MODY3 — one of the most common subtypes of MODY. Obesity in MODY3 patients modifies the disease course and complicates diagnostics at the clinical stage.

A proband was diagnosed with type 2 diabetes mellitus (T2DM) at the age of 12 years; metformin therapy was used. A family history of DM involves three generations: the mother, aunt, and maternal grandfather have suffered from insulin-dependent DM since the age of 23, 22, and 40 years, respectively. The patient was examined at the age of 14 years. Obesity was present (SDS BMI 2.3). The insulin and C-peptide levels were 4.4 μU/mL and 1.5 ng/mL, respectively. The HbA1c level was 7.3%. Under glucose load, glycemia reached diabetic values; hyperinsulinemia and insulin resistance were not detected. Specific pancreatic antibodies were absent. Metformin was discontinued, and a sulfonylurea (SU) drug was prescribed, which had a positive effect.

The presence of concomitant obesity in the patient significantly complicates the differential diagnosis, and only a careful comprehensive analysis of clinical and laboratory parameters and a family history makes it possible to suspect the diagnosis of MODY3 (requiring subsequent molecular genetic verification) and prescribe pathogenetic therapy.

**RELEVANCE**

MODY (an acronym which stands for *maturity-onset diabetes of the young* - adult-type diabetes in young people) is a rare form of diabetes mellitus (DM) with autosomal dominant inheritance, whose development is associated with mutations of various genes. There are 13 known MODY subtypes.

MODY3 is one of the most common subtypes; according to various studies, it accounts for 31–62% of all types of MODY [1—3]. In Russia, it ranks second after MODY2 [4] in terms of its incidence in the pediatric population. The development of MODY3 is associated with inactivating heterozygous mutations in the gene of the hepatocyte nuclear factor 1A (*HNF1A*) [5].

Main clinical features of MODY3 include: the onset of DM at a young age (younger than 25 years), the absence of insulin dependence 3 years after the onset of the disease, the absence of ketoacidosis, satisfactory glycemic control with a small insulin dose, detectable C-peptide level, high concentration of DM in the family (in two or more generations), absence of specific pancreatic autoantibodies (AT), characteristic for type 1 diabetes (DM1), glycosuria with glycemia <10 mmol/L, severe sensitivity to sulfonylurea (SU) drugs, absence of pronounced obesity and insulin resistance (IR) [6].

However, due to the increasing rate of obesity in the population, one should expect not only an increase in the incidence of type 2 diabetes mellitus (T2DM), but also higher incidence of a combination of obesity with various forms of diabetes. Moreover, in a patient with MODY3, obesity modifies the course of the disease and complicates diagnosis at the clinical stage, which results in misdiagnosis of patients with MODY3 as patients with adult-type diabetes in young people.
T2DM and prescription of pathogenetically unfounded and ineffective therapy.

DESCRIPTION OF THE CASE

A 14-year-old boy was admitted to the children’s department of the Scientific Research Institute of Pediatric Endocrinology with complaints of an increase in glyceremia up to 15 mmol/L and obesity.

The child from the first pregnancy which proceeded physiologically, from the first independent delivery at term. At birth his weight was 4400 g (SDS=1.8), length of the body was 57 cm (SDS=3.4). Early psychomotor development was unremarkable.

Medical history. From the age of 8, the child was observed by an endocrinologist due to obesity. (BMI 23.8 kg/m², SDS BMI +3.1). Oral glucose tolerance test (OGTT) revealed minor fasting hyperglycemia (5.9 mmol/L) and normoglycemia after 120 minutes (4.2 mmol/L).

At the age of 12, diabetic level of HbA1c was detected (7.3%). There were no clinical symptoms of DM. Fasting C-peptide and insulin levels were within the normal range — 521 pmol/L (norm: 264–1390 pmol/L) and 7.9 μU/mL (2.3–26.4 μU/mL), respectively. ICA was negative. Urine glycospiruria ++++. Considering obesity (BMI 28.4 kg/m², SDS BMI +2.7) and the absence of AT, type 2 diabetes was diagnosed, and metformin was prescribed at a dose of 1700 mg/day. One year after the start of metformin therapy, HbA1c levels remained elevated (7.3%). Glucospiruria was periodically observed in urine.

The patient was examined in FGBU ENC at the age of 14 years, 2 years after the diagnosis of type 2 diabetes.

The family medical history showed a remarkably high concentration of diabetes. The mother (36 years old) was diagnosed with non-obese DM1 at the age of 23 and was insulin therapy at a dose of 1 U/kg/day. Diabetes was diagnosed after the first pregnancy; there were no data on the state of carbohydrate metabolism during the first pregnancy. There were no data on the clinical course of diabetes and complications for the child (the patient accompanied by his grandmother at the admission). The maternal aunt (30 years old) had insulin-dependent diabetes without obesity since she was 22. The maternal grandfather had insulin-dependent diabetes from the age of 40, underwent high amputations of both limbs, and died at the age of 61. The great-grandfather had DM. The family tree is presented at Fig. 1.

Results of physical examination and laboratory and instrumental studies

Physical examination. Height 186 cm (SDS=2.8), body weight 95 kg, BMI 27 kg/m² (SDS=2.3). No acanthosis nigricans. BP 120/80 mmHg.

Laboratory data. Minor fasting hyperglycemia (5.8 mmol/L). Insulin and C-peptide levels within low normal ranges. HbA1c level was 7.3%. After a starchy break, fasting at 5 XE (after the cancellation of metformin for 3 days) (Table), the level of glycemia reached 15.3 mmol/L, the maximum level of insulin was 19.8 μU/mL, C-peptide was 4.5 ng/ml. No insulin resistance was detected: HOMA index 1.1 (norm: <3.2).

Lipid profile values were within the reference ranges: total cholesterol — 4.45 mmol/L (norm: 3.3–5.2 mmol/L), HDL cholesterol — 1.04 mmol/L (0.9–2.6 mmol/L), LDL cholesterol — 2.95 mmol/L (1.1–3.0 mmol/L), triglycerides — 1 mmol/L (0.1–1.7). Glycosuria. AT to glutamatecarboxylase (GAD) - 0.4 U/L (0–1 U/L), AT to insulin (IAA) - 2.03 U/L (0–10 U/L), AT to tyrosine phosphate (I2A) <8 U/L (0–10 U/L), AT to islet cells of the pancreas (ICA) - 0.62 U/L (0–1 U/L). HLA-typing revealed one predisposing and one neutral haplotype.

Metformin therapy was discontinued without worsening of the glycemic indices (Fig. 2).

The heredity of diabetes, as well as the absence of clinical and laboratory signs of IR and metabolic syndrome, low basal and stimulated insulin levels and lack of effect from metformin therapy put the diagnosis of diabetes mellitus in doubt. MODY was suspected. The clinical course of diabetes, a diabetic type of sugar curve, a high level of HbA1c, a history of glycosuria, insulin-dependent diabetes in relatives of the first and second degrees of kinship corresponded primarily to MODY3. A SU drug, Glimepiride, was prescribed as a trial at a dose of 1 mg/day with a positive effect (Fig. 2).

After 3 months of glimepiride therapy, the level of HbA1c decreased to 6.0%, there were no incidents of hypoglycemia.

A molecular study of the HNF1A gene revealed hetereozygous p.P291fs mutation. Therefore, the diagnosis of MODY3 was confirmed.

The further molecular genetic study was conducted on maternal half-siblings who were 1 year and 6 years of age, respectively, and had no carbohydrate metabolism disorders. Similar HNF1A mutation was detected in both. Therefore, MODY3 has been diagnosed at pre-clinical stage. The mother had the same mutation. A switch to SU drugs for the mother was postponed due to breast-feeding. No biological material for the molecular genetic study of the maternal aunt was available.

DISCUSSION

This clinical case shows that verification of the nosological form of diabetes plays the crucial role in choosing the right therapeutic tactics. Moreover, the diagnosis of the monogenic form of diabetes makes it possible to predict the course of diabetes, as well as to verify the diagnosis at the preclinical stage for the relatives in the family. MODY3 is characterized by a progressive decrease in insulin secretion response to increased glycemia. A specific feature of MODY3 is glycosuria in the compensation of carbohydrate metabolism and severe sensitivity to SU
Fig. 1. The proband’s family tree.

Fig. 2. Glycemia indicators in various treatment regimens.
Glycemia, insulin, C-peptide in the course of the test with a starchy breakfast load at 5 XE

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose (mmol/L)</th>
<th>Insulin (μU/mL)</th>
<th>C-peptide (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.8</td>
<td>4.4</td>
<td>1.5</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>12.3</td>
<td>2.3</td>
</tr>
<tr>
<td>60</td>
<td>14.7</td>
<td>9.9</td>
<td>3</td>
</tr>
<tr>
<td>90</td>
<td>15.8</td>
<td>19.6</td>
<td>4</td>
</tr>
<tr>
<td>120</td>
<td>15.3</td>
<td>19.8</td>
<td>4.5</td>
</tr>
</tbody>
</table>

drugs: hypoglycemia occurs even when low doses of the drug are administered.

The absolute criterion for the diagnosis of MODY3 is the presence of a mutation in HNF1A gene, therefore it is important to promptly refer the patient to a molecular genetic study. Together with HNF4A and HNF6, HNF1A gene forms a network of transcription factors that regulate the development and metabolic functions of hepatocytes and pancreatic islet cells [7].

Diagnosis of this disease is complicated by the polymorphism of its clinical manifestations. According to foreign studies, 80—94% of MODY cases are not diagnosed or are observed as T1DM or T2DM [1, 3]. At the pre-molecular genetic stage, it is important to suspect this form of MODY, which is possible with careful analysis of the differential diagnostic criteria for MODY3 that currently include heredity of diabetes, lack of pancreatic antibodies specific for diabetes, preserved C-peptide secretion, and absence of obesity. All the above criteria are not absolute, and each case requires an individual approach [4].

In the described case, the boy’s carbohydrate metabolism disorder was initially mistakenly interpreted as T2DM, which was due to the presence of obesity. The presence of diabetes in the mother, who was on insulin therapy, also allowed to assume DM1. Even though the absence of AT, the identification of the HLA genotype of the average risk of T1DM, the absence of insulin-dependence with a 2-year duration of the disease did not exclude the diagnosis of T1DM, they reduced its likelihood. The child did not have IR and had relatively low levels of basal and stimulated insulin (maximum 19.8 μU/mL). With T2DM, IR is present in 68.1—81.3% of cases, and the stimulated insulin level with a disease duration of 3 years reaches 80.7 μU/mL [8]. When combined with the absence of a positive effect from metformin therapy, the diagnosis of T2D was questionable. The autosomal dominant nature of the inheritance of diabetes in the family attracted attention (only 6 people with diabetes on the same line), so MODY was suspected. Clinical features of diabetes, namely, periodic glucosuria, diabetic type of sugar curve, the progression of carbohydrate metabolism disorders, were more consistent with MODY3. This diagnosis was confirmed by a molecular genetic study.

MODY3 is a progressive form of diabetes. In early childhood, carbohydrate metabolism disorders are absent in carriers of the HNF1A gene mutation, therefore, when examining a proband at the age of 8 years and its half-siblings at the age of 1 year and 6 years, no carbohydrate metabolism disorders were detected. With age, glycemia increases, and although it may remain normal for a long time under fasting conditions, HbA1c and glycemia will be elevated under load at the initial stage of the disease [9-11]. In the future, glycemia under load will reach diabetic values [4, 10]. A characteristic feature of this MODY subtype is glucosuria, even when compensating for carbohydrate metabolism, which is due to a decrease in the expression of sodium-dependent glucose transporter SGLT2 [12]. MODY3 is characterized by macro- and microvascular complications. The examination of patients with MODY3 at an age of (on average) 46.3 ± 17.4 years and with an average duration of diabetes of 17 ± 12.8 years shows that proliferative retinopathy occurs in 13%, microalbuminuria, in 19%, neuropathy, in 29%, cardio-vascular diseases, in 16% of cases [13]. The rather high incidence of diabetic complications substantiates the need for careful compensation of carbohydrate metabolism.

MODY3 verification is extremely important because it allows prescription of an effective pathogenetically based therapy. During the debut of diabetes with MODY3, compensation of carbohydrate metabolism can be achieved with a diet, but in old age it may even require insulin [14—16]. In MODY3, SU drug has the best sugar-reducing effect; their administration reduces the level of HbA1c by 1.5%. Switch to SU drugs is possible at all durations of the disease [15—18]. Our patient was able to achieve compensation of carbohydrate metabolism after prescription of a small dose of glimepiride. HbA1c levels decreased by 1.3%. The question of transferring the proband’s mother to the SU drugs was postponed due to breastfeeding.

**Conclusion**

Currently, special attention is paid to personalized medicine and an individual approach to each patient. The presented clinical case clearly demonstrates that the presence of concomitant obesity in the patient significantly complicates the differential diagnosis, and only a careful comprehensive analysis of clinical and laboratory parameters and a family history makes it possible to suspect the diagnosis of MODY3 (after molecular genetic verification) and prescribe pathogenetic therapy.

**Supplementary Information**

The patient’s consent. The patient provided written consent to the publication of data obtained during the study.

**Conflict of interest.** The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.
Shields BM, Hicks S, Shepherd MH, et al. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetesologia. 2010;53(12):2504-2508. doi: 10.1007/s00125-010-1799-4


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