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Review Article

Maturity Onset Diabetes of the Young: A Rare Monogenic Form of Diabetes

Abstract

Diabetes Mellitus is a group of metabolic disorders associated with microvascular and macrovascular complications. The rapidly increasing prevalence and incidence of this disease is causing a major worldwide health problem. Maturity onset diabetes of the young (MODY) is a rare monogenic form of diabetes resulting from mutation in a single gene. There are 13 types of MODY genes identified currently. The two main types of MODY is caused by mutations in the hepatocyte nuclear factor 1A and glycolytic enzyme glucokinase (GCK). Genetic testing is the gold standard for diagnosing MODY. It is essential to identify the MODY subtype to determine the management and treatment options.

Introduction

Maturity Onset Diabetes of the Young (MODY) is a rare, hereditary form of diabetes which is different from both Type 1 and Type 2 diabetes. It is estimated to affect 2-5% of all diabetic cases, however this may be inaccurate or under-estimated globally due to being undiagnosed or unclassified as type 1 diabetes or type 2 diabetes because of overlapping clinical features [1]. It is often developed before the age 25 years and diabetes often runs in families from one generation to the next [2].

MODY patients usually present with mild to moderate hyperglycemia started before age 25, a first-degree relative with a similar degree of diabetes, absence of positive antibodies or other autoimmunity in patient and family, persistence of a low insulin requirement, and absence of obesity or other problems associated with type 2 diabetes [3].

MODY is characterized by a Mendelian autosomal dominant mode of inheritance [2]. Understanding the genetic etiology of the disease is an important factor to consider as this will determine management and treatment options. Thus, an accurate genetic diagnosis is vital.

Fajan & Bell [4], describes the early history and genetics of MODY. A prospective long term study initiated on healthy asymptomatic first degree relatives of known diabetic patients from a diabetic clinic at the University of Michigan during the year 1949.

The result of the study disclosed in 1960, reported that mild, asymptomatic diabetes occurs in non-obese children, adolescents, and young adults of relatives of known diabetic patients. The study found out that glucose intolerance and fasting hyperglycemia improved with the administration of sulfonylurea. The study was presented at the First International congress of Endocrinology. In 1964, Fajan first used the term maturity onset of diabetes of the young and emphasized its strong familial basis at the Fifth Congress of the International Diabetes Federation. In 1974, Tattersall [4] reported three pedigrees identified with this type of diabetes and found out that it was inherited in an autosomal inherited fashion.

There are 13 subtypes of MODY genetic loci identified currently and nearly 80% of all MODY cases are attributed to highly penetrant heterozygous mutations in one of three genes: nuclear factor-1 alpha (HNF1A), 4-alpha (HNF4A), and the glycolytic enzyme glucokinase (GCK) [5]. In United States individuals less than 20 years of age, the minimum prevalence of MODY increases to 2.1 per 100,000 individuals [3]. According to Pihoker, Gilliam & Ellard [3], the United Kingdom reports a minimum prevalence of MODY estimated at 108 cases per million over the age of 1 year and out of those, 52% have HNF1A (MODY3) mutations and 32% have GCK mutation (MODY2). MODY2 and MODY3 are the most prevalent representing 20-70% of all MODY cases [6]. There are more genes that have been associated with MODY, however they are exceptionally rare having been reported once and detected in very few families [2].

MODY2

Genotype: Glucokinase (GCK)

Phenotype: Mild fasting hyperglycemia throughout life, often asymptomatic, and gestational diabetes.

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Mechanism: Pancreatic beta cells and the liver express GCK. Glucokinase gene contains an enzyme that is important for the normal regulation of insulin production. Heterozygous mutations cause re-setting of the normal threshold of glucose stimulated insulin secretion, which leads to an elevated threshold for initiation of glucose-stimulated insulin secretion. Thus it causes mild elevations in fasting blood glucose, which is the hallmark of GCK-MODY2. The mutation results in consistent elevations in fasting blood glucose with lower elevations in post- prandial glucose levels, and hemoglobin A1C level generally range 5.8-7.6% [5].

Patients are typically asymptomatic and the problem may be detected by chance during routine screenings. Patients may or may not meet the formal diagnosis for diabetes. In addition, patients may be diagnosed with gestational diabetes, with impaired fasting blood glucose levels or with type 2 diabetes. Thus, diagnosis will depend on the circumstance at hand. In GCK-MODY, the defect is present at birth, but a diagnosis may not be made for decades. Any individuals found to have GCK-MODY is recommended to stop anti-diabetic therapies and can be usually managed by exercise and diet alone. Annual monitoring of hemoglobin A1C is recommended for MODY 2 patients to identify individuals with worsening hyperglycemia due to obesity or insulin resistance. Thus, in the setting of elevating hemoglobin A1C, metformin is warranted [7].

MODY3

Genotype: Hepatocyte Nuclear Factor-1 Alpha (HNF1A)

Phenotype: Diminished renal threshold for glycosuria and marked sensitivity to sulfonylurea derivatives.

Mechanism: This gene is mainly expressed in pancreas, kidney, and liver. A mutation in the HNF1A gene results in an alteration in gene expression of proteins that are involved in glucose transport and metabolism. It also increases apoptosis of beta cells, which lead to progressive decline in beta cell function and proliferation. Ultimately causing abnormal insulin secretion. In addition, the mutation causes lower renal threshold for glucose resulting in glycosuria.

The HNF-1A, which is MODY3, is the most common form of MODY reported in studies from UK and from many European countries [8]. Because of its high penetrance nature 63% of carriers develop diabetes by 25 years of age, and almost all carriers develop diabetes by the age of 55 [5] . Strict glycemic control is pertinent due to risk of developing microvascular and macrovascular complications and decreased renal glucose reabsorption. Before being diagnosed with diabetes, carriers may develop glycosuria due to altered renal re-absorption of glucose. Since hyperglycemia may be severe and worsens over time, the risks are similar to diabetes mellitus type 1 and type 2. Therefore, tight glycemic control and close monitoring for diabetic complications are required in these patients. These patients are often misdiagnosed for type 1 diabetes and are placed on insulin therapy. Patients with HNF1A-MODY are sensitive to sulfonylurea therapy, which is recommended as first line treatment [8]. According to an observational study done by Pearson et al., [5], patients with HNF1A-MODY can be switched safely from insulin to a sulfonylurea.

Genetic testing using Sanger DNA sequencing is the gold standard for diagnosing MODY and is offered by specialist centers globally [3]. This will identify the MODY subtype that will ultimately help the management and treatment options. Thus, an accurate genetic diagnosis is vital. In addition, first degree relatives of MODY patients have a 50% probability of the same mutation [6]. Early diagnosis and initiation of appropriate treatment can reduce the risk of complications. There are some suggestions that may be helpful in determining the need for genetic testing. Recent literature provide criteria and algorithms for the consideration of genetic testing. In 2012, an approach to correctly allocate genetic testing among Caucasian patients with onset of diagnosis before the age of 35 years was published, this tool is available as an online calculator and it calculates the probability that an individual has MODY. This calculator has been shown to have high sensitivity and specificity compared to criteria of diagnosis before the age 25 years and a parent with diabetes [9].

There are many financial, and environmental barriers associated with genetic testing. Diagnosing MODY is challenging because of its relatively low prevalence in the general population. In addition, it is often misdiagnosed because of its shared clinical features with of other types of diabetes. Lack of available information on MODY and lack of knowledge among health care professionals awareness of the disease further delays correct diagnosis. However, due to the expensive cost of genetic testing from the lack of insurance coverage, genetic testing may not be feasible. Genetic discrimination is another problem as people feel that they get treated differently by their employers or insurance companies because they have a gene mutation. In addition, members of some communities especially developing countries, often fear that genetic information will be used to stigmatize them. Increase in knowledge and awareness of MODY among health care professionals and improvement of information provision for patients and family members via websites and written materials are needed to recognize the symptoms and early diagnosis of MODY. Genetic diagnosis for MODY is vital for patients and their family members because it can provide individualized treatment. According to Kim [5], diagnosing MODY is a challenge for physicians, therefore a nationwide MODY registry and systematic approaches are required for the rapid diagnosis and appropriate management of MODY.

References

1. Schwitzgebel VM (2014) Many faces of monogenic diabetes. Journal of Diabetes Investigation 5: 121-133. Link: https://bit.ly/2E5PGBW

2. Althari S, Gloyn AL (2015) When is it MODY? Challenges in the Interpretation of Sequence Variants in MODY Genes. The Review of Diabetic Studies: RDS 12: 330-348. Link: https://bit.ly/2Bw32pw

3. Amed, S, Oram R (2016) Maturity-Onset Diabetes of the Young (MODY): Making the Right Diagnosis to Optimize Treatment. Canadian Journal of Diabetes 40: 449-454. Link: https://bit.ly/2GAtxgK

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DOI: http://doi.org/10.17352/ijcem.000034

4. Fajans SS, Bell GI (2011) MODY: History, genetics, pathophysiology, and clinical decision making. Diabetes Care 34: 1878-1884. Link: https://bit.ly/2WY0Dg8

5. Kim S (2015) Maturity-Onset Diabetes of the Young: What Do Clinicians Need to Know? Diabetes & Metabolism Journal 39: 468. Link: https://bit.ly/2IaR0Yb

6. Heuvel BH, De Valk HW, Losekoot M, Westerink J (2016) Maturity onset diabetes of the young: Seek and you will find. Neth J Med 74: 193-200. Link: https://bit.ly/2WYFtPd .

7. Owen K (2014) MODY Due to Glucokinase Mutations. Link: https://bit.ly/2GAQUqi

8. Nair VV, Chapla A, Arulappan N, Thomas N (2013) Molecular diagnosis of maturity onset diabetes of the young in India. Indian Journal of Endocrinology and Metabolism 17: 430-441. Link: https://bit.ly/2SO6w08

9. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, et al. (2012) The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. Diabetologia, 55: 1265-1272. Link: https://bit.ly/2RT768B

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