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MONOGENIC DIABETES IN CURRENT MEDICAL PRACTICE

Diana MICLEA[a], Camelia ALKHZOUZ[b], Claudia BOLBA[c] and Silvia IANCU[d]

[a]Medical Genetics Department "Iuliu Hatieganu" University of Medicine and Pharmacy, 8 Babeş Street, 400012 Cluj-Napoca; Medical Genetics Department, Clinical Emergency Hospital for Children, Cluj-Napoca, 68 Motilor street, 400370, Cluj-Napoca, Romania, diana.miclea@umfcluj.ro
[b]1st Pediatric Department "Iuliu Hatieganu" University of Medicine and Pharmacy, 8 Babeş Street, 400012 Cluj-Napoca; Medical Genetics Department, Clinical Emergency Hospital for Children, Cluj-Napoca, 68 Motilor street, 400370, Cluj-Napoca, Romania, calkhuzouz@umfcluj.ro
[c]2nd Pediatric Department "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, 8 Babeş Street, 400012 Cluj-Napoca; 2nd Pediatric Clinic, Clinical Emergency Hospital for Children, Cluj-Napoca, 68 Motilor street, 400370, Cluj-Napoca, Romania, claudine.bolba@yahoo.com
[d]Clinic for Diabetes and Nutrition Disorders, County Emergency Hospital, 3-5 Clinicilor street, 400006, Cluj-Napoca, silviaiancu2004@yahoo.es

Corresponding author: Diana Miclea, diana.miclea@umfcluj.ro

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Monogenic diabetes is a rare type of diabetes determined by a pathogenic variant in a single gene. Precision medicine in diabetes is an attractive topic, especially for monogenic diabetes, not so much yet in type 1 or type 2 diabetes. In monogenic diabetes, more than 50 genetic loci are known were identified, these could be diagnosed by genes panel/exome sequencing, now an accessible testing. A better diagnosis involves a precise therapy, which could be more often seen in monogenic diabetes, a desideratum for type 1 or 2 diabetes, not so easy to accomplish, mainly due to multifactorial aetiology. Some clinical criteria are useful for a better clinical diagnosis for monogenic diabetes, allowing a diagnosis in up to 50% of patients with MODY. Thus knowing the clinical and genetical features in patients with diabetes could lead to more adequat treatment for these patients.

Keywords: monogenic diabetes, MODY, neonatal diabetes, genetics.

INTRODUCTION

Monogenic diabetes is a rare type of diabetes determined by a pathogenic variant in a single gene. The common forms of monogenic diabetes are: the maturity-onset diabetes of the young (MODY) and neonatal diabetes. Precision medicine in diabetes is an attractive topic, especially for monogenic diabetes, not so much yet in type 1 or type 2 diabetes. In monogenic diabetes, representing 1–5% of diabetes, due to the actual knowledge about the etiology and physiopathology (as congenital defects of beta cells, congenital defects of insulin action, mitochondrial diabetes), the diagnosis could be a etiological one, thus leading to a more precise therapeutic intervention[1]. The obstacles to a precision medicine in common forms of type 1 and 2 diabetes are represented by their heterogeneity and multifactorial character of the etiology, difficulty in the accurate diagnosis of different types of diabetes, incomplete understanding of the pathophysiology and limited therapies[1].

MONOGENIC DIABETES – CLINICAL PICTURE

The clinical features suggestive for a monogenic cause of the diabetes are: the autosomal dominant transmission of diabetes in the family; diabetes onset under the age of 12 months and particularly under the age of 6 months (neonatal diabetes); absent autoantibodies; mild fasting hyperglycemia (100–150 mg/dl), usually in a young asymptomatic person, without obesity, preservation of C peptide over time; an unusually low insulin requirement (≤ 0.5 U/kg/day); associated features (hearing loss, optic nerve atrophy, syndromic features – mitochondrial disorder); severe insulin resistance, in a patient without obesity (*INSR* mutations)[2].

For the clinical diagnosis of monogenic diabetes, the main data come from: clinical picture and possible associated signs, the age of onset, the family history, the body mass index (BMI), C-peptide and insulin values, autoantibodies titration (ICA, GAD2, IAA, IA-2, ZnT8)[3].

MONOGENIC DIABETES CLASSIFICATION

It has evolved from classification based on clinical features (MODY subtypes) to that based on molecular genetics (GCK-MODY), thus giving robustness to the diagnosis, defining the aetiology and the clinical course, thus indicating a more adequate treatment. The actual classification of monogenic diabetes is based on the causal gene followed by the abbreviation of the clinical phenotype (GCK-MODY or KCNJ11-TNDM – transient neonatal diabetes mellitus). It is well known that the same gene could lead to different phenotypes. If only the clinical diagnosis is established and the genetic testing has not been performed, the clinical classification is still used: MODY, TNDM, PNDM (permanent neonatal diabetes mellitus)[1].

Neonatal diabetes had an onset in neonatal period or infancy, often under six months of age and could be permanent (PNDM) or transient (TNDM). It is known that 80% of those with diabetes under six months have monogenic diabetes, thus any newborn or infant diagnosed with diabetes before six months of age should be genetically tested. Many of these patients have a diabetes which could be treated with sulfonylurea drugs. The only differential diagnosis for neonatal diabetes is type 1 diabetes, very rarely diagnosed under the age of six months. For those patients diagnosed between six and nine months, genetic testing could be indicated, for this category of age a good cost-effectiveness ratio for genetic testing was observed[1].

MODY is diagnosed in multiple individuals with diabetes from the same family, and it is characterised by autosomal dominant transmission, usually having the onset in adolescence or at young adult.

Other subtypes of monogenic obesity are represented by: genetic syndromes, mitochondrial disorders, severe insulin resistance or lipodystrophy.

The same defect that determines transient or permanent neonatal diabetes for one individual may be present in other family members with MODY.

GENETIC TESTING IN MONOGENIC DIABETES

In monogenic diabetes, more than 50 genetic loci are known were identified[1]. For diabetes developed under six months of age the genetical testing by genes panel sequencing is imperative, due to high percentage of patients with monogenic diabetes. The main reasons for genetic testing are: the possibility for a precise therapy (high dose sulfonylureas in case of ABCC8 and KCNJ11 mutations or low dose sulfonylureas in case of 6q24 methylation defect), to anticipate the prognosis and other associated features and possible early intervention for some of them (possible transitory diabetes in ABCC8 or KCNJ11 genes; exocrine pancreas deficiency in HNF1B, GATA4 genes, associated autoimmune disorders in FOXP3 or different developmental delay syndromes in KCNJ11, EIF2AK3, NKX2-2 genes)[4]. Another useful aspect is the genetic counselling derived from a precise diagnosis and the knowledge of risk recurrency.

There is no ideal combination of clinical features, family history, biomarkers that can reliably identify all cases. There must be a balance between testing more patients and the need to control costs. However, sometimes the lack of availability and the increased costs of testing could still be an obstacle.

The genetic testing methods usually used are represented by genes panel or exome sequencing.

MATURITY-ONSET DIABETES OF THE YOUNG

MODY are caused by monogenic defects of beta cell function leading to a primary defect in insulin secretion. Usually MODY are diagnosed based of clinical features.

The clinical criteria for MODY diabetes are represented by: dominant transmission with at least two (preferably three) affected consecutive generations (de novo pathology should be also considered); a typical onset before 25–30 years; MODY probability over 25% based on the MODY calculator (MODY clinical risk calculator)[5]; a distinct phenotype of stable, mild, non-progressive hyperglycaemia in asymptomatic individuals (GCK-MODY), residual insulin secretion reflected by C peptide (>0.6 ng/mL), the absence of autoantibodies associated with type 1 diabetes[1]. These criteria do not represent absolute indicators but are supportive for a good selection of the patients who can benefit from genetic testing. Strict criteria for MODY testing are represented by: diabetes in at least two or three generations, autosomal dominant transmission, diagnosis before the age of 25 in at least one of the affected subjects in the family[1]. Using these strict criteria, about half of MODY patients are diagnosed.

Even if the clinical criteria of monogenic diabetes are well-known, there is an important clinical overlap between the type 1, type 2 and monogenic diabetes, thus monogenic diabetes can be insufficiently diagnosed and treated inappropriately. It is known that 80% of MODY are not correctly diagnosed. Often it can be seen as an incidental identification in an asymptomatic patient or as a pathology which become clinically apparent during intercurrent diseases, pregnancy, puberty, thus revealing limited insulin secretion.

Today, it is more appropriate to define monogenic diabetes by genetic subgroups, thus understanding a pathogenetic features that can be sometimes influenced by a precise therapy.

The study of Todd JN *et al.* showed that for 3333 patients with type 2 diabetes genetically tested by exome sequencing, monogenic diabetes was diagnosed in 2.8% of them, in 89% of them the knowledge of this diagnosis would have changed the clinical management[6]. The most frequent mutations were observed in *GCK, HNF1A* and *HNF4A* genes[6].

GCK-MODY2

Glucokinase acts as a glucose sensor, it catalyses the phosphorylation of glucose into glucose-6-phosphate

The inactivating mutations lead to decrease in *GCK* activity, thus increasing the glucose threshold.

It is characterised by: mild fasting, asymptomatic and non-progressive hyperglycaemia (110–140 mg/dl), usually incidentally diagnosed, at a routine evaluation or during an intercurrent infection or pregnancy. The glycosylated haemoglobin is usually between 5.8–7.6%. It has a relatively high prevalence, approximately 1:1000 in general population. The need to recognize these diseases is supported by the high percentage of individuals who are unnecessarily treated with a wide variety of drugs prior to genetic diagnosis, the discontinuation of this treatment usually having no effect on glucose blood level or on glycosylated hemoglobin[7]. No treatment is indicated, except possibly during pregnancy (to try to prevent macrosomia in an unaffected foetus). It is also known the lower risk of micro- or macrovascular complication in patients with *GCK* mutations[8].

HNF4A-MODY 1

The patient or family members often have a history of macrosomia and/or hyperinsulinemic hypoglycemia at birth. In *HNF4A* gene mutations, excessive insulin secretion is observed, leading to a marked increase in birth weight (macrosomia). Neonatal hyperinsulinism can lead to persistent and prolonged hypoglycemia.

All the complications associated with diabetes could occur, depending on metabolic control.

These patients usually respond to low doses of sulfonylurea. The response to sulfonylurea could be so important that hypoglycaemia can be observed, so dose adjustments and genetic testing are necessary.

HNF1A-MODY 3

Represent the most common cause of symptomatic MODY requiring treatment. Glycosuria is common, being due to SGLT2 regulation (sodium glucose cotransporter 2) by *HNF1A*, glycosuria being observed in these patients even if the blood sugar is normal. This finding represents an early marker of the disease in children with *HNF1A* mutations (SGLT2 inhibitors are contraindicated). These patients present a higher risk for benign liver adenomas, which can rarely become larger or complicated.

The patients with *HNF1A* mutation usually respond well to low doses of sulfonylurea.

HNF1B MODY5

It is usually characterized by renal cysts and diabetes. However, some patients also present developmental delay. Diabetes onset is usually seen in adolescence or young adulthood.

These patients need insulin treatment, a characteristic of this disorder is the lower number of beta cells. A decrease in the size of the pancreatic tail is seen, thus leading to a possible exocrine pancreatic insufficiency and diminished value of faecal elastase, which may require a treatment.

HNF1B is the most common genetic aetiology of chronic kidney disease in children, being found in 20-30% of these cases.

NEONATAL DIABETES

Genetic testing will indicate a monogenic cause for diabetes diagnosed under the age of six months in 80–85% of cases. The genetic test is required to guide a specific treatment, to anticipate a possible

remission, to anticipate a familial risk of recurrence, to evaluate associated syndromes.

Two third of patients with transient form of neonatal diabetes have an overexpression of genes on 6q24 region and one third has mutations in *KATP/ABCC8* or *KCNJ11* genes.

The patients with permanent neonatal diabetes more frequently harbour *KCNJ11*, *INS* or *ABCC8* mutations (often de novo, sometimes autosomal dominant).

Most patients with KCNJ11 and ABCC8 mutations respond to high doses of sulfonylurea, leading to higher endogenous insulin secretion, improvement of HbA1c, quality of life and even the neurodevelopment, if the treatment is early initiated[9–11].

CONCLUSIONS

Monogenic diabetes is a rare form of diabetes, but with a better-known physiopathology, involving a better diagnosis, more accessible now, due to the possibility of a more affordable genetic testing. A better diagnosis involves a precise therapy, which could be more often seen in monogenic diabetes, a desideratum for type 1 or 2 diabetes, not so easy to accomplish, mainly due to multifactorial aetiology. Some clinical criteria are useful for a better clinical diagnosis for monogenic diabetes, allowing a diagnosis in up to 50% of patients with MODY. Thus knowing the clinical and genetical features in patients with diabetes could lead to more adequat treatment for these patients.

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