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Maturity Onset Diabetes of the Young (MODY) - An essence

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Maturity onset diabetes of the young (MODY) is a heterogeneous group of disorders that result in β-cell dysfunction characterized by autosomal dominantly inherited non-insulin dependent form of diabetes. It is classically presenting in adolescence or young adults before the age of 25 years [1, 2]. MODY is a rare cause of diabetes, accounting for only 1%–2% of all diabetes. It is frequently misdiagnosed as type 1 or type 2 diabetes, as MODY is often difficult to discriminate from these two forms of diabetes [1].

Identification of MODY by medical practitioners is important, as it has both therapeutic and genetic repercussions. The most pivotal differential diagnosis is IDDM, as an incorrect diagnosis may lead to inappropriate treatment. It can be very difficult to differentiate the early stages of β-cell dysfunction of MODY. Differentiation of MODY from type 2 diabetes can be done by a prominent family history in three or more generations, a young age at presentation, absence of obesity, and by the absence of the metabolic syndrome (diabetes, insulin resistance, hypertension, hypertriglyceridaemia) [3].

The diagnosis may be made by careful clinical evaluation, but exact sub-typing is possible only by genetic analysis. Several genetic factors have been identified as causative agents in MODY, each leading to a different type of the disease.

Clinical Presentation of patients with MODY

Clinical presentation of patients with MODY includes following features:

- A strong family history of diabetes of any type
- Insulin independence
- Absence of autoantibodies for pancreatic antigens and evidence of endogenous insulin production
- Lack of ketoacidosis when insulin is omitted outside the honeymoon period (typically 5 years following the diagnosis of diabetes).

Above features are atypical for type 1 diabetes, thus increasing the probability of monogenic diabetes. Clinical presentation of patients with MODY in those with apparent type 2 diabetes is the absence of insulin resistance features (lack of obesity, the absence of acanthosis nigricans, normal triglyceride levels, or elevated or normal high-density lipoprotein cholesterol) indicate the presence of monogenic forms of diabetes [1].

Genes involved in MODY [4]

Molecular genetic studies demonstrated that MODY is a clinically and hereditarily heterogeneous syndrome. Any abnormalities (mutations, deletions, or other anomalies) in at least eleven genes are responsible for MODY **(Table: 1)**. These MODY genes encode the enzymes glucokinase (GCK) (MODY 2) that is liable for the early processing of glucose in the β-cell and copious transcription factors that modulate the expression of numerous genes concerned with the demarcation and utility of β-cells. GCK mutations cause a mild, asymptomatic, and stable fasting hyperglycemia usually requiring no specific treatment. However, mutations in the HNF1A (MODY 3) and HNF4A (MODY 1) cause a progressive pancreatic β-cell dysfunction and hyperglycemia that may result in microvascular complications. Mutations in the HNF1B (MODY 5) is associated with pancreatic agenesis, renal abnormalities, genital tract malformations, and liver dysfunction. Compared to MODY 1, 2, 3, and 5, the remaining subtype of MODY

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have a much lower prevalence [4].

Table 1: Genetic classification and clinical types of MODY subtypes

Type	Gene name	Gene Function	Primary defects
MODY1	Hepatocyte nuclear factor 4α (HNF4A)	Transcription factor nuclear factor	Pancreas
MODY2	Glucokinase (GCK)	Hexokinase IV	Pancreas/liver
MODY3	Hepatocyte nuclear factor 1α (HNF1A)	Transcription factor (homeodomain)	Pancreas/kidney
MODY4	Insulin promoter factor 1(IPF-1)	Transcription factor (homeodomain)	Pancreas
MODY5	Hepatocyte nuclear factor 1β (HNF1B)	Transcription factor (homeodomain)	Kidney/Pancreas
MODY6	Neurogenic differentiation 1(NEUROD1)	Transcription factor (bHLH)	Pancreas
MODY7	Kruppel like factor 11 (KLF-11)	Transforming Growth Factor β-inducible early growth response 2	Pancreas
MODY8	Bile salt dependent lipase (CELL)	The endocrine cells of pancreas synthesize insulin and are involved in the pathogenesis of diabetes mellitus and exocrine cells are involved in the pathogenesis of pancreatic malabsorption	Pancreas
MODY9	Paired Domain Gene 4 (PAX4)	Trancription factor (paired domain gene 4)	Pancreas
MODY10	Insulin (INS)	B-cell of the islets of langerhens	NF -kappa -B
MODY11	Tyrosine kinase B-Lymphocytes specific	Tyrosine kinase (B-lymphocytes)	MIN6 beta cells

Prevalence of MODY in India

Prevalence of MODY in India was reported to be higher than the West (4.8%). Significant proportion of patients with MODY have been noticed in North India (20%) with symptomatic hyperglycemia. Degree of glucose intolerance appeared to be greater than that in the western population. Most patients were treated with diet and/or oral hypoglycemic agents. Chronic vascular complications were present in a substantial number of South Indian subjects viz., retinopathy, proliferative retinopathy, nephropathy [3].

Conclusion

Identification of MODY remains a challenge for physicians, and the condition is largely under-diagnosed. As MODY is genetically and clinically heterogeneous group of conditions, a correct genetic diagnosis of monogenic diabetes is prerequisite, as it can predict the clinical course of the patient and guide the most appropriate treatment. Health-care scientists should educate clinicians and facilitate identification of these patients. The quality of life of a patient with MODY can be improved by early, accurate genetic diagnosis and implementation of appropriate treatment which leads to considerable lifetime savings in drug therapy, reduced blood glucose monitoring, reduced clinical follow-up and better glycaemic control/early diagnosis in relatives, leading to a lower incidences of diabetic complications.

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