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Mody Diabetes

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Abstract

MODY diabetes is Maturity onset diabetes of the young. It is rare, accounting for just 1% - 2% of all diabetes. MODY patients displayed a familial form of noninsulin – depenedent diabetes. Maturity-onset of diabetes of the young, or MODY, is a form of diabetes that is caused by mutations in a number of different genes. MODY is a form of monogenic diabetes. Each different mutated gene causes a slightly different type of diabetes. The most common forms are *HNF1á*-MODY (MODY3) and GCK-MODY (MODY2), due to mutations in the *HNF1A* and *GCK* genes, respectively. MODY is typically diagnosed in late childhood, adolescence, or early adulthood. However, it has been known to develop in adults as late as their 50s. Many people with MODY are misdiagnosed as having type 1 or type 2 diabetes. However, a diagnosis of MODY could change the course of treatment and could help to identify other family members with MODY. MODY forms of diabetes are caused by at least nine different genes, some related to each other in function and some not. The commercially available MODY gene test suite only tests for six of these genes. MODY genes have one major thing in common—they are "monogenic" which means that you only need to inherit one copy of the gene to display the disorder that the gene causes. MODY forms of diabetes were long believed to affect around 2% of all people diagnosed with both type 1 and type 2 diabetes. However, a study of 586 children diagnosed with Type 1 diabetes found that a full 8% of them were actually carrying one of the three most common MODY genes. It is likely that a similar number of people diagnosed with Type 2 may also have one of these genetic forms of diabetes, too.

Keywords: MODY - Maturity onset diabetes of the young; HNF - Hepatocyte Nuclear Factor; IPF - Insulin Promoter Factor; BLK - B-lymphocyte tyrosin kinase.

Introduction

Maturity onset diabetes of the young (MODY)[1] refers to any of several hereditary forms of diabetes caused by mutations in an autosomal dominant gene (sex independent, i.e. inherited from any of the parents) disrupting insulin production.

Maturity Onset Diabetes of the Young affects approximately one or two per cent of people who have diabetes, and may often go unrecognised in its early stages.

It is a form of diabetes that develops before the patient reaches 25.

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It also runs in families, and can pass from one generation to the next. Mody does not always require insulin treatment.

Pathophysiology

The recognised forms of Mody are all due to ineffective insulin production or release by pancreatic beta cells. Several of the defects are mutations of transcription factor genes. One form is due to mutations of the glucokinase gene. For each form of Mody, multiple specific mutations involving different amino acid substitutions have been discovered. In some cases, there are significant differences in the activity of the mutant gene product that contribute to variations in the clinical features of the diabetes (such as degree of insulin deficiency or age of onset).

Signs and Symptoms

There are two general types of clinical presentation.

- Some forms of Mody produce significant

Classification

Type	Gene/protein	Description
MODY 1	hepatocyte nuclear factor 4α	Due to a loss-of-function mutation in the HNF4α gene. 5%–10% cases.
MODY 2	glucokinase	Due to any of several mutations in the GCK gene. 30%–70% cases. Mild fasting hyperglycaemia throughout life. Small rise on glucose loading.
MODY 3	hepatocyte nuclear factor 1α	Mutations of the HNF1α gene (a homeobox gene). 30%–70% cases. Tend to be responsive to sulfonylureas. Low renal threshold for glucose.
MODY 4	insulin promoter factor-1	Mutations of the IPF1 homeobox (Pdx1) gene. < 1% cases. Associated with pancreatic agensis in homozygotes and occasionally in heterozygotes.
MODY 5	hepatocyte nuclear factor 1β	One of the less common forms of MODY, with some distinctive clinical features, including atrophy of the pancreas and several forms of renal disease. Defect in HNF-1 beta gene. 5%–10% cases.
MODY 6	neurogenic differentiation 1	Mutations of the gene for the transcription factor referred to as neurogenic differentiation 1. Very rare: 5 families reported to date.
MODY 7	Kruppel-like factor 11	KLF11 has been associated with a form of diabetes[16] that has been characterized as "MODY7" by OMIM.[17]
MODY 8	Bile salt dependent lipase	CEL has been associated with a form of diabetes[18] that has been characterized as "MODY8" by OMIM.[19] It is very rare with five families reported to date. It is associated with exocrine pancreatic dysfunction.
MODY 9	PAX4	Pax4 is a transcription factor. MODY 9 is a very rare medical condition.
MODY 10	INS	Mutations in the insulin gene. Usually associated with neonatal diabetes. Rare < 1% cases.
MODY 11	BLK	Mutated B-lymphocyte tyrosin kinase, which is also present in pancreatic islet cells. Very rare.
Permanent neonatal diabetes mellitus	KCNJ11 and ABCC8	A newly identified and potentially treatable form of monogenic diabetes is the neonatal diabetes caused by activating mutations of the ABCC8 or KCNJ11 genes which encode subunits of the K_{ATP} channel. < 1% cases. Tend to respond to sulfonylureas.
Transient neonatal diabetes mellitus	ABCC8	Some forms of neonatal-onset diabetes are not permanent. < 1% cases. Tend to respond to sulfonylureas.

hyperglycemia and the typical signs and symptoms of diabetes: increased thirst and urination (polydipsia and polyuria).

- In contrast, many people with Mody have no signs or symptoms and are diagnosed either by accident, when a high glucose is discovered during testing for other reasons, or screening of relatives of a person discovered to have diabetes. Discovery of mild hyperglycemia during a routine glucose tolerance test for pregnancy is particularly characteristic.

Mody cases may make up as many as 5% of presumed type 1 and type 2 diabetes cases in a large clinic population. While the goals of diabetes management are the same no matter what type, there are two primary advantages of confirming a diagnosis of Mody.

- Insulin may not be necessary and it may be possible to switch a person from insulin injections to oral agents without loss of glycemic control.
- It may prompt screening of relatives and so help identify other cases in family members.

As it occurs infrequently, many cases of Mody are initially assumed to be more common forms of diabetes: type 1 if the patient is young and not overweight, type 2 if the patient is overweight, or gestational diabetes if the patient is pregnant. Standard diabetes treatments (insulin for type 1 and gestational diabetes, and oral hypoglycemic agents for type 2) are often initiated before the doctor suspects a more unusual form of diabetes.

Presentation

The following characteristics suggest the possibility of a diagnosis of Mody in hyperglycemic and diabetic patients:

- Mild to moderate hyperglycemia (typically 130–250 mg/dl, or 7–14 mmol/l) discovered before 30 years of age. However, anyone under 50 can develop MODY.
- A first-degree relative with a similar degree of diabetes.
- Absence of positive antibodies or other autoimmunity (e.g., thyroiditis) in patient and family. However, Urbanova *et al* found that about one quarter of Central European Mody patients are positive for islet cell autoantibodies (GADA and IA2A). Their expression is transient but highly prevalent. The autoantibodies were found in patients with delayed diabetes onset, and in times of insufficient diabetes control. The islet cell autoantibodies are absent in Mody in at least some populations (Japanese, Britons).
- Persistence of a low insulin requirement (e.g., less than 0.5 u/kg/day) past the usual "honeymoon" period.
- Absence of obesity (although overweight or obese people can get Mody) or other problems associated with type 2 diabetes or metabolic syndrome (e.g., hypertension, hyperlipidemia, polycystic ovary syndrome).
- Insulin resistance very rarely happens.
- Cystic kidney disease in patient or close relatives.
- Non-transient neonatal diabetes, or apparent type 1 diabetes with onset before six months of age.
- Liver adenoma or hepatocellular carcinoma in Mody type 3.
- Renal cysts, rudimentary or bicornuate uterus, vaginal aplasia, absence of the vas deferens, epidymal cysts in Mody type 5.

Management

Unfortunately, chronic hyperglycemia of any cause can eventually cause blood vessel damage and the microvascular complications of diabetes. The principal treatment goals for people with Mody — keeping the blood sugars as close to normal as possible ("good glycemic control"), while minimizing other vascular risk factors — are the same for all known forms of diabetes.

Tools for management are those for all forms of diabetes: blood testing, changes in diet, physical exercise, oral hypoglycemic agents, and insulin injections. In many cases these goals can be achieved more easily with Mody than with ordinary types 1 and 2 diabetes. Some people with MODY may require insulin injections to achieve the same glycemic control that another person may attain with careful eating or an oral medication.

When oral hypoglycemic agents are used in MODY, the sulfonylureas remain the oral medication of first resort. When compared to patients with type 2 diabetes, MODY patients are often more sensitive to sulphonylureas, such that a lower dose should be used to initiate treatment to avoid hypoglycaemia. Patients with MODY less often suffer from obesity and insulin resistance than those with ordinary type 2 diabetes (for whom insulin sensitizers like metformin or the thiazolidinediones are often preferred over the sulfonylureas).

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