REVIEW

Maturity onset diabetes of the young: Seek and you will find

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ABSTRACT

Maturity onset diabetes of the young (MODY) is a monogenic, autosomal dominant form of diabetes characterised by mutations in genes resulting in dysfunction of pancreatic β-cells and subsequent insulin production. We present a family with HNF1A-MODY due to a likely pathogenic mutation in HNF1A (c.59G>A, p.Gly20Glu), diagnosed a long time after the first diagnosis of diabetes. Currently 13 MODY subtypes caused by mutations in 13 genes, are known. We describe the four most prevalent forms in more detail, i.e. HNF4A-MODY, GCK-MODY, HNF1A-MODY and HNF1B-MODY, together responsible for probably 99% of MODY cases. The different forms of MODY vary in prevalence, severity of diabetes, occurrence and severity of diabetic complications and response to treatment. New tools, such as the MODY probability calculator, may be of assistance in finding those patients in whom further genetic testing for possible MODY is warranted. However, as our described family shows, a doctor's clinical eye and taking the time for a detailed family history may be equal to, or even better than, the best prediction rule.

KEYWORDS

Diabetes mellitus, HNF1A, MODY

INTRODUCTION

Diabetes mellitus is a worldwide disease associated with microvascular and macrovascular complications and still has an increasing prevalence and incidence.[1]

Although most patients with diabetes mellitus have either type 1 diabetes (~10%) characterised by primary insulin deficiency due to autoimmune β-cell destruction, or type 2 diabetes (~85%) characterised by insulin resistance and relative insulin deficiency, other types of diabetes mellitus do exist. In contrast to the more complex multifactorial origin of type 1 and type 2 diabetes mellitus, some of the less prevalent forms of diabetes have a monogenetic origin. Of these, maternally inherited diabetes and deafness with a prevalence of around 1% in de diabetic population,[2] and maturity onset diabetes of the young (MODY) constitute the most important diabetes subtypes.

MODY comprises a distinct group of monogenic and autosomal dominant inherited forms of diabetes mellitus due to β-cell dysfunction with onset at a young age. It may be difficult to distinguish from late onset type 1 diabetes and early onset type 2 diabetes, due to the absence of clear distinguishing features at diagnosis and relatively low prevalence in the population.

In the present article we set out to give an overview of MODY and describe the importance of considering and confirming the diagnosis of MODY using a family case report.

FAMILY CASE REPORT

Patient 1

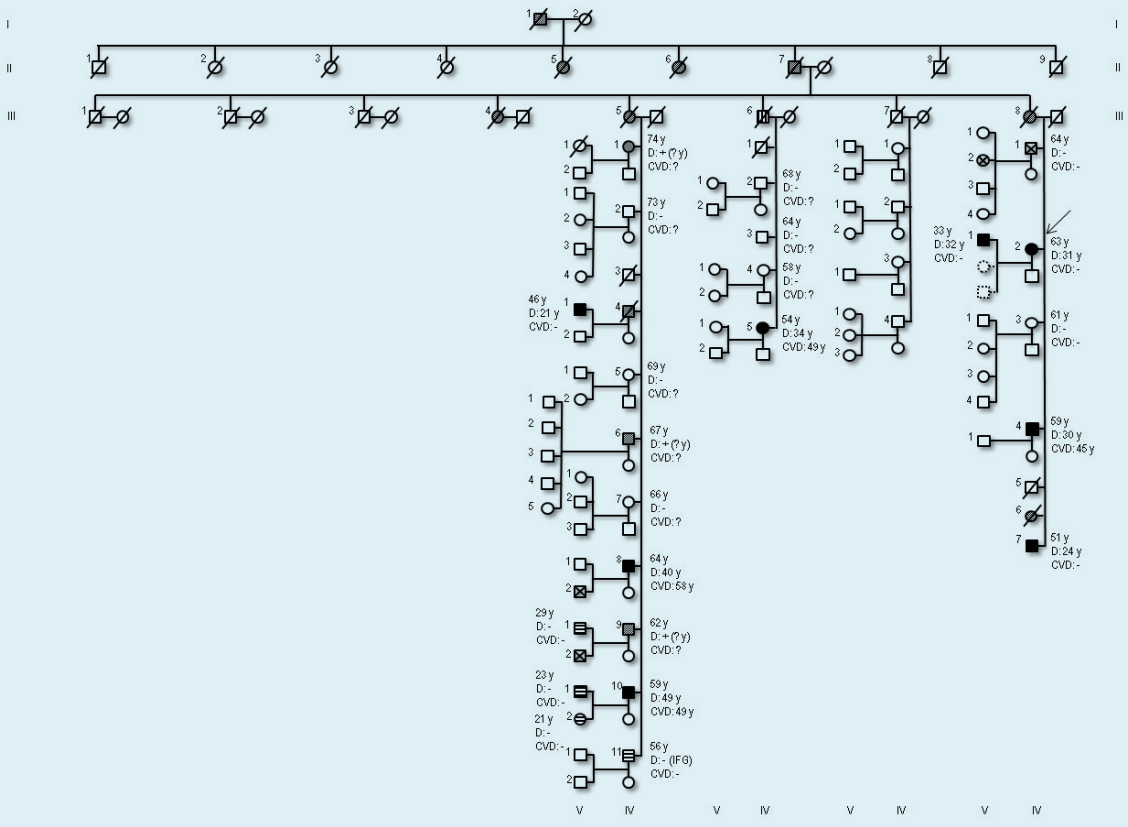
Our index patient was diagnosed with gestational diabetes at the age of 31 years. Hyperglycaemia persisted after delivery and five years later a probable diagnosis of type 2 diabetes was made. At that time her body mass index (BMI) was 25 kg/m^2 and a C-peptide test showed a good insulin reserve. After initial treatment with diet only, metformin was started but glucose regulation did not improve. A low dose of the sulfonylurea derivative tolbutamide was added and a few years later replaced by insulin therapy. Since the time of diagnosis, diabetic nephropathy (microalbuminuria) and peripheral

polyneuropathy developed. Although the patient had received care at our hospital for 25 years and earlier correspondence reported a strong positive family history of diabetes mellitus and cardiovascular disease, no detailed family history was taken. A likely autosomal dominant inheritance pattern of diabetes was discerned in her extended pedigree (*figure 1*) and genetic testing for the presence of a mutation in the HNF1A gene was performed. The patient (proband IV-8.2 in *figure 1*) was heterozygous for a variant in HNF1A (c.59G>A, p.Gly20Glu) that had not been detected previously. At the age of 61 her diagnosis was therefore changed to possible HNF1A-MODY. As a consequence, her insulin was stopped and a successful sulfonylurea derivative trial was performed. At the moment her HbA1c is stable at 55 mmol/mol (7.2%) on a diet while taking gliclazide. The patient is currently not using any insulin and reports an increase in the quality of life after stopping insulin therapy.

Patient 2

The 12 years younger brother of patient 1 (subject IV-8.7 in *figure 1*) was diagnosed with type 2 diabetes at the age of 24 years based on obesity and preserved insulin reserve during a C-peptide test, after which therapy with NPH insulin once daily was initiated. Major complications of the diabetes developed partly due to the patient's long withdrawal from care. The patient developed diabetic retinopathy and nephropathy before the age of 40, which progressed to end-stage renal disease, followed by bilateral Charcot feet. At age 44, intensive insulin therapy was started, while three years later gastric bypass surgery was performed because of persistent obesity (BMI approximately 40 kg/m^2). After his sister's diagnosis of HNF1A-MODY, the same HNF1A mutation was found to be present and the insulin was withdrawn. Trials with sulfonylurea derivatives and meglitinides (due to postprandial hypoglycaemia with a low-dose sulfonylurea

Figure 1. *Pedigree of our HNF1A-MODY family*



Squares indicate male subjects, circles female subjects. Boxes with dotted lines indicate adopted subjects. I-V indicate the five different generations. The arrow indicates the index patient
☐ No known diabetes and no further data available
■ Diabetes and genetically proven HNF1A-MODY
▨ Diabetes and clinically presumptive HNF1A-MODY
▥ Assumptive HNF1A-MODY but no available data
▤ Genetically proven HNF1A-mutation but no current diabetes
☒ No diabetes and genetically proven absence of the HNF1A mutation
IFG = impaired fasting glucose. A diagonal line through the symbol indicates that the subject has died. In the textboxes next to subjects the current age, absence or presence of diabetes with age of diagnosis (D) and absence or presence of cardiovascular disease with age of onset (CVD) are described.

derivative) were performed. Currently the patient is not using any oral glucose-lowering medication or insulin and has stable glycaemic control at 42 mmol/mol on a diet.

Family

The patients described here came from a large family of Dutch and part Indonesian ancestry. After the probable diagnosis of HNF1A-MODY in the two patients described above, multiple family members with early onset diabetes mellitus came forward for genetic testing. *Figure 1* shows the extensive pedigree of the family with the high prevalence of early diabetes and cardiovascular morbidity and mortality and a suggestive autosomal dominant inheritance pattern. Microvascular complications were present in all the known HNF1A-MODY patients in this family, except for the recently diagnosed son of the index patient (V-8.2.1 in *figure 1*). The age at diagnosis of diabetes mellitus in the family was between 21 and 40 years, with one exception, who was only diagnosed after the discovery of coronary artery disease at the age of 49. All patients from the family with a prior diagnosis of type 2 diabetes were found to be heterozygous for the earlier described variant in HNF1A (*table 1*). Subsequently, the diagnosis in these patients was changed to HNF1A-MODY and the treating physicians were informed including advice on treatment.

Table 1. *Features of the genetically tested family members*

Individual	Gender	Current age	Diabetes	HNF1A mutation
IV-5.8	M	64	Yes	Yes
IV-5.10	M	59	Yes	Yes
IV-5.11	M	56	No	Yes
IV-6.5	F	54	Yes	Yes
IV-8.1	M	64	No	No
IV-8.2 (index patient)	F	63	Yes	Yes
IV-8.4	M	59	Yes	Yes
IV-8.7	M	51	Yes	Yes
V-5.4.1	M	46	Yes	Yes
V-5.8.2	M	26	No	No
V-5.9.1	M	29	No	Yes
V-5.9.2	M	25	No	No
V-5.10.1	M	23	No	Yes
V-5.10.2	F	20	No	Yes
V-8.1.2	F	30	No	No
V-8.2.1	M	33	Yes	Yes

M = male subject, F = female subject.

In our pedigree we have 12 informative meioses in which the mutation as well as the disease segregate together. A 'rule of thumb' is that each meiosis in which the mutation segregates with the phenotype adds 0.3 to the total likelihood of odds (LOD) score, giving a total LOD score in our pedigree of ~3.6: > 3 is a significant association; we could add some additional informative meioses higher up in the pedigree and come to an estimated LOD score of ~5.4. The mutation carriers who have no symptoms (yet) fit in the reduced penetrance that is described for MODY (proband IV-5.11)[3] in combination with the relatively young age of some family members (V-5.9.1, V-5.10.1 and V-5.10.2) who may still develop diabetes in the coming years and were advised to undergo yearly check-ups.

EPIDEMIOLOGY

The prevalence of MODY remains unknown but is estimated to be responsible for 1-5% of cases of diabetes mellitus.[4-6] As MODY shares clinical features with the more common forms of diabetes mellitus, the true prevalence is probably underestimated.

At present, mutations in 13 genes linked to different types of MODY have been identified.[7-9] In *table 2* the currently known subtypes of MODY are described with their related proteins/genes and estimated prevalence.[10-14]

In general, GCK-MODY and HNF1A-MODY each represent 20-70% of all cases, HNF4A-MODY and HNF1B-MODY each account for about 5%, while the other forms are extremely rare.[14] GCK-MODY is more commonly diagnosed in countries where glucose testing of asymptomatic people and paediatric cases is routine (Czech Republic, France, Italy, Spain), whereas HNF1A-MODY is more often diagnosed in countries where random blood glucose tests are seldom done and elevated blood glucose is first found after childhood (Denmark, the Netherlands, Norway, United Kingdom).[14,15]

PATHOPHYSIOLOGY

MODY is caused by mutations resulting in pancreatic β-cell dysfunction in the production or excretion of insulin.

Normally, glucose from the circulation is taken up by the β-cell through the glucose transporter type 2 (GLUT 2) on the cell membrane. The enzyme glucokinase (GCK) converts glucose into glucose-6-phosphate which then undergoes glycolysis in the mitochondria to produce adenosine triphosphate (ATP). The increase of the ATP-ADP ratio causes the closure of the β-cell

Table 2. *Currently known types of maturity onset diabetes of the young with their associated mutations and clinical features*

MODY type	Protein/ gene	Relative prevalence	Clinical features
1	Hepatocyte nuclear factor-4 alpha (HNF4A)	~ 5 %	Neonatal hyperinsulinaemia and hypoglycaemia with associated macrosomia, gestational diabetes, low serum levels of cholesterol, marked sensitivity to sulfonylurea derivatives
2	Glucokinase (GCK)	20-70%	Mild fasting hyperglycaemia throughout life, often asymptomatic, gestational diabetes, low birth weight (with unaffected mother)
3	Hepatocyte nuclear factor-1 alpha (HNF1A)	20-70%	Diminished renal threshold for glycosuria, marked sensitivity to sulfonylurea derivatives
4	Insulin promoter factor 1 (IPF1) *or* pancreas/duodenum homeobox protein 1 (PDX1)	Rare: < 1%	Pancreatic agenesis
5	Hepatocyte nuclear factor-1 beta (HNF1B)	~ 5 %	Renal abnormalities and insufficiency at young age, diabetes often diagnosed later, hypomagnesaemia, hyperuricaemia, pancreatic atrophy or partial agenesis, exocrine pancreatic dysfunction, liver test abnormalities, genital abnormalities
6	Neurogenic differentiation 1 (NEUROD1)	Very rare	Pancreatic anomalies
7	Kruppel-like factor 11 (KLF11)	Very rare	Pancreatic malignancy
8	Carboxyl-ester lipase gene (CEL)	Very rare	Exocrine pancreatic dysfunction
9	Paired box gene 4 (PAX4)	Very rare	
10	Insulin gene (INS)	Very rare	Neonatal diabetes
11	Tyrosine kinase, B-lymphocyte specific gene (BLK)	Very rare	
12	ATP-binding cassette, subfamily C, member 8 (ABCC8)	Very rare	Neonatal diabetes, sulfonylurea derivative responsive
13	Potassium channel, inwardly rectifying, subfamily J, member 11 (KCNJ11)	Very rare	Neonatal diabetes, sulfonylurea derivative responsive

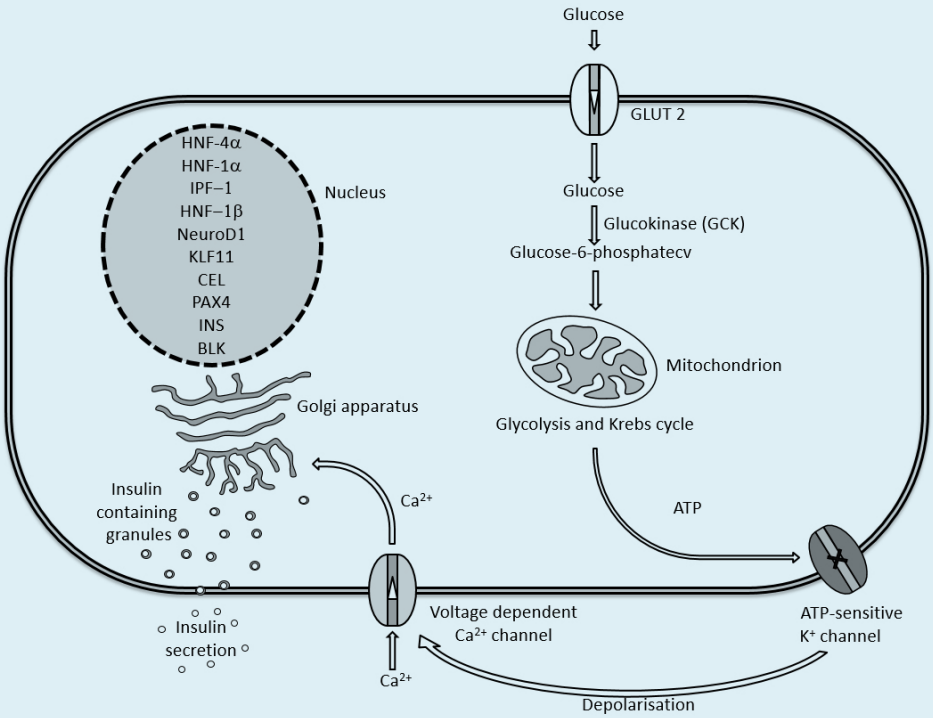
ATP-sensitive potassium channel (K_{ATP}), preventing potassium efflux, which leads to depolarisation of the membrane and subsequently causes the opening of the voltage-dependent calcium channels. The subsequent influx of calcium into the cell stimulates exocytosis of insulin-containing granules from the β-cell (*figure 2*).[16]

GCK-MODY can be described as disturbed β-cell glucose sensing. Mutations in the GCK gene cause a decrease in glucose metabolism in the β-cell and therefore a rightward shift of the dose-response curve of insulin secretion.

The hepatocyte nuclear factors (HNF)-4 alpha, -1 alpha and -1 beta are transcription factors that form part of a network of transcription factors that controls gene expression of the insulin gene and genes encoding proteins involved in glucose transport and metabolism. Mutations in the genes of these transcription factors lead to reduced expression of these genes in the β-cell and subsequently less insulin production and release. Additionally, HNF-1 beta plays a pivotal role in the development of the kidney, pancreas, liver and genital tract, and mutations subsequently lead to multi-organ consequences.

The variant in HNF1A found in the featured family is located in the highly conserved N-terminal HNF-1A dimerisation domain (up to frog considering 11 species). Mutations in this domain disrupt formation of the HNF-1A dimer and the functional DCoH-HNF-1A complex.[17] These mutations strongly argue against an obligate dominant negative mode of action and support the idea that glucose homeostasis in humans is sensitive to the dose of HNF-1A. Various *in silico* algorithms (prediction programs) indicate that the p.Gly20Glu variant is probably damaging. Two other pathogenic amino acid substitutions in the same codon (p.Gly20Arg and p.Gly20Ala)[18,19] and 25 other different amino acid substitutions in the dimerisation domain have been described in patients with MODY 3.[20] Additionally, the mutation was classified as likely

Figure 2. *Model of a pancreatic β-cell and the genes or proteins implicated in maturity onset diabetes of the young (MODY)*



pathogenic based on the American College of Medical Genetics Standards and Guidelines recently published by Richards et al.[21]

The rarer forms of MODY are caused by mutations in other nuclear transcription factors regulating pancreatic development and expression of the insulin gene, the insulin gene itself (INS-MODY), or genes of proteins involved in the ATP-sensitive potassium channel (ABCC8-MODY and KCNJ11-MODY). They also result in impaired β-cell function with reduced insulin production and/or secretion.

CLINICAL FEATURES

The mode of inheritance of MODY is autosomal dominant. In general, the main characteristics of MODY are the onset of diabetes at a young age with a prominent family history of diabetes in multiple generations and, but not necessarily, absence of obesity,[22] as was shown in our HNF1A-MODY family. Patients with MODY may easily be misdiagnosed during pregnancy as gestational diabetes in the context of increased insulin resistance, as described in our index patient. It has been shown that carriers of GCK and HNF1A mutations have an increased risk of gestational diabetes mellitus.[22,23]

An overview of the typical clinical features of the MODY subtypes is shown in *table 2*.[7-14,16,22,24-37]

TREATMENT

Patients with HNF4A- and HNF1A-MODY are very sensitive to the effect of sulfonylurea derivatives and meglitinides.[12,25,28,30,36,38] This efficacy can be explained by the binding with the sulfonylurea receptor type 1 (SUR1) subunit of the K_{ATP} causing it to close and triggering opening of the voltage-dependent calcium channels, stimulating insulin release.[28,30,36] As meglitinides cause a smaller insulin peak and have a shorter half-life, MODY patients using a meglitinide are less susceptible to hypoglycaemia than during treatment with sulfonylurea derivatives.[30,36] Despite the efficacy of sulfonylurea derivative and meglitinide treatment most of these patients will in time require insulin as β-cell dysfunction progresses.[14]

GCK-MODY, which is often asymptomatic and therefore diagnosed by screening, does not require treatment due to the mild and stable hyperglycaemia with a raised homeostatic set point (glycated haemoglobin (HbA1c) without treatment usually below 64 mmol/mol (8%)).[39]

It has been shown that HNF1B patients do not respond well to sulfonylurea derivatives and that they have a reduction

in insulin sensitivity compared with HNF1A patients.[40] If HNF1B patients are treated for their diabetes, the existing studies show that they generally receive insulin.

COMPLICATIONS

Although patients with GCK-MODY are exposed to a lifetime of, albeit limited, hyperglycaemia, microvascular and macrovascular complications in GCK-MODY seem to be limited.[41] In patients with HNF1A-MODY both microvascular and macrovascular complications are very common, as was the case in our family. The prevalence is similar to that of patients with type 1 and 2 diabetes, when matched for duration and glycaemic control,[42,43] while early detection and treatment may result in a reduced incidence of diabetic complications.[44] It has been suggested that the full spectrum of diabetes complications may also occur in HNF4A-MODY patients, particularly retinopathy and nephropathy.[10] For HNF1B-MODY it is suggested that microvascular diabetic complications are rare.[11,29,34]

CASE FINDING

Diagnosing MODY is challenging because of the relatively low prevalence in the general population (1-5%) and shared features with other types of diabetes (*table 3*). Limited awareness of MODY as a separate entity and cause of diabetes outside specialist centres combined with limited time allocated to enquiring about family history further hampers correct diagnosis, family screening and treatment. A correct diagnosis of MODY might change the treatment to oral glucose-lowering medication (HNF4A-and HNF1A-MODY) or even withdrawal of medication (GCK-MODY). Secondly, certain subtypes are associated with specific medical problems entailing additional diagnostic tests and screening. Lastly, the first-degree relatives of MODY patients have a 50% probability of the same mutation with, at least in the two most commonly occurring MODY forms, a lifetime risk of > 95% of developing diabetes.[45,46] As progression of diabetes is generally slow in MODY patients, early diagnosis and start of appropriate treatment might reduce the risk of diabetic complications as described in a Norwegian family.[44] The evidence for such an approach is, however, currently lacking and is debatable in light of the possible financial consequences for subjects with a suggestive genotype, but in the absence of diabetes. In general, two simulation studies show that screening may be cost-effective.[47,48]

Several suggestions have been published for when to consider genetic testing for MODY. Current European guidelines are highly specific, but have a low sensitivity.[49] Correspondingly, widening of the clinical criteria for genetic testing can double the number of MODY diagnoses.[50] Other recent literature describes additional criteria and Thanabalasingham et al. and Naylor et al. provided algorithms for the consideration of genetic testing.[14,51,52] In 2012 a novel approach to correctly allocate genetic testing in Caucasian patients with an onset of diabetes before the age of 35 was published.[53] This clinical prediction rule is available as an online calculator (www.diabetesgenes.org/content/mody-probability-calculator). Using the optimal cut-offs, it has an improved specificity (94% vs 91%) and especially sensitivity (91% vs 72%) for identifying MODY, compared with the criteria of diagnosis < 25 years and a parent with diabetes. Interestingly, applying the calculator to our patients would have advised

Table 3. *Comparison of the clinical and biochemical features of the most common types of diabetes*

Features	Type 1 diabetes	Type 2 diabetes	GCK-MODY	HNF1A-/ HNF4A-MODY
Age of diagnosis	10-30	> 25	Present from birth, diagnosis at any age	< 25 (15-45)
Diabetic ketoacidosis	Common	Rare	Rare	Rare
Insulin dependent	Yes	No	No	No
Parental history of diabetes	< 15%	> 50% (in young onset)	95-100%, if tested	60-90%
Obesity	Uncommon	Common	Uncommon	Uncommon
Insulin resistance	Uncommon	Common	Uncommon	Uncommon
Presence of β-cell antibodies	>90%	Negative	Rare	Rare
C-peptide concentrations	Undetectable/ low	Normal/ high	Normal	Normal
Optimal first line treatment	Insulin	Metformin	None/ diet	Sulfonylurea derivative/ meglitinide

Table 4. *Clinical features suggestive for maturity onset diabetes of the young*

Clinical features suggestive for MODY
Any of the following: • Diabetes diagnosed ≤ 30 years • Diabetes diagnosed ≤ 45 years in people without obesity/ insulin resistance/ metabolic syndrome • Diabetes diagnosed ≤ 45 years and a family history of diabetes in ≥ 2 generations in an autosomal dominant fashion
And in absence of: • Diabetic ketoacidosis • Pancreatic islet autoantibodies • No endogenous insulin production outside the honeymoon period of about 3 years (e.g. undetectable C-peptide)
Additionally, specific features of MODY subtypes may justify genetic testing: • Glycosuria at blood glucose levels < 10 mmol/l (HNF1A-MODY) • Marked sensitivity to sulfonylurea derivatives (HNF1A-/ HNF4A-MODY) • Diabetes associated with extra pancreatic features: non-diabetic renal disease, renal anomalies, genital anomalies, abnormal liver function tests (HNF1B-MODY)

against genetic testing. Probable reasons for this might be limited accounting for family history and the importance of BMI in the calculator. In addition, a specific HNF1B score focusing on the extra-diabetic features of the disease has recently been developed and validated to select patients for genetic testing of HNF1B-MODY.[37]

In *table 4* we have combined features and algorithms suggestive of possible MODY from the available literature, providing an optional tool for deciding on genetic testing.

CONCLUSION

Maturity onset diabetes of the young (MODY) encompasses distinct clinical entities causing diabetes. Our presented family illustrates the difficulties in diagnosing MODY, the consequences for treatment with the correct diagnosis as well as the long-term consequences. Correct identification of patients with MODY will probably lead to earlier diagnosis, family screening, earlier and correct treatment and hopefully improved prognosis.

Disclosures

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