

Review

Maturity onset diabetes of the young: Diagnosis and treatment options

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Abstract: Diabetes is a complicated disease, so multiple factors are involved in its development. Nevertheless some of the patients with type 1 and 2 diabetes mellitus have a monogenic form of this disease which has different treatment options and usually fewer complications. It is estimated that about 5% of patients with type 2 diabetes mellitus (T2DM) and about 10% of type 1 diabetes mellitus (T1DM) are misdiagnosed and have maturity onset diabetes of the young (MODY). We present a review study of the management of most frequent monogenic forms of diabetes such as MODY 1, 2 and 3 and the possibilities of their diagnosis including in resource limited situations.

Keywords: HNF-1a, HNF-4a, GCK, monogenic forms of diabetes.

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Introduction

The number of adults with diabetes steadily rises and is currently described as an „epidemic”. It is presumed that between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries [1]. By 2030 the number of individuals with diabetes worldwide may rise to 472 million and 80% of them will be in low and middle income countries. In some of these countries diabetic drugs and insulin are inaccessible or rather expensive and that eventually will affect the whole healthcare system [2]. Diabetes has a high rate of morbidity and mortality due to its complications, among which are vascular complications with high risk of infarction, diabetic foot, stroke, loss of vision and renal dysfunctions which result in end stage kidney disease [3]. In 2000 diabetes mellitus caused 2.9 million deaths, equivalent to 5.2% of world all-cause mortality. Depending on the country it represents 2-27% of deaths [4]. By 2010 the numbers had increased and the total number of excess deaths attributable to diabetes worldwide was estimated to be 3.96 million thus representing 6.8% of global mortality [5]. Still not all of these patients have the classical types of diabetes. Some of them may have monogenic forms with sometimes different presentations and better treatment options if they are diagnosed properly and in time. At least 13 maturity onset diabetes of the young (MODY) subtypes with distinct genetic etiologies have been identified till now. The most frequent types are MODY 1, 2 and 3 which will be furthermore discussed in the article due to their higher prevalence (up to 90% of all MODY) in the population [6, 7].

MODY incidence and prevalence

The prevalence and incidence of MODY largely depends on the country and there are often new cases MODY diagnosed in the population [8]. The minimum prevalence of MODY was reported to be 1.1-4.2% of patients with diabetes or 2.4-4.6 cases per 100,000 [9-16]. In Russian population the frequency of MODY 2 and MODY 3 possibly are the same unlike in other countries [17]. In Turkish population MODY 2 is considered to be the leading cause of MODY [18]. In the other countries the data about MODY is limited since only incidental findings were described till now [19]. In some populations MODY may have a higher incidence particularly if the community tend to maintain ethnic seclusion [20]. The current statement declares that MODY incidence and prevalence is underestimated by up to 80-95% [11, 21]. Patients with MODY are often misdiagnosed as having other types of diabetes and the lack of knowledge and awareness is still one of the important factors [22, 23].

All of the current data show that MODY is distributed unequally in different countries thus each country should perform its own population studies in order to determine the prevalence of the disease in the population [9-12].

The cost-effectiveness of diagnosing MODY should also be taken in considerations since both health and financial benefits can be found in this situation [24].

Table 1. MODY clinical features

Criteria	MODY1	MODY2	MODY3
Gene, locus	HNF-4a, 20q13.12	GCK 7, p15.3-p15.1	HNF-1a, 12q24.31
Age of diagnosis	15-45 years	Present from birth; presents at any age	15-45 years
Parental history of diabetes	60-90%	One parent usually has impaired fasting glycaemia	60-90%
Ketoacidosis	Rare, but possible	Rare, but possible	Rare, but possible
Insulin secretion	Defected with clinical presentation in adolescence or early adulthood	Can be decreased by 60%	Defected with clinical presentation in adolescence or early adulthood
Insulin resistance	Uncommon	Uncommon	Uncommon
Biochemical analysis	Low HDL, high LDL, normal C-peptide concentrations	Low free fatty acids and triglycerides	low hsCRP, high HDL, normal C-peptide concentrations
β -cell antibodies	Rare (less than 1%)	Rare (less than 1%)	Rare (less than 1%)
Vascular complications	Frequent	Rare	Frequent
Renal threshold for glucose	Normal	Can be low (glycosuria)	Low (glycosuria)

HNF, hepatocyte nuclear factor; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; GCK, glucokinase; hsCRP, high-sensitivity C-reactive protein.

MODY features and diagnosis

The genetic defects mostly affect β -cells of the pancreas and liver. These mutations cause a condition similar to type 2 diabetes mellitus (T2DM) and have no autoimmune etiology. The disease onset is usually before the age of 25. The patients are usually not overweight and respond to conservative treatment with sulfonylureas and a proper diet [6].

These mutations are characterized by high level of penetrance thus 95% of individuals that have MODY will become diabetic or will have an altered glucose metabolism before the age of 55 [25]. Misdiagnosis of MODY is a widespread problem and about 5% of patients with T2DM and about 10% type 1 diabetes mellitus (T1DM) actually may have MODY [25]. For instance in one study 20 of 247 patients clinically labeled as T1DM actually had hepatocyte nuclear factor 1a (HNF-1a) or HNF-4a mutations. From 322 patients clinically labeled as T2DM 80 had HNF-1a or HNF-4a mutations and 40 had glucokinase (GCK) mutation [26].

Patients with MODY usually have several clinical features: strong indications of diabetes inheritance in the family, early onset of the disease, relative insulin independence, absence of insulin resistance and β -cells autoimmunity (Table 1) [27].

Patients who have two or more family members with diabetes may have MODY in up to 45% of cases [28].

T1DM is characterized by the presence of islet autoantibodies, such as glutamate decarboxylase (GAD) and islet antigen-2 (IA-2) antibodies but they may be present in less than 1% of patients with MODY [29]. Thus antibodies are an effective tool in diagnosing MODY but rarely a combination of monogenic forms with T1DM may exist [30, 31]

Still the most exact diagnostic procedure that can be performed is genetic testing which is a gold standard when it comes to monogenic diseases [32]. Haplotypes may also have a significant impact when diagnosing MODY since T1DM usually is associated with specific human leukocyte antigens [33, 34].

Since some countries have no or limited access to genetic testing other data should be taken in consideration:

- diabetes diagnosed before 45 years,
- negative diabetes autoantibodies (GADA, IA-2, zinc transporter ZnT8, and insulin autoantibodies (IAA)),

- no insulin resistance,
- family history of diabetes,
- detectable C-peptide more than 0.2 nmol/l outside the honeymoon period, GST more than 0.2 nmol/l [22, 27],
- Presence of liver pathology particularly both benign and malignant primary liver cell tumors (liver adenomatosis, hepatocellular carcinoma) [35-40].

During pregnancy body mass index (BMI) <25 kg/m² and fasting glucose \geq 5.5 mmol/L can also be used as separate indicators of GCK mutation and has a sensitivity of 68% and 96% specificity. A study that involved the Atlantic Diabetes in Pregnancy cohort showed that 1.1 out of 1,000 pregnant women had GCK mutation [41]. Other studies showed that in 3% of cases GCK mutation is the cause of gestational diabetes [42].

Urinary C-peptide creatinine ratio is another test that can help to distinguish MODY from T1DM, but does not show a great distinction between MODY and T2DM. The UCPCR is <0.03-0.39 nmol/mmol for T1DM and is 2.37-5.32 nmol/mmol for MODY [43]. This test was reported to have sensitivity up to 93% and specificity up to 90% for discriminating between MODY and T1DM. [44]

MODY 1

HNF-4a regulates transcription of the insulin gene and other genes that are involved in glucose metabolism. If HNF-4a function is decreased then it affects the β -cells mainly by controlling HNF-1a which is also a transcription factor for insulin. Mutation in HNF-4a causes MODY 1 with altered response of insulin secretion in case of high glucose levels. Mutations in HNF-4a sometimes can cause neonatal hyperinsulinemic hypoglycemia and in 50% of cases macrosomia. Some gastrointestinal dysfunctions can also be present due to the fact that recent data links this transcription factor with intestinal homeostasis [27, 45, 46]. Glycosuria is not present in HNF-4a MODY, and low levels of apolipoproteins (apoA11, apoCIII, and apoB) can be a diagnostic clue in this case [47]. In some patients it is possible to switch insulin therapy to more appropriate drugs. Bazalova and coworkers reports that one patient remained on insulin therapy after 27 years of treatment due to severe complications, another one that had diabetes for 48 years was switched to a more suitable therapy which can be due to different levels of compensation of diabetes [48].

MODY 2

The GCK gene is located on 7th human chromosome p15.3–p15.1, consists of 10 exons and encodes a 456 amino-acid protein. GCK acts as a glucose sensor enzyme in the β -cells of the pancreas and in liver cells besides that it also phosphorylates glucose. By phosphorylating glucose into glucose-6-phosphate it begins the process of glucose storage or glycolysis. First GCK mutation was reported in 1992 and since then there have been described approximately 200 different mutations [46, 49].

GCK is considered to be the most stable mutation from all MODY but due to loss of sensory function of β -cells insulin secretion rate can be decreased by 60% [50]. MODY 2 is characterized as non-progressive and complications free metabolic disease probably due to lower levels of free fatty acids and triglycerides [51]. In one of the studies it was shown that children with asymptomatic hyperglycemia frequently have MODY 2 and their mothers in 5-80% of cases had gestational diabetes [45].

Bazalova and coworkers report that son and father with GCK mutation that were previously on diabetic treatment successfully started diet treatment without any medication. The uncle on the other hand remained on combined oral diabetic drugs. This underlines the importance of early diagnosis of the disease [48].

Among the other methods to identify candidate patients for MODY2 genetic testing a group of authors developed a diagnostic flowchart in order to improve the detection rate and to increase the number of properly requested tests. The flowchart is called 7-iF and consists of 7 binary "yes or no" questions. The 7-iF, in a prospective 2-year study (921 diabetic children) showed a precision of about the 76%. Also using retrospective data, the 7-iF showed a precision in identifying MODY2 patients of about 80% [52].

MODY 3

HNF-1a codes for the transcription factor HNF-1 α , which interacts with deoxyribonucleic acid (DNA) as a homodimer or a heterodimer with HNF-1 β , to regulate multiple cellular functions including glucidic metabolism, lipidic transport, and detoxication [35]. In case of HNF-1a mutations patients develop diabetes by the age of 25 in 63% and by the age of 50 in 94% of cases [46]. Several environmental and genetic factors are known to modify the age at HNF1a-MODY diagnosis, particularly intrauterine hyperglycemia and HNF-1a mutation position [53, 54]. Furthermore females are usually diagnosed earlier [53].

Patients usually have normal or even higher insulin sensitivity but their pancreatic endocrine function is directly altered and requires treatment. The condition may also be associated with hepatic adenomatosis, bile acid synthesis alteration, decreased pancreatic volume, pancreatic dysfunction and other diseases [37, 38, 55-58]. The patients also have elevated urinary glucose due to low renal threshold for glucose in this genetic subtype [59].

Several other markers may serve as a diagnostic tool such as altered glucose fucosilation of N-linked glycans on plasma proteins [6]. Serum high-sensitivity C-reactive protein (hsCRP) levels are lower in HNF-1a MODY than in other forms of diabetes. The specificity of hsCRP test is 80% and it is considered to be an easily available biomarker [60, 61]. Other test may also be useful. For instance serum 1,5-anhydroglucitol (1,5AG) performed well in discriminating GCK-MODY from other diabetes subtypes, particularly HNF1A-MODY. Mean (SD) 1,5AG levels were:

GCK-MODY 13.06 microg/ml (5.74-29.74), HNF1A-MODY 4.23 microg/ml (2.12-8.44), type 1 diabetes 3.09 microg/ml (1.45-6.57), LADA 3.46 microg/ml (1.42-8.45), and type 2 diabetes 5.43 (2.12-13.23) [62]. The receiver operating characteristic (ROC) curve analysis revealed 85.7% sensitivity and 80.0% specificity of 1,5AG in screening for HNF-1 α MODY at the criterion of <6.5 μ g/ml in patients with an A1C level between 6.5 and 9.0% [63].

It is important to mention that mutation in both GCK and HNF-1a presents as a MODY 3 probably due to the leading role of transcription factor HNF-1a in the disease [64].

MODY management

GCK mutation usually causes a mild, asymptomatic hyperglycemia. No treatment is needed for this group of patients but they should be monitored. Early diagnosis of this disease is essential for stopping the insulin therapy in time [65]. But it is important to mention that the management of pregnant women with GCK mutations is harder than those with HNF-1a mutations. An increased percentage of miscarriages in GCK pregnancies should also be considered. Since there is limited data on this subject current insulin protocols should be implemented in MODY diabetes patients who are pregnant [66].

HNF-1a and HNF-4a mutations cause more prominent hyperglycemias and with time vascular complications. The optimal treatment options in these conditions are sulfonylureas drugs. The patient should be monitored carefully since the disease is not always stable and additional lines of therapy may be helpful in future [67]. Still it is considered that approximately 70-80% of patients can successfully be treated with sulfonylureas with no insulin injections [46, 48, 68]. Some patients on the other hand remain on insulin treatment due to complications [48]. Demol and coworkers report a case where treatment with sulfonylurea was found to be a clinically ineffective alternative to insulin therapy due to a particular mutation type in HNF-1a [69].

In one of the studies 60 patients with HNF1A-MODY were matched with 60 BMI-, age-, ethnicity- and diabetes duration-matched patients with T1DM. After 84 month follow-up the majority of the cohort treated with sulfonylurea therapy remained insulin independent at 84-month follow-up (80%). The HbA1c in the HNF1a-MODY group treated with sulfonylurea therapy alone improved significantly over the study period. The rate of retinopathy was significantly lower in the HNF1a-MODY group than that in the T1DM group as well as a lower rate of microalbuminuria and cardiovascular disease [68].

Other medications can also be useful, for instance glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase IV inhibitors, meglitinide analogues showed excellent results in controlling glucose levels as well [70-73].

The presence of monogenic diabetes does not give protection from having metabolic syndrome or elements of T2DM and patients with some of the genetic variations are more likely to develop these metabolic diseases over time [74, 75]. There are also rare reports of patients with MODY who later developed T1DM [30, 31].

Macrovascular risk factors are more frequent in T2DM still 23% of MODY patients may have dyslipidemia and 10% hypertension [76]. Liver and pancreatic functions should be carefully monitored in MODY 3 [37, 38, 55-58].

The data involving MODY patients and surgical outcomes is limited and currently mostly involves transplantation surgery outcomes. Simultaneous pancreas and kidney transplantation in MODY is discussed in several articles with good postoperative results [77, 78].

The implementation of registry for monogenic diabetes should also be a helpful tool since it provides data about the incidence rates and clinical presentation of diabetes in a particular population [79, 80]. It also has low cost and allows collecting a wide range of longitudinal data on rare patients from diverse geographic locations [81].

Conclusion

In the last decade there is growing attention toward monogenic forms of diabetes and their frequency in the population may be higher than it was firstly presumed. Careful study of the patient's family history and more accurate laboratory testing may be useful to find patients with MODY. Still the best method for any monogenic disease remains genetic testing but due to limited financial support in some countries alternative methods can be successfully used for MODY screening. Further investigation in this area can improve the possibilities for diagnosis and treatment of genetic diabetes, its complications and improve the quality of life and life expectancy.

Conflict of interest

The authors declare that they have no conflict of interest.

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