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THE ROLE OF MODY DIABETES IN THE STRUCTURE OF DIABETES MELLITUS INCIDENCE AMONG YOUNG PATIENTS

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Annotation: In the last decade, it has become clear that not all cases of diabetes that develop during childhood and adolescence are type 1 diabetes. Increasingly, it is possible to identify diabetes mellitus in children and adolescents 2type 2 (DM 2), MODY type, as well as rarer syndromic forms of diabetes. MODY includes several clinically and genetically heterogeneous subtypes. Recent research has changed the understanding of MODYdiabetes. It has been found that MODY can develop into full-blown diabetes even at age 50. Thus, the problems of differential diagnosis of diabetes mellitus are still relevant in our time.

Keywords: Diabetes mellitus, MODYdiabetes, heredity, young patients, genetic studies.

Recently, all cases of diabetes mellitus (DM) in childhood were classified as type 1 diabetes (DM1), but in the last decade it has become obvious that not all diabetes is an autoimmune form of the disease and leads to the destruction of pancreatic β-cells with absolute failure insulin. Currently, type 2 diabetes (DM2) is increasingly being identified in children and adolescents, as well as adult-type diabetes in young people - MODY (Maturnity-onset diabetes of the young). According to Pearson E., McAlpine R., among patients under 35 years of age with newly diagnosed diabetes, T1DM predominates, accounting for 74% of all cases; T2DM is less common among younger patients, but the likelihood of development increases with age and degree of obesity; MODY is the most rare, with an incidence of 0.3–2.4%, although these figures are likely underestimated due to the high cost of genetic testing [1]. There is a need to carry out a differential diagnosis between various forms of diabetes, as this makes it possible to predict the clinical course of the disease, promptly screen for complications, identify diseases associated with diabetes, and is also crucial in determining the treatment strategy. Verification of the diagnosis is also of great importance for the patient's relatives, since it can lead to correction and proper treatment of other family members with diabetes, if monogenic diabetes is detected, as well as medical genetic counseling [2]. T1DM is characterized by an absolute deficiency of insulin secretion. It begins acutely, often with ketoacidosis, with high levels of hyperglycemia. In 85–90% of people with hyperglycemia, serological markers of the autoimmune process are detected - antibodies to glutamate decarboxylase (GAD), islet cell cytoplasmic autoantibodies (ICA), anti-insulin antibodies (IAA) [2]. According to Titovich E.V. et al., among patients with T1DM, 73% were positive for antibodies, and 27% were negative for autoantibodies at the time of examination [3]. T2DM develops due to pancreatic β-cell dysfunction and insulin resistance. Most patients diagnosed with T2DM were overweight or obese. T2DM is also associated with arterial hypertension, dyslipidemia, non-alcoholic fatty liver disease, and polycystic ovary syndrome [4, 5]. MODY is a heterogeneous group of diseases that are based on mutations of various genes and are characterized by β-cell dysfunction, onset at a young age (before 25 years), and autosomal dominant inheritance [6]. In many countries, such as the UK, the Netherlands, Denmark, the most common form of monogenic diabetes is MODY3, which is based on

mutations in the HNF-1α (hepatocyte nuclear factor-1α) gene, but in Spain, Italy, France, Germany, and the Czech Republic it is more common MODY2 is found [7]. In the Russian population, no differences were found in the frequencies of occurrence of MODY2 and MODY3 [8].The clinical picture depends on the type and location of the mutation [7]. With a mutation affecting the HNF1A (A) isomer (exons 8–10), the disease was diagnosed at an average age of 25.5 years; with mutations affecting three isomers (exons 1–6), the manifestation of diabetes is observed earlier - on average at 18. 0 years [9]. More than 350 mutations of the HNF-1α gene are known, which can vary the clinical severity of the disease, as well as the age of manifestation. This form of diabetes most often manifests in postpubertal age with hyperglycemia without ketoacidosis and/or with glycosuria at a relatively low level of glycemia.

There may be a family history of diabetes in two, three or more generations. Patients at the onset of the disease can only be on diet therapy, but in most cases they need to be prescribed glucose-lowering drugs [10]. Sulfonylurea drugs effectively reduce glycemic levels in MODY3 diabetes, which allows some patients to be switched from insulin therapy to tablet drugs [11]. However, some of these patients will eventually require insulin treatment as β-cell secretory failure progresses [12, 13]. MODY3 is often misdiagnosed as T1DM or T2DM [14]. In the UK, it is estimated that more than 80% of MODY cases are missed or misdiagnosed as T1DM or T2DM [15]. Clinical characteristics of T1DM, T2DM and monogenic diabetes are presented in Table 1. Currently, many works are devoted to atypical manifestations of diabetes and the difficulties of differential diagnosis. For example, in the work of Bowden SA, Hoffman RP, a clinical case of a combination of T1DM with the presence of a mutation in the gene characteristic of MODY3 in an obese adolescent was described [14]. We present our own observation. In a boy with a family history of T2DM and overweight, for the first time at the age of 11 years, a clinical examination revealed an increase in fasting glycemia to 6.8 mmol/l. Birth weight was 3900 g, height 52 cm. Hyperglycemia was not observed at neonatal age. Hyperglycemia detected at 11 years of age was not accompanied by polydipsia or polyuria. Excess body weight has been noted since the age of 3, when the child received inhaled hormonal therapy (Flexatide) due to bronchial asthma, but currently does not receive hormonal therapy. The boy's father, overweight, has been suffering from diabetes since he was 26 years old; for 6 years he received glibenclamide at a dosage of 10 mg/day, then at 32 years old, due to the ineffectiveness of therapy and the development of vascular complications, he was transferred to basal bolus insulin therapy with human gene-based insulin. engineered insulins of medium duration (insulin-isophane) and short-acting insulins in a total daily dose of 0.5–0.6 U/kg. There are specific complications of diabetes: preproliferative retinopathy (a condition after laser coagulation of the retina of both eyes at the age of 35 years), diabetic polyneuropathy, diabetic foot syndrome, neuroischemic form. The glycemic level currently ranges from 4 to 8 mmol/l. Glycated hemoglobin HbA1c in August 2011 – 7.1%, body mass index (BMI) 26.5 kg/m2. When carrying out a food load with breakfast with carbohydrates, the following results were obtained: fasting glucose - 10.4 mmol/l, at 120 minutes - 15.0 mmol/l; C-peptide on an empty stomach – 1.1 ng/ml, at 120 min – 2.0 ng/ml (Table 2). Thus, 10 years after the manifestation of diabetes, against the background of ongoing insulin therapy, preserved secretion of intrinsic insulin without hyperinsulinism and insulin resistance is revealed. A great-uncle on his father’s side was diagnosed with T2DM at the age of 29 and has been on insulin therapy for the last 16 years.A paternal great-aunt also experienced a transient increase in glucose levels due to stress. There were no cases of diabetes on the mother's side, but the maternal grandmother and great-grandmother were obese. The proband was examined at the Federal State Budgetary Institution Research Center 4 months after the detection of elevated fasting blood glucose levels. Fasting glycemia was 7.1 mmol/l, HbA1c – 6.7% BMI 26 kg/m2 (SDSmt +2.4). Blood pressure 120/70 mm Hg. Art. No manifestations of acanthosis nigricans on the skin were noted. The levels of total cholesterol, HDL, and LDL were within the normal range; an increase in the level of triglycerides was detected (2.9 mmol/l; the norm was 0.05–2.26 mmol/l).

When performing an oral glucose tolerance test (OGTT) with a glucose load (75 g), the level of fasting glycemia was 7.1 mmol/l, after 2 hours – 12.8 mmol/l; level of immunoreactive insulin (IRI) on an empty stomach – 6.7 μU/ml, after 2 hours – 41.4 μU/ml; Fasting C-peptide – 2 ng/ml; after 2 hours – 6.1 ng/ml (Table 3). Insulin resistance indices: Matsuda=4.26 (N>3.4), HOMA=2.11 (N0.3), thus, the glycemic profile is characteristic of diabetes, hyperinsulinemia, insulin resistance was not detected. The patient was prescribed metformin at a dose of 1000 mg/day. A repeat examination was carried out after 9 months. Diabetes control was insufficient: he did not follow the diet, he took metformin at a dose of 500 mg/day due to dyspeptic symptoms. HbA1c level increased to 7.8%. BMI was 27.34 kg/m2, SDSIMI +2.67, weight gain over 9 months was 7 kg. Blood pressure is within 130/90–140/100 mmHg. When performing an OGTT with a glucose load (75 g), the fasting glucose level was 7.7 mmol/l, the maximum glucose level was 17.0 mmol/l at 60 minutes; basal insulin level – 4.7 μU/ml, maximum insulin level 27.7 μU/ml at 90 minutes; the basal level of C-peptide is 2 ng/ml, the maximum level of C-peptide is 5.6 ng/ml at 120 min (Table 4). Glucosuria, ketonuria, and microalbuminuria were not noted. The lipid profile values were outside the normal range: triglycerides 2.5 mmol/l (with a normal range of 0.05–2.26 mmol/l), total cholesterol 5.7 mmol/l (with a normal range of 3.3–5.2 mmol /l), LDL cholesterol 3.3 mmol/l (normal 1.1–3.0 mmol/l). An instrumental examination revealed fatty liver hepatosis. GAD, ICA, IAA were not identified. Thus, over 9 months there was an increase in HbA1c levels, body weight, the appearance of arterial hypertension, and an increase in dyslipidemia. Considering the presence of diabetes in three generations, as well as the absence of hyperinsulinemia and insulin resistance, a molecular genetic study of the HNF-1α gene was carried out. Using PCR and subsequent direct sequencing, a heterozygous insertion (ins 1 bp CCA→CCCA) was identified, leading to a reading frame shift: Pro 291 frame shift, in the HNF-1α gene, which determines the diagnosis of MODY3. The same mutation was detected in the father. Second degree relatives were not examined. Discussion In children with impaired carbohydrate metabolism in combination with obesity, T2DM or the onset of T1DM due to obesity can be diagnosed. During 4 months of observation, our patient had hyperglycemia without glycosuria, ketonuria and ketoacidosis, as well as the absence of polydipsia, polyuria, and weight loss characteristic of T1DM. During the examination, antibodies to GAD, ICA, and IAA were not detected, however, the absence of autoantibodies is not an absolute diagnostic criterion [3], since when T1DM manifests itself in 20% of cases, specific autoantibodies are not detected, while at the same time, up to 15% of cases have autoantibodies are determined in T2DM [16–18]. The literature has described clinical cases in which patients diagnosed with type 1 diabetes mellitus, in whom autoantibodies were not detected,found mutations characteristic of MODY. Some of these patients were successfully converted from insulin therapy to sulfonylureas. For example, Lambert RA et al. described a clinical case: a proband diagnosed with T1DM, with a high concentration of diabetes in the family, on insulin therapy at a dose of 0.74 units/kg, glycated hemoglobin 7.6%, after identifying a mutation in the HNF-1α gene, he was switched to sulfonylurea drugs (gliclazide) at a daily dose of 160 mg, after transfer the HbA1c level was 7.8% [11]. In our patient, C-peptide was within normal limits, which cannot clearly exclude the diagnosis of T1DM, since at the early preclinical stage of the disease, insulin secretion, and therefore the level of C-peptide, remained intact for a long time; In addition, in adolescents with obesity and T1DM, insulin resistance provokes an earlier manifestation of the disease, at the stage of normal C-peptide secretion [19]. The presence of a high family concentration of diabetes (diabetes in the father and great-uncle, transient disorder of carbohydrate metabolism in the great-aunt), the absence of insulin resistance and hyperinsulinemia, and the absence of acantosis nigricans allowed us to assume that the child and his father had a monogenic form of diabetes. Establishing the MODY subtype is important when choosing therapeutic tactics and determining the prognosis of the disease. Patients with MODY2 diabetes in childhood and adolescence in most cases can only be on a diet, and patients with MODY1 and 3 diabetes are often sensitive to sulfonylureas [10]. The development of MODY2 is associated with a mutation in the glucokinase gene. The average level of glycemia is in the range of 5.5–8 mmol/l, hyperglycemia, as a rule, does not progress [7,13]. HbA1c is generally slightly below or slightly above the upper limit of normal

(5.5–5.7%), the increase in glucose level when performing a glucose tolerance test 2 hours after a glucose load is insignificant [2], which does not fit into our clinical case. MODY 1 (HNF-4α) and MODY 3 (HNF-1α) have a similar phenotype, as the HNF-4α gene regulates the expression of the HNF-4α gene, except that in MODY1 there is no low renal threshold, but glycosuria is not a mandatory manifestation MODY3. The age of manifestation of MODY1 is usually higher [2]. However, it is impossible to clinically reliably determine the type of MODY; genetic testing, which is the gold standard for diagnosing MODY, has the greatest specificity and sensitivity [1, 20]. The patient and his father were found to have a mutation in the HNF-1α gene. Genetic confirmation of the mutation is of great importance for the relatives of the proband, as this allows early suspicion and detection of diabetes before the onset of clinical manifestations. Hepatocyte nuclear factor-1α (HNF-1α) is a transcription factor that is involved in the expression of several liver genes and also acts as a weak transactivator of the insulin gene.In persons with developed diabetes and in carriers of mutations, impaired insulin secretion is detected in response to glucose administration. Until the age of 10, most carriers have normoglycemia on an empty stomach; in older children, fasting glycemia slightly exceeds the upper limit of normal, then a progressive disturbance of carbohydrate metabolism is noted due to impaired glucose tolerance. When performing an OGTT, the type of curve characteristic of diabetes is revealed, fasting C-peptide is within normal limits, insulin resistance is not detected [9, 19]. Patients with MODY 3, as a rule, do not have excess body weight [2], dyslipidemia and arterial hypertension, acanthosis nigricans [21], which distinguishes this type of diabetes from T2DM. Taking into account the presence in a child who has a mutation in the HNF-1α gene, the presence of excess body weight, high blood pressure, and an abnormal lipidemic profile, we can assume a combination of T2DM and MODY3 type. However, as obesity spreads in the population, various forms of diabetes, including type 1 diabetes and MODY diabetes, will also be combined with obesity, which modifies the clinical picture of the diseases. Bowden SA, Hoffman RP described a clinical case in which a 17-year-old obese girl (BMI 36.4 kg/m3), with a family history of T2DM (father, grandmother, aunt and uncle), had positive autoantibodies and was diagnosed with a mutation in the gene HNF-1α [14]. The father, who has the same mutation, was diagnosed with diabetes later than his son - at 26 years old. Due to low compliance (the patient never followed the diet), glibenclamide therapy was not effective enough. However, even 10 years after the diagnosis of diabetes, the patient had a significant level of C-peptide, although half that of his son. Rapidly developing retinopathy (after 6 years) is obviously a consequence of decompensation of diabetes in the first years of the disease. It should also be noted that the course of diabetes was quite stable - in the absence of self-control, the HbA1c level on insulin therapy was 7.1%, and the low need for insulin was 0.5 U/kg body weight. The presented clinical case demonstrates the need for molecular genetic research in children and adolescents with the T2DM phenotype for MODY in the absence of insulin resistance in the case of dominant inheritance in the family.the presence of excess body weight, high blood pressure, a violation of the lipidemic profile, a combination of T2DM and MODY3 type can be assumed. 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