

Case Report

Atypical Presentation of Diabetes Mellitus

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Maturity onset diabetes of the young (MODY) is a subtype of diabetes of autosomal dominant inheritance characterized by anomalous B cell activity, decreasing insulin production ability of the pancreas for glucose utilization, and an early onset of hyperglycemia typically presenting before the age of 25.¹ It consists of a genetically heterogeneous group of monogenic disorders having more than 10 variants.²

Patients with this kind of diabetes are frequently misdiagnosed as having either type 1 or type 2 diabetes mellitus (DM). Unlike DM1 and DM2 which are polygenic, MODY is caused by a single gene mutation including Glucokinase (GCK), Hepatocyte Nuclear Factor (HNF1A, HNF4A, HNF1B), Insulin (INS), NEURO1, Pancreatic and Duodenal Homeobox (PDX1), Paired box (PAX4), ATP Binding Cassette Subfamily C Member (ABCC8), Potassium Inwardly Rectifying Channel Subfamily J Member 11 (KCNJ11), Krüppel-like family of transcription factors (KLF11), Carboxyl Ester Lipase (CEL), Tyrosine-protein kinase BLK (BLK), and Amyloid Beta Precursor Protein (APPL1) diagnosed by molecular genetic testing out of which mutations in hepatocyte nuclear factor (HNF)4A (MODY1), glucokinase (GCK) (MODY2), and HNF1A (MODY3) genes total to almost 99% of the cases.^{3,4}

Mild, asymptomatic hyperglycemia in a child, adolescent, or young adult with a family history of autosomal dominant diabetes is the most common symptom of MODY.⁵ Patients with mutations in HNF1A and HNF4A are more likely to have polydipsia and polyuria, however, those with mutations in GCK are more likely to have a moderate increase in blood glucose on standard testing.⁵

MODY-HNF1A is most prevalent in the UK, Netherlands, and Denmark, whereas Spain, Italy, France, Germany show a higher occurrence of MODY-GCK.⁶ Even though Asian patients have a higher prevalence of diabetes, their limited referral for UK MODY testing under-

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represents them.⁷ The estimated incidence of MODY in children and adolescents under the age of 15 with newly diagnosed DM is 2.4% for which glucose-lowering medications such as sulfonylureas, meglitinides, and insulin in combination with a low carbohydrate diet have been set as the standard treatment.^{8,9}

Case Report

A 24-year female patient, previously healthy and non-obese, presented to the endocrinology clinic with complaints of increasing urine frequency, increased appetite, and early fatigability for the past 4-5 months. According to the patient, increased urinary frequency was not associated with fever, pain, or burning sensation. She checked her blood sugar at home which was over 250 mg/dl so she followed for further work up. Her father and mother were both diagnosed Type 2 diabetics and father died due to chronic inflammatory demyelinating polyneuropathy.

On presentation, patient's vitals were BP 146/72 mmHg, Pulse 94 bpm, RR 20/minute, O2 saturation 96% room air. Her height and weight were 160.5 cm and 56 kg respectively, and her body mass index was calculated to be 21.7, falling in the healthy range for age and sex. On inspection, there was no evidence of goitre or acanthosis nigricans, and the rest of the systemic examination was also unremarkable.

On lab workup her HbA1c was 10 with fasting blood sugar of 190 mg/dl. Her anti islet cell and anti GAD 65 antibodies were negative. TSH was 9.8. Keeping in view of the history, examination and lab workup patient was diagnosed as MODY and was started on sulphonylurea (Diamicron MR 30mg) BBF and Thyroxine 50mcg QAM. Her HbA1c on next visit after 2 months drop to 5.40 % which further decrease to 5.0% after five month of diagnosis.

On next visit after a year of diagnosis of Diabetes mellitus, patient complain of urinary, fecal incontinence and incomplete bladder emptying since 2-3 months. MRI

Thoracic-lumbar spine was performed which showed subtle abnormal T2 hyper intense signals in the distal cord at the level of T11-L1 without any evidence of cord expansion or post contrast enhancement. Mild disc bulging at L4-L5 and L5-S1 resulting in mild thecal sac indentation without any lateral recess narrowing was also identified. Neurologist advise ANA workup which came out to be negative. EMG was done which showed autonomic dysfunction affecting upper and lower extremities with absent sympathetic skin response and a chronic neurogenic process due to intraspinal canal lesion (radiculopathy) affecting bilateral L5-S1 myotome, moderate to severe in degree without active motor axon loss changes.

Two and half year after the diagnosis of Diabetes mellitus, her HbA1c was 5.1 % on diamicron MR 30mg QAM. Her MODY genetic workup was done which came out to be negative. In October 2020 her diamicron MR 30mg QAM was changed to amaryl 1mg QAM, her HbA1c on next visit was 5.3 with FBS of 77 mg/dl. Her amaryl was stopped and OGTT was done after 2 weeks of stopping amaryl, the result of OGTT showed FBS: 95 and after 2 hour of 75 gm glucose it was 98 mg/dl. Her amaryl was stopped and she was called for follow up after 4 months. On next follow up her HbA1c raised to 7.3% so amaryl was restarted.

This is an intriguing instance of atypical diabetes mellitus that meets the clinical criteria for MODY yet has a negative genetic test for the disease. In these circumstances, other causes of atypical diabetes, such as mitochondrial or other atypical causes, should be addressed.

Discussion

Maturity onset diabetes of the young (MODY) is a term that refers to genetic, metabolic, and clinical heterogeneity that is frequently misinterpreted as type 1 (insulin-dependent) and type 2 (noninsulin-dependent) diabetes with a single etiology.¹ Patients with MODY typically present with a strong family history of diabetes of any type, absence of autoantibodies for pancreatic antigens, and insulin dependence along with evidence of endogenous insulin production⁹ which all our patient presented with. MODY is an autosomal dominant condition with over ten different subtypes. According to recent research, MODY has a wide range of clinical manifestations, ranging from asymptomatic hyperglycemia to severe insulin-dependent diabetes. Patients are often non-obese with low C-peptide levels, which indicate B cell malfunction.¹

There are currently no screening tests available for MODY. Given the disease's limited frequency, direct gene sequencing as a screening method is still prohibitively expensive. While high-sensitivity C-reactive

protein has been shown to be a sensitive test for distinguishing MODY from T2DM caused by a mutation in HNF1A, most previously investigated screening biomarkers lacked insufficient sensitivity and specificity

Table 1: Common MODY variants with 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

for diagnosing MODY.⁴

MODY1 does not have glycosuria, whereas MODY3 does. In most cases, hyperinsulinism caused by MODY1 goes away throughout childhood, followed by a steady decline in internal insulin levels and the onset of diabetes in adolescence.¹⁰ MODY2 patients are frequently asymptomatic. The majority are identified via normal prenatal checkups or urine glucose screening tests at schools. MODY2 is seen in 2–6% of pregnant women with gestational diabetes and may be recognized by clinical signs and symptoms as well as fasting glucose levels.¹¹ 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.¹² MODY 4 is a very rare subtype. MODY5 patients develop dyslipidemia, characterized by low high-density lipoprotein levels and increased triglyceride levels. Diabetes normally develops in adolescence or early adulthood and proceeds to an insulin-dependent condition as a result of pancreatic hypoplasia, with hepatic insulin resistance developing at a younger stage of the disease.¹³

Because diabetes is more frequent among males in tropical areas, the increased frequency of MODY among female participants in this sample is intriguing. This might be because young women with MODY type diabetes are identified at a young age as a result of standard blood testing performed during pregnancy.¹⁴

Undiagnosed, chronic hyperglycemia can have potentially catastrophic repercussions if it is not diagnosed and treated early. Early detection in our patient's situation likely rescued her from the need for extensive insulin therapy. Microvascular problems such as retinopathy, nephropathy, and neuropathy are among these effects.¹⁵

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