MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

1. What is MODY?

Maturity-Onset Diabetes of the Young or MODY is a monogenic form of diabetes that usually occurs during adolescence or early adulthood. It affects 1-2% of people with diabetes, although it often goes unrecognised. The 3 main features of MODY are:

- Diabetes often develops before the age of 25
- Diabetes runs in families from one generation to the next
- Diabetes may be treated by diet or tablets and does not always need insulin treatment

2. What causes MODY?

MODY is caused by a number of different gene mutations all of which limit the ability of the pancreas to produce insulin. This leads to high blood glucose levels that may lead to complications particularly from the eyes, kidneys, nerves, and blood vessels. Mutations in the genes GCK, HNF1A, HNF4A, HNF1B, KCNJ11, ABCC8 account for the vast majority of MODY cases. However, there are MODY cases with a still unknown genetic cause.

3. What are the features of MODY?

Clinical features of MODY depend on the gene mutation a person carries. People with certain types of mutations may have slightly high blood sugar levels that remain stable throughout life, have mild or no symptoms of diabetes, and therefore avoid any long-term complications. Their high blood glucose levels may only be discovered during routine blood tests. However, other mutations require specific treatment with either insulin or a type of oral diabetes medication called sulfonylureas and may be accompanied by other features, i.e renal cysts. Knowing the type of MODY a person has makes us able to predict how their diabetes will progress in the future.

MODY may be confused with type 1 or type 2 diabetes. In the past, people with MODY have generally not been overweight or obese, or have other risk factors for type 2 diabetes, such as high blood pressure or abnormal blood fat levels. However, as more people become overweight or obese, people with MODY may also be overweight or obese. Moreover, it is possible for an individual with MODY to develop other types of diabetes that require treatment. Patients have the same risk of developing Type 2 diabetes as other members of the general population. Type 2 diabetes is common in older people especially if they are overweight and can need tablet or insulin treatment.

Although both type 2 diabetes and MODY can run in families, people with MODY typically have a family history of diabetes in multiple successive generations, meaning MODY is present in a grandparent, a parent, and a child.

MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

4. How is MODY inherited?

MODY runs in families because of a change in a single gene which is passed on by affected parents to their children. Most forms of MODY are caused by autosomal dominant mutations, meaning that the condition can be passed on to children when only one parent carries or has the disease gene. With dominant mutations, all children of an affected parent with MODY have a 50% chance of inheriting the affected gene and developing MODY themselves.

However, there are also types of monogenic diabetes that are inherited by autosomal recessive pattern. In those cases, the mutation must be inherited from both parents and every child of the family has a 25 percent chance of having monogenic diabetes.

While not as common, it is possible to inherit mutations from the mother only (X-linked mutations). Also, not as common are mutations that occur spontaneously.

It is important to know that although the same mutation is most probably present in one of the parents, the child and other family members, it does not mean that the "severity" of their diabetes will be identical. On the contrary, there can be considerable variations within the same family tree. Moreover, the course of diabetes and the presence of complications also depend on how well blood sugar is controlled.

5. How is MODY diagnosed?

Genetic testing can diagnose most forms of monogenic diabetes. A correct diagnosis with proper treatment should lead to better glucose control and improved long term health.

Genetic testing is recommended if:

- diabetes is diagnosed within the first 6 months of age
- diabetes is diagnosed in children and young adults, particularly those with a strong family history of diabetes, who do not have typical features of type 1 or type 2 diabetes, such as the presence of diabetes-related autoantibodies or obesity, respectively.
- a person has stable, mild fasting hyperglycemia, especially if obesity is not present

Genetic testing for the common mutations that are responsible for MODY diabetes in the Greek population is performed at the Choremeion Research Laboratory, inside the premises of "Aghia Sophia" Children's Hospital.

Abnormal results can determine the gene responsible for diabetes in a particular individual or show whether someone is likely to develop a monogenic form of diabetes in the future. Genetic testing can be helpful in selecting the most appropriate treatment for individuals with monogenic diabetes. Testing is also important in planning for pregnancy and to understand the risk of having a child with monogenic diabetes if you, your partner, or your family members have monogenic diabetes.

MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

6. What is the treatment of MODY?

Treatment varies depending on the specific gene mutation that caused monogenetic diabetes. People with certain forms of MODY can be treated with sulfonylurea, an oral diabetes medicine that helps the body release more insulin into the blood. Other people may need insulin injections. Some people with MODY may not need medications and are able to manage their diabetes with lifestyle changes alone, including physical activity and healthy food choices.

6.1. GCK mutations (MODY 2)

Glucokinase (GCK) is a gene which plays an important role in recognising the levels of blood glucose. It acts as the "glucose sensor" for the pancreas, so that when the blood glucose rises, the amount of insulin produced also increases. This means that the blood glucose does not become too high if glucokinase is functioning normally. If there is a mutation in the GCK gene, this means that it works slightly differently so that the blood glucose is "reset" at a higher level than in people without this change. Affected people may be diagnosed with diabetes although this rise in blood glucose is mild and usually does not need treatment. In people without a change in GCK, the blood glucose is usually less than 100 mg/dl, whereas in people with a change (a mutation) in the glucokinase gene, the fasting blood glucose is typically between 100 and 160 mg/dl. The blood glucose is typically raised from birth and is stable throughout life. Unlike other types of diabetes, the increase in blood glucose after eating is usually small. A glucose tolerance test may be performed to identify if an individual has diabetes. With a GCK gene mutation the rise in blood glucose during this test is usually small (less than a 55 mg/dl increase in 70% of patients at 2 hours). Because the rise in glucose that occurs with mutations in the GCK gene is mild there are usually no symptoms so it is often only identified during routine screening (for example during pregnancy). Complications of diabetes are very rare; therefore, usually no treatment is needed. If diabetes treatment is started, it may make very little difference to blood glucose levels as the body will keep trying to maintain the blood glucose at the raised level. The presence of a change in the GCK gene is most significant in pregnancy.

MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

6.2. HNF1A mutations (MODY 3)

Mutations in the HNF1A gene cause diabetes by lowering the amount of insulin that is produced by the pancreas. It allows insulin to be produced normally in childhood but the amount of insulin is progressively reduced. Therefore, diabetes usually presents during adolescence or early adulthood, although some people are diagnosed later. It is important to keep blood glucose controlled in this type of diabetes as it can lead to diabetic complications. This can be prevented if blood glucose levels are kept well controlled. The risk of coronary heart disease is also raised in HNF1A mutations even though levels of HDL are usually high, so early treatment (at least from the age of 40) with cholesterol lowering medications to protect the heart is recommended. People with mutations in the HNF1A gene often pass increased amounts of glucose in their urine so may have glucose detected on urine testing while their blood glucoses are normal. Individuals with HNF1A diabetes are often particularly sensitive to the blood glucose lowering effects of a group of tablets called sulphonylureas that work by stimulating the pancreas to produce insulin. People with HNF1A diabetes who have been taking insulin from diagnosis prior to a genetic test may be able to stop insulin and convert to sulphonylureas instead. However, there is often an increasing need for treatment as the affected individual gets older and so most people will progress to the addition of other tablets or a background dose of insulin in combination with sulphonylureas to prevent their blood glucose becoming too high. This progression may take place over many years. Those with HNF1A diabetes who are overweight or with a higher HbA1c may also require a background dose of insulin in combination with sulphonylureas to achieve good blood glucose control. Keeping physically active and slim is still important and helps to keep the blood glucose controlled.