Diagnostic and Therapeutic Stratagies in Maturity Onset Diabetes of the Young

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BACKGROUND AND OBJECTIVE

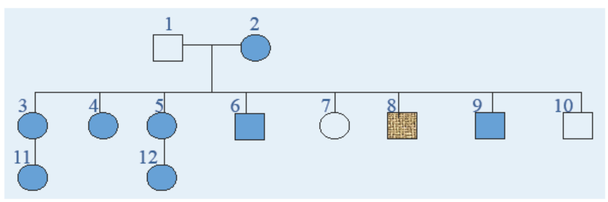
Maturity Onset Diabetes of the Young (MODY) has an estimated prevalence of 1-5% in the diabetic population, but misdiagnosis as type 1 or type 2 diabetes is common. It comprises a heterogeneous group of monogenic diseases characterized by primary dysfunction of b-cell, young onset, autosomal dominant inheritance, without autoimmunity and without ketosis. Early diagnosis remains a challenge with important future implications, since it allows treatment optimization, prognosis definition and genetic counseling of family members.

OBJECTIVE: Characterize the parameters for the diagnosis of MODY.

PATIENTS AND METHODS

We studied 9 cases in three successive generations of a family of 12 elements, with assessment of age at diagnosis, gender distribution, clinical manifestations, initial treatment and subsequent need for insulin. We analyzed the levels of glucose, HbA1c, C-peptide, the presence of ketosis and anti-β cell antibodies. Molecular analysis of GCK (glucokinase) and HNF-1α (hepatocyte nuclear factor 1α) genes was performed to detect MODY mutations – MODY 2 and 3 are the most frequent subtypes, accounting for 50-70% and 20-30% of cases, respectively ⟹ *Institut de Biologie de Lille, Philippe Froguel*

RESULTS



	Age (years)
1- No diabetic – 2 siblings without diabetes	66
2- Diabetic since 38 years – without insulin	66
3- Diabetic since 30 years – without insulin	45
4- Diabetic since 19 years – start insulin at 25 years	43
5- Diabetic since 28 years – without insulin	41
6- Diabetic since 16 years – start insulin at 32 years	39
7- No diabetic – 3 sons, without diabetes	38
8- Diabetic since 34 years – without insulin	39
9- Diabetic since 33 years – without insulin	33
10- No diabetic	28
11- Diabetic since 17 years – without insulin	22
12- Diabetic since 20 years – without insulin	21

MODY n=9	
Age of diagnosis (years)	**26.1 ± 8.2 years**
Gender (%)	66.7% F (n=6) 33.3% M (n=3)
Disease duration (years)	12.7 ± 10.6 years
Fasting Glucose (mg/dL)	200 ± 48 mg/dL
Hb A1c (%)	8.5 ± 1.5%
Glucosuria (%)	100% (n=9)
Diabetic retinopathy (%)	66.7% (n=6) No proliferative
Diabetic nephropathy (%) Albumin excretion rate (µg/min)	44.4% (n=4) 215 ± 48 µg/min
C-peptide (ng/mL)	**2.5 ± 1.1 ng/mL**
Anti-β cell antibodies (%)	**100% Negative** (n=9)
Ketosis (%) Ketonuria (%) β-hidroxibutirate (%)	**0%** (n=0) 0% (n=0) 100% Undetectable (n=9)

Characteristics	MODY	DM1	DM2
Age of diagnosis	15-45 years	5-20 years	>25 years
Parental history	60-90%	<15%	10-40% (>50% in early onset DM2)
Heredity	**Autosomal dominant**	Polygenic	Polygenic
Obesity	Uncommon	Uncommon	Common
Metabolic Syndrome	Uncommon	Uncommon	Common
Insulin Resistance	Uncommon	Uncommon	Common
Diabetic Ketoacidosis	Rare	Common	Rare
Anti-β cell Antibodies	Absent	**Present**	Absent
C-Peptide	**Normal**	**No detectable/** Low	Normal/**High**
First-line Treatment	Sulfonylurea (MODY 1,3,4) Diet (MODY 2)	Insulin	Metformin

Genetic testing revealed a **mutation in exon 6** (stop mutation Ser 371 OCH) of **gene HNF-1α (MODY3)**

Only 2 (22.2%) patients, diagnosed at 16 and 19 years, required insulin therapy, at 32 and 25 years respectively. The remaining 7 (77.8%) patients kept up with glibenclamide treatment (2.5-15mg/day).

The 9 diabetics studied had clinical characteristics of **MODY**:
Asymptomatic hyperglycemia at early age; autosomal dominant transmission; several carriers of the disease in three generations of the same family

Characteristics	MODY 2	MODY 3
Frequency	Common form, especially in **children** and in women with a history of **gestational diabetes**	More frequent form in clinical activity in **adults**, in most populations
Mutations	> 130 mutations on **gene GCK** All races and ethnic groups	> 120 mutations on **gene HNF-1α** All races and ethnic groups
Primary β-cell dysfunction	Impaired sensitivity to glucose in β-cells	Impairment of insulin secretion pathways in the β-cell
Manifestations	Moderate hyperglycaemia and asymptomatic	Normal fasting glucose levels in infancy Glucose levels in **OGTT** significantly greater than in MODY 2
Evolution	Relatively stable, with little deterioration lifelong	Hyperglycemia increases with disease progression **Progressive decrease of insulin secretion (1 to 4% annually)**

Characteristics	MODY 2	MODY 3
Treatment **Insulin requirement**	Good metabolic control only with **dietary measures** Exceptionally, some individuals with severe hyperglycemia require insulin (<2%)	**ADO ou insulin are needed** 30 to 40% require insulin
Chronic complications	Rare	Risk of microvascular complications, particularly retinopathy and nephropathy, similar to DM1 and DM2
Particularities		Decreased renal reabsorption of glucose and **glycosuria** Marked sensitivity to insulin secretagogues (sulfonylureas)

CONCLUSION

The clinical presentation of hyperglycemia without ketosis, no anti-β cell antibodies and C-peptide levels allowed to exclude type 1 diabetes. Genetic testing enabled to confirm mutations in gene HNF-1a and guide treatment according to clinical evolution.

References: Thanabalasingham G, Owen KR. BMJ 2011; Henzen C. Swiss Med Wkly 2012; Fajans et al. NEJM 2001; Bonnefond A, Vaxillaire M, Froguel P. PLoS One 2012