DOI: 10.7860/JCDR/2025/77139.22165

Case Series

Internal Medicine Section

From Misdiagnosis to Precision: Genetic Testing Reveals MODY in Adolescents Initially Treated as Type 1 Diabetes

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ABSTRACT

Maturity-Onset Diabetes of the Young (MODY) is a heterogeneous form of clinical monogenic diabetes caused by genetic abnormalities resulting in an autosomal dominant mode of inheritance. MODY accounts for approximately 4.8-10.9% of diabetes cases worldwide; its clinical characteristics often resemble those of Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM), causing underdiagnosis. In this study, we have presented three cases, initially diagnosed with T1DM but later identified as Monogenic Diabetes (MODY) caused by mutations in the HNF1A and HNF4A genes. All patients, despite insulin therapy, suffered from recurrent Diabetic Ketoacidosis (DKA) and poor glycaemic control, prompting further investigation. Genetic analysis revealed two instances of HNF1A (MODY3) mutations and one case of HNF4A (MODY1) mutation. These findings were pivotal in reclassifying the patients' conditions from T1DM to MODY. Understanding the genetic mutations, the patients were switched to a minimal sulfonylurea regimen, resulting in significant improvement in blood glucose control and a reduction in DKA episodes. The studies emphasise the significance of genetic testing in accurately diagnosing MODY and tailoring a personalised treatment with oral sulfonylureas.

Keywords: Diabetes mellitus, Maturity-onset Diabetes of the young, Oral sulfonylureas

CASE REPORT

Diabetes Mellitus (DM) is a chronic condition that is increasingly recognised as a lifestyle-related disease, characterised by a range of phenotypically distinct forms. It is situated within a continuum that includes two vaguely defined types: T1DM and T2DM [1]. T1DM is defined by the autoimmune destruction of pancreatic beta cells, resulting in a complete deficiency of insulin. The incidence of MODY globally is reported to be between 1 and 5 cases per 10,000 individuals, particularly prevalent among European cohorts. MODY encompasses 14 distinct subtypes, each associated with mutations in various genetic factors [2]. The most frequently encountered subtype is MODY 3, followed by MODY 2 and MODY 1, which together account for around 80% of all MODY cases [3]. The rarer subtypes include MODY 5, 6, and 10, while the remaining subtypes collectively make up approximately 1% of MODY cases [4].

Certain genetic forms of diabetes, particularly MODY, can mimic T1DM and often go undiagnosed because of their similar clinical presentations. MODY consists of a group of monogenic disorders caused by mutations that affect insulin secretion. Among these, the HNF1A and HNF4A mutations stand out due to their specific clinical features and differing management strategies [5,6]. This case series discusses three patients who were initially diagnosed with T1DM but were later identified as having MODY, resulting in a modification of their treatment strategies.

CASE SERIES

Case 1

A female patient, aged 18 years, with a body weight of 50 kg and a height of 158 cm, presented to the Emergency Department (ED) due to three instances of vomiting lasting for two days that were non-projectile with abdominal discomfort for a day. The patient was diagnosed with T1DM at the age of three years and was on insulin therapy. Human Actrapid 46 units/day and Human Insulatard 44 units/day were administered, but the diabetes subtype was not evaluated. She had a history of recurrent DKA, occurring at least three times each year, with ongoing hyperglycaemia despite high insulin doses. Family history showed no relevant comorbidities. Management included Intensive Care Unit (ICU) admission for DKA treatment, where laboratory tests were negative for autoantibodies. Genetic testing revealed an HNF1A mutation (MODY type 3), and further details are provided in [Table/Fig-1]. Consequently, the patient was transitioned to a minimal sulfonylurea regimen of 1 mg Glimepiride twice a day and insulin. After monitoring for a week, the patient was confirmed with an optimal glycaemic control and later she was discharged with regular follow-up up to six months and no further episodes of DKA were reported.

Case 2

A 21-year-old male with a body weight of 65 kg and a height of 171 cm, arrived at the ED, presented with severe abdominal pain for three days, dull aching, fever with high grade accompanied by chills and rigours for two days, vomiting for a day, with shortness of breath with no palpitation for the two days. His medical history reveals a diagnosis of T1DM at the age of 11 years, for which he has been on insulin therapy. He has experienced multiple hospitalisations for DKA, at least twice yearly, and one episode of hyperosmolar hyperglycaemic syndrome that required ICU care. Despite receiving maximum insulin doses, his glycaemic control has been inadequate. Family history showed no significant comorbidities. After receiving treatment in the ICU for DKA, autoantibody testing was negative, leading to genetic testing that revealed an HNF4A mutation (MODY type 1) [Table/Fig-1]. He was subsequently prescribed a minimal dose of sulfonylurea, which improved his blood glucose levels, and he was discharged with proper follow-up. Each patient was initially followed up after discharge for one week and subsequently for every month for three months until the glycaemic report was under control. No further follow-up was done if no incidents of DKA were reported.

Case 3

A 17-year-old female with a body weight of 58 kg and a height of 163 cm, presented to the ED with three episodes of vomiting and abdominal pain lasting for two days and dull aching with no other significant symptoms has been reported. While looking into her past medical history, she was diagnosed with T1DM at the age of 3 years. She was also on insulin therapy and had experienced DKA at least once a year. Despite maximum insulin administration, her blood glucose levels remained poorly controlled and family history analysis revealed no significant comorbidities. On examining the physical characteristics, she had a low Body Mass Index (BMI) of 15.1, severe dehydration, and a respiratory rate of 42 cycles per minute. For further details, refer to [Table/Fig-1]. After ICU admission for DKA treatment, investigations showed negative autoantibodies. Genetic testing revealed the presence of an HNF1A mutation (MODY type 3). She was shifted to sulfonylureas, which resulted in effective glycaemic control and a lack of subsequent episodes of DKA during initial follow-up for one week after discharge.

Parameters	Case 1	Case 2	Case 3
Day 0			
CBG (mg/dL)	High	High	High
RBS (mg/dL)	890	635	825
Urine ketone	Positive	Positive	Positive
Urine sugar	Nil	4+	Nil
Autoantibodies testing:			
Gad 65	Negative	Negative	Negative
IAA	Negative	Negative	Negative
ZnT8	Negative	Negative	Negative
IA-2A	Negative	Negative	Negative
C Peptide level	Normal limit	Normal limit	Normal limit
Genetic panel testing			
Protein description	pGly31Asp	p.Gly41Ser	p.Ser142Phe
GAD antibody	Negative	Negative	Negative
HbA1c (%)	10.1	9.7	11
Initial diagnosis	T1DM with DKA	T1DM with DKA	T1DM with DKA
Initial treatment	Insulin 1 U/kg/day	Insulin 1 U/kg/ day	Insulin 1 U/kg/ day
Genetics	Novel heterozygous HNF1A gene in Exon 1 G92c>A (p.Gly31Asp)	Novel heterozygous variation in the HNF4A gene in Exon 8 C.261c>T (p.Gly41ser)	Heterozygous variation HNF1A gene in the Exon 2 c425C>T (p.Ser142Phe)
Final diagnosis	HNF1A MODY	HNF4A MODY	HNF1A MODY
Change in treatment	Sulfonylureas	Sulfonylureas	Sulfonylureas

[Table/Fig-1]: Detailed analysis of various parameters checked for the case series at the time of admission.
CBG: Capillary blood glucose; RBS: Random blood sugar; IAA: Insulin autoantibodies; ZnT8: Zinc transporter 8; IA-2A: Insulinoma associated-2 autoantibodies; GAD: Glutamic acid decarboxylase antibodies; HbA1c: Glycated haemoglobin A1c; T1DM: Type 1 Diabetes mellitus; DKA- Diabetic ketoacidosis; MODY: Maturity-onset diabetes of the young; HNF1A: Hepatocyte nuclear factor 1 alpha; HNF4A: Hepatocyte nuclear factor 4 alpha

DISCUSSION

The monogenic defects are due to a single mutation in the specific gene responsible for the development of β-cell and insulin secretion, causing diabetes, including MODY, genetic syndrome, Permanent Neonatal Diabetes (PNDM), and transient neonatal diabetes [7]. MODY is attributed to a heterozygous mutation in a specific gene, with many cases recognised as haploinsufficiency disorders [8]. A recent discovery has identified a homozygous mutation that also leads to MODY. It is important to consider a MODY diagnosis in individuals with diabetes who lack the typical features of T1DM or T2DM, especially when there is a family history of diabetes in one parent or a first-degree relative. MODY cases involved two instances of the HNF1A gene mutation and one on the HNF4A gene mutation. The MODY reported the first case in 2020 among Africans, in which 5.9% of gene mutation was for HNF1A [9]. Narasimhegowda M et al., have reported similar cases of MODY in a private hospital in Bangalore, but in our case, we had a genetic variant HNF1A and HNF4A. They had genetic variants of HNF1A, HNF1B, and KCNJ11 [10]. The phylogenetic study involved all variant reference sequences for the HNF1A and HNF4A genes accessible in NCBI. This analysis was executed using MEGA 11, resulting in the construction of a phylogenetic tree using the Kimura 2-parameter model with a bootstrapping of 1000. Interestingly, mutations in the HNF1A gene were identified in two instances, and it is significant to note that none of the three cases had a family history of diabetes. Generally, MODY occurs at a younger age, especially when the mutation HNF1A/HNF4A-MODY is reported in adolescence or early adulthood. The present study has also reported on the two gene mutations of patients of the adolescent stage, which agrees with the statement reported on the MODY gene [11]. In all our cases, we experienced that the patients had a lower BMI, especially for case 3 with a BMI of 15.1, which is believed to be a characteristic feature of MODY specifically for HNF1A-MODY and HNF4A-MODY [12].

The initial clinical presentations of these patients led to a diagnosis of T1DM, prompting the recommendation for insulin therapy. Yet, due to recurrent episodes of DKA and insufficient glycaemic control despite maximum insulin doses, further investigation became necessary. The absence of autoantibodies indicated a non-autoimmune cause, thus underscoring the importance of genetic evaluation. MODY is frequently misdiagnosed as T1DM due to overlapping symptoms. The identification of specific genetic mutations, including HNF1A and HNF4A, can have a profound impact on management strategies. These genes are essential for the regulation of insulin secretion in pancreatic β-cells, and mutations can disrupt this process, leading to diminished insulin secretion in genotype-positive prediabetic individuals, who show a reduced insulin response to high glucose levels [13].

Individuals with HNF1A-MODY are typically at increased risk for complications related to diabetes, as glycaemic control tends to deteriorate over time [14]. The presence of these mutations is correlated with the preservation of beta-cell function, enabling successful management using oral hypoglycaemic agents and consequently preventing complications that may arise from insulin therapy, including DKA. The switch to sulfonylureas not only led to better glycaemic control but also improved these patients' quality of life by minimising hospitalisations and DKA complications. This is due to the fact that HNF1A- and HNF4A-related diabetes has an increased sensitivity to sulfonylureas, a group of drugs that stimulate the release of insulin [15]. This process is initiated when the sulfonylureas bind to the subunit of the KATP channel; as a result, depolarisation occurs in the β-cell and thus initiates the release of insulin. Sulfonylurease is much better than metformin in patients with HNF1A- and HNF4A-MODY [16]. This case series strongly supports the need for genetic testing in younger patients exhibiting atypical diabetes symptoms to ensure accurate diagnosis and customised treatment plans. By integrating genetic testing into routine diabetes diagnostic procedures, healthcare professionals can create more tailored and effective management plans, ultimately improving patient outcomes.

CONCLUSION(S)

This case series emphasises the significance of genetic screening in young patients with T1DM, mainly those encountering recurrent DKA with poor metabolic control. Early detection of MODY can substantially influence the treatment regime and transition to oral medications, eventually enhancing glycaemic control and reducing the complications associated with diabetes ketoacidosis. This study

highlights the importance of considering MODY in individuals with atypical diabetes and a family history, ultimately leading to more effective and tailored care strategies.

REFERENCES

[1] Aarthy R, Aston-Mourney K, Mikocka-Walus A, Radha V, Amutha A, Anjana RM, et al. Clinical features, complications, and treatment of rarer forms of maturity-onset diabetes of the young (MODY) - A review. J Diabetes Complications. 2021;35(1):107640.

[2] Caballero LS, Gorgogietas V, Arroyo MN, Igoillo-Esteve M. Molecular mechanisms of β-cell dysfunction and death in monogenic forms of diabetes. Int Rev Cell Mol Biol. 2021;359:139-256.

[3] Nkonge KM, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). Clin Diabetes Endocrinol. 2020;6(1):20.

[4] Szopa M, Ludwig-Galezowska AH, Radkowski P, Skupien J, Machlowska J, Klupa T, et al. A family with the Arg103Pro mutation in the NEUROD1 gene detected by next-generation sequencing - Clinical characteristics of mutation carriers. Eur J Med Genet. 2016;59(2):75-79.

[5] Warncke K, Kummer S, Raile K, Grulich-Henn J, Woelfle J, Steichen E, et al. Frequency and characteristics of MODY 1 (HNF4A Mutation) and MODY 5 (HNF1B Mutation): Analysis from the DPV database. J Clin Endocrinol Metab. 2019;104(3):845-55.

[6] World Health Organization. Classification of diabetes mellitus. Geneva: World Health Organization. 2019.

[7] Ferrer J. A genetic switch in pancreatic beta-cells: Implications for differentiation and haploinsufficiency. Diabetes. 2002;51(8):2355-62.

[8] Matsha TE, Raghubeer S, Tshivhase AM, Davids SF, Hon GM, Bjorkhaug L, et al. Incidence of HNF1A and GCK MODY variants in a South African population. Appl Clin Genet. 2020;13:209-19.

[9] Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, et al. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. PLoS Med. 2007;4(4):e118.

[10] Narasimhegowda M, Nagarajappa VH, Palany R. A case series of maturity-onset diabetes of the young highlighting atypical presentations and the implications of genetic diagnosis. Arch Endocrinol Metab. 2024;68:e230239. Doi: 10.20945/2359-4292-2023-0239.

[11] Yau D, Colclough K, Natarajan A, Parikh R, Canham N, Didi M, et al. Congenital hyperinsulinism due to mutations in HNF1A. Eur J Med Genet. 2020;63(6):103928.

[12] Misra S, Hassanali N, Bennett AJ, Juszczak A, Caswell R, Colclough K, et al. Homozygous Hypomorphic HNF1A alleles are a novel cause of young-onset diabetes and result in sulfonylurea-sensitive diabetes. Diabetes Care. 2020;43:909-12.

[13] Byrne MM, Sturis J, Menzel S, Yamagata K, Fajans SS, Dronsfield MJ, et al. Altered insulin secretory responses to glucose in diabetic and nondiabetic subjects with mutations in the diabetes susceptibility gene MODY3 on chromosome 12. Diabetes. 1996;45(11):1503-10.

[14] Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. Diabet Med. 2009;26(4):437-41.

[15] Pearson ER, Liddell WG, Shepherd M, Corrall RJ, Hattersley AT. Sensitivity to sulphonylureas in patients with hepatocyte nuclear factor-1alpha gene mutations: Evidence for pharmacogenetics in diabetes. Diabet Med. 2000;17(7):543-45

[16] Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet. 2003;362(9392):1275-81.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Dec 20, 2024
- Manual Googling: Sep 15, 2025
- iThenticate Software: Sep 17, 2025 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Dec 19, 2024**
Date of Peer Review: **Feb 19, 2025**
Date of Acceptance: **Sep 19, 2025**
Date of Publishing: **Dec 01, 2025**