Global Pediatric Health
Volume 6: 1–3

DOI: 10.1177/2333794X19874215
journals.sagepub.com/home/gph
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A Case of a 13-Year-Old Female With Maturity Onset Diabetes of the Young (MODY) Identified by School-Based Cardiovascular Screening

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Received July 3, 2019. Received revised July 22, 2019. Accepted for publication July 25, 2019.

Introduction

Maturity onset diabetes of the young (MODY) is a rare type of autosomal dominant diabetes with an estimated prevalence of 1.2% within the pediatric diabetic population.[1] Approximately 99% of cases of MODY result from mutations in hepatocyte nuclear factor (HNF)4A (MODY1), glucokinase (GCK) (MODY2), and HNF1A (MODY3) genes. HNF4A and HNF1A are expressed in pancreatic β cells and hepatocytes. While the underlying mechanism is not well understood, these mutations relate to reduced insulin secretion in response to rising blood glucose levels. The presentation of MODY is heterogeneous, which makes identification of these patients difficult.[2] The clinical phenotype and progression among patients with the same underlying mutation can be variable, reflecting the effect of the environment on gene expression. The most common presentation of MODY is mild, asymptomatic hyperglycemia in a child, adolescent, or young adult with a family history of autosomal dominant diabetes. While patients with mutations in HNF1A and HNF4A often present with polydipsia and polyuria, those with mutations in GCK are more likely to present with a mild elevation in blood glucose on routine screening. Other symptoms may include nocturia, gastrointestinal symptoms, and rarely diabetic ketoacidosis.[1] Patients do not typically present with features of insulin resistance such as hypertension, dyslipidemia, fatty liver, or acanthosis nigricans that often accompany type 2 diabetes (T2DM). These patients are often young at diagnosis (between the second to fourth decades of life), with most recent data by Pihoker and colleagues[1] reporting a diagnosis at 11.5 ± 3.9 years. MODY should be clinically suspected when the following criteria are met: age of diagnosis <25 years, non-insulin dependent, and an autosomal dominant family history of diabetes. MODY can be distinguished from type 1 diabetes (T1DM) by the absence of islet cell autoantibodies and from T2DM by the absence of features of insulin resistance. Screening hemoglobin A1C (HgbA1C), blood glucose levels, and islet cell autoantibodies are used in the initial diagnosis of MODY; however, confirmatory direct gene sequencing is required for diagnosis if the presentation and clinical history suggest MODY. Patients with the more common forms of MODY can initially be treated successfully with a combination of (1) oral sulfonylurea drugs, specifically in cases of mutations in HNF1A and HNF4A; (2) low-carbohydrate diets; and (3) exercise; however, some will progress to requiring insulin therapy long term.

We present the case of a 13-year-old patient who was discovered to have MODY via an asymptomatic comprehensive cardiovascular screening that included screening for diabetes, lipid abnormalities, and hypertension in a middle school clinic. In this case report, we argue for the potential unexpected benefit of community cardiovascular screenings, as has been reported by Siegel and colleagues.[3]

Ethical Approval and Informed Consent

Per Cincinnati Children's Internal Review Board guidelines, guardian and patient gave verbal assent for patient information to be included in this case report. Written consent was not required by institution guidelines.

Case Report

The patient is a 13-year-old, previously healthy, non-obese female with no past medical history who presented

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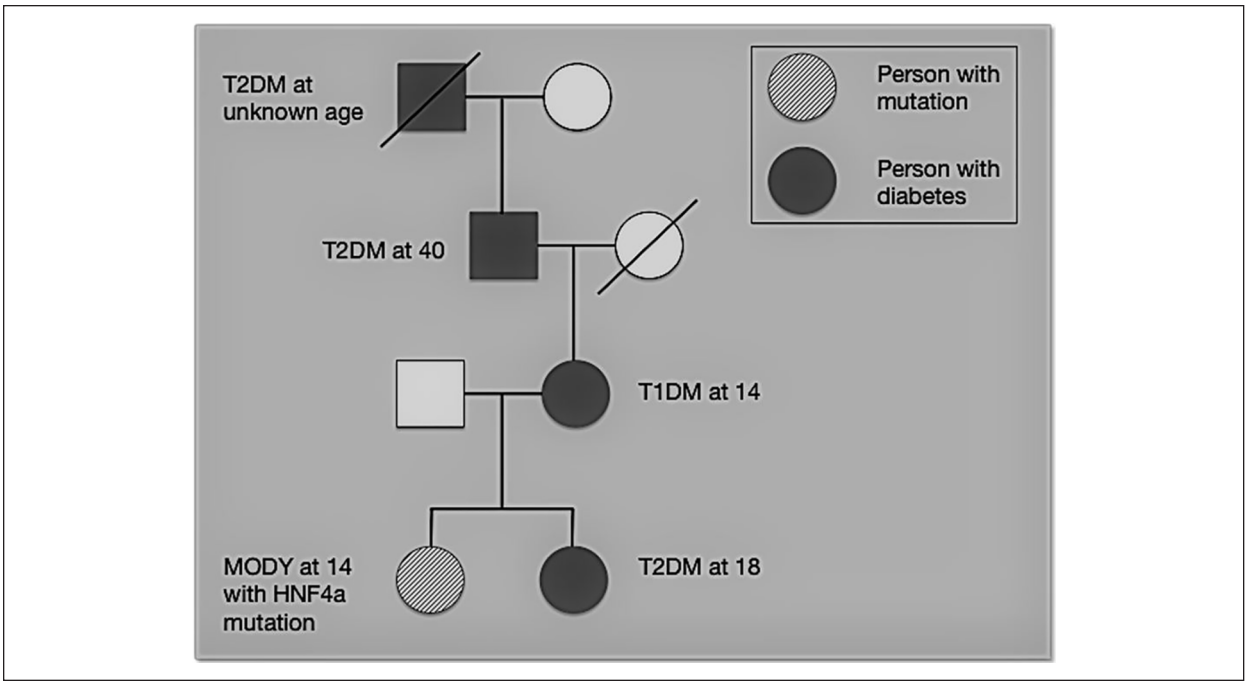

Figure 1. Family pedigree.

to a school-based cholesterol and diabetes screening. Her height and weight were 155 cm and 39.5 kg, respectively, and her body mass index was at the 20th percentile for age and sex. Her vital signs were within normal limits, her blood pressure was not elevated, and she was well-appearing. Her screening lipid panel was within normal limits (cholesterol 125 mg/dL, high-density lipoprotein 49 mg/dL, low-density lipoprotein 63 mg/dL, and triglycerides 68 mg/dL). Point-of-care screening HgbA1C was significant for a value of 8.5% with a repeat value of 8.7%. The endocrinology team was consulted by phone and the patient denied symptoms of weight loss, polydipsia, polyuria, nocturia, and polyphagia; however, a strong family history of diabetes was reported (Figure 1).

In the setting of a new diagnosis of diabetes, she was referred to the Cincinnati Children's Hospital Medical Center Emergency Department for further evaluation and management. On evaluation in the emergency department additional laboratory studies were sent to confirm the diagnosis of diabetes and evaluate its etiology. Laboratory studies included a repeat serum HgbA1C, electrolytes, urinalysis, and an islet cell autoantibody screen. Additionally, routine new-onset diabetes screening laboratory tests, which included a thyroid stimulating hormone, immunoglobulin A (IgA), and tissue transglutaminase IgA, were also sent. On laboratory evaluation, she had no evidence of acidosis or urine ketones and a random serum glucose was within normal limits (111 mg/dL) but with glycosuria. In the setting of a normal random serum glucose and absence of acidosis in a well-appearing patient, she was discharged home with the plan for close endocrine follow-up.

The repeat serum HgbA1C resulted after the patient was discharged and was elevated at 10.3% and her islet cell autoantibody screen and all other screening labs returned as negative. On telephone follow-up, the patient remained asymptomatic and a family history obtained was significant for diabetes spanning 4 generations (see Figure 1 for pedigree). To further confirm a diagnosis of new-onset diabetes an oral glucose tolerance test was performed. Fasting glucose (89 mg/dL) and insulin (3.8 μIU/mL) were both within normal limits. However, her oral glucose tolerance test results were consistent with the diagnosis of diabetes, with glucose elevation to 313 mg/dL at 2 hours. In the setting of new-onset diabetes, a negative islet cell autoantibody screen and a family history of autosomal dominant diabetes, a diagnosis of MODY was suspected. Confirmatory gene sequencing was sent and revealed a heterozygous mutation in HNF4A gene designated c.200G>A (p.Arg67Gln) consistent with MODY1. This variant has been reported previously. Ophthalmic examination and renal function laboratory tests were both within normal limits. To date, the patient's glycemic control has been successfully maintained to reduce microvascular comorbidities with glipizide and diet without the need of intensive insulin therapy.

Discussion

This patient's diagnosis of MODY was discovered on participation in a school-based comprehensive cardiovascular screening program. Although the prevalence of MODY is much smaller than that of other forms of diabetes, the diagnosis of this condition is often delayed or misdiagnosed as either T1DM or T2DM. This patient's case raises several important questions about current screening practices and the importance of early diagnosis of MODY to reduce associated microvascular comorbidities.

Currently, no screening tests exist for MODY. Direct gene sequencing as a screening tool is currently cost-prohibitive given the low prevalence of this disease. While high sensitivity C-reactive protein has been demonstrated as a sensitive test to distinguish MODY due to a mutation in HNF1A from T2DM, most previously studied screening biomarkers have had inadequate sensitivity and specificity for detecting MODY.[4] Although the American Academy of Pediatrics and the American Diabetes Association both endorse the screening of older school-age children for diabetes, a majority of children are not screened for diabetes in primary care offices. Siegel and colleagues[3] demonstrate the feasibility and high yield of screening children in this age group for diabetes, through which individuals like this patient can be identified.

Early diagnosis and appropriate management can aid in preventing potentially irreversible consequences of undiagnosed, persistent hyperglycemia. In our patient's case, early diagnosis likely saved her from needing to be placed on intensive insulin therapy. Among these consequences are microvascular complications such as retinopathy, nephropathy, and neuropathy.[5] In patients with T1DM, tight glycemic control is encouraged to prevent potential disturbances in central nervous system development that chronic hyperglycemia and glucose variability pose.[6]

Conclusion

We present a case of a 13-year-old previously healthy female with a multigenerational family history of diabetes diagnosed with MODY due to a mutation in HNF4A after an elevation in HgbA1C was detected at a school-based comprehensive cardiovascular screening program. While more data are needed to justify universal screening for diabetes with tests such as HgbA1C, practitioners should be vigilant with family history screening for diabetes. In families with 2 or more generations of diabetes, there should be a low threshold for asymptomatic screening with a serum HgbA1C.

Author Contributions

KG: Contributed to design; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MY: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
RS: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
KS: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Ethicon Inc.

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