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Etiology and Epidemiology of Maturity-onset Diabetes of the Young

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Evidence indicates that Maturity-onset diabetes of the young (MODY) exhibits an autosomal dominant inheritance and is the most common type of monogenic diabetes. However, it should be noted that misdiagnosis of the condition is very common, as patients are usually mistaken for both types I and type II diabetes mellitus. In the present study, we have discussed the etiology, pathogenesis, and epidemiology of MODY based on an extensive literature review. Genetic

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mutations are mainly attributed to the development of the disease, which usually manifests throughout the second to fifth decades of life. Pancreatic islet cell destruction, impaired insulin secretion, defects regarding threshold to serum glucose levels, and other pathological events are usually observed in these patients. Data regarding the epidemiology of the condition is not adequately reported in the literature, especially among non-European populations, indicating the need to conduct future investigations. Ethnic and age variations are potentially epidemiological characteristics of the disease. However, not enough data are present in the literature to support such conclusions.

Keywords: Diabetes mellitus; phenotypes; maturity-onset diabetes of the young; etiology; epidemiology; MODY.

1. INTRODUCTION

The term maturity-onset diabetes mellitus of the young (MODY) was first reported by Tattersall in 1974 [1]. Evidence indicates that MODY exhibits an autosomal dominant inheritance and is the most common type of monogenic diabetes. However, it should be noted that misdiagnosis of the condition is very common, as patients are usually mistaken for both types I and type II diabetes mellitus. In addition, the clinical manifestations of the condition are usually observed before 25 years of age. However, it should be noted that affected cases do not usually have pancreatic autoantibodies, and the disease is non-ketotic. Moreover, the main etiology of the condition is usually attributed to beta-cell dysfunction [2,3].

Establishing an adequate diagnosis of the condition is based on understanding and recognizing the most susceptible patients to conduct adequate diagnostic modalities. Although the condition usually exhibits autosomal dominant inheritance, evidence indicates that the condition's behavior, treatment, and prognosis are difficult to predict [4]. Among the different studies in the literature, evidence indicates that the currently reported subtypes of MODY are six. However, with further research ongoing, further data regarding novel subtypes are suspected, indicating the importance of research in this field [5,6]. It should be noted that the epidemiology of the disease is also hugely variable across the different populations. In the present literature review, we will discuss the epidemiological and etiological findings from relevant studies in the literature discussing MODY.

2. LITERATURE REVIEW

2.1 Etiology and Pathophysiology

The pathogenesis of MODY is usually initiated by a defect in insulin secretion secondary to impaired development of pancreatic islet cells. Patients usually have heterozygous mutations, and the disease is usually inherited in an autosomal dominant pattern. However, evidence that expressivity and penetrance of the disease are usually remarkably variant across the different populations and affected patients, even within a single-family. The genes involved in the pathogenesis and etiology of the condition are the main determinant of the clinical phenotype of the disease. Different mechanisms have been proposed by which genetic abnormalities can affect insulin secretion in patients with MODY. Some of these mechanisms include the activation of adenosine triphosphate (ATP)-dependent potassium channels, impaired glucose metabolism in beta cells, and inducing defects regarding insulin sensing. A single-gene defect is usually observed among patients with polygenic type I and type II diabetes mellitus, which significantly leads to a defect in glucose metabolism secondary to impaired insulin secretion. Evidence also indicates that autosomal dominant transmission is usually observed with most of the genetic defects in these patients. However, it has been reported that autosomal recessive variations are also reported in the literature and are usually observed in cases of neonatal diabetes. The older classification and nomination of the different subtypes of MODY have been conducted numerically (i.e., from 1 to 6). However, recent data classified these subtypes based on the relevant genetic defects observed in these patients. In this context, studies show that at least 14 mutations of MODY can be detected, leading to the development of different subtypes of the condition. These include APPL1, BLK, CEL, KLF11, KCNJ11, ABCC8, PAX4, PDX1, NEURO1, INS, HNF1B, HNF4A, HNF1A, and GCK. Different factors can attribute to the variable genetic mutations. These include the presence of extra-pancreatic manifestations, response to treatment, and stage of onset. The

commonest genetic mutations based on evidence from the relevant studies in the literature include gene mutations in glucokinase (GCK), the hepatocyte nuclear factor 1 alpha (HNF1A), hepatocyte nuclear factor 1 beta (HNF1B), and the hepatocyte nuclear factor 4 alpha (HNF4A) which are usually detected in 30-60%, 30-60%, 5%, and 5-10% of patients with MODY [7].

Evidence shows that the pathology in MODY3 subtypes is mainly attributed to the significant inhibition of mitochondrial metabolism and glucose transport and metabolism in pancreatic cells by influencing the key steps in these cascades. HNF1A is usually detected in the intestine, kidney, and liver together with pancreatic tissues. It is usually associated with remarkably beta-cell dysfunction and destruction. Besides, the affected patients usually exhibit a reduced renal threshold, leading to remarkable glucosuria. Most patients with these genetic mutations are usually diagnosed with MODY between 21-26 years of age. High penetrance was also reported for this genetic mutation. Studies show that 96%, 79%, and 63% of these genetic carriers usually develop diabetes mellitus by 45, 35, and 25 years old, respectively [8,9]. On the other hand, studies show that the etiology in patients with GCK genetic mutations, higher fasting glucose levels are usually detected in these patients secondary to resitting insulin secretion related threshold of serum glucose levels. In this context, a mild increase in serum levels of glucose is usually observed by oral glucose tolerance testing [10,11]. On the other hand, the pathology of MODY reported with patients with HNF4A mutations is usually similar to type II diabetes mellitus, including mainly a defect in HDL-C, which is remarkably reduced [12,13]. These findings indicate that extensive research and diagnostic approaches should be exerted to investigate more about the genetic status of these types to enhance a better prognosis for the affected patients.

2.2 Epidemiology

Many previous literature investigations have reported the epidemiological data of MODY, which will be discussed in the current section. Evidence indicates that MODY diagnosis is usually established within the 2nd to 5th decades of life [14]. However, not much data is available concerning the condition's global burden since large worldwide population-based investigations are rare in the literature. Furthermore, studies regarding the incidence of the disease are not widely available in the literature. Many reasons can attribute to the minimum data regarding the incidence of the condition among the different worldwide investigations. First, MODY is frequently misdiagnosed because of the insidious onset of symptoms. Second, the clinical manifestations of the condition are usually overlapped with the clinical manifestations of the other two types of diabetes mellitus. Besides, clinicians lack awareness about the condition, which significantly impacts the referral rate of high-risk children for early and comprehensive genetic evaluation. On the other hand, the estimated prevalence rates are more common and widely available in the literature [15-18]. Overall, the estimated prevalence among the different worldwide populations usually ranges between 1-5% of all patients with diabetes mellitus [14,19]. However, most of these rates are obtained from European investigations, which also indicate that the prevalence of the condition is variable among different populations.

Previous studies from Germany reported that the prevalence of MODY is 23.9 per million, while the incidence is 2.4% [20,21]. The estimated prevalence of the condition in Italy, Lithuania, Sweden, and Norway is 5.5%, 3.14%, 1.2%, and 0.94-6.5%, respectively [22-26]. Besides, studies from the United Kingdom also show that the prevalence of the condition ranges between 68-108 per million [15,27]. On the other hand, the estimated prevalence in the Netherlands has also been reported to be 30 per million. Studies within other countries outside Europe were also conducted and also showed variable findings. For instance, a previous epidemiological study in the United States by Pihoker et al. [16] reported that the prevalence of MODY is 1.2%. Moreover, Davis et al. [20] estimated that the prevalence of MODY in their Australian population is 89 per million. Among the different studies in the literature, it has been reported that the least prevalence of MODY was reported by Amed et al. [28] in Canada, which reported that the prevalence is 0.2 per 100,000 in their included children and young youth (<18 years old).

Although no ethnic disparity regarding the prevalence of MODY was reported in the literature, it has been previously suggested that ethnicity can significantly impact the development and prevalence of the condition [15]. This can also be attributed to the availability and access to diagnostic modalities and genetic

testing among certain populations over others. Variations of the prevalence of the disease were also documented. For instance, it has been estimated that the prevalence of the condition is usually 1 per 23,000 in children and 1 per 10,000 in adults. It should also be noted that the fact that evidence regarding the prevalence of the condition among different European countries is usually attributed to the fact that genetic testing and the availability of relevant diagnostic resources are widely available in these countries [16]. For instance, studies from the United Kingdom indicate this by reporting high prevalence rates of monogenic diabetes, estimated to be 2.5%. Moreover, other studies also estimated a minimum prevalence of MODY that ranges between 68 to 108 cases per 1,000,000 population [15,27,29,30]. Studies also show that certain subtypes of MODY are more prevalent than others, including NF1A-MODY and GCK-MODY, by 52% and 32%, respectively. On the other hand, other subtypes were also detected but not as prevalent as these two subtypes. These include HNF4A-MODY, HNF1B-MODY, and Insulin (INS)-MODY or Neurogenic differentiation 1 (NEUROD1)-MODY, by 10%, 6$, and <1%, respectively [15,27]. Although the prevalence of these conditions seems to be relatively high compared to other worldwide rates, it should be noted that the estimated rates across the Kingdom are reported to be potentially underreported because of the high rate of misdiagnosis of MODY secondary to reduced referral and awareness of the condition and genetic predisposition [27]. Estimates also indicate that the prevalence of MODY in other European countries (Poland, Germany, Netherlands, and Norway) is usually comparable with the estimated prevalence in the United Kingdom, as previously discussed [15,17,19,21,25,31].

It should also be noted that the prevalence rates of MODY might also be significantly impacted by the way participants are chosen in these population-based studies. For instance, it has been observed that if patients with negative autoantibody are recruited, the prevalence of genetically confirmed MODY is usually higher, as reported in Lithuania, Sweden, and Norway (3.14%, 1.2%, and 6.5%, respectively) [22,24,26]. In the same context, recruiting patients with only impaired fasting glycemia is also associated with higher prevalence rates, as reported in Italy, with an estimated prevalence rate for MODY of 5.5% [23]. Although little data is known regarding the prevalence of MODY outside Europe based on the scarcity of reports, evidence from these few studies indicates that ethnic and geographic variations can significantly impact the prevalence of the condition. For instance, a previous study from the United States shows that for youth < 20 years of age, the estimated minimum prevalence of monogenic diabetes is 21 per 1,000,000, while the prevalence of the condition among all pediatric patients with diabetes mellitus is 1.2% [16]. Compared with the United States, a previous study in Western Australia reported that the minimum prevalence of MODY in the whole Australian population is 89 cases per 1,000,000 population, which corresponds to a rate of 0.24% of patients with diabetes that are < 35 years of age [32].

Not much epidemiological data was found in Asian, African, Middle Eastern, and South American populations, which makes it difficult to draw any conclusive data regarding the behavior of MODY in these countries. In addition, evidence from Saudi Arabia also indicates that the epidemiological data regarding MODY is scarce, and little is known about the condition [33-35]. However, a previous report suggested that it is important to screen for the disease because of the potential misdiagnosis of many cases across the Kingdom [36]. Accordingly, further studies are needed, especially among non-European countries, to adequately estimate the prevalence and epidemiological characteristics of the disease globally. However, it should be noted that a novel frameshift mutation was first detected in a previous report in Brazil, which is considered the first case of NEUROD1-MODY in Latin America [37]. Therefore, such data indicate that studying epidemiology with countries where multiethnic variations are present can adequately establish elaborate more about epidemiological characteristics and pathogenesis of the condition.

3. CONCLUSION

In the present study, we have discussed the etiology, pathogenesis, and epidemiology of MODY based on an extensive literature review. Genetic mutations are mainly attributed to the development of the disease, which usually manifests throughout the second to fifth decades of life. Pancreatic islet cell destruction, impaired insulin secretion, defects regarding threshold to serum glucose levels, and other pathological events are usually observed in these patients.

Data regarding the epidemiology of the condition is not adequately reported in the literature, especially among non-European populations, indicating the need to conduct future investigations. Ethnic and age variations are potentially epidemiological characteristics of the disease. However, not enough data are present in the literature to support such conclusions.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Tattersall RB. Mild familial diabetes with dominant inheritance. The Quarterly journal of medicine. 1974;43(170):339-57.
2. Colom C, Corcoy R. Maturity onset diabetes of the young and pregnancy. Best practice & research Clinical endocrinology & metabolism. 2010;24(4):605-15.
3. Burlina S, Lapolla A. Maturity-Onset diabetes of the young: Epidemiology and management in pregnancy.
4. Nyunt O, Wu JY, McGown IN, Harris M, Huynh T, Leong GM, et al. Investigating maturity onset diabetes of the young. The Clinical biochemist Reviews. 2009;30(2):67-74.
5. Anık A, Çatlı G, Abacı A, Böber E. Maturity-onset diabetes of the young (MODY): An update. Journal of pediatric endocrinology & metabolism : JPEM. 2015;28(3-4):251-63.
6. McDonald TJ, Ellard S. Maturity onset diabetes of the young: Identification and diagnosis. Annals of clinical biochemistry. 2013;50(Pt 5):403-15.
7. Gardner DS, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). Diabetes, metabolic syndrome and obesity : targets and therapy. 2012;5:101-8.
8. Brunerova L, Rahelić D, Ceriello A, Broz J. Use of oral antidiabetic drugs in the treatment of maturity-onset diabetes of the young: A mini review. Diabetes/metabolism research and reviews. 2018;34(1).
9. Kim SH. Maturity-onset diabetes of the young: What do clinicians need to know? Diabetes & Metabolism Journal. 2015;39(6):468-77.
10. Wędrychowicz A, Tobór E, Wilk M, Ziółkowska-Ledwith E, Rams A, Wzorek K, et al. Phenotype Heterogeneity in Glucokinase-Maturity-Onset Diabetes of the Young (GCK-MODY) Patients. Journal of Clinical Research in Pediatric Endocrinology. 2017;9(3):246-52.
11. Bansal V, Gassenhuber J, Phillips T, Oliveira G, Harbaugh R, Villarasa N, et al. Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6888 individuals. BMC medicine. 2017;15(1):213.
12. Horikawa Y. Maturity-onset diabetes of the young as a model for elucidating the multifactorial origin of type 2 diabetes mellitus. Journal of Diabetes Investigation. 2018;9(4):704-12.
13. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology and clinical decision making. Diabetes Care. 2011;34(8):1878-84.
14. Nkonge KM, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). Clinical Diabetes and Endocrinology. 2020;6(1):20.
15. Kleinberger JW, Pollin TI. Undiagnosed MODY: Time for Action. Current diabetes reports. 2015;15(12):110.
16. Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: Results from the SEARCH for Diabetes in Youth. The Journal of Clinical Endocrinology and Metabolism. 2013;98(10):4055-62.
17. Weinreich SS, Bosma A, Henneman L, Rigter T, Spruijt CM, Grimbergen AJ, et al. A decade of molecular genetic testing for MODY: A retrospective study of utilization in The Netherlands. European journal of human genetics: EJHG. 2015;23(1):29-33.
18. Sanyoura M, Letourneau L, Knight Johnson AE, Del Gaudio D, Greeley SAW, Philipson LH, et al. GCK-MODY in the US Monogenic Diabetes Registry: Description of 27 unpublished variants. Diabetes Res Clin Pract. 2019;151:231-6.
19. Firdous P, Nissar K, Ali S, Ganai BA, Shabir U, Hassan T, et al. Genetic testing

of maturity-onset diabetes of the young current status and future perspectives. Frontiers in Endocrinology. 2018;9:253.
20. Galler A, Stange T, Müller G, Näke A, Vogel C, Kapellen T, et al. Incidence of childhood diabetes in children aged less than 15 years and its clinical and metabolic characteristics at the time of diagnosis: data from the Childhood Diabetes Registry of Saxony, Germany. Hormone Research in Paediatrics. 2010;74(4):285-91.
21. Neu A, Feldhahn L, Ehehalt S, Hub R, Ranke MB. Type 2 diabetes mellitus in children and adolescents is still a rare disease in Germany: A population-based assessment of the prevalence of type 2 diabetes and MODY in patients aged 0-20 years. Pediatric diabetes. 2009;10(7):468-73.
22. Carlsson A, Shepherd M, Ellard S, Weedon M, Lernmark Å, Forsander G, et al. Absence of islet autoantibodies and modestly raised glucose values at diabetes diagnosis should lead to testing for MODY: Lessons from a 5-year pediatric swedish national cohort study. Diabetes Care. 2020;43(1):82-9.
23. Delvecchio M, Mozzillo E, Salzano G, Iafusco D, Frontino G, Patera PI, et al. Monogenic Diabetes Accounts for 6.3% of Cases Referred to 15 Italian Pediatric Diabetes Centers During 2007 to 2012. The Journal of Clinical Endocrinology and Metabolism. 2017;102(6):1826-34.
24. Stankute I, Verkauskiene R, Blouin JL, Klee P, Dobrovolskiene R, Danyte E, et al. Systematic genetic study of youth with diabetes in a single country reveals the prevalence of diabetes subtypes, novel candidate genes, and response to precision therapy. Diabetes. 2020;69(5):1065-71.
25. Irgens HU, Molnes J, Johansson BB, Ringdal M, Skrivarhaug T, Undlien DE, et al. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. Diabetologia. 2013;56(7):1512-9.
26. Johansson BB, Irgens HU, Molnes J, Sztromwasser P, Aukrust I, Juliusson PB, et al. Targeted next-generation sequencing reveals MODY in up to 6.5% of antibody-negative diabetes cases listed in the Norwegian Childhood Diabetes Registry. Diabetologia. 2017;60(4):625-35.
27. 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(12):2504-8.
28. Amed S, Dean HJ, Panagiotopoulos C, Sellers EA, Hadjiyannakis S, Laubscher TA, et al. Type 2 diabetes, medication-induced diabetes, and monogenic diabetes in Canadian children: a prospective national surveillance study. Diabetes Care. 2010;33(4):786-91.
29. Kropff J, Selwood MP, McCarthy MI, Farmer AJ, Owen KR. Prevalence of monogenic diabetes in young adults: a community-based, cross-sectional study in Oxfordshire, UK. Diabetologia. 2011;54(5):1261-3.
30. Shepherd M, Shields B, Hammersley S, Hudson M, McDonald TJ, Colclough K, et al. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. Diabetes Care. 2016;39(11): 1879-88.
31. Fendler W, Borowiec M, Baranowska-Jazwiecka A, Szadkowska A, Skala-Zamorowska E, Deja G, et al. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. Diabetologia. 2012;55(10):2631-5.
32. Davis TM, Makepeace AE, Ellard S, Colclough K, Peters K, Hattersley A, et al. The prevalence of monogenic diabetes in Australia: the Fremantle Diabetes Study Phase II. The Medical journal of Australia. 2017;207(8):344-7.
33. Habeb AM, George ET, Mathew V, Hattersley AL. Response to oral gliclazide in a pre-pubertal child with hepatic nuclear factor-1 alpha maturity onset diabetes of the young. Ann Saudi Med. 2011;31(2):190-3.
34. Habeb AM, Al-Magamsi MS, Eid IM, Ali MI, Hattersley AT, Hussain K, et al. Incidence, genetics, and clinical phenotype of permanent neonatal diabetes mellitus in northwest Saudi Arabia. Pediatric diabetes. 2012;13(6):499-505.
35. Udezue E, Mohamed F. Non-ketotic diabetes in Saudi Arabian youths: MODY or early onset of type 2 diabetes? International Journal of Diabetes and Metabolism. 2007;15(2):60.
36. Mohamed S, Elkholy S, El-Meleagy E, Abu-Amero K, Hellani AM. Clinical and

molecular characterization of maturity onset-diabetes of the young caused by hepatocyte nuclear factor-4 alpha mutation: red flags for prediction of the diagnosis. Ann Saudi Med. 2014;34(3): 217-21.

37. Abreu GM, Tarantino RM, Cabello PH, Zembrzuski VM, da Fonseca ACP, Rodacki M, et al. The first case of NEUROD1-MODY reported in Latin America. Molecular Genetics & Genomic Medicine. 2019;7(12):e989.

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