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 cotransporter-2 (SGLT2) inhibitor dapaglifl ozin 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
Maturity-onset diabetes of the young (MODY) is a heterogeneous group of diseases that occur as a result of gene mutations that cause pancreatic β-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 of 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 (HbA1c) 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 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.

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 HbA1c 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...
blood glucose level was up to 7 mmol/L, postprandial glucose level was up to 11 mmol/L, HbA1c 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 HbA1c 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 periventricular white matter of the hemispheres, signs of atrophic changes in brain tissue in the structure of the basal nuclei and in the white matter of the brain 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.

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).

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

After 6 months of therapy, the patient’s HbA1c 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 HbA1c 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 

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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 ß-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 ß-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

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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. Shahstshneider 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.