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MOLECULAR GENETIC AND CLINICAL VARIANTS OF MODY2 AND MODY3 IN CHILDREN IN UZBEKISTAN

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Annotation

For a long time, it was believed that only type 1 diabetes mellitus (DM1) was characteristic of childhood. However, it is now known that other types of diabetes occur in childhood and adolescence, among which the most common are type 2 diabetes (T2DM), as well as monogenic forms of diabetes, which include MODY (maturityonset diabetes of the young - adult diabetes type in young people), neonatal diabetes and some other forms. In most European countries, T1DM accounts for more than 90% of diabetes cases in childhood and adolescence, with incidence ranging from 0.1 to 57.6 per 100,000 children [1]; in the Republic Uzbekistan it is 12.43 per 100,000 children [2]. T2DM and monogenic forms of diabetes are much less common. The prevalence of monogenic diabetes in the UK is 10.8:100,000 [3]. Recent independent studies have shown that in children and adolescents. The increasing frequency of monogenic forms of diabetes is 1.1–4.2% of all forms of diabetes, the prevalence in the population is 2.1–4.6:100,000 [4–6]. To date, 13 genes are known that lead to the development of MODY. The most common forms of this pathology are MODY2 and MODY3, which are caused by mutations in the genesGCKAndHNF1arespectively. The "gold standard" for diagnosing MODY is the identification of mutations through molecular genetic testing. At the stage of clinical examination, it is important to suspect this form of diabetes based on the characteristics of the disease in order to refer the patient for a molecular genetic study. The clinical course may not fit into the classical characteristics of this form of diabetes; only 50% of patients with genetically confirmed MODY have a course of the disease that meets its classical criteria [3]. It remains relevant to study the variability of the clinical course and laboratory characteristics of MODY, primarily its most common subtypes - MODY2 and MODY3.

Keywords

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diabetes mellitus, MODY2, MODY3, C –peptide, insulin, manifestation, remission, hyperinsulinemic, normoglycemic

Purpose of the study— study the molecular genetic and clinical features of MODY2 and MODY3 in children.

Material and methods. Molecular genetic study of genes *GCK*And*HNF1a*was carried out in 169 patients under the age of 18 years, in whom glycemic disorders were clinically interpreted as manifestations of MODY - mild manifestation, long period of clinical and laboratory remission (no need for insulin or need less than 0.4 units/kg), preserved secretion of C -peptide with a disease duration of more than 2-3 years and/or a family history of diabetes of the autosomal dominant type. MODY2 was diagnosed when a heterozygous mutation in the gene was detected*GCK*, MODY3 - heterozygous mutation in the gene*HNF1a*. Molecular genetic study of the gene*GCK* carried out on 10 siblings and 21 parents of probands with verified MODY2 and gene*HNF1a*— 3 siblings and 9 parents of probands with MODY3. Molecular genetic research was carried out by direct sequencing of exons 1a, 2-10 and adjacent sections of gene introns *GCK*, exons 1-10 and adjacent regions of gene introns*HNF1a*. Genomic DNA was isolated from peripheral blood using QIAamp DNA blood kits (Qiagen, USA). With PCR amplified exon sequences after purification (QIAquick PCR Purification kit, Qiagen, USA), an elongation termination reaction was performed (Big Dye Terminator Cycle Sequencing kits V1.1 Ready Reaction, ABI PRISM/PE Biosystems, USA), the reaction product was purified and analyzed using capillary electrophoresis (ABI PRIZM 310 Genetic Analyzer, ABIPRISM/PE Biosystems, USA).

Results. The diagnosis of MODY2 was verified in 85 people (62 probands, 5 siblings and 18 parents), MODY3 - in 27 people (18 probands, 1 sibling and 8 parents). The ratio of MODY2 to MODY3 in probands was 3.4:1. In the group of patients with MODY2, boys predominated, their share was 61.2% versus 31.6% in the group of patients with MODY3 (p<0.05). In singleton pregnancies at a gestational age of 38–41 weeks (92.5%), the average birth weight was lower in patients with MODY2 - 3140±500 g versus 3640±500 g in MODY3 (R<0.05), the average body length did not differ (51.3±2.3 and 52±2.2 cm, respectively).*Diagnosis of diabetes mellitus.*Disorders of carbohydrate metabolism in MODY2 were diagnosed earlier than in MODY3 - the median age was 7.8 years (4.0; 10.5) versus 11.8 years (9.7; 13.5) (p<0.01). In persons with MODY2, in 9 (13.4%) cases, carbohydrate metabolism disorders were detected before the age of 1 year

(minimum age of diagnosis - 1 month). The minimum age of diagnosis for MODY3 is 8 years. Diagnosis was random (during clinical examination or examination for a concomitant disease) in 75.8% for MODY2 and 55.6% for MODY3 (p>0.05); in 11.1% of MODY3 cases, the reason for examination was detected glycosuria (p<0.01). The examination was carried out in connection with heredity aggravated by diabetes in 16.1% of cases with MODY2 and in 27.7% with MODY3 (p>0.05). Clinical manifestations of diabetes occurred only in 8.1% of patients with MODY2 and in 16.7% with MODY3 (p>0.05). The degree of disturbances in carbohydrate metabolism was less in MODY2: the level of fasting glycemia was 6.8 mmol/l (6.5; 7.4) versus 7.7 mmol/l (6.9; 9.3) in MODY3 (p<0.01), HbA1c level - 6.5% (6.1; 6.7) versus 6.8% (6.5; 7.9) (p<0.05). At initial diagnosis, insulin was prescribed in 3% of cases with MODY2 and in 27.7% with MODY3 (p<0.01). Clinical and laboratory characteristics of the patients are presented. The median age of patients at examination was 10.6 years (7.8; 15) in MODY2 and 14.4 years (11.3; 17.5) in MODY3. Disease duration: 2.0 years (0.7; 4.5) for MODY2 and 2.9 years (1.0; 4.1) for MODY3. Patients with MODY3 were more likely to be obese (SDS BMI ≥2) (33.3%) than those with MODY2 (8.6%) (p<0.05). In the Russian population, obesity occurs in 5.5% of children living in rural areas and 8.5% in cities [7]. The HbA1c level below the diagnostic level (<6.5%) was determined in 41.3% of patients with MODY2, and in 45% with MODY3, which indicates insufficient diagnostic information value of this indicator in children and adolescents with MODY. The median fasting glucose level was higher in patients with MODY2 [6.6 mmol/l (6.0, 7.0)] than in MODY3 [5.5 mmol/l (5.0, 6.8)] (p<0.05). At the same time, a normal level of fasting glycemia was determined in 12.1 and 58.8% (p<0.01), impaired fasting glycemia - in 58.6 and 35.3% of patients (p>0.05), diabetic level - in 29.3 and 5.9% of children (p<0.05) at MODY2 and MODY3, respectively. The median stimulated glycemic level in MODY2 [9.4 mmol/l (8.3, 10.9)] was lower than in MODY3 [14.3 mmol/l (12.4, 15.4)] (p<0.01). It should be noted that in 21.6% of children with MODY2 the level of glycemia at 120 min of the test reached diabetic values and in 66.7% corresponded to impaired carbohydrate tolerance; in 11.7% it was normal. In MODY3, the glycemic level during OGTT reached diabetic values in all patients. In MODY2, in 22.4% of cases, all indicators of carbohydrate metabolism (HbA 1c level, fasting glycemic level and at the 120th minute of the test) were below diabetic values. Basal insulin and C-peptide levels were not significantly different between MODY2 and MODY3. Stimulated insulin level and C-peptide at the 60th minute of the test were higher in patients with MODY2. Insulin resistance

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(HOM index>3.2) was detected in 11.7% of patients with MODY2 and in 11.1% with MODY3.

Discussion. Currently, it is believed that monogenic diabetes accounts for 1–4% of all forms of diabetes among children and adolescents [4–6]. MODY is one of the most common forms of monogenic diabetes. This form includes non-immune cases of diabetes with an autosomal dominant type of inheritance, which are based on mutations in various genes. The clinical picture of MODY is variable both among subtypes and within each of them: from asymptomatic carriers of the mutation to insulin-requiring diabetes. The most common and studied are MODY2 and MODY3. For the first time in Uzbekistan, a literature review on MODY was published in 2000 [27]. The prevalence of MODY in Russia is unknown; currently, small groups of patients with this type of diabetes have been described: the first cases of MODY2 were described in 2009 in 5 families with diabetes [28], 9 cases of MODY3 were identified in 3 families [29], an analysis of 18 probands was published with MODY3 [30], and individual clinical cases have also been described [31, 32]. Our study is the largest of those presented previously. The development of MODY2 is caused by inactivating mutations in the gene*GCK*. The connection between such mutations and the development of β-cell dysfunction was described in 1992 [33], and by 2009, 620 mutations in this gene had been described [15]. Gene*GCK*located on chromosome 7, consists of 12 exons, is expressed in the pancreas, liver, brain, and intestinal endocrine cells [34] and encodes glucokinase, a key regulatory enzyme of β-cells that catalyzes the first reaction of the glycolytic metabolic pathway and ensures the phosphorylation of glucose. Glucokinase plays a critical role in the regulation of insulin secretion, it is the link between the level of glycemia and the onset of insulin secretion, it is also called the glucose sensor in β-cells (the rate of glucose phosphorylation in cells changes depending on the concentration of glucose in the blood) [35]. Heterozygous inactivating mutations in*GCK*lead to an increase in glycemic levels, at which insulin is secreted, which is the main cause of hyperglycemia in MODY2 [36]. In the gene*GCK*no frequent mutations were identified; each of them was identified predominantly in the aquatic family. We identified 30 previously undescribed mutations, and the p.C372X mutation was identified in two probands with diabetes. MODY3 is caused by mutations in the gene*HNF1a*. In 1996, K. Yamagata et al. [22] first reported that the gene*HNF1a*, encoding the transcription factor HNF1A, is associated with the development of MODY3 [26]. Gene*HNF1a*mapped to the q arm of chromosome 12 and consists of 10 exons encoding 631 amino acids. It is expressed in various tissues, such as liver, kidney, intestine, and pancreas [37]. In the pancreas, HNF1A

is involved in the embryonic development of islets [38], and in mature β-cells it regulates the expression of many genes involved in glucose metabolism and transport (including by regulating pyruvate kinase, the glucose transporter GLUT2), and also regulates the expression of the insulin gene and key enzymes of glucose metabolism in mitochondria [38–40]. The most common mutation is p.P291fs in the polycytosine tract [41]. In our study, this mutation was also the most common.,detected in 27.8% of cases. The ratio of MODY2 and MODY3 is different in different populations. Among the adult population, as a rule, there is a predominance of MODY3 [42]. In Poland, the frequency of MODY2 is 83% of all cases of monogenic diabetes [6], in the USA, among patients under the age of 20 years, MODY2 accounts for 30% of all cases of MODY, MODY3 - 55% [4], in Norway the frequency of MODY2 is 35%, MODY3 - 58% [5]. In our study, MODY2 was 3.4 times more common in childhood and adolescence than MODY3. According to the literature [43], the median age for diagnosis of MODY3 is 18–25 years. In children with a mutation in the gene*HNF1a*up to 10 years, as a rule, carbohydrate metabolism disorders are not detected. In our study, the median age of diagnosis of carbohydrate metabolism disorders was 11.8 years. According to the literature [44], at the onset of diabetes in patients with MODY3, fasting normoglycemia is more often observed, and during OGTT - an increase in glycemia by 4.5 mmol/l or more. Fasting blood glucose levels gradually increase as the disease progresses [45]. In carriers of inactivating mutations in the gene*GCK*Fasting hyperglycemia is detected from birth, but the degree of carbohydrate metabolism disturbance does not progress with age [46]. In our MODY2 group, 13.4% of patients were diagnosed with carbohydrate metabolism disorders before the age of 1 year, also without significant progression in the degree of carbohydrate metabolism disorders. Taking this into account, it can be assumed that the ratio of the two subtypes of diabetes among people over 18 years of age will shift towards MODY3. The criteria for selecting patients for molecular genetic research play an important role in determining the ratio of MODY subtypes. When including patients with a degree of carbohydrate metabolism disorder that meets the criteria for a diagnosis of diabetes, many MODY2 cases will not be verified. The estimated prevalence of MODY2 has been shown to be greatly underestimated. Of 5,500 pregnant women, 390 with a fasting glycemic level of more than 5.1 mmol/l underwent a gene study*GCK*. In the absence of data on In the presence of diabetes in parents, active examination made it possible to diagnose carbohydrate metabolism disorders in 4.8% of cases with MODY2 and in 5.6% with MODY3. The degree of these disorders in MODY3 more often met the criteria for diabetes than in

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MODY2. The secretion of C-peptide and insulin in patients with MODY2 was higher than in patients with MODY3, which is explained by a more profound defect in function β-cells in MODY3. Insulin resistance according to the HOMA index was detected in 11.7% of patients with MODY2 (*n*=8), 2 of whom were obese, and 2 (11.1%) patients with MODY3 (obesity in all cases). In patients with MODY3, insulin resistance could be due to concomitant obesity, although this explanation is not always applicable [48]. In patients with MODY2 without obesity Insulin resistance can be explained by the characteristics of gluconeogenesis in the liver and the secretion of glucagon. A small study by E. Guenat [49] showed that in response to hypoglycemia, the concentration of glucagon in patients with MODY2 exceeds that in healthy people; the threshold concentration of glucose in the blood at which glucagon is secreted was 22% higher than in healthy people, Liver glucose production was recorded at higher glycemic levels than in healthy people. Thus, with MODY2, there is an early counter-regulatory response to hypoglycemia (increased glucagon secretion, activation of gluconeogenesis in the liver). According to the author, this can be explained by reduced glucokinase activity in glucose-sensitive cells of the central nervous system. In our study, in 2 patients with MODY2, moderate insulin resistance was confirmed by the behavior of a hyperinsulinemic normoglycemic clamp test, and in 1 patient with extremely high insulin levels. Clinical studies show that approximately 80% of adult patients with monogenic diabetes are diagnosed with T1DM or T2DM [3]. In childhood, increased glycemia in patients with MODY is often regarded as the onset of T1DM and insulin therapy is prescribed, which does not improve glycemia in MODY2 and is not the treatment of choice in MODY3, although it is invasive for patients. In our group of patients, before verification of the diagnosis, insulin therapy was prescribed in 11.3% of cases for MODY2, and in 27.8% for MODY3. In 5.3% of patients with MODY2, insulin therapy was continued after verification of the diagnosis due to worsening glycemic parameters when insulin was discontinued. Its administration in most MODY2 cases does not affect the average HbA1c level [50]. Patients with MODY3 exhibit hypersensitivity to SM drugs. When prescribing SM, their fasting blood glucose levels are reduced 5.2 times more effectively than when prescribing metformin; Gliclazide is 3.2 times more effective in MODY3 than in T2DM [51]. Patients with an initial diagnosis of T1DM who are receiving insulin can be switched to SU drugs.

Conclusions. 1. Among children with disorders of carbohydrate metabolism that do not fit the diagnostic criteria for T1DM, a mild course of the disease without

insulin requirement or with a requirement of less than 0.4 units/kg/day for more than 2 years and with preserved β-cell function, MODY2 and MODY3 were identified in 47.3% of cases (MODY2 is 3.4 times more common than MODY3). 2. Fasting hyperglycemia is more typical for MODY2: diabetic level of glycemia or impaired fasting glycemia was determined in 87.9% of cases versus 41.2% of such cases in MODY3. Glycemia levels during OGTT were below diabetic values in 78.4% of children and adolescents with MODY2 and reached diabetic values in all patients with MODY3. 3. The presence of obesity and insulin resistance does not exclude the diagnosis of MODY. Obesity occurred in 8.6% of cases in MODY2 and in 33.3% in MODY3. Insulin resistance was detected in 11.7% of patients with MODY2 and in 11.1% with MODY3. 4. Glucosuria in MODY3 is detected even with compensation of carbohydrate metabolism and is absent in MODY2.

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