Current Perspectives in MODY Management— A Narrative Review

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Abstract: Maturity-onset diabetes of the young (MODY) is associated with familially inherited monogenic diabetes. It is characterized by genetic mutations leading to pancreatic β-cell dysfunction and subsequent insulin production. Clinical features of MODY include young-onset hyperglycemia associated with a lack of beta cell autoimmunity or insulin resistance. Glucose-lowering agents are the main therapeutic options for MODY. In this review, we have outlined the particular aspects of the most common types of MODY in order to assist clinical practitioners in this field.

Keywords: MODY; genetic mutations; oral antidiabetics

Introduction

Maturity-onset diabetes of the young (MODY) is a rare form of familial diabetes with autosomal dominant transmission spanning at least three generations (grandparents, parents and children).

In 1964, the term MODY was first mentioned by Fajans at the Fifth Congress of the International Diabetes Federation in Toronto [1]. This entity includes Caucasians with normal weight, young-age onset of the disease and a therapeutic response to tolbutamide, being a form of mild diabetes mellitus (DM) [2–4]. In 1928, Cammidge observed a good evolution of DM among children, even in the absence of insulin therapy for several years. Finally, Tattersall concluded that patients with this mild type of diabetes are asymptomatic with normal weight; they do not develop ketosis and do not necessarily require insulin treatment [5]. The World Health Organisation includes MODY in the category of other specific types of DM, including monogenic, with genetic defects in pancreatic beta cell function. The classifications of juvenile-onset diabetes and adult-onset diabetes are also used [6].

The prevalence of MODY varies by geographical region, ranging from 1.2% in Sweden to 6.5% in Norway [7,8]. In Africa, Asia, South America and the Middle East, data on the prevalence of MODY are unclear, necessitating further study [9]. Among children diagnosed with DM who do not have autoantibodies, 6.5% have a specific MODY genetic mutation [10].

Diagnosis of MODY

MODY can be suspected in patients with DM who do not phenotypically develop features of type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). Most of the time, MODY is diagnosed at onset as T2DM due to a lack of insulin requirements. With the increasing worldwide incidence of childhood obesity, about 15% of cases diagnosed with MODY are overweight; therefore, the etiological diagnosis is overlooked from the beginning. The underdiagnosis of MODY is related to the borrowing of features from T1DM and T2DM (Table 1), in addition to the missing information needed to establish diagnoses within the family. MODY diagnosis represents a gap in clinical research due to the high cost of genetic mutation investigations [11–13].

Diagnostic criteria for MODY include:

- Onset of the disease under the age of 25 years, with a history of DM in one or more family members;
- Lack of insulin requirement at least 3–5 years after diagnosis;
- Autosomal dominant inheritance (similar phenotype in successive generations);
- Body mass index (BMI) below 25 kg/m²; obesity is not an exclusion criterion for MODY;
- Heterogeneity of insulin secretion, with values frequently within a normal range, but low in relation to blood glucose;
- Lack of pancreatic autoantibody positivity.

The MODY diagnostic algorithm is currently not standardized in clinical practice [14].

Table 1. Differential diagnosis between T1DM, T2DM and MODY [15].

Characteristics	T1DM	MODY	T2DM
Prevalence	<10%	1–5%	90%
Age onset	6 months to 30 years	Under 25 years	Above 30 years
Symptomatology onset	Acute, fast (ketosis)	Variable	Variable (slow to fast)
Genetic profile	Polygenic	Monogenic	Polygenic
Autoantibodies	Positive	Negative	Negative
C peptide value at onset	Low to absent	Normal values	Variable
BMI	Below 25 kg/m²	Below 25 kg/m²	Above 25 kg/m²
Acanthosis nigricans	No	No	Yes
Family history of DM	No (2–4%)	Yes (90%)	Yes (80%)
Need for insulin therapy	From onset	3–5 years after onset	Depending on glycemic control

The Pathophysiology of MODY

In the pathophysiology of MODY, the main mechanism is characterized by genetic mutations in the pancreatic beta cell, leading to altered insulin secretion. The transmission of most genetic mutations is an autosomal dominant mechanism; consequently, the presence of the mutation in one of the parents leads to a 50% risk of transmission to the child. Nowadays, 14 types of MODY are known, of which MODY 1, 2 and 3 account for about 85% of all cases [14,16,17].

The contemporary classification of MODY is based on genetic mutations, these being glucokinase (GCK), hepatocyte nuclear factor-1 alpha (HNF1A), hepatocyte nuclear factor-4 alpha (HNF4A), hepatocyte nuclear factor-1 beta (HNF1B), insulin (INS), neuronal differentiation 1 (NEURO D1), pancreatic and duodenal homeobox 1 (PDX1), paired box 4 (PAX4), ATP binding cassette subfamily C member 8 (ABCC8), potassium inwardly rectifying channel subfamily J member 11 (KCNJ11), Krüppel-like factor 11 (KLF11), carboxyl ester lipase (CEL), BLK proto-oncogene, src family tyrosine kinase (BLK) and adaptor protein, phosphotyrosine interacting with the PH domain and leucine zipper 1 (APPL1) [18].

The age of onset of the disease is a defining criterion in suspecting the diagnosis of MODY and differentiating it from T1DM and T2DM, although the clinical presentation is often atypical and it can be difficult to fit it into the diagnostic criteria [19–22].

Differential diagnosis between MODY types is based on different therapeutic responses (Table 2). Patients with GCK mutations do not require diet, pharmacological or insulin treatments [23]. HNF1A and HNF4A MODY patients have an efficiently therapeutic response to sulfonylurea administration [24], whereas patients with HNF1B mutations require insulin treatment [25,26].

Table 2. Classification of MODY [15,19,27–30].

Classification	Gene Mutation	Prevalence	Characteristics	Treatment
MODY 1	HNF-4A	5–10%	Progressive beta cell disfunction, adolescent/young adult, neonatal transient hyperglycemia, large-for-gestational-age	Response to sulfonylureas
MODY 2	GCK	30–70%	Stable mild fasting glucose, minor increase in blood glucose at 2 h of OGTT	No pharmacological treatment or diet
MODY 3	HNF-1A	30–70%	Low renal glucose threshold (glycosuria), significant increase in blood glucose at 2 h of OGTT	Response to sulfonylureas
MODY 4	IPF-1/PDX1	Very rare	Persistent neonatal DM	Diet/oral antidiabetics/insulin
MODY 5	HNF-1B	5–10%	Cystic kidney disease, genitourinary abnormalities, pancreatic atrophy, hyperuricemia (gout)	Insulin
MODY 6	NEURO D1	Very rare	Hyperglycemia, adult onset, pancreatic and neurological damage	Oral antidiabetics/insulin
MODY 7	KLF11	Very rare	Similar to T2DM	Oral antidiabetics/insulin
MODY 8	CEL	Very rare	Described in Norway, endocrine and exocrine pancreatic dysfunction (small and fibrotic pancreas, low fecal elastase)	Oral antidiabetics/insulin
MODY 9	PAX4	Very rare	Described in Thailand, predisposition to ketoacidosis, retinopathy and diabetic nephropathy	Diet/oral antidiabetics/insulin
MODY 10	INS	<1%	At any age	Oral antidiabetics/insulin
MODY 11	BLK	Very rare	Overweight, obesity, insulin secretion deficiency	Diet/oral antidiabetics/insulin

Table 2. *Cont.*

Classification	Gene Mutation	Prevalence	Characteristics	Treatment
MODY 12	ABCC8	<1%	Persistent neonatal DM	Response to sulfonylureas
MODY 13	KCNJ11	<1%	Persistent neonatal DM	Oral antidiabetics/insulin
MODY 14	APPL1	Very rare	At any age	Diet/oral antidiabetics/insulin

Particular Aspects of GCK-MODY

Glucokinase-MODY, known as MODY 2, has a prevalence of up to 70% of MODY patients. GCK is a key enzyme in glucose metabolism, stimulating insulin secretion dependent on the glucose plasma levels. The GCK gene mutation, located at chromosome 7, region 7p15-p13, acts as a glycemic sensor in the pancreatic beta cells; therefore, the stimulation of insulin secretion will occur at glycemic thresholds higher than physiological levels. At the hepatic level, these mutations damage the process of glycogenogenogenesis, and at the pancreatic level, they disturb glucagon secretion in hypoglycemia states. Subsequently, glucagon acts at lower hypoglycemic values than in patients with T2DM [31].

Paraclinical picture revealed by laboratory tests is characterized by mild stable fasting hyperglycemia with blood glucose ranging between 100 and 150 mg/dL, glycosylated hemoglobin (HbA1C) between 5.6 and 7.6% [32]. Hence, postprandial glycemic values at OGTT are slightly increased. Blood glucose values in these patients are 40% higher compared to people without DM and approximately with 100 mg/dL lower compared to patients with T2DM.

Routine periodical screening can lead to the identification of these slightly elevated blood glucose values. Approximately 3% of women with gestational diabetes actually have a diagnosis of GCK-MODY [33,34], in the presence of a positive family history of hyperglycemia and mildly modified OGTT values. Suspicion of GCK-MODY is raised in cases with a presence of glucose metabolism disorders in at least two generations in the family [23,35–38].

Clinically, patients do not exhibit symptoms, obesity or insulin resistance, or associated risk factors such as hypertension, dyslipidemia and atherosclerosis [39,40].

The prevalence of diabetes complications in GCK-MODY patients is much lower compared to other genetic mutations in MODY. Microvascular complications such as diabetic retinopathy, nephropathy and neuropathy are rarely seen or even absent, whereas significant macrovascular complications such as peripheral arterial disease and cardiovascular disease have a low prevalence [41,42].

Treatment is not necessary in this category of patients, because they have an excellent long-term prognosis, similar to people without diabetes. If GCK-MODY is discovered during pregnancy, then two possibilities are considered. The presence of the GCK mutation only in the mother can lead to prolonged exposure of the fetus to hyperglycemia during pregnancy. At birth, the fetus may present with macrosomia, neonatal hypoglycemia and malformations, as a consequence of the early initiation of insulin therapy on the mother; frequent monitoring of the pregnancy at risk is necessary [43–45].

The presence of GCK mutations in both the mother and fetus does not require insulin treatment, because the glycemic set point is similar in both, resulting in a normal birth [43,46].

Particular Aspects of HNF-1A-MODY

The HNF-1A gene is present in the liver, intestine, pancreatic beta cells and kidneys. Mutations are found on chromosome 12 in the 12q24.2 region, with a prevalence of up to 30–70% of MODY cases.

The HNF-1A gene is involved in the transcription of insulin (INS), glucose transporters 1 and 2 (GLUT 1 and 2) and sodium/glucose cotransporter 2 (SGLT2) [47,48]. The pathophysiological mechanism of HNF-1A mutations encompasses decreased beta-cell function with impaired glucose metabolism. Decreased renal glucose reabsorption is a consequence of reduced SGLT2 activity, all of which leads to glycosuria before hyperglycemia, and is an important marker used as a screening assay for this mutation. Compared with patients with T2DM, they show lower insulin resistance, better lipid profiles and increased proinsulin/insulin ratios. Compared with GCK-MODY, complications occur more frequently in these patients, with a good glycemic control being more difficult to achieve [49].

Diagnosis in the initial stages of the disease can also be sustained by OGTT, if a marked increase in blood glucose levels over 90 mg/dL is observed two hours after glucose intake [50].

Diagnosis of HNF-1A-MODY can be suspected in patients aged 4 up to 18 years with initially normal blood glucose values, glycosuria and modified OGTT after two hours. The treatments involve low-carbohydrate diet and low-dose sulfonylureas. Due to gradual beta cell dysfunction, insulin therapy is not necessary from baseline, but can be initiated if optimal glycemic targets are not achieved or in pregnancy. Sulfonylureas are a group of drugs that act through increased insulin secretion.

In those patients who were initially treated with insulin, having been misdiagnosed with T1DM, sulfonylurea therapy can be initiated without the risk of ketoacidosis, and insulin can be ceased. The effectiveness of switching medication can be assessed by achieving a better glycemic control and a reduction in HbA1C values [51].

The advantages of this intervention include much greater flexibility in mealtimes and lifestyle, and considerably lower pill prices, which can improve the patient compliance with medication and the quality of life.

Initiation of sulfonylureas (e.g., glyburide and glibenclamide) is performed at low doses to minimize the risk of hypoglycemia and to assess interindividual tolerability. Metiglinides may also be used, because they are non-sulfonylurea insulin secretagogue agents, which decrease postprandial blood glucose levels and present a reduced risk of hypoglycemia than sulfonylureas.

The glucagon-like peptide 1 receptor agonist (GLP-1 RA) class is increasingly used in the management of diabetes, due to the superior cardiovascular benefits and protection, and the reduced risk of hypoglycemia compared to sulfonylureas. They are especially recommended for obese patients, having catabolic effects, as well as for patients with renal impairment (e.g., liraglutide) [52].

Particular Aspects of HNF-1B-MODY

HNF-1B is the gene which regulates organogenesis, starting in the embryonic period, and is involved in the development of the urogenital tract, liver and pancreas. HNF-1B mutations are present on the chromosome 17, region 17 cen-q21.3, with a prevalence of 5–10% in all MODY cases.

The clinical picture at presentation is mainly dominated by renal damage: 75% of patients have renal cysts. Among the extra-renal manifestations, DM is present early, following renal disease, the association of DM with renal cysts is also known as renal cysts and diabetes syndrome (RCAD). The presence of structural abnormalities from birth evolves over time to impairment functions of the involved organs. Regarding kidney function, about 50% of patients may require dialysis or kidney transplantation [53]. In addition to renal malformations (such as unique kidney, renal hypoplasia), patients may also present malformations of the urinary tract, internal and external genitalia, pancreatic atrophy, gout and hyperuricemia [54].

Kidneys present single or bilateral hyperechogenic cysts with normal or low renal parenchyma. Renal function is secondarily impaired, leading to renal magnesium loss and uric acid accumulation with hyperuricemia, and later to renal stone build-up and gout [55].

Therapeutic management of HNF-1B-MODY requires early therapy to prevent micro- and macrovascular complications [25,56,57], as well as long-term nephrological follow-up. In contrast to HNF-1A, sulfonylurea administration is not recommended for this category of patients.

Particular Aspects of HNF-4A-MODY

The HNF-4A gene is expressed in the pancreas, liver and kidneys, with its mutation located at chromosome 20, region 20q12-q13.1, mainly affecting carbohydrate and lipid metabolism. Apoprotein concentrations (apoAII, apoCIII, and apoB) are lower than those met in T2DM, as well as lipoprotein lipase activity. Paraclinical features include elevated glycemic values, altered lipid profiles with increased low-density lipoprotein and decreased high-density lipoprotein and triglycerides [58].

Another important feature is the presence of neonatal transient hyperglycemia with fetal macrosomia; however, the diagnosis of DM is confirmed later in adolescence [59]. The first-line treatment is characterized by a low-carbohydrate diet and sulfonylureas, with insulin therapy being elective in pregnancy. Glycemic control can also be achieved by the administration of meglitinide or GLP-1 RA in patients who have frequent hypoglycemia upon therapy with sulfonylureas [60].

Neonatal Diabetes Mellitus

Neonatal diabetes mellitus (NDM) is defined as part of monogenic DM, diagnosed until the age of 6 months old. It can be permanent neonatal diabetes mellitus (PNDM) or transient neonatal diabetes mellitus (TNDM), the definite diagnosis being disturbed at onset because the clinical presentation is limited, and differentiation being based on extra-pancreatic features. TNDM abates within 12 weeks, but the risk of recurrence later in life remains. At onset, blood glucose levels are between 200 and 900 mg/dL, requiring insulin treatment and ceasing after the normalization of blood glucose values. These patients require yearly follow-up; in cases of relapse, the patients can be managed with a diet either associated or not with insulin. Oral antidiabetic drugs are not a successful choice.

NDM occurs due to mutations in the KCNJ11, ABCC8, IPF-1/PDX1, HNF-1B and GCK genes, most commonly found in KCNJ11 and ABCC8 mutations [61]. Screening of MODY during pregnancy has the potential for early diagnoses and to facilitate optimal therapeutic management [62,63]. Genetic testing is recommended in both subtypes of NDM [64].

Future Perspectives

The real incidence of patients with MODY is not fully known, due to misdiagnoses as T1DM or T2DM, as well as expensive genetic testing. A thorough medical history, correlated with hereditary history and paraclinical examinations, would allow a more frequent prediction of MODY patients. The gold standard in diagnosis is genetic testing, which is difficult to perform in clinical practice. MODY calculators can contribute to estimations of the possibility of identifying MODY in patients diagnosed with DM, and it is useful in diagnostic stratification [65].

A multidisciplinary team, including a geneticist, is essential for genetic counseling. The autosomal dominant inheritance mechanism of disease should be explained to patients and their families, and this should be considered in subsequent medical decisions.

Conclusions

MODY is a rare disease, situated within monogenic DM. The diagnosis of MODY in adulthood is overlooked because of its phenotypic similarity to T1DM and T2DM. Its particular features are autosomal dominant inheritance in 2–3 successive generations and a lack of insulin requirements for at least 3–5 years. For the appropriate diagnosis of patients with MODY, family screening and further investigations to establish the type of diabetes enable the initiation of proper treatment and improvements in long-term prognoses. Regarding NDM, clinical practice now advises the suspicion and search for possible signs and symptoms, so that a certain diagnosis of MODY is not overlooked.

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