ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Commentary

When We Must Think to MODY Type of Diabetes?

Daniel Zamanfar[1]*, Mohamad Bagher Hashemi Soteh[2], Mobin Ghazaiean[3] and Somayeh Rostami Maskopaii[4]

[1]*Associated Professor, Pediatric Endocrinologist, Diabetes Research Center of Mazandaran, Mazandaran University of Medical Sciences, Sari, Iran*

[2]*Immunogenic Research Center, Molecular and Cell Biology Research Center, Faculty of Medical Sciences, Sari, Iran*

[3]*School of Medicine, Mazandaran university of Medical Sciences, Sari, Iran*

[4]*Mazandaran University of Medical Sciences, Sari, Iran*

***Corresponding Author:** Daniel Zamanfar, Assistant Professor, Pediatric Endocrinologist, Diabetes Research Center of Mazandaran, Mazandaran University of Medical Sciences, Sari, Iran.

Received: August 23, 2022; **Published:** September 01, 2022

Diabetes is a group of metabolic illnesses characterized by poor insulin manufacturing, glucose sensing, channelopathy, and endoplasmic reticulum dysfunction, all of which limit beta cell expression and function [1-4]. Diabetes, which encompasses both type 1 and type 2 diabetes, is genetically polygenic in general [2]. MODY, NDM (TNDM, PNDM), and syndromic diabetes are examples of monogenic diabetes [1,3,4]. Insulin-dependent diabetes, often known as type 1 diabetes, is an early form of autoimmune disease. Non-insulin-dependent diabetes, on the other hand, can be polygenic or monogenic, with type 2 diabetes being an example of non-insulin-dependent polygenic diabetes [2,5]. NDM, MODY, and other unusual diabetes-related disorders are examples of non-insulin-dependent monogenic diabetes [1,3-5]. MODY is a non-classic NIDDM, which means that insulin secretion and function are unaffected [6]. In fact, single gene changes in beta cells decrease the progression of the disease [6,7]. MODY is characterized by a set of criteria based on the clinical presentation and symptoms of the patient.

Early signs and symptoms

In reality, at least two members of the family under the age of 25 could be participating. Depending on the number of persons in the family, diagnostic testing, and anticipation, this cut-off can be adjusted. The anticipation effect has resulted in the disease's age decreasing as more and more generations of the family become engaged. The disease has been diagnosed at an early age thanks to the development of diagnostic tests [8,9]. Involvement in a family member as well as a moderate form of diabetes, on the other hand, will be detected at a later age, such as in MODY 3, when ages are taken into account 10 - 60 [10]. Non-insulin dependent diabetes mellitus (NIDDM) is a kind of diabetes defined by a certain quantity of C-peptide or the absence of the requirement for insulin treatment within 5 years after diagnosis. In situations of IDDM, where a person's hyperglycemic condition may be maintained by food and hypoglycemic medicines for a honeymoon period, this kind of diabetes is suspected [8]. MODY is a kind of non-insulin-dependent diabetes mellitus (NIDDM) that can develop both type 1 and type 2 diabetes. In reality, it is suspected of having type 2 diabetes due to two characteristics: NIDDM and a positive family history. On the other hand, in some type 1 diabetes instances, beta cells are gradually destroyed, making it harder for a person to require beginning insulin therapy [11-15]. MODY inheritance is a dominant or pseudo-dominant autosomal type of inheritance. A single gene is involved in dominant inheritance. Polygenic diseases are implicated in the pseudo-dominant. Both horizontal and vertical transmission can be noticed during pregnancy. The early signs of NIDDM in family members are more likely to be caused by a single gene. A good family history is indicated by autosomal dominant inheritance. According to reports, the majority of young persons with diabetes who have no

family history of the disease do not have a MODY diagnosis. However, some patients are left out due to a lack of understanding about their family history [9,16]. MODY is caused by more than ten genes [17]. MODY is caused by mutations on distinct chromosomes.

Types 1 through 5 are caused by chromosomal 20q, 7p, 12q, 13q, and 17q abnormalities, respectively (7). MODY 1: HNF-4 functions as an HNF-1 regulator in the steroid/thyroid branch, regulating the action of hormone receptors [7,17]. This kind of MODY appears between the ages of 7 and 15. Despite the fact that insulin function is unaffected, the first and second stages of insulin production are gradually disrupted, with up to 30% of patients eventually requiring insulin due to insulin resistance [6,7]. MODY 2: Different types of diabetes can be caused by mutations in the GCK gene, depending on the type of mutation; MODY (heterozygous mutation) or NDM (non-diabetes mellitus) (homozygous mutation). The most prevalent MODY variation is caused by this mutation [5,18,19]. This enzyme works as a glucose sensor and is a limiting enzyme in the process of insulin release in beta cells in response to glucose uptake [20]. These patients exhibit mild hyperglycemia, which can lead to insulin resistance over time, but the vascular consequences are unexpected due to the non-progressive nature of this mutation [5,19,21-23]. Blood and urine (glucosuria) tests are used to diagnose these patients before puberty [22]. The infant may increase weight, lose weight, or be normal weight depending on the mutation and the parents [24]. MODY 3 is the most frequent MODY variant in Asia, Europe, and North America, and it is caused by a mutation in the HNF-1 gene [21]. It can be found in the liver, kidneys, and pancreas, among other organs [25,26]. This mutation, unlike the GCK mutation, is progressive, resulting in a decrease in pancreatic endocrine secretion in response to stimulation [17]. This MODY manifests itself in adulthood as abnormal glucose tolerance tests (GTT) and insulin resistance, which are not visible before puberty [10]. The nephropathy manifested as glucosuria, aminoaciduria, and albuminuria due to proximal tubule damage [26]. MODY 4: The IPF-1, like HNF-factors, plays a role in the development and function of beta cells [27,28]. Different forms of diabetes can result from mutations in this gene, depending on whether the endocrine or exocrine systems are involved. MODY 4 is produced if the illness is solely endocrine, and PNDM is produced if it is both endocrine and exocrine [29,30]. MODY 4 has symptoms that are similar to MODY 1 [31]. Hyperinsulinemia and obesity at a young age are the most notable features of MODY 4 [32]. Vascular problems such as retinopathy and nephropathy can occur as a result of hyperglycemia [27,32,33]. MODY 5 is caused by a mutation in HNF-1, which is important in the development of the pancreas, kidney, and genitalia [34,35]. On the other hand, heterozygous HNF-1 mutations can result in syndromic NDM [36-38]. GTT and plasma glucose levels were normal until the age of ten, as they were in MODY 3 and MODY 4, but as the patient's age increased, so did their glucose control and GTT [34,35]. Urogenital involvement, such as renal cysts (the most common finding), renal dysplasia, and genital abnormalities, are examples of extra pancreatic observations [31,36,39]. Renal problems can occur without the presence of nephropathy or the beginning of diabetes [40]. Family history is not relevant to diagnosis due to a spontaneous mutation in the HNF-1 gene [41]. Clinical findings were utilized to confirm the condition, and laboratory data was used to rule out alternative kinds of diabetes in the MODY diagnosis. Age at commencement of disease, non-insulin dependence, autosomal dominant inheritance, BMI, and laboratory data such as islet auto-antibody, OGTT, and serum C-peptide levels are among the clinical findings [42,43]. The best way to tell the difference between MODY and type 2 diabetes is to look at how old you are [44]. Antibodies against islet antigen 2 are among the autoantibodies utilized in the diagnosis of diabetes. Islet cells and glutamic acid decarboxylase [45]. The sensitivity of plasma indicators such as autoantibodies, high-sensitivity C-reactive protein (CRP), lipid profile, and C-peptide in the diagnosis varies [46-51]. Patients with diabetes have been diagnosed despite modest auto-antibody titration, and auto-antibody titration diminishes as the disease advances, therefore auto-antibodies are not a trustworthy criterion. Because a level of C-peptide was discovered to be discriminable in patients with early and chronic diabetes, C-peptide is not a sufficient criterion for diagnosis [52]. The lipid profile of all patients with the HNF-4 mutation decreased, whereas LDL rose [53,54]. When compared to the normal condition, people with GCK mutation have a higher HbA1c and a lower lipid profile (HDL-cholesterol) [55]. Because HNF-1 is involved in protein fucosylation as well as CRP's proper function, both the CRP and plasma glycoprotein profile are useful in detecting the HNF-1 mutation [49,56-60]. Patients with the HNF-1 and GCK mutations have significantly lower CRP than those with the GCK mutation [56]. To distinguish type 1 diabetes with HNF-1 and HNF-4 mutations, urine and postprandial C-peptide are employed [47]. The absence of glycosuria in individuals with HNF-4, as well as low levels of plasma apolipoproteins such as apoA, apoB, and apoC, are among the differences that can

be made between HNF-1 and HNF-1 [61]. When a young non-obese child with a positive family history and abnormal tests such as FBS, OGTT, and negative auto-antibody does not suffer any stress, genetic analysis is undertaken [62]. The most essential aspect of the sequencing method at the moment is determining the pathogenicity of the variation [63]. Common mutations induce less impairment in beta cell function and plasma glucose, according to a study of phenotypic variants of dominant genes [64]. The three genes HNF-4, HNF-1, and GCK are responsible for about 80% of MODY instances [42]. It is critical to identify MODY patients as soon as possible in order to reduce vascular problems and insulin resistance [21]. Nephropathy is one of the vascular problems in MODY patients. Mild hyperglycemia in MODY 2 seldom leads to vascular problems among MODY patients [5,19,21]. MODY 1 and 4 are caused by a lack of glycemia regulation, resulting in nephropathy [17,19,21,31]. Both micro and macrovascular problems affect MODY 3 individuals [10,65]. Renal involvement, on the other hand, refutes a Fanconi syndrome in these patients [26]. Renal problems in MODY 5 patients can result in hypoplastic glomerulocystic disease due to the production of renal cysts [40]. MODY can also be diagnosed based on medication, as young persons with diabetes who are not fat respond well to sulphonylurea therapy [66]. The K-channels are closed by hypoglycemic drugs like sulphonylurea. Treatment of patients with the GCK mutation does not lower glucose levels or HbA1c because it reduces endogenous insulin secretion in these patients [67]. Patients with HNF-1 and HNF-1 mutations receive comparable treatment, which begins with a low-dose sulphonylurea [53]. Insulin, dipeptidyl peptidase-4 (DPP-4) and glucagon-like peptide-1 (GLP-1) receptor agonists can be administered if sulphonylurea treatment fails in patients with HNF-1 and HNF-4 mutations [68]. In patients with the IPF-1 mutation, insulin and hypoglycemic medications may be administered [34,35]. In patients with HNF-1 mutations, unlike HNF-1 and HNF-4 mutations, insulin is the first line of treatment [68,69].

Bibliography

1. Murphy R., *et al*. "Clinical implications of a molecular genetic classification of monogenic β-cell diabetes". *Nature Clinical Practice Endocrinology and Metabolism* 4.4 (2008): 200-213.

2. McCarthy MI. "Biological and translational insights from T2DM genetics". *Nature Reviews Endocrinology* 13.2 (2017): 71-72.

3. Philipson LH., *et al*. "Genetic testing in diabetes mellitus: a clinical guide to monogenic diabetes". *Genetic Diagnosis of Endocrine Disorders* (2010): 17-25.

4. Porter JR and Barrett TG. "Monogenic syndromes of abnormal glucose homeostasis: clinical review and relevance to the understanding of the pathology of insulin resistance and β cell failure". *Journal of Medical Genetics* 42.12 (2005): 893-902.

5. Velho G and Froguel P. "Genetic determinants of non-insulin-dependent diabetes mellitus: strategies and recent results". *Diabetes and Metabolism* 23.1 (1997): 7-17.

6. Mellitus D. "Diagnosis and classification of diabetes mellitus". *Diabetes Care* 28.S37 (2005): S5-S10.

7. Polonsky KS. "The β-cell in diabetes: from molecular genetics to clinical research". *Diabetes* 44.6 (1995): 705-717.

8. Tattersall R and Mansell P. "Maturity onset-type diabetes of the young (MODY): one condition or many?" *Diabetic Medicine* 8.5 (1991): 402-410.

9. Hattersley A. "Genetic factors in the aetiology of non-insulin-dependent diabetes". *Molecular Pathology of Diabetes Mellitus* 22 (1997): 157-178.

10. Isomaa B., *et al*. "Chronic diabetic complications in patients with MODY3 diabetes". *Diabetologia* 41.4 (1998): 467-473.

11. Yokoyama H., *et al*. "Existence of early-onset NIDDM Japanese demonstrating severe diabetic complications". *Diabetes Care* 20.5 (1997): 844-847.

12. Yamada S., *et al*. "Identification of mutations in the hepatocyte nuclear factor (HNF)-1α gene in Japanese subjects with IDDM". *Diabetes* 46.10 (1997): 1643-1647.

13. Møller A., *et al*. "Mutations in the hepatocyte nuclear factor-1α gene in Caucasian families originally classified as having type I diabetes". *Diabetologia* 41.12 (1998): 1528-1531.

14. DiMeglio LA., *et al*. "Type 1 diabetes". *The Lancet* 391.10138 (2018): 2449-2462.

15. Parkkola A., *et al*. "Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children". *Diabetes Care* 36.2 (2013): 348-354.

16. Froguel P., *et al*. "Familial hyperglycemia due to mutations in glucokinase--definition of a subtype of diabetes mellitus". *New England Journal of Medicine* 328.10 (1993): 697-702.

17. Fajans SS and Brown MB. "Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young". *Diabetes Care* 16.9 (1993): 1254-1261.

18. Njølstad PR., *et al*. "Neonatal diabetes mellitus due to complete glucokinase deficiency". *New England Journal of Medicine* 344.21 (2001): 1588-1592.

19. Velho G and Froguel P. "Genetic, metabolic and clinical characteristics of maturity onset diabetes of the young". *European Journal of Endocrinology* 138.3 (1998): 233-239.

20. Appleton M., *et al*. "Clinical characteristics of HNF1 alpha (MODY3) and glucokinase mutations". Diabetologia PRINGER VERLAG 175 FIFTH AVE, NEW YORK, NY 175 (1997): 10010.

21. Hattersley A. "Maturity-onset diabetes of the young: clinical heterogeneity explained by genetic heterogeneity". *Diabetic Medicine* 15.1 (1998): 15-24.

22. Clement K., *et al*. "Assessment of insulin sensitivity in glucokinase-deficient subjects". *Diabetologia* 39.1 (1996): 82-90.

23. Byrne MM., *et al*. "Insulin secretory abnormalities in subjects with hyperglycemia due to glucokinase mutations". *The Journal of Clinical Investigation* 93.3 (1994): 1120-1130.

24. Colom C and Corcoy R. "Maturity onset diabetes of the young and pregnancy". *Best Practice and Research Clinical Endocrinology and Metabolism* 24.4 (2010): 605-615.

25. Yamagata K., *et al*. "Mutations in the hepatocyte nuclear factor-1α gene in maturity-onset diabetes of the young (MODY3)". *Nature* 384.6608 (1996): 455-458.

26. Pontoglio M., *et al*. "Hepatocyte nuclear factor 1 inactivation results in hepatic dysfunction, phenylketonuria, and renal Fanconi syndrome". *Cell* 84.4 (1996): 575-585.

27. Stoffers DA., *et al*. "Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence". *Nature Genetics* 15.1 (1997): 106-110.

28. Staffers DA., *et al*. "Early-onset type-ll diabetes mellitus (MODY4) linked to IPF1". *Nature Genetics* 17.2 (1997): 138-139.

29. Melloul D., *et al*. "Pancreatic Duodenal Homeobox (PDX-1) in health and disease". *Journal of Pediatric Endocrinology and Metabolism* 15.9 (2002): 1461-1472.

30. Thomas IH., *et al*. "Neonatal diabetes mellitus with pancreatic agenesis in an infant with homozygous IPF-1 Pro63fsX60 mutation". *Pediatric Diabetes* 10.7 (2009): 492-496.

31. Bingham C., *et al*. "Abnormal nephron development associated with a frameshift mutation in the transcription factor hepatocyte nuclear factor-1β1: 1See Editorial by Woolf, p. 1202". *Kidney International* 57.3 (2000): 898-907.

32. Fajans SS., *et al*. "Obesity and hyperinsulinemia in a family with pancreatic agenesis and MODY caused by the IPF1 mutation Pro63fsX60". *Translational Research* 156.1 (2010): 7-14.

33. Gragnoli C., *et al*. "IPF-1/MODY4 gene missense mutation in an Italian family with type 2 and gestational diabetes". *Metabolism* 54.8 (2005): 983-988.

34. Ryffel G. "Mutations in the human genes encoding the transcription factors of the hepatocyte nuclear factor (HNF) 1 and HNF4 families: functional and pathological consequences". *Journal of Molecular Endocrinology* 27.1 (2001): 11-29.

35. Iwasaki N., *et al*. "Splice site mutation in the hepatocyte nuclear factor-1β gene, IVS2nt+ 1G> A, associated with maturity-onset diabetes of the young, renal dysplasia and bicornuate uterus". *Diabetologia* 44.3 (2001): 387-388.

36. Edghill E., *et al*. "Hepatocyte nuclear factor-1 beta mutations cause neonatal diabetes and intrauterine growth retardation: support for a critical role of HNF-1β in human pancreatic development". *Diabetic Medicine* 23.12 (2006): 1301-1306.

37. Yorifuji T., *et al*. "Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1β gene due to germline mosaicism". *The Journal of Clinical Endocrinology and Metabolism* 89.6 (2004): 2905-2908.

38. D'Amato E and Lorini R. "Letter Re: Neonatal diabetes mellitus and mutation in the HNF-1beta gene". *The Journal of Clinical Endocrinology and Metabolism* 90.10 (2005): 5906-5907.

39. Edghill EL., *et al*. "Hepatocyte nuclear factor-1β gene deletions-a common cause of renal disease". *Nephrology Dialysis Transplantation* 23.2 (2008): 627-635.

40. Bingham C., *et al*. "Mutations in the hepatocyte nuclear factor-1β gene are associated with familial hypoplastic glomerulocystic kidney disease". *The American Journal of Human Genetics* 68.1 (2001): 219-224.

41. Ulinski T., *et al*. "Renal phenotypes related to hepatocyte nuclear factor-1β (TCF2) mutations in a pediatric cohort". *Journal of the American Society of Nephrology* 17.2 (2006): 497-503.

42. Ellard S., *et al*. "Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young". *Diabetologia* 51.4 (2008): 546-553.

43. Owen KR., *et al*. "The clinical application of non-genetic biomarkers for differential diagnosis of monogenic diabetes". *Diabetes Research and Clinical Practice* 86 (2009): S15-S21.

44. Shields B., *et al*. "The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes". *Diabetologia* 55.5 (2012): 1265-1272.

45. Howson JM., *et al*. "Genetic analysis of adult-onset autoimmune diabetes". *Diabetes* 60.10 (2011): 2645-2653.

46. Jones A and Hattersley A. "The clinical utility of C-peptide measurement in the care of patients with diabetes". *Diabetic Medicine* 30.7 (2013): 803-817.

47. Besser RE., *et al*. "Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-α/ hepatocyte nuclear factor 4-α maturity-onset diabetes of the young from long-duration type 1 diabetes". *Diabetes Care* 34.2 (2011): 286-291.

48. McDonald TJ., *et al*. "Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes". *Diabetic Medicine* 28.9 (2011): 1028-1033.

49. Thanabalasingham G., *et al*. "A large multi-centre European study validates high-sensitivity C-reactive protein (hsCRP) as a clinical biomarker for the diagnosis of diabetes subtypes". *Diabetologia* 54.11 (2011): 2801-2810.

50. McDonald TJ., *et al*. "High-sensitivity CRP discriminates HNF1A-MODY from other subtypes of diabetes". *Diabetes Care* 34.8 (2011): 1860-1862.

51. Shields B., *et al*. "Integration of biomarkers and clinical characteristics provides the best method for identifying patients with MODY". *Diabetologia* (2012): 55.

52. Oram RA., *et al*. "The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells". *Diabetologia* 57.1 (2014): 187-191.

53. Pearson E., *et al*. "Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4α mutations in a large European collection". *Diabetologia* 48.5 (2005): 878-885.

54. Shih DQ., *et al*. "Genotype/phenotype relationships in HNF-4alpha/MODY1: haploinsufficiency is associated with reduced apolipoprotein (AII), apolipoprotein (CIII), lipoprotein (a), and triglyceride levels". *Diabetes* 49.5 (2000): 832-837.

55. Spégel P., *et al*. "Metabolite profiling reveals normal metabolic control in carriers of mutations in the glucokinase gene (MODY2)". *Diabetes* 62.2 (2013): 653-661.

56. Owen KR., *et al*. "Assessment of high-sensitivity C-reactive protein levels as diagnostic discriminator of maturity-onset diabetes of the young due to HNF1A mutations". *Diabetes Care* 33.9 (2010): 1919-1924.

57. Thanabalasingham G., *et al*. "Mutations in HNF1A result in marked alterations of plasma glycan profile". *Diabetes* 62.4 (2013): 1329-1337.

58. Bacon S., *et al*. "Circulating CD36 is reduced in HNF1A-MODY carriers". *PLoS One* 8.9 (2013): e74577.

59. Nowak N., *et al*. "Cystatin C is not a good candidate biomarker for HNF1A-MODY". *Acta Diabetologica* 50.5 (2013): 815-820.

60. Nowak N., *et al*. "Circulating ghrelin level is higher in HNF1A–MODY and GCK–MODY than in polygenic forms of diabetes mellitus". *Endocrine* 50.3 (2015): 643-649.

61. Lehto M., *et al*. "Mutation in the HNF-4alpha gene affects insulin secretion and triglyceride metabolism". *Diabetes* 48.2 (1999): 423-425.

62. Owen K and Hattersley AT. "Maturity-onset diabetes of the young: from clinical description to molecular genetic characterization". *Best Practice and Research Clinical Endocrinology and Metabolism* 15.3 (2001): 309-323.

63. MacArthur D., *et al*. "Guidelines for investigating causality of sequence variants in human disease". *Nature* 508.7497 (2014): 469-476.

64. Estrada K., *et al*. "Association of a low-frequency variant in HNF1A with type 2 diabetes in a Latino population". *The Journal of the American Medical Association* 311.22 (2014): 2305-2314.

65. Velho G., *et al*. "Diabetes complications in NIDDM kindreds linked to the MODY3 locus on chromosome 12q". *Diabetes Care* 9.9 (1996): 915-919.

66. Colclough K., *et al*. "Mutations in the genes encoding the transcription factors hepatocyte nuclear factor 1 alpha and 4 alpha in maturity-onset diabetes of the young and hyperinsulinemic hypoglycemia". *Human Mutation* 34.5 (2013): 669-685.

67. Stride A., *et al*. "Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia". *Diabetologia* 57.1 (2014): 54-56.

68. Pearson ER., *et al*. "Contrasting diabetes phenotypes associated with hepatocyte nuclear factor-1α and-1β mutations". *Diabetes Care* 27.5 (2004): 1102-1107.

69. Horikawa Y., *et al*. "Mutation in hepatocyte nuclear factor–1β gene (TCF2) associated with MODY". *Nature Genetics* 17.4 (1997): 384-385.

Volume 5 Issue 9 September 2022