Case Report

A rare case of maturity onset diabetes of young (MODY)

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Abstract

Maturity Onset Diabetes of Young (MODY) refers to any of the several hereditary forms of Diabetes Mellitus (DM) caused by mutations in an autosomal dominant gene disrupting insulin production or insulin secretion. MODY is often referred to as "Monogenic Diabetes" to distinguish it from the more common types of diabetes mellitus (especially type1 and type 2). MODY 3 caused by hepatocyte nuclear factor1 alpha (HNF 1 alpha) mutation is the most common form of MODY accounting for 52-65% of all MODY cases. We present a challenging case of young adult male with MODY 3 due to HNF 1 alpha mutation who was treated as type 1 diabetic with insulin for 6 years. His A1C remained well controlled but at the expense of frequent hypoglycemic episodes. He finally received an accurate diagnosis of MODY 3 with genetic analysis. Insulin was transitioned to low dose sulfonylurea with a decrease in the frequency of hypoglycemic episodes. Our case highlights the importance of MODY gene analysis for diagnostic confirmation in such rare patients as a right diagnosis has clinical and therapeutic implications.

Key Word: maturity onset diabetes of young.

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CASE PRESENTATION

Patient was a 24 year old non Caucasian American male who was initially diagnosed with Diabetes mellitus in 2012 at the age of 18 on routine physical examination. He did not require any treatment for diabetes for the first 8 months until he was hospitalized for severe sinus infection and noted to have hyperglycemia with blood glucose in 400s. He did not develop DKA or HHS. He reported symptoms of polyuria, polydipsia without weight loss. He was not overweight or obese at the time of diagnosis. He was started on insulin glargine and Lispro and was on a total daily dose of about 20-25 units. He was told by an outside physician that he had type 1 diabetes mellitus. Details of these were unclear to patient. Patient reported strong family history of suspected type 2 diabetes mellitus in his parents, brother and maternal grandparents. All of them were treated with oral hypoglycemic agents. Age at the time of diagnosis of DM in relatives was unknown. At his first clinic visit, diagnosis of type 1 DM was questioned given history of multigenerational diabetes, lack of DKA episode despite not being on insulin for the first 8 months after diagnosis and good glycemic control with A1C ranging from 5.8% to 7.1% with minimal insulin requirements. Phenotypic features of type 2 diabetes were absent. Workup for autoimmune diabetes including glutamic acid decarboxylase 65 antibody (GAD 65) and Islet cell antibody was negative. Fasting C peptide on two occasions was 0.7 ng/ml and 0.6 ng/ml with concomitant blood glucose of 133 mg/dl and 117 mg/dl respectively. Off note, patient was on glargine and Lispro insulin at the time of testing. HDL and fasting triglycerides were normal. He was not hypertensive, overweight or obese. Fasting blood glucose average was around 110 mg/dl. 2

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hour post meal blood glucose rangedbetween 150-200 mg/dl. He reported frequent hypoglycemic episodes especially during the late evening and bedtime. He admitted partial compliance with diet and good compliance with exercise. His weight since 12/2015 was stable and ranged between 135-142 lbs. with BMI of 20-23 kg/m2. His clinical picture raised suspicion for monogenic diabetes. Genetic analysis for MODY was delayed due to insurance issues. He finally had genetic analysis done in 01/2018 which confirmed MODY type 3 as he had hepatocyte nuclear factor 1 alpha (HNF 1 alpha) mutation. Insulin was stopped and patient was transitioned to glipizide 2.5 mg twice daily. He initially tolerated it well but then hadfrequent hypoglycemic episodes which improved with proper timing of Glipizide with meals. Alternatives including meglitinides were discussed as therapeutic options if hypoglycemia persisted with Glipizide. He was educated about the autosomal inheritance pattern of MODY and was encouraged to have other family members checked for monogenic diabetes.

DISCUSSION

The term "MODY" maturity onset diabetes of young was first described in 1964. It is a common form of monogenic diabetes, the other being neonatal diabetes. MODY is autosomal dominant, nonketotic, usually noninsulin dependent diabetes with onset typically before 25 years of age with two to three consecutively affected generations confirming autosomal dominant inheritance pattern. Patients typically lack significant obesity or metabolic features of type 2 DM. Pancreatic autoantibodies are negative. Studies show that less than 50% of individuals with a genetic diagnosis of MODY fit the classic description. Although the exact prevalence of MODY is not known, current estimates suggest that MODY might account for 1% to 5% of all cases of diabetes in the United States. There are eleven different types of MODY caused by changes in eleven different genes. Greater than 99% of MODY with a known genetic etiology results from mutations in Hepatocyte nuclear factor (*HNF)-1 alpha* (MODY 3), Glucokinase (MODY 2) and HNF 4 alpha (MODY 1). MODY 3 accounts for 52-65% of all MODY cases. HNF1-alpha is a nuclear transcription factor (also known as transcription factor 1, TCF1) that is expressed in liver, kidneys and pancreas. A mutation results in abnormal glucose metabolism that leads to decrease in ATP which in turn affects the function of K dependent ATP channel resulting in defect in insulin secretion. Sulfonylureas bypass the defective ATP pathway and augment insulin secretion in patients with MODY 1 and MODY 3, making them excellent therapeutic option in these patients [2]. MODY patients usually require low dose of sulfonylurea (SU) due to increased sensitivity of SU receptor. These patients are at risk of SU induced hypoglycemia. MODY patients with frequent hypoglycemia with low dose of SU can be treated with Meglitinides given their favorable pharmacokinetics.[3] GLP-1 analogue Liraglutide has shown promising results in this subset of MODY patients. However, the loss of insulin secretory capacity is slowly progressive and 30-40% of patients eventually need insulin[4] Except for MODY 2 which is managed with life style changes, all other types of MODY cause complications typical of type 1 or type 2 Diabetes Mellitus, including increased risk of microvascular and macrovascular complications.

CONCLUSION

Our patient was treated as type 1 diabetic for almost 6 years. He had frequent hypoglycemic episodes associated with insulin therapy. His clinical presentation was highly suggestive of MODY. After a genetic analysis confirmed MODY 3 due to HNF 1 alpha mutation, he was successfully transitioned from insulin to low dose sulfonylurea with improvement in hypoglycemic episodes. Because of rarity of this disorder and variable presentation, diagnosis requires a high degree of suspicion and is often delayed or misdiagnosed, resulting in inappropriate treatment and morbidity for the patients especially at high risk of hypoglycemia due to insulin therapy. Goals of management are to maintain a normal blood glucose level and offer genetic counselling and prenatal diagnosis for appropriate patients. Meglitinides and GLP-1 analogues can be considered as therapeutic alternatives in select MODY patients with frequent hypoglycemic episodes with low dose sulfonylureas.

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