MATURITY ONSET DIABETES OF THE YOUNG

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Abstract

Maturity-onset diabetes of the young (MODY), named also as "genetic defects of β cell function", is a type of diabetes mellitus determined by a single mutation of a single gene. There are nine known genes that lead to the occurrence of different subtypes of MODY, with different phenotype and prognosis. When diabetes mellitus is diagnosed during pregnancy, one has to think about the possibility that this is a MODY type (frequent determined by glucokinase mutations). The therapy ranges from diet only to diet and insulin therapy, the aim being a good glycemic control in order to prevent chronic complications. It is important to diagnose MODY because this implies a correct therapy, prognosis and genetic advice for both patient and family members.

key words*: monogenic diabetes, glucokinase mutations, transcription factors mutations, pregnancy*

The term of "maturity-onset diabetes of the young" (MODY) was used for the first time by Fajans in 1964 for a rare form of familal non-insulin-dependent diabetes mellitus (DM), having juvenile onset and favorable response to tolbutamide, which interested normal weight Caucasians. The first pieces of information related to this entity dates, however, from 1928, when Cammidge noticed children with DM with slow evolution, with an obvious family history and which, for many years, did not present any characteristic symptoms, even in the absence of insulin therapy [1]. Much later, in 1974, Tattersall and co-workers forwarded the hypothesis that some youngsters with DM without obesity, which do not develop ketosis and are treated for some time without insulin, would suffer from a dysfunction of β cells, consequence of a mutation at the level of a single gene [2]. Subsequently, along with the increase of the number of described cases and with the decoding of responsible mutations, MODY gains a well defined place in DM systematization proposed by the World Health Organization, being framed as "genetic defects of β cell function" [3].

MODY is defined as that type of DM characterized by a dysfunction of β cells, which results as a consequence of a single mutation of a single gene and is inherited following an autosomal-dominant pattern. The definition is supported by the description of genetic defect and, although it has changed

with years, the name of MODY, based on the old classification of DM in "juvenile onset diabetes" and "adult onset diabetes", was kept [4, 5].

The diagnosis criteria of MODY are represented by [6-8]:

1. early diagnosis of diabetes, before the age of 25 years, in one or, ideally, two members of the family;

2. insulin independence for at least 5 years after the diagnosis (as alternative, the insulin treated patients need the presence of significant concentrations of C peptide);

3. autosomal-dominant inheritance (presence of DM cases with similar phenotype for two or even three generations);

4. normal weight or underweight (obesity is not excluded, but it is not needed for MODY to appear);

5. insulinemia frequently found within normal limits, having however low values related to glycemia (diabetes is a consequence of β cell dysfunction).

Some remarks are imposed related to the defining criteria of MODY.

The early diagnosis, below the age of 25 years, represents an essential feature of MODY. It was noticed, in most of the families with this type of DM, the phenomenon of "anticipation", that is diagnosis established at younger and younger ages at the new generations (probably as a consequence of the larger impact DM has in the general population). It is accepted, however, that the patients with MODY are diagnosed as well after the age of 25, under the conditions the diagnosis is acknowledged by genetic testing [7].

The insulin independence for at least 5 years helps for the differentiation from type 1 DM, for which potential remissions are pretty rare after this period. The decision of insulin therapy is subjective in most of the cases, as it belongs to the attending physician. It can sometimes happen that when a young and normal weight patient, with unknown family history, is diagnosed with DM, he/she shall be considered as suffering from type 1 DM and the insulin therapy shall be initiated. In these cases, marking out a C normal peptide after 5 years from the diagnosis orients towards MODY type of DM. In order to prevent such errors, it is very useful to determine pancreatic autoantibodies, especially glutamic acid decarboxylase antibodies, positivity of which is very rare in case of MODY [8].

The autosomal dominant inheritance of MODY is an important diagnosis criterion. It means that DM must exist for two generations (ideal for three generations). However, marking out this mode of autosomal dominant transmission of MODY is not very exact. A polygenic disease, like type 2 DM, may manifest "pseudo-dominance" and be transmitted to various generations of the same family. Furthermore, in case both parents have type 2 DM (frequent situation for the population with increased prevalence of the disease), it can appear to the offspring even at young ages (the phenomenon of "double gene dose"). In these cases, for the establishment of MODY diagnosis and not of type 2 DM, the following elements can help:

- presence of non-insulin-dependent DM, with onset at young ages, in various branches of the genealogic tree (1st and 2nd cousins);
- the absence of glycemic disorders to one of the parents;
- absence of obesity and of other suggestive features for insulin resistance (like atherogenic dyslipidemia).

The absolutely compulsory consideration of the criterion of dominant transmission leads to MODY underdiagnosis, seeing that the family history can be unknown by some of the patients, diabetes is not diagnosed at the parents or it can result as a consequence of a *de novo* mutation (in this latest case, the children of the subject have 50% chances to develop DM and then the diagnosis is retroactively established) [7, 9].

The factors reducing insulin sensitivity (infections, puberty, pregnancy, obesity) have no significant role in the occurrence of MODY, but their presence may increase the value of glycemia, making the diagnosis obvious.

The prevalence of MODY in Europe is of about 1-2% amongst the cases with non-insulin-dependent DM. It is different from one country to the other, depending on the author [6].

The differential diagnosis of MODY must be performed with other types of DM which can be diagnosed before 25 years (Table 1).

Table 1. Differential diagnosis of MODY at the youngster [1]

Feature	DM type 1	DM type 2	MODY
Age at onset	Peaks at 10-15 years	Adolescence, youngsters	<25 years
Ethnic group	Caucasians	Afro-Americans, Hispanics	Caucasians
Gender M/F	1.1/1	1/1.5	1/1
Severity at onset	High	Reduced or medium	Reduced or medium
Autoimmunity	+	–	–
HLA DR3, DR4	High frequency	Normal frequency	Normal frequency
Ketoacidosis	Frequent	Rare	Rare
Natural evolution	Insulindependent	Non-insulindependent	Non-insulindependent
Obesity	Rare	≥90%	Rare
Transmission mode	Non-Mendelian, sporadic	Non-Mendelian, but with strong family aggregation	Autosomal dominant
Involved genes	Polygenic	Polygenic	Monogenic
Pathogenesis	Insulinopenia by β cell destruction	Insulin resistance + insulinopenia	Insulinopenia

Table 2. MODY systematization [6-8]

MODY subtype	Gene localization	Prevalence
MODY produced by mutations of GCK (GCK-MODY)		
GCK-MODY = MODY 2	7 p15-p13	14%
MODY produced by mutations of TF (TF-MODY)		
HNF-4α MODY = MODY 1	20 q12-q13.1	3%
HNF-1α MODY = MODY 3	12 q24.2	69%
IPF-1 MODY = MODY 4	13 q12-1	<1%
HNF-1β MODY = MODY 5	17 cen-q21.3	3%
NeuroD1/BETA2 MODY = MODY 6	2 q32	<1%
MODY produced by other mutations		
KLF11 = MODY 7	2 p25	<1%
CEL = MODY 8 (MODY 7, according to other authors)	9 q34	<1%
PAX4 = MODY 9	7 q32	<1%
MODY not yet described		

Legend: MODY=maturity onset diabetes of the young; GCK=glucokinase; TF=transcription factors; HNF=hepatocyte nuclear factor; IPF=insulin promoter factor-1; NeuroD1/BETA2=neurogenic differentiation 1; KLF11=Kruppel-like factor 11; CEL=carboxyl ester lipase.

Depending on the genetic defect, various MODY subtypes have been described. They were named, in the order of the discovery, MODY 1, MODY 2, MODY 3 etc. Nowadays, there is the tendency to replace figures with the name of the responsible gene, so that the subtypes are named HNF-4α MODY, GCK-MODY, HNF-1α etc. The presence of some clinical associated features brings for suspicion of a certain type of MODY, the precise diagnosis being set as a consequence of genetic testing. A systematization of MODY subtypes is shown in Table 2.

GCK-MODY

Glucokinase (GCK) is the enzyme which limits the rate of glycolysis, catalyzing its first step, phosphorylation of glucose in glucose-6-phosphate. It has an extremely important function in the β cells, but exercises as well metabolic roles in the hepatocyte, pancreatic α cell and hypothalamus. Unlike other hexokinases, it has a low affinity for the glucose and is not inhibited by its product, glucose-6-phosphate. As a consequence of these unique pharmacokinetic properties, the rate of glucose phosphorylation is related only to the enzyme concentration, thus allowing β cell and hepatocyte have a proper response to glycemic values. As a result, GCK functions like a true glycemic sensor in the β cells [7].

Heterozygote mutations of GCK gene lead to a reset of the glycemic sensor, which "accepts" as normal higher glycemia. After a glucose load, the patients with GCK-MODY have the capacity to correspondingly increase the secretion of insulin. This is the reason for which only small increases in glycemia are recorded at the oral glucose tolerance test (OGTT). GCK mutations determine, at hepatic level, the reduction of glycogen synthesis (GCK being the enzyme limiting as well the speed of this process), and in α cell, the alteration of glucagon secretion, as a response to hypoglycemia (the response of α cell takes place at lower values of the glycemia compared to those of patients with type 2 DM) [8].

Regardless which of the least 130 known mutations of GCK is present, GCK-MODY is the combined result of faulty perception of hyperglycemia and diminished glycogen synthesis. Fasting hyperglycemia is present from the birth, its values being contained between 100 and 145 mg/dl. It aggravates very slowly with time. If OGTT is performed, the glycemic excursions are low, not exceeding 55 mg/dl. Therefore, most of the patients with GCK-MODY are diagnosed as having DM on the grounds of the fasting glycemia and not of that postprandial. Generally, the glycemic values are about 40 mg/dl higher than in non-diabetics, but 100 mg/dl lower than in patients with type 2 DM. The value of HbA_{1c} is placed around the upper limit of normal range. The proinsulin/insulin ratio is normal, showing that this type of MODY is a consequence of glycemic sensor abnormality and not of another malfunction of β cell, as the case, for example, in type 2 DM [7].

Many times, the diagnosis of GCK-MODY is set in pregnancy. It is estimated that about 3% of Caucasian women with gestational DM actually have GCK-MODY. The identification of these cases is important, seeing the different clinical evolution, both during pregnancy, and afterwards. The criteria bringing forward the suspicion of a mutation of GCK are represented by persistent fasting

hyperglycemia (≥100 mg/dl), low glycemic excursion (<55 mg/dl) at OGTT and family history of hyperglycemia [10].

Regarding GCK mutations and pregnancy, some remarks are mandatory. Depending on the manner the pathological gene is transmitted, one can meet one of the following 3 situations:

– the mother is affected and the fetus is not (50% of the GCK-MODY cases to the mother);
– the mother is not affected, but the fetus is (the gene is inherited from the father);
– both the mother and the fetus are affected (50% of the GCK-MODY cases at the mother).

In the first case, the fetus suffers from hyperglycemia during the gestation, which stimulates the secretion of insulin and, consequently, of the growth factors mediated by it. Therefore, its weight will be higher for the gestational age. In the second situation, as the insulin-secretor response of the fetus is decreased, the weight at birth will be about 500 g lower than normal. This can represent an alternative explanation for the association between low weight at birth and the occurrence of diabetes at the adult age (it actually is GCK-MODY and not type 2 DM). Finally, in the last case, the fetus suffers from hyperglycemia during the pregnancy, but its low insulin-secretor response prevents synthesis in large quantities of the increase factors. Its weight at birth is usually normal [7].

The diagnosis of GCK-MODY is established by chance (within the pregnancy or with the occasion of accidental glucose measurements) or as a consequence of family studies. The symptoms are discrete or absent and do not make the patient consult a physician. Sometimes, the diagnosis is set at the adult or old age, being difficult to differentiate MODY from type 2 DM. The existence of obesity and insulin resistance are not needed for the installation of GCK-MODY. Microangiopathic complications are rare, being in concordance to a mild increase of glycemic level. The prevalence of macroangiopathic complications is difficult to estimate, seeing the relatively low number of patients. Fasting insulinemia is similar to that of non-diabetic individuals, being however disproportionately low compared to glycemic values [7, 8].

TF-MODY

Mutations of transcription factors (TF) affect the secretion of insulin in mature β cell, alter its life cycle (decreased rate of development and proliferation, high rate of apoptosis) and decrease the concentration of proteins with essential role in the metabolism of glucose, like key enzymes of mitochondrial metabolism of glucose. There are proves that 4 of the transcription factors: hepatocyte nuclear factors (HNF) 1α, 4α and 1β and insulin promoter factor (IPF) 1, work in a complex network and that alterations at any of its level determine a deterioration of β cell, probably by joint mechanism. HNF-1α and HNF-4α are mutually stimulated at the level of pancreas. In their turn, HNF-1β and IPF-1 stimulate the action of HNF-4α. The loss of the function of any of these factors determines a decrease of the mass and functionality of β cells [7].

All the patients with TF mutations have a similar hyperglycemic pattern, which is totally different from of the patients with mutations of GCK. They arise with normal glucose

tolerance. β-cell function progressively deteriorates, the DM diagnosis being set for 63% of the cases by the age of 25. At OGTT, fasting glycemia is frequently normal, but the glycemic excursion exceeds 90 mg/dl. The subjects are lean and insulin sensitive, unlike the patients with type 2 DM, who are obese and insulin resistant. The microvascular complications are frequent, especially if the treatment is not adequate [8].

Depending on the subtype, the patients can present some particular features.

HNF-4α MODY

The patients have plasma levels of apoproteins AII, CIII and possibly B and a, lower by 25% than normal, which makes them different from the patients with type 2 DM. The concentrations of triglycerides are 50% lower, and the activity of lipoproteinlipase is diminished, as a consequence of the decreased apoprotein concentrations [11].

HNF-1α MODY

There have been described by now more than 65 mutations of HNF-1α. The patients present decreased renal thresholds for glucose, due to a diminished glucose reabsorbtion in the proximal contort tube, consequence of reduced the activity of sodium and glucose transporter 2 (SGLT-2). This anomaly appears before the installation of hyperglycemia, which makes useful the screening of the mutation by determining the glycosuria. The patients present aminoaciduria that accompanies glycosuria and has no characteristic features. Seeing the high sensitivity to insulin (significantly higher compared to that of patients with type 2 DM with the same body mass index) and the role played by TF in the synthesis of lipoproteins, the lipid profile of patients with TF mutations is favorable, being characterized by increased serum concentrations of HDL cholesterol. The proinsulin/insulin ratio is high, the same as in type 2 DM [7, 12].

IPF-1 MODY

The most obvious particularity of patients IPF-1 mutations (factor involved as well in organogenesis) is that, when the subject is homozygote, pancreatic agenesis occurs, with marked hyperglycemia and exocrine insufficiency from the very birth [8, 13].

HNF-1β MODY

HNF-1β plays an important role in the intrapartum development of the uro-genital apparatus. The most striking extra-pancreatic feature is represented by renal anomalies, which dominate most of the times the clinical picture, making the patient to consult first a nephrologist. More than 75% of the patients present renal cysts, visible at the antenatal echography. This association of renal cysts with DM was named as well RCAD syndrome ("renal cysts and diabetes"). The renal involvement does not have, however, the same aspect in all the patients, being also met, next to cystic dysplasia, oligomeganephronia, familial hypoplastic glomerulocystic kidney disease, single kidneys or familial gouty nephropathy. The renal function is affected in various degrees, about 50% of the patients needing dialysis or renal transplant. Next to renal suffering, the patients can also have anomalies of the uterus or external genital organs (30% of the cases), stature-weight underdevelopment and, unlike other MODY subtypes, insulin resistance and hiperuricemia

(accompanied or not by gout). Macroscopically, the pancreas of these patients is atrophic [14, 15].

NeuroD1 MODY

The patients do not present other alterations than hyperglycemia. Most of the described cases have been diagnosed after the age of 40 and few of them needed insulin for glycemic control [16].

MODY produced by other mutations

KLF11 MODY

The patients with mutations of Kruppel-like factor 11 (KLF-11) have no characteristic features which can allow the orientation towards this subtype [17].

CEL MODY

This subtype has only been described in 2 families from Norway. It is characterized by the presence, besides DM, of a dysfunction of the exocrine pancreas, which is usually the first diagnosed. The subjects have a deficit of fecal elastase and other suggestive clinical parameters for the insufficiency of exocrine pancreas (abdominal pain, loose stools). The exocrine insufficiency can be met in other members of the family as well, even without the presence of DM. The imagistic investigations mark out the existence of a small pancreas. This intravitam finding was acknowledged by the autopsy performed to one of the patients, which showed a small and fibrotic pancreas, characterized from a histopathologic standpoint by marked fibrosis, mucinous metaplasia and absence of islets and acinary cells [18].

PAX4 MODY

It was described to some families in Thailand. The patients rapidly develop retinopathy and diabetic nephropathy leading to chronic renal insufficiency [19].

MODY Treatment

The objective for treating patients with MODY is, similary to any type of DM, to obtain a value of HbA_{1c} <7%, as, contrary, there is an increased risk of chronic complications [1].

In cases of GCK-MODY, the medication is very rarely needed, the optimization of the lifestyle being enough. The therapeutic response to any hypoglycemic agent is poor, the correction of fasting hyperglycemia being difficult due to the increase of the activity of counter regulatory hormones. The administration of insulin usually determines decrease of endogenous insulin-secretion, and the glycemic values are maintained high. Due to this reason, the risk of hypoglycemia is low in these patients. A special situation is represented by the pregnant woman with GCK mutations. In this case, the main purpose of the treatment is to reduce the fetal risk. The intrauterine development of the fetus depends not only on the glycemic control of the mother, but also on the transmission or not of the mutant gene. If the mother has a good glycemic control and the fetus inherited the gene, it shall be small for the gestational age (which would not happen if the glycemia had been higher at the mother). For a change, if the fetus did not inherit the gene and the mother has high glycemia, the weight of the fetus will be higher (which would have not happened in case the mother has had good glycemia). Therefore, the intensity of the

treatment must be guided by the rhythm of fetal growth, echographically marked out. Postpartum, the mothers with GCK-MODY usually don't need pharmacological therapy, even if during their pregnancy they were administered large doses of insulin [7, 8].

The patients with mutations of TF can be treated only with diet (⅓ of the cases), with diet and oral antidiabetic drugs (⅓ of the cases) and with diet and insulin (⅓ of the cases). If most of the patients with type 2 DM present similar glycemic response to metformin and sulphonylureas, the patients with HNF-1α MODY have a 4 times better response to sulphonylureas compared to metformin (the values of HbA_{1c} are 4-5% higher in case of treatment with metformin) [20, 21]. The treatment begins with small doses of sulphonylureas, of approx. ¼ of the usual start dose at adults (for example, 20 mg gliclazide once or twice a day). If hypoglycemia occurs even for these doses, the drug can be replaced with an extended release formulation or with meglitinide. Unlike the patients with HNF-1α MODY, which promptly respond to sulphonylureas, the patients with HNF-1β MODY are not sensitive to them and usually need insulin [7].

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