth, her fasting

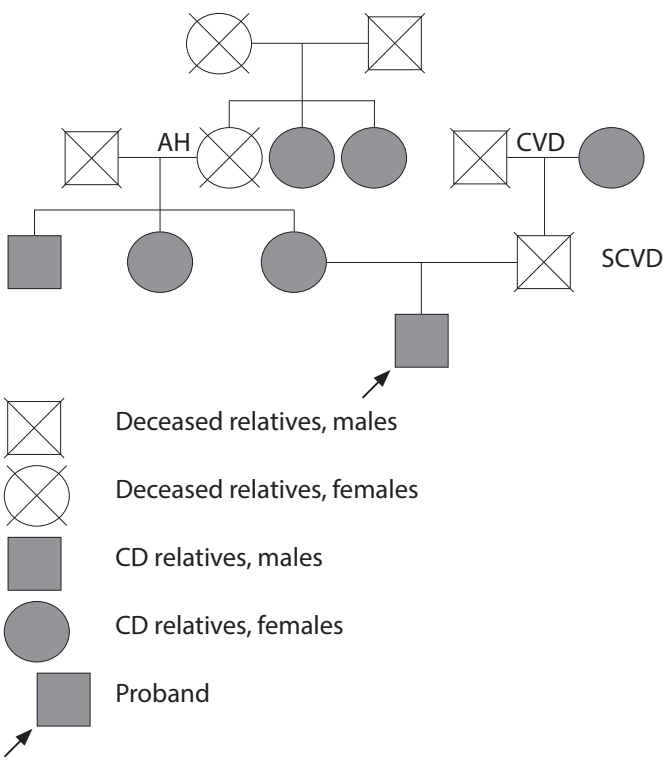

Fig. 1. Patient's family tree
Notes: AH–arterial hypertension, CVD–cardiovascular disease, SCVD–sudden cardiovascular death, RTA–road traffic accident.

blood glucose level was up to 7 mmol/L, postprandial glucose level was up to 11 mmol/L, HbA_{1c} was 8.1% and C-peptide level was 0.8 ng/mL (normal for her was 0.9 to 7.1 ng/mL). Her concomitant conditions included verified grade 1 arterial hypertension, dyslipidaemia with a predominance of low-density lipoprotein cholesterol and peripheral neuropathy. She took glimepiride 4 mg/day and metformin 2000 mg/day. The relatives on the father's side had cardiovascular disease (coronary heart disease and sudden death) in two generations.

Upon examination of the patient, his height was 165 cm, weight was 68 kg, body mass index was 25 kg/m2, pulse was regular at 88 beats/min, blood pressure was 140/85 mm Hg, and there were no signs of internal organ pathology. Blood chemistry revealed a moderate increase in the level of transaminases (ALT 78.6 U, AST 68.2 U), uric acid (422.1 μmol/L) and low-density lipoprotein cholesterol (3.41 mmol/L). Other indicators remained within normal limits. The HbA_{1c} level was 5.9%, C-peptide was 1.35 ng/mL (normal for patient was 0.9–7.1 ng/mL) and urinary albumin excretion was 57.3 mg/L.

With daily monitoring of the patient's blood pressure, average values of 157/96 mm Hg were recorded during the day, whereas those at night were 155/92 mm Hg; the time index of systolic and diastolic hypertension increased during the day (99% and 93%, respectively). Ultrasound of the heart revealed intact valves, two additional chords of the left ventricle and an ejection fraction of 62%. Ultrasonic Doppler examination showed atherosclerosis of the brachiocephalic arteries at the extracranial level and a haemodynamically insignificant plaque in the left common carotid artery with spread to the internal carotid artery. No abnormalities were found during the ultrasound examination of the thyroid gland, abdominal cavity, and kidneys. Electromyography revealed severe distal sensory neuropathy. An MRI of the brain revealed single small chronic nonspecific foci in the structure of the basal nuclei and in the white matter of the hemispheres, signs of atrophic changes in brain tissue in the periventricular white matter of the hemispheres of a dyscirculatory nature and reduction of blood flow in the right vertebral artery.

With insulin therapy with glargine 10 U in the evening and insulin lispro 4 U before dinner, the following glycaemic values were registered: 5.2 mmol/L at 08:00, 3.7 mmol/L at 11:00, 7.4 mmol/L at 13:00, 13.7 mmol/L at 17:00 and 7.6 mmol/L at 20:00.

Given the characteristics of the course of disease (familial aggregation of DM, frequent hypoglycaemia with the administration of small doses of insulin, intact level of C-peptide and absence of anti-islet antibodies), the presence of MODY was suggested. A whole-exome sequencing of genes associated with the known subtypes of MODY 1 to 14 was performed. The His321Pro missense mutation in the PAX4 gene was revealed (associated with MODY 9), as well as an Ala1457Thr mutation in the *ABCC8* gene (associated with MODY 12). The replacements were confirmed using Sanger automatic sequencing. The mutation of His321Pro in the PAX4 gene, identified in the heterozygous variant, is a high-frequency polymorphism and does not lead to the development of clinical manifestations. A mutation in position 1457 of the

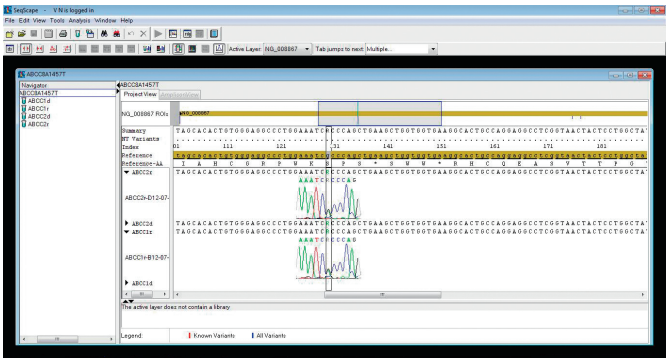

Fig. 2. Mutation of p.Ala1457Thr identified in the proband.

ABCC8 gene is rare, leading to replacement of alanine by tryptophan in the structure of the encoded protein (Fig. 2). The mother and uncle of the proband also exhibited the Ala1457Thr mutation in the *ABCC8* gene.

Using the PolyPhen-2 tool to predict the impact of the amino acid substitution on protein structure, we discovered a high probability of damaging effects of the Ala1457Thr mutation on the function of sulphonylurea receptor 1, the *ABCC8* gene product.

Considering the presence of dyslipidaemia in the patient, a molecular genetic study of a number of genes involved in the regulation of lipid metabolism was performed, namely, *APOA1, APOA2, APOA4, APOA5, APOB, APOC3, APOD, LDLR, LDLRAP1, LPL, PCSK9, SCARB1* and *SREBF2*. The Gly2Ser polymorphism in exon 1 of the *SCARB1* gene encoding the SRB1 protein, a high-density lipoprotein receptor as well as the nonsense mutation of Ser474Ter in exon 9 of the *LPL* gene encoding lipoprotein lipase can contribute to the development of dyslipidaemia in this patient.

After obtaining the results of the molecular genetic study, an attempt was made to cancel the patient's insulin therapy and gliclazide MB was administered at a dose of 60 mg/day. During his treatment with gliclazide MB for 1 week, significant glycaemic excursions were noted (3.6–12.9 mmol/L). Continuous glucose monitoring was conducted in real time using the Medtronic Paradigm MMT-722 system, and the results on days 4 to 7 of treatment are presented in Fig. 3.

Considering the patient's significant variability in glycaemia, episodes of hyperglycaemia and tendency to fasting hypoglycaemia, a further increase in the gliclazide dose seemed inappropriate. Therefore, the combination therapy of gliclazide MB 60 mg/day and dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, 10 mg/day was prescribed. On this treatment regimen, a

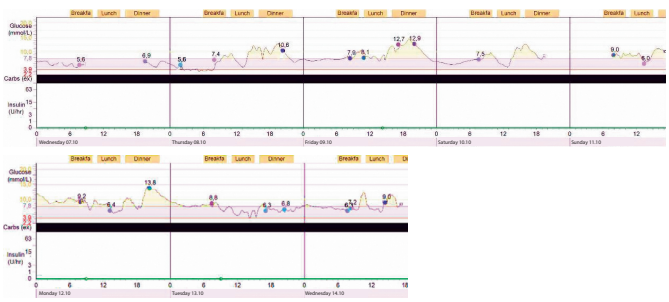

Fig. 3. Results of continuous monitoring of glycaemia in the patient while receiving gliclazide MB 60 mg/day (top panel) and while receiving the combination therapy (bottom panel).

decrease in the patient's glycaemic excursions was noted, and episodes of hypoglycaemia were not recorded.

After 6 months of therapy, the patient's HbA_{1c} level was 6.0%, plasma fasting glucose was 4.3 to 6.2 mmol/L and during the day random glucose was 6 to 7 mmol/L (self-monitoring glucose data from glucose metre). There was no decrease in glucose level below 3.8 mmol/L, and there were no clinical manifestations of hypoglycaemic conditions. The patient's body weight decreased by 4 kg. After 1.5 years, the patient continued to take the prescribed antihyperglycaemic therapy, and the target blood glucose levels were achieved.

Following verification of the proband's mother's mutation in the *ABCC8* gene, she also underwent corrective therapy: instead of glimepiride, gliclazide MB 60 mg/day was prescribed, and metformin was cancelled. While on monotherapy, the patient's mother did not achieve the target values of carbohydrate metabolism; hypoglycaemia was noted with increased doses of glimepiride. Considering the positive effect of glimepiride in combination with dapagliflozin in the proband, a drug in the SGLT2 inhibitor class was also recommended for his mother; therefore, she started to take empagliflozin 25 mg/day in addition to the gliclazide MB 60 mg/day. After a month, her level of glycaemia was within target values, and after 3 months, her HbA_{1c} level was 7.4%.

DISCUSSION

The case presented here demonstrates the special aspects of the course of DM associated with a rare mutation in the *ABCC8* gene encoding sulphonylurea receptor 1. As is well known, type 1 DM, type 2 DM or monogenic forms of DM can all be verified in young patients with impaired carbohydrate metabolism. In this patient, at the onset of disease, some symptoms characteristic of the most common types of DM were absent. The absence of ketonuria, ketoacidosis and antibodies to pancreatic islet cells and glutamate decarboxylase was not quite typical as they are detected in more than 70% of cases during the manifestation of type 1 DM *[*11]. Additionally, the C-peptide level was normal; however, this can be observed in the early stages of the clinical course of type 1 DM. The patient was not obese and had no clinical manifestations of insulin resistance, such as acanthosis nigricans, which are characteristic of early onset type 2 DM *[*6]. The possibility of MODY was indicated by the presence of DM in at least three generations of the patient's family, the sustained C-peptide secretion and the obvious signs of insulin overdose with administration of relatively small doses during year 2 of the clinical course. The time of onset of hyperglycaemia in this patient is unknown, and an asymptomatic disease course before the clinical onset cannot be ruled out.

A specific feature of DM in the patient we observed was the relatively late (at the age of 27 years) clinical manifestation of the disease. This was accompanied by an increase in glycaemia to high values, the absence of ketosis, the development of microvascular complications (retinopathy, nephropathy and neuropathy) after a short duration of the disease, rapid progression of DR, the combination of diabetes with arterial hypertension, dyslipidaemia, hyperuricaemia, neurological pathology and early (relative to age) signs of atherosclerosis of the brachiocephalic arteries. The literature does not describe diabetic complications associated with MODY 12; however, in this case, early microvascular complications were diagnosed in the patient, the development of which may be associated with changes in lipid metabolism genes. Missense replacement of rs4238001 (p.Gly2Ser) in the SCARB1 gene in the homozygous variant for the rare T allele (MAF = 0.06) was verified in the patient. Using the online PolyPhen-2 programme for predicting the impact of mutations on protein structure, there was a high probability (PolyPhen-2 score of 1.000) of detrimental effects of rs4238001 on the function of the protein encoded by the SCARB1 gene. The SCARB1 gene product, scavenger receptor class B member 1, is one of several cell surface receptors that play an important role in regulating lipoprotein metabolism by participating in the transport of cholesterol esters *[*12]. The SCARB1 gene polymorphism is associated with plasma levels of high-density lipoprotein cholesterol, triglycerides and apolipoprotein B, and mutations in the gene can cause dyslipidaemia *[*13]. According to the literature, nonsense replacement in the *LPL* gene (rs328, p.Ser474Ter) is associated with the development of hypertriglyceridaemia *[*14]. Dyslipidaemia in a patient may occur because of structural changes in the genes of lipid metabolism and lead to a more severe course of diabetes and early development of cardiovascular complications. Changes in lipid metabolism genes were also detected in our patient's mother.

The molecular genetic study we performed revealed a mutation in the *ABCC8* gene, which led to replacement of alanine by tryptophan in the sulphonylurea receptor 1 protein encoded by this gene. This protein is the second subunit of the ATP-sensitive potassium channels of the pancreatic β-cells. The first subunit, the Kir6.2 protein, is encoded by the *KCNJ11* gene associated with the development of MODY 13. Four Kir6.2 subunits form the pores of the channel, and each of them is associated with the sulphonylurea receptor 1 subunit, which regulates the operation of the channel *[*15]. Closing the ATP-sensitive potassium channels is necessary for glucose-stimulated insulin secretion by β-cells, but opening of these channels inhibits insulin secretion. The ATP-dependent potassium channel encoded by the *KCNJ11* and *ABCC8* genes is a therapeutic target for sulphonylurea drugs *[*16]. Most mutations in these genes lead to the development of neonatal DM and do not differ in clinical manifestations *[*17]. Some mutations in *ABCC8* cause the development of hypoglycaemic hyperinsulinism in infancy *[*18].

ABCC8 mutations are associated with the development of MODY 12, type 2 DM, gestational DM and neonatal DM. The literature describes isolated cases of *ABCC8*-related MODY, which differ in clinical course. The mutation we detected in the *ABCC8* gene was present in three generations of the same family, and the clinical presentation of these family members resembled that of glucokinase deficiency (MODY 2), which includes 'mild' hyperglycaemia that does not require medical treatment *[*19]. A previously published clinical case is

of interest as childhood convulsions of unknown origin occurred in that patient's father, who had MODY 12. XXXX also had verified DM associated with a mutation in the *ABCC8* gene at the age of 28 years [20]. The patient we present also had a convulsive syndrome in childhood, although epilepsy and other organic neurological diseases were ruled out. Convulsions in combination with neonatal diabetes are the clinical manifestations of developmental delay, epilepsy and neonatal diabetes (DEND syndrome) [21]. This syndrome is associated with mutations in the *KCNJ11* gene. With pathological changes in this gene, the function of Kir6.2 in the ATP-sensitive potassium channels located not only in the β-cells of the pancreas but also in neurons is impaired, which manifests in neurological symptoms. In the case of mutations in *ABCC8*, channel dysfunction is also observed, but it occurs from the sulphonylurea receptor 1 subunit located in the pancreas and neurons. The presence of seizures in MODY 12 may be a consequence of a mutation in the *ABCC8* gene and, like in DEND syndrome, appears in combination with the development of DM, but at a later age. However, this assumption requires further study.

Carriers of mutations in the *ABCC8* gene are usually sensitive to sulphonylurea drugs, consistent with the effect of this class of drugs on sulphonylurea receptors, whose function is impaired in MODY 12 [18]. Several clinical cases have been described in which hypoglycaemia in response to small doses of insulin was observed in MODY 12 patients, and they all had high sensitivity to sulphonylurea drugs [22, 23]. In the patient we describe, treatment with gliclazide MB within the therapeutic range was quite effective but was accompanied by significant glycaemic variability (GV). Accumulated evidence suggests that high GV is a risk factor for the development of microvascular complications and macroangiopathies [24]. Given the rapid development of vascular lesions in the patient, it was important to avoid episodes of hypoglycaemia and hyperglycaemia, thereby reducing GV. Thus, we needed a second antihyperglycaemic drug with minimal risk of hypoglycaemia that reduced GV and had an insulin-independent mechanism of action [25]. All these characteristics are intrinsic to SGLT2 inhibitors, such as dapagliflozin [26, 27]. Therefore, a combination of gliclazide and dapagliflozin was prescribed to the patient, which had a positive effect. The patient's mother also achieved target values for carbohydrate metabolism when taking a sulphonylurea drug and SGLT2 inhibitor. Previously, the use of SGLT2 inhibitors among monogenic forms of DM was described only in MODY 3, and it was recommended they be prescribed with care since the mutation in the *HNF1A* gene associated with MODY 3 causes the renal threshold for glucose to be reduced and the administration of this class of drugs may cause dehydration and urogenital infection [28]. As far as we know, this is the first report in the Russian literature of the use of an SGLT2 inhibitor in the treatment of MODY patients. The insulin-independent mechanism of action of SGLT2 inhibitors makes these drugs a very promising treatment for patients with genetically determined β-cell dysfunction without ketoacidosis when sulphonylurea drugs prove inefficient or ineffective.

CONCLUSIONS

This case demonstrates the features of the clinical course of DM associated with a mutation in the *ABCC8* gene encoding sulphonylurea receptor 1 (MODY 12) and the tailored treatment that was necessary. A personalised approach to diagnosis and treatment is especially important in identifying and managing nonclassical DM in young people.

ADDITIONAL INFORMATION

Financing of the work. Molecular genetic studies were performed at the Research Institute of Therapy and Preventive Medicine, Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, at the expense of a grant from the Russian Science Foundation (No. 14-15-00496-P). The clinical examination of the patient was performed at the Research Institute of Clinical and Experimental Lymphology, Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, at the expense of the state task.

Conflict of interest. The authors declare no conflict of interest associated with the publication of this article.

Patient consent. The work conducted complies with GCP standards. The protocol and the patient informed consent form for participation in the study were reviewed and approved by the Ethical Committee of the Research Institute of Therapy and Preventive Medicine, protocol No. 2 dated 11.02.2014. Patients voluntarily signed informed consent to the publication of personal medical information in the journal 'Diabetes mellitus'.

Contribution of authors. A.K. Ovsyannikova was engaged in collection and processing of material, analysis of the data obtained, and writing the text. O.D. Rymar created the concept and design of the study and edited the text of the manuscript. E.V. Shahtshneider performed molecular genetic study and wrote the text. V.V. Klimontov conducted clinical examination of the patient and wrote the text. E.A. Koroleva performed clinical examination of the patient and wrote the text. M.I. Voevoda created the concept and design of the study.

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ЦИТИРОВАТЬ:

Овсянникова А.К., Рымар О.Д., Шахтшнейдер Е.В., Климонтов В.В., Королева Е.А., Воевода М.И. Сахарный диабет, связанный с мутацией гена ABCC8 (MODY 12): особенности клинического течения и терапии // *Сахарный диабет*. — 2019. — Т. 22. — №1. — С. 88-94. doi: 10.14341/DM9600

TO CITE THIS ARTICLE:

Ovsyannikova AK, Rymar OD, Shakhtshneider EV, Klimontov VV, Koroleva EA, Voevoda MI. Diabetes mellitus associated with the mutation of the ABCC8 gene (MODY 12): features of clinical course and therapy. *Diabetes Mellitus*. 2019;22(1):88-94. doi: 10.14341/DM9600