MONOGENIC DIABETES-GENETICAL ASPECTS AND DIAGNOSIS CRITERIA

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ABSTRACT. The most common forms of diabetes, type 1 and type 2, are polygenic, meaning the risk of developing these forms of diabetes is related to multiple genes. Some rare forms of diabetes result from mutations in a single gene and are called monogenic. In most cases of monogenic diabetes, the gene mutation is inherited. In the remaining cases the gene mutation develops spontaneously. Most mutations in monogenic diabetes reduce the body's ability to produce insulin, a protein produced in the pancreas that helps the body use glucose for energy. Maturity-onset diabetes of the young (MODY) is a form of monogenic diabetes. MODY usually first occurs in children or adolescents but may be mild and not detected until adulthood. The authors described the most important clinical aspects of the MODY diabetes.

KEYWORDS: diabetes, monogenic, genetical aspects, clinical aspects, MODY

INTRODUCTION.

The diagnosis of mellitus diabetes (DM) at a child is based either on a random detection of a hyperglycemia on an asymptomatic patient, or on clinical signs that mark the clinical debut (polyuro-polydipsic syndrome) or on an acute complication (cytoacidosis).

Types of diabetes.

Type 1 diabetes recognizes the autoimmune mechanism which destroys the insulin providing pancreatic cells.

Type 2 diabetes is multiple etiologies disorder. MODY diabetes (maturity onset diabetes of the young) is a rare monogenic familiar form of DM with autosomal dominant transmission ((AD), early debut which represents approximately 2-5% from the total cases of DM non-insulin-dependent(Velho, 2007). In 1990 there have been discovered 6 genes that are associated with this type of diabetes. In some cases with a phenotype evoking MODY DM where no genetically anomaly was documented.

The disease complications are identical to the ones we may upperhand in DM type 1, even though hyperglycemia is moderate and the patient is asymptomatic. The most frequent forms are MODY 2 and MODY 3. Knowledge of this type of DM allows us to establish an early diagnosis, and therapeutic attitude adapted to each case separately.

MODY diabetes may occur as a child, adolescent or young adult. Recently there have been established 5 diagnosis criteria which synthesize the most important aspects of the disease (Fajens et al, 2001)

1. Hereditary factor: the passing of DM along 3 generations;
2. The absence of obesity or overweight;
3. Hyperglycemia present before the age of 25 at one or 2 family members;
4. Normal insulin or low in concerning a hyperglycemic patient;

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5. Absence of insulin treatment 4 years after the diagnosis or low level of C peptide on an insulin dependent patient.

On the basis of genetic abnormality, clinical manifestations and evolution there have been described 5 types of DZ Mody:

1. DM MODY 1:
The debut is marked between 7-40 years age and the presumptive diagnosis is based on a “a jeune” hyperglycemia. The genetical anomaly associated to this type of MD is a heterozygotic mutation of the HNF4α gene, situated in the 20th chromosome (Pearson et al, 2007). The physiopathological consequence is the disturbance of the insulin secretion which is being developed by the β Langerhans cells, the intracellular transport and the glucose metabolism. The penetrance is quasi complete, with a variable phenotype expression. In some families there are diabetic subjects that are not mutation carriers but are usually obese. Usually the patient and overweight at birth. The evolution is based on a progressive insulin-secretion loss. Micro or macro vascular complications may occur and they impose a hypoglycemiant treatment.

2. DM MODY 2:
This pathology is due to a genetical mutation of the glucokinase gene situated on the 7th chromosome. The penetrance is complete: all the mutation carriers are hyperglycemic. 3 Hyperglycemic family generations may sustain the diagnosis. Metabolic anomalies may be present at birth or even during the intrauterine period. Birth weight of the carriers is more reduced compared to the healthy newborn which suggests an insulin secretion descend.

The glycemic level that launches insulin secretion is quite high, the biological consequence to this being a moderate and permanent hyperglycemia, with slight chances to evolve at a young, normal or underweight patient.

Sometimes hyperglycemic historical isn’t present amongst the family members, but may be highlighted in some pathological situations (surgical interventions, infectious disease, corticotherapy) or on the occasion of a biological exam. The persistence of “a jeun” moderate hyperglycemia may also be MODY2 diabetes.

In this case the hyperglycemia is present at birth and remains constant over several years. The micro vascular complications are rare, even though normally the patient pose a high cardio-vascular risk.

The treatment objective is to maintain a normal glycaemia, and presumes a diet in 2/3 cases, in rare cases it also implies insulin.

3. DM MODY 3
3% of DM type 2 are in Great Britain, and this is due to the genetical mutation of HNF1α (Hepatocyte Nuclear Factor 1 α) gene situated in chromosome 12, having a phenotype expression different from one individual to another even concerning the same family members. Some individuals are hyperglycemic others hypoglycemic. “a jeun”: hyperglycemia remains moderate similar to the one we find in DM Mody 2, but much higher after the glucose loading. Insulin secretion is reduced even if stimulated.

The diagnosis is based on the post puberty period, and the clinical debut is initiated based on the polyuro-polydipsic syndrome simulating the debut of an insulin-dependent diabetes. Familiar aspect (autosomal dominant transmition), and the absence of imuno-genetical markers are arguments in favor of this type of DM. Evolution may vary and necessitate insulin therapy as in DM type 1. Micro and macro vascular complications may occur (retinopathy and nephropathy), and the hypoglycemiant treatment becomes necessary. Weight excess sustains the hyperglycemia, that’s why cautious measures should be applied. The genetical carriers even though they don’t have diabetes must be supervised closely.
4. DM MODY 4

The IPF1 (Insulin Promoter Factor 1) gene mutation, also called PDX1, in heterozygotic states determines this type of MD. In condition to the homozygotic mutation, a pancreatic agenesis presence is possible associated with a neonatal diabetes and a exocrine pancreatic insufficiency. The heterozygotic form diagnosis is early made in comparacy to the other forms of MD MODY.

5. DM MODY 5

In this type of DM an HNF1β gene mutation has been identified, in heterozygotic states, localizes on the 17th chromosome. The diabetes is associated with renal morphopathy anomalies (cysts, progressive renal failure) and genital development anomalies, pancreatic hypoplasia, or hepatic tests anomalies.

6. MD MODY 6

This is a rare form of DM and it is due to a D1 gene mutation (Neurogenic Differentiation Factor), situated on the 2nd chromosome. This gene might influence the development of the central nervous system and the pancreas.

CONCLUSIONS

The possibility of identifying genes has opened new perspectives in the understanding how the pancreatic cells work. MODY genetical variations don’t seem to play an important role in the DM type 2 pathology in its common form. Knowing the genetic profile helps us adapt the therapy and have a more precise prognosis, a more realistic view on the investigations we propose for the family, and further more gives us the power to anticipate complications on a long term. Clinical diagnosis and the absence of a genetical profile is easier if the hyperglycemia appeared over 3 generations and the clinical evolution may identify the gene mutations that have to be studied -MODY 2 in case on moderate hyperglycemia, MODY 3 in case of DM with ketosis, MODY 5 in case of renal anomalies.

REFERENCES

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