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A Young Patient with HNF1A-MODY and an Elevated HbA1c

Paola Atallah[1] Helena Fahmi[1]

[1] Department of Endocrinology and Metabolism, Saint George Hospital University Medical Center, Beirut, Lebanon

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Address for correspondence Paola Atallah, MD, Department of Endocrinology and Metabolism, Saint George Hospital University Medical Center, Beirut, Lebanon (e-mail: pjatallah@stgeorgehospital.org).

Abstract

Background Maturity-onset diabetes of the young (MODY) is the predominant form of monogenic diabetes, affecting 1 to 5% of diabetes patients. It has autosomal dominant inheritance but occasional de novo mutations. Its clinical features encompass early-onset hyperglycemia, residual pancreatic function, and absence of insulin resistance or beta cell autoimmunity, which are managed primarily with glucose-lowering medications. Increasing awareness of MODY's clinical importance among health care professionals, researchers, and policymakers may enhance screening and diagnostic approaches.

Case Presentation We describe the case of a 16-year-old adolescent boy presenting with polyuria and polydipsia. He had no significant past medical history but a notable family history of diabetes, including prediabetes and type 2 diabetes, across three generations. On evaluation, his vitals were stable. Initial investigations revealed hyperglycemia with a point-of-care glucose of 222 mg/dL, HbA1c of 10.4%, and no ketonuria. C-peptide levels were 0.9 ng/mL, and diabetes autoantibodies were negative. The patient was started on insulin therapy and transitioned to basal-bolus insulin. Genetic testing was performed due to strong familial history and absence of autoantibodies, revealing a heterozygous *HNF1A* gene mutation consistent with HNF1A-MODY. He was switched to gliclazide 60 mg daily, achieving excellent glycemic control with an HbA1c of 5.3% at 3 months of follow-up. First-degree relatives were referred for MODY genetic testing.

Conclusion In HNF1A–MODY, the glycemic profile typically presents with slight fasting hyperglycemia and notably elevated glucose levels post-glucose intake, accompanied by a gradual decline in insulin secretion and deteriorating glucose regulation, necessitating treatment. It is generally uncommon to have significant hyperglycemia and elevation of HbA1c in MODY patients, as seen in the case discussed. Clinicians need a comprehensive grasp of MODY's epidemiology and pathogenesis to precisely diagnose patients, tailor individualized treatment plans and monitoring, and screen relatives of those affected by diabetes mellitus.

Keywords

- maturity-onset diabetes
- MODY
- monogenic diabetes
- *HNF1A* gene

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Introduction

Maturity-onset diabetes of the young (MODY) is a relatively common group of inherited non-autoimmune diabetes disorders that often go undiagnosed, even as awareness of it grows. It refers to a group of inherited non-autoimmune diabetes disorders that typically appear at a young age. Mutations in over 15 genes have been linked to a MODY-monogenic phenotype, leading to various treatment approaches. Monogenic defects that lead to beta-cell dysfunction, such as MODY-monogenic diabetes, account for a small yet significant percentage of diabetes cases of less than 5%. Distinguishing MODY from other types of diabetes can be challenging. Therefore, obtaining a thorough family history, performing a comprehensive clinical assessment, and conducting detailed biochemical testing are essential for accurate diagnosis. This case report highlights one specific subtype of MODY caused by a mutation in the *HNF1A* gene, emphasizing the diagnostic challenges and treatment considerations associated with monogenic diabetes.

Case Description

We present the case of a 16-year-old male patient who presented to the clinic for evaluation of polyuria and polydipsia. He had no past medical history. His father had diet-controlled prediabetes, his maternal grandmother had mild type 2 diabetes controlled on metformin, and his paternal grandfather had long-standing insulin-dependent type 2 diabetes. In the clinic, the patient's vitals were the following: blood pressure (BP), 130/80 mm Hg; pulse, 53 bpm, and body mass index (BMI), 24.22 kg/m^2. His point-of-care testing for glucose was 222 mg/dL. He was admitted to the hospital on the same day for investigation of his hyperglycemia. No ketonuria was detected during the investigation, and 4+ glucose was present on the urine dipstick. He had normal electrolytes and kidney function, a thyroid-stimulating hormone (TSH) level of 0.5 mIU/L, HbA1c of 10.4%, and C peptide of 0.9 ng/mL (*N*: 0.8–4.2) after breakfast. The patient was started on IV insulin and switched to basal-bolus therapy the next day. He was discharged on insulin glargine 10 units at bedtime and insulin aspart premeals around 2 to 4 units. The autoantibody profile was negative: anti-GAD, 2.3 U/mL ($N < 17$); anti-IA2, <5 U/mL, and Zinc transporter 8 Ab < 10 U/mL ($N < 15$). The laboratory parameters on presentation are presented in ►**Table 1**. The patient was then referred to genetic testing to evaluate for MODY in view of a strong family history and negative diabetes antibody profile, and the results revealed a heterozygous mutation in the *HNF1A* gene. He was then switched to gliclazide 60 mg daily, which achieved proper glycemic control. Follow-up HbA1c 3 months later was 5.3%. The patient's first-degree relatives were also referred for MODY genetic testing.

Table 1 Laboratory evaluation on presentation

Parameter	Result	Reference range
Plasma glucose	222 mg/dL	80–120 mg/dL
Urinary glucose	++++	–
HbA1c	10.4%	4–6.4%
Thyroid-stimulating hormone	0.5 mIU/L	0.35–4.5 mIU/L
Serum C-peptide	0.9 ng/mL	0.8–4.2 ng/mL
Anti-GAD antibody	2.3 U/mL	<17 U/mL
Anti-IA2 antibody	<5 U/mL	<5 U/mL
Zinc transporter 8 antibody	<10 U/mL	<15 U/mL

Discussion

Monogenic defects affecting beta-cell function lead to early-onset hyperglycemia, typically before the age of 25 years, though diagnosis may occur later. These defects impair insulin secretion due to disruptions in beta-cell-specific gene pathways, while insulin action remains largely unaffected in the absence of obesity. Most cases follow an autosomal dominant inheritance pattern. Genetic testing is recommended for individuals with MODY due to its important implications for treatment, family screening, cost-effectiveness, and increasing availability. The clinical characteristics that differentiate MODY from other forms of diabetes are outlined in ►**Table 2**. Furthermore, Broome et al have proposed an algorithm (illustrated in ►**Fig. 1**) that can aid in identifying and diagnosing monogenic diabetes, including MODY.[1]

HNF1A-MODY, previously known as MODY-3, is the most frequently reported genetic variant, accounting for 30 to 65% of all MODY cases, and results from heterozygous mutations in the *HNF1A* gene encoding the transcription factor hepatocyte nuclear factor 1 alpha.[1,2] These genes are found to be expressed in several tissues, particularly in the islets of Langerhans,[3] and mutations would result in β-cell function impairment, leading to a gradual decline in glucose tolerance and an increasing need for treatment.[2] HNF1A-MODY is characterized by a fasting glucose level of at least 126 mg/dL and HbA1c of ≥6.5%, with a progressive course. Patients may present with osmotic symptoms, including polyuria and polydipsia, though some individuals remain asymptomatic. Diagnosis typically occurs in adolescence or early adulthood, often with a strong family history (90%), consistent with its autosomal dominant inheritance. Unlike type 2 diabetes, obesity is uncommon. C-peptide remains detectable, and pancreatic autoantibodies are absent, distinguishing it from type 1 diabetes.[4] Progressive hyperglycemia results from impaired insulin secretion and HbA1c levels at diagnosis, which can vary widely among individuals and be influenced by factors such as the age of onset, duration of hyperglycemia before diagnosis, and individual genetic differences. While some patients may present with HbA1c levels below 6.5%, others can exhibit significantly higher values. In a literature review by Zhao et al discussing the clinical characteristics of patients with HNF1A-MODY, the average HbA1c was 7.9% among Asians versus 7.3% in non-Asian populations, attributed to higher postprandial glycemia in the former population.[5]

Table 2 Clinical characteristics of MODY monogenic diabetes

Family history: • Parents affected by MODY monogenic diabetes
Early-onset diabetes: • Develops in adolescence or young adulthood, typically before the age of 35 y (increased likelihood if before the age of 25 y)
Atypical features for type 1 diabetes: • No pancreatic antibodies at diagnosis • Low insulin requirement for treatment (e.g., <0.5 U/kg/d) • Sustained endogenous insulin production beyond 3–5 y after diagnosis (C-peptide >0.6 ng/mL when glucose >72 mg/dL) • Absence of ketoacidosis when insulin is stopped
Atypical features for type 2 diabetes: • Diabetes onset before the age of 45 y with normal or low BMI • Absence of acanthosis nigricans • Normal triglycerides and/or normal or elevated HDL-C (seen in HNF1A-MODY)
Other indicators: • Mild, stable fasting hyperglycemia that does not significantly progress or respond to medication • Extreme sensitivity to sulfonylureas • Extrapancreatic features. (e.g., renal, hepatic, gastrointestinal)
Personal or family history: • Neonatal diabetes or neonatal hypoglycemia • Family history pattern consistent with autosomal dominant inheritance
Distinguishing MODY from type 1 and 2 diabetes: • Type 1 diabetes: Often sporadic; only 2–6% have an affected parent • Type 2 diabetes: Commonly familial with shared environmental/risk alleles, typically presenting after the age of 45 y with obesity • MODY: Onset before the age of 35 y without obesity, unlike type 2 diabetes

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; MODY, maturity-onset diabetes of the young.

Additionally, it was noted that patients with noncoding mutations exhibited the highest HbA1c levels, averaging 9.5%.[5] There are documented cases of individuals with HNF1A-MODY presenting with HbA1c levels exceeding 10%. In a case report, a 20-year-old woman was initially misdiagnosed with type 1 diabetes at the age of 14 years and treated with multiple daily insulin injections. At diagnosis, her HbA1c was 10.9%. Upon reevaluation, she was correctly identified as having HNF1A-MODY, which led to a change in her treatment regimen.[6]

As for the treatment approach, sulfonylurea (SU) is the first-line treatment in patients with HNF1A-MODY since it bypasses the defective β-cells and increases glucose-independent insulin secretion through potassium-sensitive ATP (K_{ATP}) channels. SU should start with the lowest dose and be titrated according to the blood sugar target.[2] Glyburide (glibenclamide) is the most commonly used SU in the United States. A single study on the nateglinide analog, nateglinide, showed that, compared to the SU glyburide, it resulted in lower postprandial glucose levels and a lower hypoglycemia incidence due to its shorter duration of action.[7] With any SU therapy and depending on the age at which it was initiated, blood sugar control is expected to decline over a period ranging from 3 to 25 years.[8] Insulin or glucagon-like peptide-1 receptor agonists (GLP-1 RA) can be added to SU therapy for patients not maintaining adequate blood sugar control with SU alone. GLP-1 receptor agonists are an alternative to SUs for treating beta-cell failure, as they lower fasting and postprandial glucose levels similarly to glimepiride but with a lower risk of mild hypoglycemia. GLP-1 RA stimulates insulin secretion by activating adenylate cyclase and protein kinase A, bypassing the beta-cell ATP deficiency and directly affecting the K_{ATP} channel. HNF1A-MODY patients have a comparable risk of all-cause mortality and cardiovascular disease to those with type 2 diabetes.[9] In that light, GLP-1 RAs are recommended as add-ons to SU, given their cardiovascular benefits and insulin release mechanism independent of the genetic defect. However, their potential as a first-line therapy is still under investigation.

Sodium-glucose transport protein 2 (SGLT- 2) inhibitors are not recommended for HNF1A-MODY due to increased risks of severe dehydration, diabetic ketoacidosis (DKA), and other complications. This is attributed to reduced SGLT-2 expression in these patients, leading to excessive glycosuria and higher adverse effects compared to those with type 2 diabetes. Moreover, dipeptidyl peptidase-4 (DPP-4) inhibitors show modest efficacy and can be considered an additional treatment.[10] In a trial, linagliptin improved glycemic control and variability without increasing hypoglycemia risk in HNF1A-MODY patients as an add-on therapy to glimeperide.[11]

Conclusion

This case highlights the diagnostic and therapeutic complexities of managing HNF1A-MODY, the most common

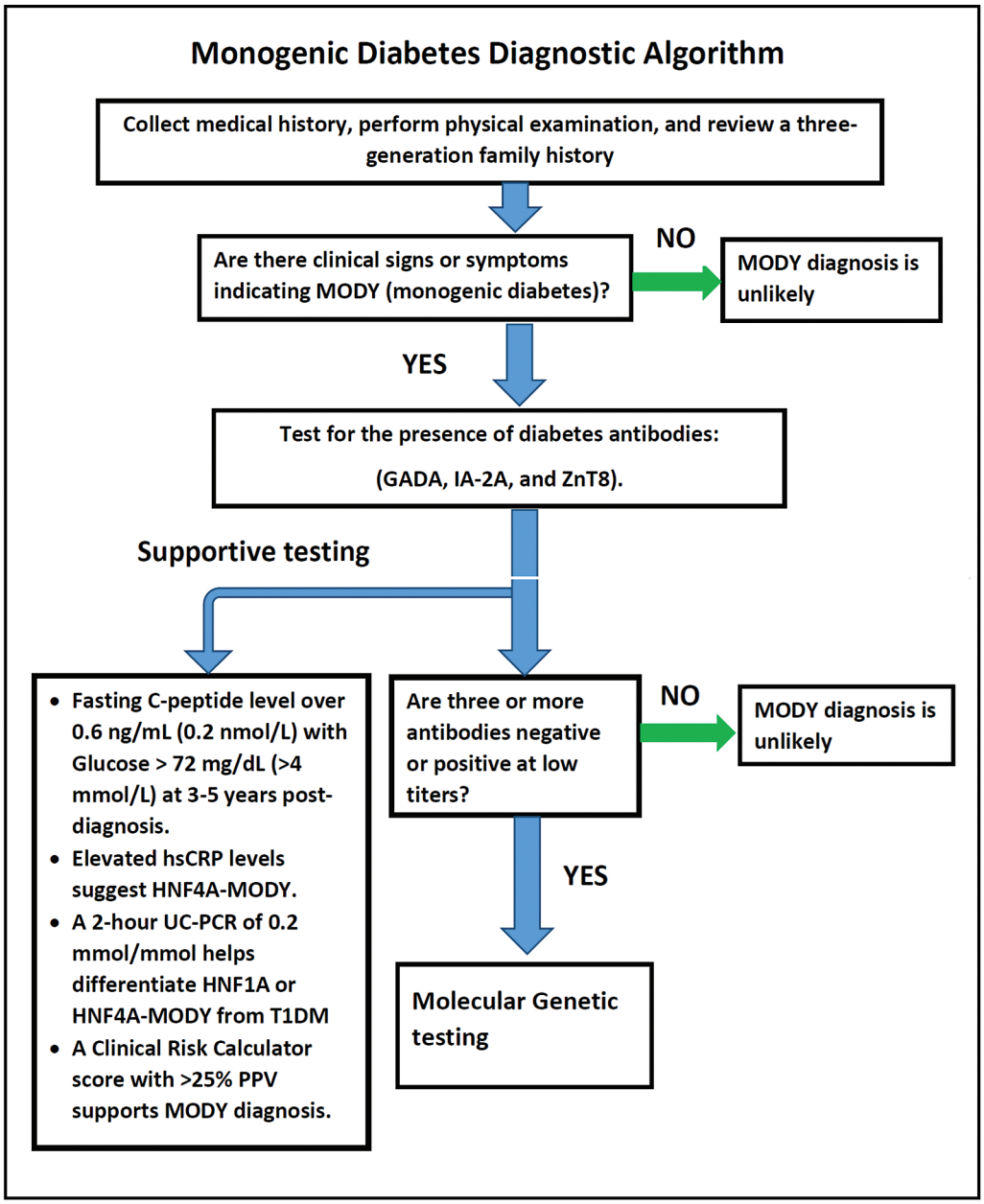

Fig. 1 Maturity-onset diabetes of the young (MODY) monogenic diabetes diagnostic algorithm.

form of monogenic diabetes. Early identification through a thorough family history, clinical evaluation, and genetic testing is essential for differentiating MODY from other diabetes types. In this case, a definitive diagnosis allowed for a shift from insulin to SU therapy, achieving excellent glycemic control with minimal risk of hypoglycemia. Understanding the pathophysiology of HNF1A-MODY enables clinicians to optimize treatment, with SUs as the first-line therapy, given their efficacy in bypassing beta-cell dysfunction. Individualized care remains paramount, while other therapeutic options, such as GLP-1 receptor agonists, DPP-4 inhibitors, and insulin, may complement or replace SUs over time. Moreover, genetic testing of at-risk family members facilitates early detection and intervention, potentially mitigating long-term complications. This case underscores the importance of clinician awareness and a systematic approach in diagnosing and managing monogenic diabetes to achieve favorable outcomes and improve patient and familial care.

Patient Consent Statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Authors' Contributions

H.F. contributed to the drafting of the case report. P.A. clinically reviewed and managed the patient and, as the corresponding author, supervised the preparation of the manuscript and coordinated the submission process. All authors reviewed and approved the final version of the case report.

Compliance with Ethical Principles

No prior ethical approval is required for single case reports and small series provided informed consent is obtained from the patients.

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None.

Conflict of Interest

None declared.

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