Maturity-Onset Diabetes of the Young

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Maturity-onset diabetes of the young (MODY) is a group of several conditions characterized by abnormally high blood sugar levels. These forms of diabetes typically begin before age 30, although they can occur later in life. In MODY, elevated blood sugar arises from reduced production of insulin, which is a hormone produced in the pancreas that helps regulate blood sugar levels. Specifically, insulin controls how much glucose (a type of sugar) is passed from the blood into cells, where it is used as an energy source.

Keywords: genetic conditions

1. Introduction

The different types of MODY are distinguished by their genetic causes. The most common types are *HNF1A*-MODY (also known as MODY3), accounting for 50 to 70 percent of cases, and *GCK*-MODY (MODY2), accounting for 30 to 50 percent of cases. Less frequent types include *HNF4A*-MODY (MODY1) and renal cysts and diabetes (RCAD) syndrome (also known as *HNF1B*-MODY or MODY5), which each account for 5 to 10 percent of cases. At least ten other types have been identified, and these are very rare.

HNF1A-MODY and *HNF4A*-MODY have similar signs and symptoms that develop slowly over time. Early signs and symptoms in these types are caused by high blood sugar and may include frequent urination (polyuria), excessive thirst (polydipsia), fatigue, blurred vision, weight loss, and recurrent skin infections. Over time uncontrolled high blood sugar can damage small blood vessels in the eyes and kidneys. Damage to the light-sensitive tissue at the back of the eye (the retina) causes a condition known as diabetic retinopathy that can lead to vision loss and eventual blindness. Kidney damage (diabetic nephropathy) can lead to kidney failure and end-stage renal disease (ESRD). While these two types of MODY are very similar, certain features are particular to each type. For example, babies with *HNF4A*-MODY tend to weigh more than average or have abnormally low blood sugar at birth, even though other signs of the condition do not occur until childhood or young adulthood. People with *HNF1A*-MODY have a higher-than-average risk of developing noncancerous (benign) liver tumors known as hepatocellular adenomas.

GCK-MODY is a very mild type of the condition. People with this type have slightly elevated blood sugar levels, particularly in the morning before eating (fasting blood sugar). However, affected individuals often have no symptoms related to the disorder, and diabetes-related complications are extremely rare.

RCAD is associated with a combination of diabetes and kidney or urinary tract abnormalities (unrelated to the elevated blood sugar), most commonly fluid-filled sacs (cysts) in the kidneys. However, the signs and symptoms are variable, even within families, and not everyone with RCAD has both features. Affected individuals may have other features unrelated to diabetes, such as abnormalities of the pancreas or liver or a form of arthritis called gout.

2. Frequency

MODY is estimated to account for 1 to 3 percent of all cases of diabetes.

3. Causes

MODY can be caused by a mutation in one of several genes. *HNF1A*-MODY, *GCK*-MODY, *HNF4A*-MODY, and RCAD, are caused by mutations in the *HNF1A*, *GCK*, *HNF4A*, and *HNF1B* gene, respectively. All of these genes provide instructions for making proteins involved in the production of insulin to control blood sugar levels in the body. In particular, the proteins are important in specialized cells in the pancreas called beta cells, which secrete insulin.

The proteins produced from the *HNF1A*, *HNF4A*, and *HNF1B* genes all act as transcription factors, which means they control the activity of other genes. In particular, these proteins regulate genes that direct the development and function of beta cells. *HNF1A*, *HNF4A*, or *HNF1B* gene mutations result in production of an altered transcription factor that is unable to function normally. These changes alter gene activity in cells, impairing normal beta cell development and function. As a result, beta cells are less able than normal to produce insulin in response to sugar in the blood, which means the body cannot control blood sugar. Elevated blood sugar results in the signs and symptoms of MODY. Some of these MODY-related genes play roles in the development of other body systems, in addition to beta cells. Disrupted development of these systems underlies additional signs and symptoms in particular forms of MODY. For example, the *HNF1B* gene is involved in kidney development, which helps explain the kidney abnormalities in people with RCAD.

The protein produced from the *GCK* gene acts as a sensor that recognizes when the amount of glucose in the blood rises. In response, the protein helps stimulate the release of insulin from beta cells so sugar can be taken up and used by cells for energy. This protein also helps determine when excess sugar should be taken into liver cells and stored. Mutations in the *GCK* gene limit the protein's ability to sense a rise in blood sugar, so levels remain elevated.

Other genes involved in controlling blood sugar cause rare types of MODY. It is likely that additional genes that have not been identified are also involved in the condition.

3.1. The Genes Associated with Maturity-Onset Diabetes of the Young

- ABCC8
- GCK
- HNF1A
- HNF1B
- HNF4A
- INS
- KCNJ11

3.1.1. Additional Information from NCBI Gene:

- APPL1
- BLK
- CEL
- KLF11
- NEUROD1
- PAX4
- PDX1

4. Inheritance

MODY is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In most cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

5. Other Names for This Condition

- MODY

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