REVIEW ARTICLE

MATURITY ONSET DIABETES OF THE YOUNG

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ABSTRACT

MODY is a rare endocrinopathy originated from various genetic mutations that, independently of each other, express in the patient characteristics of a specific subtype of MODY, thirteen of which have been identified to date, however, only some of these subtypes have been delimited due to, among other factors, levels of overlapping of clinical characteristics and the need for genetic tests as the only definitive diagnostic resource.
The primary defect in pancreatic cell function, the absence of debut by ketoacidosis, the disease will affect three family generations, the diagnosis in childhood or adolescence, the low obesity index and evolution of slow progress without insulin treatment in the early stages of the disease, are the general characteristics of the Maturity Onset Diabetes of the Young. On the other hand, the diagnosis of MODY X is given to the identified patients whose genetic tests do not express mutations known to be associated to MODY but that present the clinical criteria

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BACKGROUND

Diabetes mellitus (DM) is one of the noncommunicable diseases (NCDs), with a marked degree of severity and the most frequent range of complications in the world, which demonstrates its relevance at the level of public health; it is estimated that of 56 million deaths in 2012, 68% were caused by an NCD; diabetes is among the diseases with the highest mortality rate along with cardiovascular diseases, cancer and chronic lung diseases. The WHO, in 2014, estimated that the global prevalence of diabetes is 10% (2), the value of individual variation in relation to the degree of development and social, demographic and cultural characteristics of the population, and with the recent increase in prevalence of obesity, diabetes has increased. In Ecuador, the National Institute of Statistics and Census (INEC) reported diabetes mellitus as the second cause of death in 2014, the leading cause of death in females and the third in men (3). Diabetes MODY (Maturity Onset Diabetes of the Young) was originally described by Stefan S. Fajans, an American researcher, who studied a family group, with children and adolescents, with a previous family background of DM type 2; years of studying allowed to determine that MODY is a monogenic disease whose transmission mode is autosomal dominant (4,5); it affects a single gene, whose mutation has a 50% probability of being present in direct descendants, without the influence of sexual genes. The American Diabetes Association (ADA) classifies DM into Type 1 diabetes; Type 2 diabetes; gestational diabetes mellitus, and specific types of diabetes due to other causes, among which is MODY (6). MODY is a heterogeneous subtype of Type 2 DM in which a patient debuts before the age of 25, there is evidence of deficient insulin secretion and absence of insulin. Insulin resistance is present on family background of at least 3 generations of diabetic patients and usually does not need treatment with insulin during the first 5 years after diagnosis (7).

METHODS

A systematic search was performed in databases such as SciElo, ScienceDirect, LILACS, Redalyc, IntechOpen, PubMed, with selection criteria such as: bibliographies no greater than 5 years old, clinical criteria such as presentation less than 25 years, low rate of obesity, 3 consecutive family generations affected, affected genes (HNF-4α, GCK, TCF-1, IPF1, HNF-1β, NEUROD1). Approximately 20,000 results, between articles, books and other types of publications, and 35 were selected that fulfilled the selection criteria.

DIABETES MELLITUS

DM is a clinical syndrome cataloged among the noncommunicable diseases, it is characterized by the alteration of the metabolism or intermediate due to faults of the action of the insulin on the tissues due to decrease of the sensitivity of these to the hormone and/or alteration on the insulin secretion by the pancreatic cells, which constitutes 60-70% of the endocrine component in the human pancreas (8-10), these conditions can be isolated or coexist in the same patient. Its clinical manifestation is elevated blood glucose levels; however, its more severe expression leads to ketoacidosis and hyperosmolar non-ketotic syndrome (8). The treatment of diabetes depends on to the multifactorial reduction of risks produced in long term; micro and macrovascular damage in different structures such as feet, eyes, kidneys, nerves, heart and vessels (6).

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The ADA, in 2017, classified MODY in other

specific types of diabetes, more specifically in genetic defects of the beta cell. Nowadays, specific mutations have been studied in thirteen types of MODY (6,11,12), despite this, there are unclear limits and unspecified results between subtypes with a low morbidity rate. It has been defined that MODY type 1, 2 and 3 are the most common forms of this monogenic disease with autosomal dominant inheritance with incomplete penetrance (6,11,13). There are patients that does not show alterations in the genes identified for MODY, but they have clinical criteria, so MODY X (7.13) is diagnosed.

MODY is characterized by presenting familial non-ketotic hyperglycemia, starting in childhood, adolescence or young adulthood, classically before the age of 25, however, the diagnosis can be made years later, an indicator for this is the presence of DM in at least three generations. There have been cases with the absence of that criterion (12,14-16). It is associated with primary alterations in insulin production, and defects in the action of this hormone are minimal or non-existent, so 2-5% of diabetes are not dependent on insulin treatment (6, 11,12,16), a fact that remains constant during the first 5 years of development of the endocrinopathy (16), which expresses its unusual appearance, without relegating its relevance in public health, where it has been identified at least 1,200 genes that induce various pathologies and phenological traits, which some are discussed below.

MODY 1: MUTATION IN THE HEPATIC NUCLEAR FACTOR 4 ALPHA GENE (HNF-4α)

Mutation of the HNF-4A gene located on chromosome 20q13.12 (17) is one of the less frequent MODY subtypes, with few cases reported outside from Michigan (US), where it was identified for the first time in the offspring of a couple who emigrated from Germany (18). This gene codes Hepatic Nuclear Factor 4 alpha, of its super-family of nuclear receptors of thyroid and steroid hormones. Under physiological conditions, they regulate the secretion of insulin by pancreatic islets in the presence of high levels of glucose, they also take charge of the expression of genes related to the metabolism of glucose and lipids such as fatty acids and cholesterol (11,18). The insulin sensitivity is conserved with defective stimulation on the secretion of this hormone by glucose intervention, gradual decrease and early deficiency of insulin secretion by pancreatic cells, hyperglycemia; vascular complications such as microangiopathy, rarely are obese and they respond positively to insulin treatment (11,18).

MODY 2: MUTATION IN THE GLUCOKINASE GENE (GCK)

It was identified for the first time in French families (18), but it is currently distributed throughout the planet, the main ethnic groups are Caucasians, 12.5% in British families and 63% in French and Pacific Islander families, not found in Japanese families. No predominance has been reported by sex (19). The mutation of the GCK gene present in chromosome 7p13 affects Glucokinase (17), an enzyme that mediates glucose catabolism in glucose-6-phosphate in the first reaction of glycolysis, is considered a blood glucose sensor, variable in function of which initiates or inhibits the metabolic pathway (20 -22).

Glucokinase is expressed especially in pancreatic cells and hepatocytes (17,21). In the pancreas it regulates the function of glycolysis, thus reversing and producing adenosine triphosphate; energy, and the secretion of insulin, under normal conditions, fulfils its function as a sensor efficiently (19), however, patients with MODY 2 require plasma glucose at higher than normal levels, so patients have basal hyperglycemia and mild diabetes due to changes in sensitivity that

induce abnormal glucokinase activity, which is total dysfunction or functional interference. Unusual cases have been reported where the mutation boosts enzyme activity, which increases insulin secretion with consequent hypoglycemia (16,18). In the liver it participates in the storage of glucose in the form of glycogen (17,18). In MODY 2, there are heterozygous mutations of an allele and patients receive diet therapy and oral antidiabetics for presenting little or no chronic complications such as obesity, hypertension, or others. Patients who inherit two alleles with mutations in the GCK gene have neonatal diabetes with a deficiency in insulin production that requires lifelong insulin treatment (21,22). The inheritance of MODY 2 is direct and each child has a 50% chance of having the same mutation in the gene for the enzyme GCK, except in de novo mutations. The probability of inheriting the mutation is 75% when both parents are carriers (19).

MODY 3: MUTATION IN THE HEPATIC NUCLEAR FACTOR 1-ALPHA GENE (HNF-1α)

The most common appearance of MODY diabetes in countries where research has been done is the mutation of the HNF-1α gene, encoded on chromosome 12q24.2(17,19,23). It accounts for 70% of cases (24) and there are marked variations depending on the ethnic group involved in the disease (7). The HNF-1α gene activates genetic transcription of insulin (25,26). Lack or deprivation of HNF-1α function leads to severe defects in the results of insulin secretion to glucose and leucine (26). Cell functions affected by the HNF-1α mutation induce a deficiency in pancreatic beta cells at the molecular pathway level (27). The defect of the pancreatic beta cell in this type of diabetes is progressive naturally (28). Carriers of the HNF-1α mutation who do not yet have diabetes show normal blood glucose levels when fasting, but when the glucose level is higher than 140 mg/dl are unable to increase insulin secretion. Prior to the onset of diabetes, the carriers of this mutation manifest a glucose overload, which causes glycosuria; to determine whether a person is a carrier of this mutation, a glycosuria test is performed two hours after the oral glucose overload, which test leads to a subsequent evaluation of the carriers (25). It is frequently diagnosed in the post-pubertal age group (19), between the ages of 14 and 30, although in adolescence it occurs with greater incidence. Hyperglycemia and insulin deficiency are severe in this type of MODY, prevailing in the Caucasian and Japanese ethnic groups (26). Frequently, MODY 3 is associated with dyslipidemia and high blood pressure, and obesity is not common (23). In the first 10 years of life, patients have normal blood glucose levels, with subsequent deterioration of pancreatic function, but from the third decade of life onwards insulin secretion decreases, requiring treatment (26). Diabetics with the HNF-1α MODY mutation are more sensitive to insulin and to sulfonylureas that lower blood sugar levels than type 2 diabetics. This alteration is the response of the white tissue to a drug, induced by the pharmacogenetics of underlying etiology to MODY 3(25). Several studies show the weighting of HDL levels over triglycerides in patients with MODY 3 in relation to patients with T1DM (15,29). Several clinical studies have shown that patients with the MODY 3 inducer mutation can control their glycemia level by meticulously administering sulfonylureas treatment with low doses that guarantee an effect with short non-hypoglycemic prolongation, however, it will be necessary to progressively inhibit drug treatment of this nature due to the tendency to deteriorate glycemic control (30). Diet therapy and oral or insulin pharmacological treatment similar to that of patients with type 1 diabetes mellitus is recommended (26,31).

MODY 4: MUTATION IN THE INSULIN PROMOTER FACTOR-1 GENE (IPF-1)

The genetic mutation of chromosome 13q12.2 of the insulin promoter factor-1 (IPF-1), causes a rare type of diabetes, called MODY 4. Under normal conditions, this gene is essential to normalize insulin synthesis via transcription and organogenesis of the pancreas (19). However, the mutation limits the protein binding that promotes the insulin gene and alters the development of pancreatic beta cells. In IPF-1 mutations, when the affected gene is heterozygous, it produces MODY, but if it is homozygous, it causes pancreatic agenesis (26). 1% of all reports of MODY type diabetes are diagnosed in young adults, which characterizes the low prevalence, treatment requires the administration of insulin and oral antidiabetics (23), although 30% of people diagnosed only require insulin (19,32,33). MODY 4 diabetes has a lower risk of chronic complications compared to MODY 1, MODY 3 and MODY 5(19).

MODY 5: MUTATION IN THE HEPATOCYTE NUCLEAR FACTOR-1 BETA GENE (HNF – 1β)

The genetic mutation of chromosome 17q21.3(25) of hepatocyte nuclear factor-1 beta (HNF – 1β) causes MODY 5-type diabetes. This nuclear transcription factor is found in the pancreatic islets, and under normal conditions has the function of homodimer or heterodimer with HNF-1β, which normalizes the genetic presence in tissues of organs such as the pancreas and kidney, so that when the mutation occurs, it impairs pancreatic and renal function and organogenesis (26). It frequently appears in adolescence or in young adulthood, and describes a wide clinical spectrum (34), so it must be diagnosed in specific clinical situations. It is considered the least common, in 5 to 10% of cases, including de novo mutations, the primitive description of this association between early diabetes and renal pathology with the appearance of cysts (35). MODY 5 diabetes is similar to MODY 3, since it can present renal, pancreatic, hepatic complications and genital malformations, the diagnosis of diabetes in intrauterine conditions can be anticipated. Probably due to the decrease in the action of HNF-1β in the liver and kidney, patients have a low level of liver sensitivity to insulin, so the administration of an oral treatment such as metformin would be the primary option after the application of insulin (23).

MODY 6: MUTATION IN THE NEUROGENIC DIFFERENTIATION FACTOR 1 GENE

A rare type of diabetes is MODY 6, which is caused by the mutation on chromosome 2q32 and genetically affects neurogenic differentiation factor 1 (NEUROD1 or BETA2). Commonly the NEUROD1 factor has functions such as: regulating the formation of the endocrine pancreas (25), as a protein regulating pancreatic development, with tissue expression in the pancreas, intestine and central nervous system (26). When the NEUROD1 factor mutation occurs, it causes moderate or severe diabetes, with ranges in various age groups (19). Some authors mention that it affects mostly young adults (25). MODY 6 is expressed in the brain, intestine and pancreatic islets, resulting in long-term progressive hyperglycemia (23).

CONCLUSIONS

It is important to determine clinically when it is a question of type 1 and 2 diabetes mellitus, and when MODY is considered in any of its types, bearing in mind that the majority of cases of MODY type diabetes coincide with patients with a low rate of obesity, of less than 25 years of age, affected by 3

consecutive generations and these patients do not require insulin treatment in the early stages of this disease, it tends to be confused with type 1 or type 2 diabetes mellitus, for this reason it should be noted that the clinic in addition to genetic tests contribute to the diagnosis of MODY diabetes in any of its types, in order to start specific treatment and avoid future complications. This disease is of scientific, medical and social interest, the high incidence of diabetes mellitus in the Latin American population and the little available information on MODY diabetes in the context of the countries that make up this disease, motivates the scientific community to continue conducting studies to determine the incidence of this pathology at the continental level, since the current literature is poor with respect to this variant of diabetes mellitus.

Conflicts of Interest:
The authors declare no conflicts of interest.

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REFERENCES

1. Hammer GD, McPhee SJ. Fisiopatología de la enfermedad : una introducción a la medicina clínica [Internet]. 7th ed. México, D.F.; 2015. 777 p. Disponible en: http://www.ingebook.com/ib/NPcd/IB_BooksVis?cod_primaria=1000187&codigo_libro=6712
2. Organizacion Mundial de la Salud. Informe sobre la situación mundial de las enfermedades no transmisibles. WHO. 2014;1–18.
3. Ministerio de Salud Pública., Ministerio de Salud Pública. Guía de Práctica Clínica (GPC) de la Diabetes Mellitus tipo 2. Minist Salud Pública. 2017;1:1–87.
4. Oliveira CSV, Furuzawa GK, Reis AF. Diabetes Mellitus do Tipo MODY. Arq Bras Endocrinol Metabol [Internet]. 2002;46(2):186–92. Disponible en: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302002000200012&lng=pt&tlng=pt
5. Cesar Paz Y Miño ALC. Genetica Molecular y Citogenética Humana. In: Genetica Molecular y Citogenetica Humana Funadamentos Aplicaciones e investigacines en el Ecuador. 1st ed. Quito, Ecuador; 2014.
6. American Diabetes Association. Standards of Medical care in diabetes - 2017. J Clin Appl Res Educ. 2017;40:1–142.
7. Ben Khelifa S, Martinez R, Dandana A, Khochtali I, Ferchichi S, Castaño L. Maturity Onset Diabetes of the Young (MODY) in Tunisia: Low frequencies of GCK and HNF1A mutations. Gene [Internet]. 2018;651(2017):44–8. Disponible en: https://doi.org/10.1016/j.gene.2018.01.081
8. Vélez H, Rojas W, Borrero J, Restrepo J. Fundamentos de Endocrinología [Internet]. 7th ed. Colombia: CIB (Corporacion para Investigaciones Biologicas); 2012]. Disponible en: http://booksmedicos.org/fundamentos-de-medicina-endocrinologia-7a-edicion/
9. Hall JE. Tratado de Fisiología Médica. 13th ed. Elsevier; 2016. 1168 p.
10. Pawlina W, Michael H. Ross P. Histología TEXTO Y ATLAS Correlación con biología celular y molecular [Internet]. 7th ed. Philadelphia: Wolters Kluwer Health; 2015. 1071 p.
11. Sanzana G. MG, Durruty A. P. Otros Tipos Específicos De Diabetes Mellitus. Rev Médica Clínica Las Condes [Internet]. 2016;27(2):160–70. Disponible en: http://linkinghub.elsevier.com/retrieve/pii/S0716864016300050
12. AlSaraj F. Pathogenesis of Type 2 Diabetes Mellitus. In: Croniger C, editor. Treatment of Type 2 Diabetes patients [Internet]. 1st ed. InTech; 2015. Disponible en: http://www.intechopen.com/books/treatment-of-type-2-diabetes
13. Grupo de trabajo de la Guía de Práctica Clínica sobre Diabetes mellitus tipo 1. Guía de Práctica Clínica sobre Diabetes Mellitus Tipo 1. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad y Política Social. Agencia de Evaluación de Tecnologías Sanitarias del País Vasco-Osteba. España; 2012.
14. Li Q, Cao X, Qiu H-Y, Lu J, Gao R, Liu C, et al. A three-step programmed method for the identification of causative gene mutations of maturity onset diabetes of the young (MODY). Gene [Internet]. 2016 Aug;588(2):141–8. Disponible en: http://dx.doi.org/10.1016/j.gene.2016.05.021
15. Lima RA, Alves C, Dotto RP, Franco LF, Dib SA, Dias-da-Silva MR, et al. Maturity-onset diabetes of the young (MODY) in Brazil: Establishment of a national registry and appraisal of available genetic and clinical data. Diabetes Res Clin Pract [Internet]. 2017;123:134–42. Disponible en: http://dx.doi.org/10.1016/j.diabres.2016.10.017
16. Liu GY. Molecular Pathogenesis of MODYs. Matschinsky FM, Magnuson MA, editores. Switzerland: Karger; 2009.
17. Dorantes A, Martínez C, Ulloa A. Endocrinología Clínica. 5th ed. Endocrinología clínica. Manual Moderno; 2016.
18. Cooper DS, Ladenson PW. Greenspan Endocrinología básica y clínica. 2012.
19. Sánchez-Reyes L, Fanghänel G, Márquez-Cid ME, Salazar Rocha R, Labastida-Sánchez C, Solís-Pérez A, et al. Actualización en los diferentes subtipos de diabetes tipo MODY. Rev Endocrinol y Nutr Rev Endocrinol y Nutr Enero-Marzo [Internet]. 2001;9(1). Disponible en: http://www.medigraphic.com/pdfs/endoc/er-2001/er011b.pdf
20. Lachance CH, Baillargeon M. Should the Clinical Criteria for Suspecting Glucokinase Mutation-Related Hyperglycemia (MODY-2) Be Revisited During Pregnancy?

Can J Diabetes [Internet]. 2017;1–3. Disponible en: http://dx.doi.org/10.1016/j.jcjd.2017.07.003
21. Pollak C. F, Lagos L. M, Santos M. JL, Poggi H, Urzúa C. A, Rumié C. H. Diabetes mellitus por mutación en el gen de glucokinasa. Caso clinico. Rev Med Chil. 2017;145(9):1203–7.
22. Aykut A, Karaca E, Onay H, Gökşen D, Çetinkalp Ş, Eren E, et al. Analysis of the GCK gene in 79 MODY type 2 patients: A multicenter Turkish study, mutation profile and description of twenty novel mutations. Gene [Internet]. 2018;641:186–9. Disponible en: http://dx.doi.org/10.1016/j.gene.2017.10.057
23. Barrio R. Seminarios de diabetes: Diabetes Monogénicas. Av en Diabetol [Internet]. 2007;23(5). Disponible en: http://www.avancesendiabetologia.org/gestor/upload/revistaAvances/23-5.pdf
24. Rees K, Reed A, Banerjee A, Pasupathy D. Maturity onset diabetes of the young in pregnancy: diagnosis, management and prognosis of MODY in pregnancy. Obstet Gynaecol Reprod Med [Internet]. 2017;27(5):144–7. Disponible en: http://dx.doi.org/10.1016/j.ogrm.2017.02.005
25. Jara Albarrán A, Sánchez García-Cervigón P, Arranz Martín A, Andía Melero VM. Endocrinología. Madrid: Editorial Médica Panamericana; 2011.
26. Ibis DA, González C, Teresa D, González Calero M. Aspectos más recientes en relación con la diabetes mellitus tipo MODY Most recent aspects about type MODY diabetes mellitus. Rev Cuba Endocrinol Rev Cuba Endocrinol [Internet]. 2012;2323(22). Disponible en: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1561-29532012000200008
27. Karaca E, Onay H, Cetinkalp S, Aykut A, Göksen D, Ozen S, et al. The spectrum of HNF1A gene mutations in patients with MODY 3 phenotype and identification of three novel germline mutations in Turkish Population. Diabetes Metab Syndr Clin Res Rev [Internet]. 2017;11:S491–6. Disponible en: http://dx.doi.org/10.1016/j.dsx.2017.03.042
28. Hattersley AT. Maturity-onset diabetes of the young: clinical heterogeneity explained by genetic heterogeneity. Diabet Med [Internet]. 1998 Jan 1 [cited 2018 Apr 12];15(1):15–24. Disponible en: http://doi.wiley.com/10.1002/%28SICI%291096-9136%28199801%2915%3A1%3C15%3A%3AAID-DIA562%3E3.0.CO%3B2-M
29. Piccini B, Artuso R, Lenzi L, Guasti M, Braccesi G, Barni F, et al. Clinical and molecular characterization of a novel INS mutation identified in patients with MODY phenotype. Eur J Med Genet [Internet]. 2016;59(11):590–5. Disponible en: http://dx.doi.org/10.1016/j.ejmg.2016.09.016
30. 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 [Internet]. 2000 Jul;17(7):543–5. Disponible en: http://www.ncbi.nlm.nih.gov/pubmed/10972586
31. Jha S, Siddiqui S, Waghdhare S, Dubey S, Krishna S, Subramanian K, et al. Identification of a novel glucokinase mutation in an Indian woman with GCK-MODY. Lancet Diabetes Endocrinol [Internet]. 2016;4(4):302. Disponible en: http://dx.doi.org/10.1016/S2213-8587(16)00040-1
32. Giuffrida FMA, Reis AF. Genetic and clinical characteristics of maturity-onset diabetes of the young. Diabetes, Obes Metab [Internet]. 2005 Jul;7(4):318–26. Disponible en: http://www.ncbi.nlm.nih.gov/pubmed/15955117
33. Staffers DA, Ferrer J, Clarke WL, Habener JF. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. Nat Genet [Internet]. 1997 Oct 1 [cited 2018 Apr 12];17(2):138–9. Disponible en: http://www.nature.com/articles/ng1097-138
34. Bellanné-Chantelot C, Chauveau D, Gautier J-F, Dubois-Laforgue D, Clauin S, Beaufils S, et al. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med [Internet]. 2004 Apr 6;140(7):510–7. Disponible en: http://www.ncbi.nlm.nih.gov/pubmed/15068978
35. Timsit J, Saint-Martin C, Dubois-Laforgue D, Bellanné-Chantelot C. Searching for Maturity-Onset Diabetes of the Young (MODY): When and What for? Can J Diabetes [Internet]. 2016;40(5):455–61. Disponible en: http://dx.doi.org/10.1016/j.jcjd.2015.12.005