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CASE REPORT

A CASE OF MODY 2 - ASSOCIATED HYPERGLYCEMIA DIAGNOSED AS GESTATIONAL DIABETES

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ABSTRACT

Maturity-onset diabetes of the young (MODY) is the most common monogenic form of diabetes, accounting for 1-2% of all diabetes cases. At least 14 different MODY subtypes have been identified the most common of which is MODY 2 caused by mutations in the glucokinase (*GSK*) gene. The mild hyperglycemia of MODY 2 is often first detected during pregnancy. Patients with MODY are usually misdiagnosed as either idiopathic type 1 or type 2 diabetes. The recognition of MODY 2 during pregnancy has important clinical implications as the management of hyperglycemia may differ from the established algorithm in gestational diabetes. Fetus development could be seriously affected in case it has inherited the *GSK* mutation and maternal hyperglycemia is insulin treated to the pregnancy adopted glycemic targets.

The case report describes the stepwise diagnostic approach to a 43-year-old woman with a history of gestational diabetes and persistent prediabetes who was found to be a carrier of a heterozygous pathogenic variant in *GSK* (c.184G>A) and discusses the possible genotype of her two children according to their birth weight.

Key words monogenic diabetes, MODY 2, gestational diabetes

INTRODUCTION

Maturity-onset diabetes of the young (MODY) is the most common monogenic form of diabetes related to defects in beta-cell development and insulin secretion, inherited in an autosomal dominant pattern and affecting 1-2% of patients with diabetes. Still, it is largely unrecognized due to the expensive diagnosis requiring genetic testing. Patients with MODY are usually misdiagnosed as either idiopathic type 1 or type 2 diabetes, and sometimes the specific form of diabetes is not even suspected. The entity of MODY encompasses 14 different subtypes and many novel candidate genes are currently being investigated. In countries where routine genetic screening is performed, MODY 2 is reported as the most common subtype. MODY 2 is caused by mutations in the glucokinase (*GSK*) gene, encoding a key enzyme of the beta-cell that is responsible for glucose sensing and insulin secretion. Individuals with MODY 2 are characterized by mild, benign, and asymptomatic fasting hyperglycemia, generally not requiring pharmacologic treatment. Diagnosis of MODY is important in terms of choosing the correct treatment approach as well as for the timely diagnosis of potentially affected family members [1-4]. The recognition of MODY 2 during pregnancy is crucial as the conventional insulin treatment during pregnancy may negatively affect the development of the fetus in case it has inherited the GSK mutation [5].

CASE PRESENTATION

A 43-year-old woman was referred to the department of Diabetology for assessment of glucose tolerance. She had a history of gestational diabetes during her first pregnancy at the age of 26 with fasting glucose concentrations of 7 to 8 mmol/l. She did not receive insulin therapy during pregnancy and her glucose tolerance was not reassessed after delivery nor during her second pregnancy. Both babies weighted below 4 kg at birth – 3650 g and 3000 g, respectively, but the first delivery was 2 weeks preterm. In the following years her fasting glucose was constantly within the range of 6.5 to 8.2 mmol/l and metformin therapy was initiated. The patient had concomitant autoimmune thyroiditis and beta thalassemia. The family history was abundant - her father had elevated fasting glucose values around 8 mmol/l though he was never treated for hyperglycemia, her mother had Grave's disease and vitiligo, one of the patient's

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sons, a first cousin, and a nephew all had beta thalassemia. Physical examination revealed no abnormalities, the patient had a BMI of 19.5 kg/m^2, waist circumference of 71 cm and blood pressure of 120/70 mmHg.

Clinical investigation

- *Assessment of glucose tolerance and insulin resistance* - oral glucose tolerance test (OGTT) was performed after discontinuation of metformin and revealed a state of prediabetes - impaired fasting glucose. Fasting insulin was low normal and calculated HOMA IR was within range. (Table 1) HbA1c was 5.2% in the setting of hemoglobin concentration of 126 G/l.
- *Assessment of immunologic markers* - islet cell antibodies - anti-GAD 65-Ab, anti-IA 2-Ab and anti-ZnT8-Ab, were negative.
- *Assessment of insulin secretion* - intravenous glucose tolerance test (IVGTT) demonstrated preserved endogenous insulin secretion. (Table 2)
- *Assessment of glycemic control* - continuous glucose monitoring (CGM) (FreeStyle Libre) showed good glycemic control and no need of pharmacologic therapy at this stage. (Figure 1)
- *Other* - serum lipids and TSH were within normal range.

Genetic testing

- *NGS sequencing*

Based on clinical suspicion of a specific monogenic form of diabetes running in her family the patient was referred for genetic testing. Genomic DNA was extracted from a blood sample taken after informed consent was signed. A custom panel was used for library preparation that included the exons and exon-intron boundaries of 99 genes associated with different syndromic and non-syndromic causes of monogenic diabetes. All 14 genes implicated in the different subtypes of MODY were included in the gene panel. Next-generation sequencing (NGS) was performed on an Illumina MiSeq platform.

Table 1. Oral glucose tolerance test

	0 min	**120 min**
Glucose mmol/l	6.77	6.83
Insulin mIU/l	2.8	11.8
HOMA-IR	0.84	

Table 2. Intravenous glucose tolerance test

	0 min	**1 min**	**3 min**	**30 min**	**60 min**
Glucose mmol/l	6.5	16.4	16.2	13.1	9.6
Insulin mIU/l	3.9	32.4	24.3	18.6	11.6

- *NGS data analysis and variant classification*

MiSeq reporter software was used for standard bioinformatic analysis. The generated VCF file was annotated using wANNOVAR software [6]. After common polymorphisms were filtered out, all remaining rare variants were classified according to the ACMG guidelines [7]. The patient was found to be a carrier of a heterozygous pathogenic variant in *GCK* (c.184G>A).

DISCUSSION

The presented case has the typical characteristics of MODY: early onset, generally before the age of 25 years, no signs of autoimmunity or insulin resistance, as well as the related traits of the metabolic syndrome, preserved endogenous insulin secretion and family history consistent with autosomal dominant pattern of inheritance [1-3]. The presentation of MODY as gestational diabetes is also rather typical [3, 4]. Although dysglycemia during pregnancy is usually considered a main risk factor for future development of type 2 diabetes, the phenotype of a patient with MODY, who generally does not have the characteristics of the metabolic syndrome, should be considered for further diagnostic

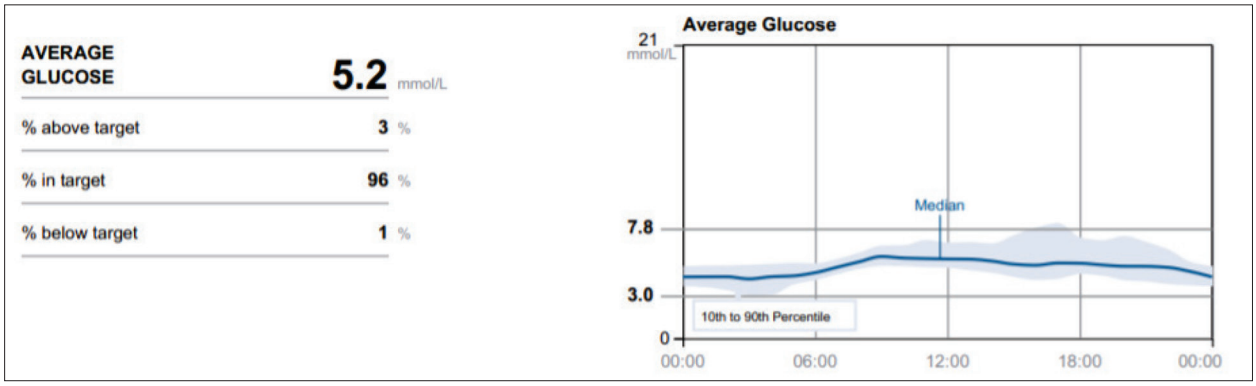

Figure 1. Continuous glucose monitoring report

assessment. Our patient had BMI in the low-normal range, no concomitant hypertension or dyslipidemia, no history of PCOS or other traits of the insulin resistance state. Still, a specific form of diabetes had not been suspected, and the patient had received the standard pharmacologic approach to subjects with prediabetes or newly diagnosed type 2 diabetes with metformin. Generally, the mild hyperglycemia of MODY 2 does not require pharmacologic treatment and the administration of different agents does not usually affect the HbA1c level [3]. Metformin therapy, in our case, supports this observation, as fasting glycemia was not influenced by this therapy throughout the years.

However, a treatment approach to MODY 2 during pregnancy, when glycemic targets are at their lowest levels, is a rather complicated situation. It may negatively affect the development of the fetus depending on whether it carries the *GSK* pathogenic variant or not. In the case that the fetus has inherited the mutation, achievement of glycemic targets by insulin treatment would lead to decreased insulin secretion in the fetus, as the normal maternal glucose levels cannot stimulate the defective beta-cells. As a result, fetal weight could be severely affected. If the baby does not carry the mutation, maternal hyperglycemia would stimulate fetal insulin secretion that will result in approximately 500 g additional weight and fetal macrosomia. That is why it is recommended to use insulin treatment during pregnancy in women with MODY 2, based on the presence of ultrasound signs of fetal macrosomia not on maternal glucose concentrations [5]. In our case, insulin was not administered during both pregnancies, but this decision was not based on the presence of MODY 2, as the diagnosis was not established at that time. We do not have data on the genotype of the two children, as the parents decided not to perform genetic testing at this point. Based, however, on their birth weight and a difference of 650 g between the babies, preterm in the case of the larger baby, we can speculate that a possible scenario could be that the first child does not carry the mutation, as the untreated maternal hyperglycemia during pregnancy resulted in a relatively large gestational aged baby - approaching the 90th percentile according to both the original and revised Fenton charts [8]. Yet the second child probably carries the mutation, as the untreated maternal hyperglycemia has resulted in a normal weight for the baby. In case both the mother and the fetus carry the mutation, fetal growth is not affected because the insulin secretion of the fetus is triggered at the same glycemic threshold as that of the mother [5].

Regarding the genetic background, the detected pathogenic variant in the *GCK* gene in our patient is a substitution of cytosine with thymine at position 44192924 on chromosome 7 (GRCh37/hg19). It is denoted as c.184G>A at transcript level (NM_000162.5) and results in the substitution of valine with methionine at codon 62 (V62M) of the amino acid sequence of the protein (NP_000153.1). This variant (rs1064793998) is extremely rare and is not reported in large population databases, such as gnomAD, ExAC and GenomeAsia 100K. V62M in *GCK* has been found, however, in multiple individuals with MODY 2 around the world [9-11] and is classified as pathogenic in the ClinVar database (Variation ID: 419624). There is a clinical correlation between our patient and other carriers of the V62M variant, as they also had elevated fasting plasma glucose levels [9, 11]. Heterozygous inactivating mutations in *GCK* cause MODY 2, while heterozygous activating mutations result in hyperinsulinemic hypoglycemia [12]. Functional studies about the consequences of the V62M variant detected in our patient demonstrated that the mutation leads to lowered catalytic activity, mild thermal instability, weaker glucose binding and diminished interaction with the glucokinase regulatory protein [9, 13, 14]. Therefore, the expected inactivating effect of the mutation is consistent with the MODY 2-related hyperglycemia phenotype observed in our patient.

The presented case clearly illustrates that the mild fasting hyperglycemia of MODY 2 may not necessarily fulfill the criteria for diabetes. Thus, not only some patients with diabetes, but also a certain proportion of the subjects with prediabetes with atypical phenotype, are candidates for further diagnostic evaluation and genetic testing. Fasting hyperglycemia in our patient was almost constantly in the range of impaired fasting glucose. The normal 2-hour value during OGTT is also typical for MODY 2 and the underlying glucokinase defect and the shifted to the right dose-response curve of glucose concentrations and insulin secretion [1].

Apart from the typical characteristics, the presented case is interesting for two additional issues also of genetic character that elaborate the diagnosis and management of the patient: the concomitant autoimmune disease and beta-thalassemia. The presence of autoimmune thyroid disease in the patient together with the constellation of autoimmune polyglandular syndrome type 3c in her mother suggested the possibility of autoimmune diabetes. Although the long evolution of dysglycemia was not supportive of this hypothesis, the absolute differentiation between the entities of MODY and type 1 diabetes were the negative immunologic markers and mainly the preserved endogenous insulin secretion during IVGTT. The presence of the other monogenic disease - beta thalassemia, compromised the usage of HbA1c as a criterion for the assessment of glucose tolerance and glycemic control of the patient [15]. The limitations of HbA1c were overcome with the new metrics of glycemic control derived from CGM.

In conclusion, MODY could be diagnosed at any stage of glucose dysregulation, including the early stages of glucose intolerance. Each patient with any degree of dysglycemia and clinical and laboratory findings that do not match the standard profile of type 1 and type 2 diabetes

should undergo genetic testing for a specific form of diabetes. The recognition of MODY 2 during pregnancy has important clinical implications, as the treatment approach may differ from those established in gestational diabetes. In many countries like Bulgaria, where routine screening is not performed, national healthcare systems should be involved in the reimbursement of the genetic testing of the suspected patients and the family members of the detected individuals. CGM could be useful in patients with mild hyperglycemia like the one observed in MODY 2 when deciding whether to initiate pharmacologic therapy.

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Declaration of interest

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