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A Review on the Cause, Clinical Presentation and Management of Most Common Types of Maturity Onset Diabetes of the Young (MODY)

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***Abstract*: Maturity Onset Diabetes of the Young (MODY), first noticed by Andrew Cammidge in 1928, and first reported by Tattersall RB and Fajans SS (Father of MODY) in 1975, is a monogenic form of diabetes that is characterized by increased blood glucose level due to mutation of specific genes which are transferred from parent to child. Mutations in any of the transcription factors or the enzyme glucokinase or mainly hepatocyte nuclear factor genes lead to insufficient insulin release from pancreatic β- cells causing MODY. MODY was first used to characterize any asymptomatic hyperglycemia in children or young adults that did not progress to diabetic ketosis or ketoacidosis (a diabetic complication where the body produces excess ketone bodies). The diagnosis is usually made before the age of 25. MODY is frequently misdiagnosed as type 1 or type 2 diabetes mellitus, so for determining the treatment, a correct diagnosis for MODY is very important. Different types of MODY are identified based on the mutated genes. Molecular testing helps in confirming the type of MODY. The most frequent cause of MODY in all populations is due to the mutation in the GCK (Glucokinase), HNF1A (Hepatocyte nuclear factor 1 α), and HNF4A (Hepatocyte nuclear factor 4 α) which constitutes about 95% of all Maturity Onset Diabetes cases. This review summarizes the pathophysiology, diagnosis, and treatment options for the most common types of MODY i.e. GCK MODY, HNF1A MODY, HNF4A MODY.**

***Keywords*: HNF1A, GCK, MODY, HNF4A, Mutation, Diabetes, gene.**

1. Introduction

Diabetes is a metabolic disorder that causes high glucose levels in the body due to numerous etiologies and primarily because of defects in insulin secretion, insulin activity, or both. Diabetes is a serious, long-term condition that causes a major impact on the lives and wellbeing of individuals, families worldwide. It is estimated that 8.8% of the adult population around the world suffers from diabetes, with type 2 diabetes comprise about 90% of the cases. Although type 1 diabetes is the most frequent in children, other kinds such as type 2 diabetes and monogenic diabetes must also be considered, with the latter accounting for 1%–6% of all diabetes cases. Neonatal diabetes, mitochondrial diabetes, and Maturity Onset Diabetes of the Young (MODY) are the three types of monogenic diabetes.

MODY (Maturityonset diabetes of the young) was coined in the 1970s to characterize a kind of diabetes that is distinct from type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes [1]. MODY is a monogenic form of diabetes that is characterized by an increased blood sugar level due to mutation of specific genes that are transferred from parent to child. Mutations in any of the transcription factors or the enzyme glucokinase and mainly hepatocyte nuclear factor genes lead to insufficient insulin release from pancreatic β- cells causing MODY. The diagnosis is usually made before the age of 25. MODY is frequently misdiagnosed as type 1 or type 2 diabetes mellitus, so for determining the treatment, a correct diagnosis for MODY is very important. There are 14 known subtypes of MODY. The most frequent cause of MODY in all populations is due to the mutation in the GCK (Glucokinase), HNF1A (Hepatocyte nuclear factor 1 α), and HNF4A (Hepatocyte nuclear factor 4 α) genes which constitutes about 95% of all Maturity Onset Diabetes cases.

2. HNF4A-MODY or MODY1

Mutations in transcription factor genes are responsible for a number of the abnormalities. The mutation in the HNF4A gene on chromosome 12 causes MODY1.HNF4A is a transcription factor that affects the expression of genes involved in glucose transport and metabolism, particularly in the liver, pancreas and kidney [2]. Hence the mutation of HNF4A leads to increased blood glucose level.

1) Clinical presentation

MODY1 is defined by a continuous rise in blood glucose levels over time. Before the age of 30, mild to severe hyperglycemia (usually 130–250 mg/dl, or 7–14 mmol/l) is observed. Microvascular problems such as diabetic retinopathy, nephropathy are commonly observed in people with MODY1 [3]. The production of apolipoproteins and triglycerides is also

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affected by HNF4A deficiency, resulting in reduced serum concentrations [4]. Early onset of neonatal hyperinsulinemia and micrsomia is common. Prolonged neonatal hypoglycemia is also observed. Normal renal threshold is maintained in most of the patients (180 mg/dl).

2) Management

It is recommended to put a patient on a low-carbohydrate diet when their blood glucose and glycated hemoglobin (HbA1c) levels are still in the "non-diabetic" range at the time of diagnosis and in the early stages of the disease. Switching to sulfonylureas can achieve better glycemic control than insulin when the diet appears to be ineffective. Sulfonylureas work by increasing the insulin secretion from the beta cells of pancreas. Kyithar et al. found that two individuals on metformin had excellent blood glucose control (HbA1c 6.15%) after 15 years of MODY diabetes [5]. Patients who are not showing a good response to sulfonylureas and metformin are treated with insulin injections.

3) GCK-MODY or MODY2

Mutations in the GCK (Glucokinase) genes lead to MODY 2(GCK-MODY). GCK is a glucose sensor produced in pancreatic -cells that catalyze the conversion of glucose to glucose-6-phosphate and consequently regulates glucose-mediated insulin production. Mutation of this leads to impaired glucose synthesis [6].

4) Clinical presentation

The fasting blood sugar of GCK-MODY patients ranges from 5.5 to 8.0 mmol/L. GCK-MODY hyperglycemia is present at birth and lasts a lifetime, but it is usually asymptomatic and only detectable by routine glucose testing. Diabetes-related problems are uncommon in GCK-MODY; multiple studies on patients indicate that the rate of microvascular and macrovascular complications in GCK-MODY is less compared to other types of MODY in the general population [7]. Patients are screened for genetic testing if their fasting glucose is 5.5–8.0 mmol/L and 2 hr increment <4.6 mmol/L on a 75 g OGTT (glucose tolerance test) and if there is a family history of type 2 diabetes [8] .

5) Management

Individuals with GCK-MODY are now advised not to treat their hyperglycemia, except for during pregnancy. Glucose-lowering medication, including insulin, is said to have a negligible effect on glucose levels in GCK-MODY patients. In one trial, there was no difference in HbA1c levels between people with GCK-MODY who received glucose-lowering medication (oral glucose-lowering drugs or insulin) and those who did not. They will be at risk for complications if they develop these more prevalent types of diabetes, and they will almost certainly require further monitoring and treatment [9].GCK-MODY is mainly managed with diet.

3. HNF1A-MODY or MODY 3

MODY 3 (HNF1A-MODY) is caused by mutations in the HNF1α gene (a home box gene), which accounts for 30–70% of cases and is the most common type of MODY in populations. MODY3-related hyperglycemia can be progressive and worsening. The risks of microvascular and macrovascular problems in these people are comparable to those seen in patients with type 1 and type 2 diabetes [10].

1) Clinical presentation

HNF1A–MODY has a glycemic pattern that includes modest fasting hyperglycemia and extremely high glucose concentrations after glucose infusion. Insulin secretion declines with time in individuals with HNF1A–MODY, and glucose control deteriorates, necessitating medication.63% of patients with this diabetes is diagnosed before the age of 25, 79% before the age of 35, and 96% by the age of 55[11]. The renal tubular transport of glucose is reduced in HNF1A–MODY, resulting in a low renal glucose reabsorption threshold. Patients with MODY3 have been observed with glycosuria before they develop severe hyperglycemia [12].

2) Management

MODY 3 is most commonly caused by mutations in the HNFA-1 gene. Treatment for HNF1A-MODY patients is determined by their age and HbA1c level. If HbA1c is less than 6.5 percent, the first-line treatment is a low-sugar diet; otherwise, sulphonylureas may be recommended [13]. Sulphonylureas are recommended as first-line treatment by the International Society for Paediatric and Adolescent Diabetes/International Diabetes Federation and the American Diabetes Association because they stimulate insulin release from beta cells, improving glycemic control [14]. When glycemic control with OHAs fails, insulin injections should be initiated. Inhibitors of the sodium-glucose co-transporter-2 (SGLT-2) have also been investigated. It has been established that a single dosage of the SGLT-2 inhibitor dapagliflozin (10 mg) given as an adjuvant in conventional treatment has helped in obtaining glycemic control. Its potential role as a long-term treatment alternative has yet to be investigated [15]. Administration of meglitinide analogs was also found effective in adults in lowering postprandial glucose levels in patients with HNF1A MODY [16].

4. Conclusion

60 years ago, there was only a little information available about diabetes genetics and pathology. Initially, MODY was assumed to be a rare kind of diabetes. MODY is now known to be highly widespread, often appearing as type 1 or, more commonly, type 2 diabetes. The prevalence of MODY among diabetic patients is believed to be 1–2%. MODY and other monogenic forms of diabetes are now recognized as distinct kinds of diabetes. The most frequent cause of MODY in all populations is due to the mutation in the GCK (Glucokinase), HNF1A (Hepatocyte nuclear factor 1 α), and HNF4A (Hepatocyte nuclear factor 4 α) which constitutes about 95% of all Maturity Onset Diabetes cases. Newer studies on these types of diabetes have helped to gain more information and also helped to spread awareness among people. MODY genetic testing is becoming frequent, and it helps in the right diagnosis and treatment of the disease.

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