HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2022.88886
Haydarpasa Numune Med J 2024;64(1):125–127

CASE REPORT

Maturity-Onset Diabetes of the Young-2 (MODY2) in Youth

Ayşe Gümüş Özçelik, Akın Dayan, Memet Taşkın Egici

University of Health Sciences Turkiye, Haydarpasa Numune Training and Research Hospital, Family of Medicine, Istanbul, Turkiye

Abstract

Maturity-Onset Diabetes of the Young (MODY) is an autosomal dominant inherited monogenic disease that emerges in youth. The primary defect is a loss of beta-cell function, impairing insulin secretion. Its prevalence among all diabetes cases varies between 2% and 5%. The most common forms, MODY2 and MODY3, are caused by mutations in the glucokinase and hepatocyte nuclear factor 1-alpha genes, respectively. MODY2, resulting from heterozygous inactivating mutations of the glucokinase gene, is characterized by mild fasting hyperglycemia. It can be controlled by diet and is considered in cases of familial diabetes, impaired glucose tolerance, or gestational diabetes. This case presents a patient diagnosed with diabetes during pregnancy, who was later found to have the heterozygous p.MET394Thr(c.1181T>C) variation in the GCK gene mutation analysis, a finding also present in her child. Clinically recognizing MODY cases and differentiating them from Type 1 and Type 2 diabetes is crucial in treatment selection. Primary care physicians should consider MODY in the differential diagnosis for diabetes patients, as it can guide early diagnosis and treatment choices.

Keywords: Glucokinase; Hepatocyte Nuclear Factor 1-Alpha; Hyperglycemia.

Maturity-Onset Diabetes of the Young (MODY) in youth is caused by autosomal dominant mutations in a single gene, leading to dysfunction in beta cells.[1] Characteristics suggesting a MODY clinical diagnosis include autosomal dominant inheritance with a similar glycemic pattern across at least three generations, diagnosis before the age of 25, absence of pancreatic autoantibodies, ongoing endogenous insulin production, and measurable C-peptide levels in the state of hyperglycemia.[1-6] These features are atypical for Type 1 diabetes, but the early onset overlaps with Type 1 diabetes. In Type 2 diabetics, the absence of obesity and acanthosis nigricans, normal triglyceride levels, normal or increased high-density lipoprotein (HDL) cholesterol levels, and the lack of insulin resistance suggest monogenic diabetes.[4]

Definitive diagnosis of MODY requires sequencing of MODY genes.[7] MODY is a heterogeneous disease with different genetic and clinical characteristics, so its true prevalence is difficult to determine. According to studies supported by laboratory methods and genetic analyses used for MODY detection, its prevalence among all diabetes cases varies between 2-5%.[8-9] Currently, mutations in 14 different genes are known to play a role in the etiopathogenesis of MODY.[10] Among these, the Hepatocyte Nuclear Factor 1-alpha (HNF1A) and glucokinase (GCK) genes are the most well-known, observed in approximately 52-65% and 15-32% of MODY patients, respectively.[11-13] Glucokinase enzyme mutations leading to MODY are characterized by asymptomatic, mild, and non-progressive fasting hyperglycemia and generally do not require pharmacological treatment.

In contrast, mutations in HNF1A and HNF4A in other MODY

Correspondence: Ayşe Gümüş Özçelik, M.D. University of Health Sciences Turkiye, Haydarpasa Numune Training and Research Hospital, Family of Medicine, Istanbul, Turkiye
Phone: +90 536 705 40 27 **E-mail:** gumusayseee@gmail.com
Submitted Date: 13.04.2022 **Revised Date:** 10.06.2022 **Accepted Date:** 20.06.2022

subtypes are associated with progressive insulin secretion disorders, hyperglycemia, and vascular complications due to this glycemic state.[4,14] Glucokinase, one of the enzyme isoforms that catalyzes the phosphorylation of glucose to glucose-6-phosphate, is the first step in glucose metabolism. A moderate diabetic phenotype is associated with impaired glucose sensitivity in beta cells. Moderate elevation in fasting glucose levels is present in early childhood and typically remains stable for the rest of life. The age of diagnosis varies depending on when blood glucose measurement is first performed. Differentiating MODY2 from Type 1 and Type 2 diabetes is essential in treatment selection. MODY3, caused by mutations in the Hepatocyte Nuclear Factor 1-alpha (HNF-1A) genes, is a more severe form of diabetes than GCK-MODY. It is characterized by reduced expression of SGLT2 in the proximal tubules and renal tubular dysfunction resulting in renal glucosuria. It is sensitive to low doses of sulfonylureas. In cases where diabetes onset occurs later, insulin treatment is highly needed. Micro and macrovascular complications can appear similarly to T1DM and T2DM. The frequency and mortality of cardiovascular disease have increased.[15]

Case Report

A 39-year-old female patient with no known chronic diseases other than a diagnosis of diabetes presented during her first pregnancy (2009) at 26 years of age. In the 27th week of her pregnancy, she was diagnosed with gestational diabetes based on Oral Glucose Tolerance Test (OGTT) results and started on insulin therapy. Post-pregnancy, she was treated with oral antidiabetics for a Type 2 diabetes diagnosis. During her second pregnancy (2012), she was again managed with insulin therapy. Her family history revealed that her mother also had diabetes, controlled with oral antidiabetics. Since 2014, the patient has been monitored in a Family Medicine clinic, with fasting blood sugar levels between 117-134 mg/dL, glycosylated hemoglobin (HbA1c) levels of 5.8-6.2%, C-peptide levels of 1.18-1.24, HDL cholesterol levels of 48-61 mg/dL, LDL cholesterol levels of 56-75.6 mg/dL, and triglyceride levels of 35-52 mg/dL. Her postprandial plasma glucose levels never exceeded 200 mg/dL. Physical examination revealed a weight of 55 kg, height of 166 cm, and a Body Mass Index (BMI) of 20 kg/m^2. Her waist circumference was 78 cm, and her blood pressure measured in the clinic was 110/75 mmHg. Her medications included Metformin 2x1000mg. No micro or macro complications of diabetes were found upon examination and testing. Considering parameters such as high fasting blood sugar levels, low postprandial plasma glucose levels, regular insulin and C-peptide levels, and the absence of overweight or obesity, a preliminary diagnosis of Maturity-Onset Diabetes of the Young (MODY) was considered, and genetic testing was requested. The genetic test identified that she carries the heterozygous p.Met394Thr(c.1181T>C) variation in the analyzed GCK gene.

In 2012, her male child, born weighing 2920 grams at 38 weeks of gestation, started to exhibit excessive drinking and frequent urination at the age of 9 (2021). Due to these symptoms, his family took him to a pediatric endocrinology and metabolism clinic. Knowing the mother's MODY2 diagnosis, genetic testing was requested for the child. The genetic test revealed that he, like his mother, carries the heterozygous p.Met394Thr(c.1181T>C) variation in the analyzed GCK gene.

Discussion

Maturity-Onset Diabetes of the Young (MODY) is an autosomal dominant inherited monogenic form of diabetes exhibiting genetic, metabolic, and clinical heterogeneity. GCK-MODY, one of the most common types among MODY, typically progresses asymptomatically and is diagnosed through incidental findings of hyperglycemia. Many cases have a family history and a history of gestational diabetes. Our case was asymptomatic, but high blood sugar levels measured during the OGTT in her pregnancy led to a diagnosis of gestational diabetes. Characteristics distinguishing GCK-MODY patients from other MODY types include mild fasting hyperglycemia, a modest increase in glucose levels at the 120th minute of the OGTT, and generally HbA1c levels below 8%.[1-16]

Genetic testing for MODY subtyping plays a significant role in determining complications' risk and choosing treatment. GCK-MODY cases with mild hyperglycemia do not typically exhibit microvascular complications.[17] Although there is insufficient data regarding macrovascular complications, it is believed that the risk of cardiovascular disease is not increased.[18] Consistent with these findings, no micro or macrovascular complications were observed in our patient diagnosed with GCK-MODY.

Martin et al.[19] reported that GCK-MODY patients showed increased body mass index and blood sugar levels and decreased insulin sensitivity. Therefore, it is recommended that HbA1c levels be monitored annually for GCK-MODY patients. In line with these recommendations, we have followed up our patient with annual HbA1c controls.

Diagnosing MODY cases through genetic screening is also essential for providing genetic counselling services for their

future offspring. Genetic counselling provided to our patient diagnosed with GCK-MODY could have facilitated an earlier diagnosis for her son, who carries the same variation.

Conclusion

In patients followed for Type 1 and Type 2 Diabetes Mellitus (DM) diagnoses but exhibiting atypical progressions, considering monogenic diabetes in the diagnosis and confirming it with appropriate molecular tests plays a crucial role in treatment decisions. Increasing awareness of MODY among primary care physicians can facilitate timely diagnosis, proper treatment of patients, and provide genetic counselling, enabling screening of individuals at risk.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept: A.D.; Design: A.G.Ö.; Supervision: A.G.Ö., A.D.; Materials: A.G.Ö., A.D.; Data Collection or Processing: A.G.Ö., A.D.; Analysis or Interpretation: M.T.E.; Literature Search: A.G.Ö.; Writing: A.G.Ö.; Critical Review: A.D., M.T.E.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. McDonald TJ, Ellard S. Maturity onset diabetes of the young: Identification and diagnosis. Ann Clin Biochem 2013;50:403–15.[CrossRef]
2. Agarwal SK, Khatri S, Prakash N, Singh NP, Anuradha S, Prakash A. Maturity onset diabetes of young. J Indian Acad Clin Med 2002;3:271–7.
3. Bosma AR, Rigter T, Weinreich SS, Cornel MC, Henneman L. A genetic diagnosis of maturity-onset diabetes of the young (MODY): Experiences of patients and family members. Diabet Med 2015;32:1385–92.[CrossRef]
4. Gardner DS, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). Diabetes Metab Syndr Obes 2012;5:101–8.[CrossRef]
5. Nakhla M, Polychronakos C. Monogenic and other unusual causes of diabetes mellitus. Pediatr Clin North Am 2005;52:1637–50.[CrossRef]
6. Ovsyannikova AK, Rymar OD, Shakhtshneider EV, Klimontov VV, Koroleva EA, Myakina NE, et al. ABCC8-related maturity-onset diabetes of the young (MODY12): Clinical features and treatment perspective. Diabetes Ther 2016;7:591–600 .[CrossRef]
7. Oliveira SC, Neves JS, Pérez A, Carvalho D. Maturity-onset diabetes of the young: From a molecular basis perspective toward the clinical phenotype and proper management. Endocrinol Diabetes Nutr (Engl Ed) [Article in English, Spanish] 2020;67:137–47.[CrossRef]
8. McDonald TJ, Colclough K, Brown R, Shields B, Shepherd M, Bingley P, et al. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet Med 2011;28:1028–33.[CrossRef]
9. Thanabalasingham G, Owen KR. Diagnosis and management of maturity onset diabetes of the young (MODY). BMJ 2011;343:d6044.[CrossRef]
10. 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;6:20.[CrossRef]
11. Naylor R, Philipson LH. Who should have genetic testing for maturity-onset diabetes of the young? Clin Endocrinol (Oxf) 2011;75:422–6.[CrossRef]
12. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): How many cases are we missing? Diabetologia 2010;53:2504–8.
13. Yamagata K, Furuta H, Oda N, Kaisaki PJ, Menzel S, Cox NJ, et al. Mutations in the hepatocyte nuclear factor-4alpha gene in maturity-onset diabetes of the young (MODY1). Nature 1996;384:458–60.[CrossRef]
14. Hattersley AT, Patel KA. Precision diabetes: Learning from monogenic diabetes. Diabetologia 2017;60:769–77.[CrossRef]
15. Vaxillaire M, Froguel P. Monogenic diabetes in the young, pharmacogenetics and relevance to multifactorial forms of type 2 diabetes. Endocr Rev 2008;29:254–64..[CrossRef]
16. Matschinsky F, Liang Y, Kesavan P, Wang L, Froguel P, Velho G, et al. Glucokinase as pancreatic beta cell glucose sensor and diabetes gene. J Clin Invest 1993;92:2092–8.[CrossRef]
17. Velho G, Blanché H, Vaxillaire M, Bellanné-Chantelot C, Pardini VC, Timsit J, et al. Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families. Diabetologia 1997;40:217–24.[CrossRef]
18. Schober E, Rami B, Grabert M, Thon A, Kapellen T, Reinehr T, et al. Phenotypical aspects of maturity-onset diabetes of the young (MODY diabetes) in comparison with Type 2 diabetes mellitus (T2DM) in children and adolescents: Experience from a large multicentre database. Diabet Med 2009;26:466–73.[CrossRef]
19. Martin D, Bellanné-Chantelot C, Deschamps I, Froguel P, Robert JJ, Velho G. Long-term follow-up of oral glucose tolerance test-derived glucose tolerance and insulin secretion and insulin sensitivity indexes in subjects with glucokinase mutations (MODY2). Diabetes Care 2008;31:1321–3.[CrossRef]