

Case Report

An interesting case of young onset diabetes mellitus

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ABSTRACT

A 24 years old female, was admitted with symptoms of urinary tract infection. She was married and had bad obstetric history. She was known diabetic for 16 years of age and was on regular treatment with injection human insulin mixtard since the time of diagnosis, but had no episode of diabetic ketosis/ ketoacidosis. She had a positive family history of diabetes. She was further evaluated and was found to have normal C peptide levels and islet cell antibodies were found to be negative. Hence, the possibility of MODY (monogenic diabetes) was considered. Her genetic testing could not be done due to financial constraints. But a trial of sulfonylureas was given along with reduction in the dose of insulin to which she responded well and is presently well controlled.

Keywords: C Peptide, Diabetes mellitus, Islet cell antibody, MODY, Sulfonylureas

INTRODUCTION

Maturity onset diabetes of young (MODY) comprises of a heterogeneous group of monogenic disorders characterized by β cell dysfunction.

MODY is a subtype of diabetes characterized by autosomal dominant inheritance, early onset of hyperglycemia (usually before 25 years of age) and impaired insulin secretion.

More than 10 variants of MODY are known.¹ These variants are caused by mutations in the genes encoding islet- enriched transcription factors or glucokinase. These factors most likely affect islet development or the expression of gene important in glucose stimulated insulin secretion or the maintenance of beta cell mass.

Diagnosis of MODY should be considered in patients with early onset of hyperglycemia, positive family history of diabetes, absence of features of insulin resistance and absence of β cell autoimmunity.

CASE REPORT

A 24 years old female was admitted with complaints of high grade fever with chills.

She was a known case of Diabetes mellitus for 16 years of age, on insulin since diagnosis, at present receiving human mixtard insulin (18U---0---10U). At the time of diagnosis of diabetes at age 16, her complaints were generalized weakness, weight loss and polyuria. Her BSL at onset was (F) 300; (PP1) 350. There was no history of any episode of diabetic ketoacidosis/ ketosis.

She also had a bad obstetric history. She was married at the age of 21, conceived after a year of marriage. During pregnancy, her blood sugars were uncontrolled, she had hyperemesis in the 2nd trimester and history of recurrent UTI. Her USG at 5 months of gestation showed B/L Acute Pyelonephritis and oligohydromnios. She had an IUD at 6½ months of gestation. She was also diagnosed to have hypertension post-delivery. She is Apla -ve.

Her father was a diabetic, diagnosed at 35 years of age and died due to kidney failure after 5 years of diagnosis of diabetes. Her father's brother and sister are also diabetic.

During present admission blood sugars were high, her urine routine was suggestive of albumin 2+, sugars 3+, 10-12 pus cells; urine culture s/o no growth; all other lab parameters were within normal limits. Her fever subsided and urine routine came down to normal after 7 days of antibiotic therapy. The patient was further evaluated for the type of diabetes. Her C-peptide was normal and islet cell antibody was negative.

Since our patient was a case of non-obese, young onset diabetes with strong family history with normal C-peptide levels, negative for islet cell antibodies and no history of diabetic ketosis/ ketoacidosis, the possibility of MODY was considered. Thus, the patient was given a trial of sulfonylureas with reduced doses of insulin and she responded well. She has been kept on tight control of diabetes, as she is likely to conceive again.

DISCUSSION

Maturity-onset of diabetes mellitus of the young (MODY) is a rare form of diabetes mellitus in children that includes several disorders caused by monogenic defects in β -cell function. It comprises of a heterogeneous group of monogenic disorders characterized by β cell dysfunction.¹ MODY is not a single entity but represents a genetic, metabolic and clinical heterogeneity.

The term maturity onset diabetes of the young (MODY) was first used in the 1970s, to describe inheritable diabetes distinct from type 1 (insulin-dependent) and type 2 (noninsulin-dependent) diabetes.

Approximately 1-2% of cases of diabetes are misdiagnosed as type 1 and type 2 diabetes but have a monogenic cause of diabetes.

MODY is an autosomal dominant disorder with more than 10 known variants. Recent studies suggest that the clinical presentation of MODY is broad, ranging from asymptomatic hyperglycemia to a severe insulin requiring diabetes. Patients are usually non-obese and have low C-peptide levels characteristic of β cell dysfunction.²

Although early onset, non-insulin dependent and autosomal dominant inheritance is used to define MODY, other important features include β cell dysfunction and lean body habitus.³

MODY accounts for 1-2% of non-insulin dependent diabetes, the relative prevalence of different subtypes of MODY are 14% glucokinase mutation; 75% transcription factor and 11% MODYx (MODYx includes families that fulfill criteria for MODY but no specific mutation is found).⁴

A clinical criterion for diagnosing MODY was first proposed by Tattersall and Fajans in 1975, which is as follows:

- Early onset of diabetes (<25 years)
- Early onset diabetes in at least 2 or ideally 3 family members
- Autosomal dominant mode of inheritance
- Non-insulin dependence (not requiring insulin even after 5 years of diagnosis)
- Detectable C-peptide levels and negative antibody testing.⁵

Genetic mutation can occur spontaneously, but usually runs in the family.⁶ MODY is associated with mutation in gene encoding islet enriched transcription factor or glucokinase. These mutations affect islet cell development or maintenance of β cell mass or expression of gene mediating insulin secretion.

Table 1: Common variants of MODY and their associated mutation.

Locus	Gene name
MODY 1 (20q)	HNF4A
MODY 2 (7p)	GCK
MODY 3 (12q)	HNF1A
MODY 4 (13q)	IPF1
MODY 5 (17q)	TCF2
MODY 6 (2q)	NEUROD1

To date over 800 different mutations have been detected in association with MODY.⁷ Mutation of gene HNF4A, Glucokinase (GCK) and HNF1A comprise the most common causes of MODY, approximately in about 70% individuals.⁷

MODY presents with hyperglycemia and common symptoms such as weight loss, fatigue, polyuria and polydipsia. It is important to note that diabetic ketoacidosis is rarely associated with MODY.⁸

MODY 1 (HNF4A MODY) and MODY 3 (HNF1A MODY) present with progressive decline in glycemic control and are often misdiagnosed as type 1 diabetes. This type to MODY responds well to OHAs like sulfonylureas.

MODY 2 (GCK MODY) presents with mild to moderate stable hyperglycemia, which does not respond to OHAs and usually do not require treatment.^{1,4,8,9}

the mechanism behind MODY 2 is that the mutation in GCK catalyzes the formation of glucose 6 phosphate from glucose, which is important glucose utilization as glucose 6 phosphate is required for eliciting insulin secretory response from pancreatic β cells. Also, patients with GCK MODY are unlikely to develop diabetic complications.⁹

Genetic testing is important to confirm the clinical diagnosis of MODY. Once the associated mutation is established the management and monitoring of the disease can be planned accordingly.

Certain subtypes of MODY are associated with specific medical conditions, for example HNF1B MODY is associated with renal involvement, thus evaluation of the subtype disease becomes important in screening of patients for associated conditions and monitoring its progress.

Genetic testing is not only helpful for the patient but also his family as first-degree relatives are also likely to have MODY, the chances of the sibling of the diseased of inhering the same mutation are as high as 50%. Thus, in such families genetic testing can be used as a modality of predictive testing in asymptomatic members.⁹

Unfortunately, the facility of molecular genetic techniques is not freely available in our country due to lack of finances and expert manpower.¹⁰

CONCLUSION

Our patient is MODY type of diabetes, according to criteria, and maybe having the HNF1B mutation, because she presented with a renal involvement, possibly a nephritis, and she has family history of father being Diabetic at a young age, and developing Renal Failure within 5 years of diagnosis to which he succumbed.

Clinical implications: MODY is a clinically and genetically heterogeneous group of monogenic disorders causing diabetes in the younger population.⁷

Possibility of MODY should be considered in patients whose features are atypical of their diagnostic label. Genetic diagnosis of this disorder has huge therapeutic and prognostic benefits both for patient and family.

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