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Case Report

Differentiating Among Type 1, Type 2 Diabetes, and MODY: Raising Awareness About the Clinical Implementation of Genetic Testing in Latin America

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ABSTRACT

Objective: To describe a case of maturity-onset diabetes of the young (MODY) to highlight the importance of a correct diabetes diagnosis.
Methods: We describe a Mexican family misdiagnosed with T1D and T2D.
Results: A 36-year-old woman with diabetes and adverse outcomes during 2 pregnancies had been diagnosed with T2D 10 years ago. Genetic testing was performed due to clinical and family history, which showed a pathogenic heterozygous variant c.544G>T (p.Val182Leu) in the *GCK* gene. This mutation was also confirmed in most of the family members who had been diagnosed with diabetes.
Conclusion: This case highlights the need for a correct diabetes classification. Reassessment of diabetes etiology is justified, especially in individuals with unclear clinical presentation or when family history is suggestive.

Introduction

Maturity-onset diabetes of the young (MODY) is a subset of monogenic diabetes characterized by an autosomal dominant inheritance that can be transmitted by either parent or occur as a *de novo* mutation. It is classically characterized by a non-acute and non-ketotic presentation in lean subjects, typically before 25 years of age.[1] MODY can be misclassified as type 1 diabetes (T1D) due to young age at presentation. It can also be misclassified as early-onset type 2 diabetes (T2D) because of the low risk of ketosis and coexistence with overweight or obesity in some cases.[2,3] Similarly, in adults, T2D is the most frequent diagnosis; however, a small percentage have MODY.[4]

More than 14 genetic subtypes of MODY have been identified with mutations in corresponding genes. Despite the presence of well-defined characteristics for the most common forms of MODY, genetic testing is warranted to establish a precise diagnosis, which has consequences for treatment selection and family screening.[5]

In this report, we describe a Mexican family with misclassified diabetes that resulted in unnecessary treatment, possibly during pregnancy as well, and fetal complications. Upon re-diagnosis of the patient and family members, oral antidiabetic drugs were suspended and down-titration of insulin was started.

Case Report

A 36-year-old Hispanic woman, diagnosed with Crohn disease in August 2019 and currently being treated with adalimumab, was referred to our endocrinology outpatient clinic for further evaluation of suspected monogenic diabetes. She had first presented 10 years ago to her primary care physician with a 2-week history of fatigue. Initial evaluation was notable for a fasting plasma glucose of 156 mg/dL (normal, <100 mg/dL) and glycated hemoglobin (HbA1c) concentration of 6.4% (46 mmol/mol) (normal, <5.7%

Abbreviations: HbA1c, glycated hemoglobin; MODY, maturity-onset diabetes of the young; T1D, type 1 diabetes; T2D, type 2 diabetes.

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Table
Relevant Family History of the Index Case

Family member	Current age (y)	Age at diagnosis (y)	Treatment
Mother	64	T2D, 33	Glimepiride + metformin
Sister	46	T1D, 14	Insulin
Sister	43	T2D, 40	Metformin + empagliflozin
Son	17	T1D, 7	Insulin
Daughter	2	*GCK*-MODY, 2	No treatment
Niece	26	T1D, 11	Insulin
Nephew	13	*GCK*-MODY, 13	No treatment

[39 mmol/mol]). A diagnosis of T2D was made and thrice-daily metformin was started. At that time, her height was 153 cm, weight was 58.0 kg, and body mass index (BMI) was 24.8 kg/m^2. She had no signs of insulin resistance. She made changes in her diet and lost 10 kg of body weight over a 6-month period. Her HbA1c level was 6.6% (49 mmol/mol) and metformin was lowered to twice daily. She reported an obstetric history of a twin pregnancy when she was 19 years old that was complicated by the death of one of the products and subsequent delivery through cesarean delivery at 32 weeks of gestation. The newborn was otherwise well and weighed 2.4 kg. He developed polyuria and hyperglycemia at the age of 7, was diagnosed with T1D, and has been treated with insulin since then. He had never presented with an episode of diabetic ketoacidosis. She became unintentionally pregnant with her second child at the age of 32 and her pre-pregnancy BMI was 26.9 kg/m^2. Metformin was continued throughout the pregnancy and insulin therapy was started at 4 weeks of gestation due to elevated glucose levels. Toward the end of the pregnancy, her insulin requirement for glycemic control was 43 units/d (0.98 U/kg). The pregnancy was complicated by premature rupture of membranes, which required delivery by urgent cesarean delivery. The child was born at 28 weeks of gestation, weighed 1.09 kg, and had hyperglycemia after birth.

At the time of her first visit, her BMI was 25.1 kg/m^2 and physical examination was unremarkable. Laboratory test results were fasting plasma glucose 106 mg/dL, HbA1c 5.7% (39 mmol/mol), LDL-cholesterol 173 mg/dL (normal, <130 mg/dL), and creatinine 0.75 mg/dL (normal, 0.7-1.3 mg/dL). Due to lack of certainty in her T2D diagnosis, antibodies against glutamic decarboxylase 65 and C-peptide levels were evaluated, with a result of 0.27 U/mL (normal, 0.8-4.2 U/mL) and 1.62 ng/mL (normal, 0.8-4.2 ng/mL), respectively. At this timepoint, her treatment was empagliflozin and linagliptin. She is the youngest child in a family with 4 siblings (2 sisters and 1 brother). Her sisters had been diagnosed with T1D and T2D at 14 years and 40 years of age, respectively. Her 40-year-old sister has a daughter who had been diagnosed with T1D at the age of 11, with no history of diabetic ketoacidosis. Her mother was diagnosed with T2D at the age of 33. Because of her family history, BMI <25 kg/m^2 at diagnosis, and non-acute presentation of her relatives diagnosed as T1D, genetic analysis for MODY was performed. Testing identified a pathogenic variant c.544G>T (p.Val182Leu) in the in *GCK* gene, which was confirmed by Sanger sequencing, as recommended by the American College of Medical Genetics. The same mutation was also confirmed in all family members who had a diagnosis of diabetes. Furthermore, 2 asymptomatic family members were also identified as having the same mutation, including her 40-year-old sister's 13-year-old son and the patient's 2-year-old daughter (Table and Figure).

With these new results of genetic analysis, we suspended empagliflozin and linagliptin. We decided to suggest life-style changes and nutritional follow-up. Currently, she only requires medications related to her Crohn disease. Her most recent HbA1c was 5.7% (39 mmol/mol). The patient's son has transitioned to discontinue insulin therapy. Her family members were advised of their genetic condition and were referred to their endocrinologists.

Discussion

Up to 6% of all cases of diabetes are MODY, which is a group of well-known monogenic diseases that are mainly caused by mutations in *HNF4A*, *GCK*, and *HNF1A* genes.[6,7] *GCK* encodes glucokinase, which is an enzyme that catalyzes the phosphorylation of glucose

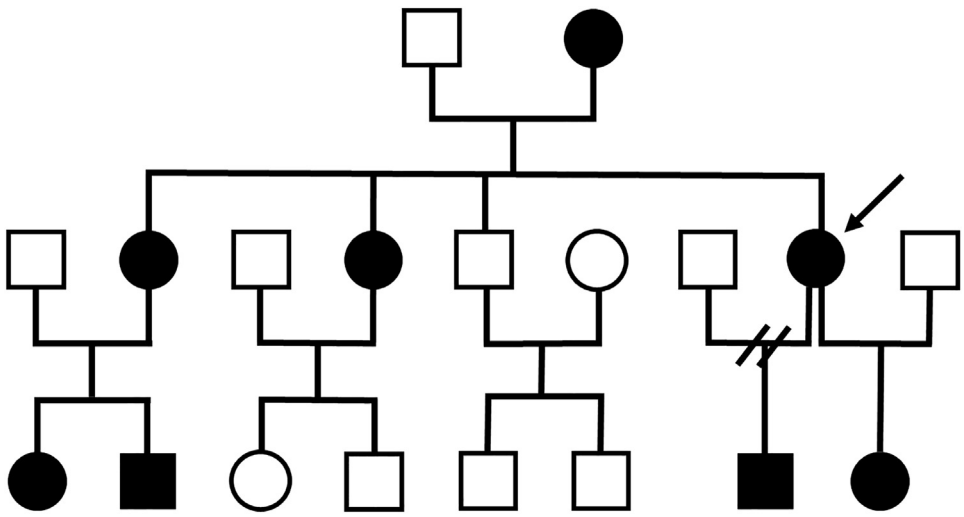

Fig. Patient's pedigree. The patient's family members were diagnosed with the heterozygous pathogenic variant c.544G>T (p.Val182Leu) in the *GCK* gene (closed circles and squares). The double diagonal line indicates divorce/not together. The closed circle with arrow shows the proband.

and, therefore, acts as a sensor of blood glucose levels in the pancreatic beta cell.[8] *HNF4A* and *HNF1A* encode hepatocyte nuclear factors 4A and 1A, respectively, and both are transcription factors that promote gene transcription related to insulin production and pancreatic beta cell development.[9,10] A correct molecular diagnosis is critical for providing optimal treatment or no treatment at all, as in *GCK*-MODY patients. It has been estimated that the time elapsed since the diabetes presentation to molecular diagnosis is >10 years and that around 80% of MODY patients are frequently misdiagnosed as T1D or T2D.[11] Our patient received the correct diagnosis 10 years after clinical presentation. The lack of molecular tests resulted in misclassification of diabetes in her and in all her family members. If her family members would have had the right diagnosis in a timely fashion, unnecessary treatment could have been avoided. It has been shown that genetic diagnosis of MODY can improve patient well-being.[12]

Our patient was treated for T2D diabetes during pregnancy. Both pregnancies were complicated by premature deliveries and a dead fetus. *GCK*-MODY can have clinical implications during pregnancy, especially when there is discordance between maternal and fetal genotypes. If the only the mother is affected, maternal hyperglycemia causes fetal hyperinsulinemia and increased birth weight.[13] Conversely, when the fetus inherits a paternal *GCK* mutation, levels of maternal glucose are not enough to stimulate adequate fetal insulin to sustain optimal growth and birth weight will be lower. When both the mother and the fetus have a *GCK* mutation, birth weight can be normal if the mother's hyperglycemia is not treated. However, if her hyperglycemia is treated during pregnancy, birth weight can be compromised.[14] We can speculate that both pregnancies with low birthweight products were caused by the latter mechanism. Based on the aforementioned observations, it is recommended that pregnant mothers with hyperglycemia due to a *GCK* mutation be treated only when there is ultrasound evidence of accelerated fetal growth.[15]

Over 600 different *GCK*-MODY mutations have been described in a variety of populations, mainly from Europeans countries.[11] In contrast, regions including Africa, Latin America, and the Middle East, have a paucity of studies that include MODY populations.[16] Regarding the frequency of MODY in Latin America, there are only small studies from Brazil and Mexico.[17] It is possible that a lack of resources for performing genetic studies and research directives is the main cause of virtually no monogenic diabetes studies.

Our patient's scenario highlights the diverse implications when diabetes is misclassified. It is of uttermost importance that clinicians treating diabetes consider monogenic etiologies when adults have been diagnosed at a younger age, in individuals with non-ketotic hyperglycemia before the age of 25, or if evidence of autosomal dominant inheritance is present.[18] However, there are several case reports that describe *de novo* variants in monogenic diabetes.[19] The *GCK* Val182Leu mutation has been previously described to be associated with MODY.[20] The Val182Leu change severely affects glucose affinity, which suggests that it performs poorly as a glucose phosphorylating enzyme under physiologic conditions.

Conclusion

This case exemplifies one of the many hypothetical cases of diabetes misclassification in Mexican families that has implications from unnecessary treatment to pregnancy and fetal complications. Latino populations, being one of the major populations with the highest prevalence of diabetes, are in great need of research in the field of monogenic diabetes and immediate clinical implementation of genetic testing. Reassessment of diabetes etiology is justified, especially in individuals with unclear previous diagnostic criteria or if the family history is suggestive.

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Disclosure

The authors have no multiplicity of interest to disclose.

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