CLINICAL VIGNETTE

Early Diagnosis of MODY

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Case Presentation

The patient is a 19-year-old female who presented for Endocrinology consultation for evaluation of newly diagnosed diabetes mellitus with fasting glucose of 134 mg/dL, HbA1c 7.1%, and 3+ glucose on urinalysis. She had presented to her primary care physician for recent onset of light-headedness with presyncopal episodes that lasted for seconds. She also reported increased urinary frequency without dysuria. She denied history of hypoglycemia, diabetic ketoacidosis, or prior hospitalizations for diabetes. Her medical history was otherwise insignificant. She was not on any medications and did not have any known drug allergies. Family history was significant for diabetes in her maternal grandmother and paternal grandfather. Her mother did not have diabetes and father's medical history was unknown due to lack of medical care. Vitals signs were unremarkable with a blood pressure of 96/52 and pulse of 76. She was 5'4" in height, weighed 68 kg with a corresponding BMI of 18.0 kg/m2. Physical examination was unremarkable without any signs of insulin resistance such as acanthosis nigricans.

During the initial consultation, the patient was educated on diabetic disease and diet and was prescribed a glucometer and prandial insulin to use on a sliding scale basis only. Further laboratory evaluations demonstrated a c-peptide of 1.33 ng/mL (0.80 – 3.10) with corresponding glucose of 167 mg/dL (70 – 99). Pancreatic autoantibodies tests were negative for glutamic acid decarboxylase (GAD 65) < 1.0 U/mL (1.0 or less), islet antigen 2 (IA-2) <0.8 U/mL (<0.8), and insulin autoantibody <0.4 U/mL (<0.4).

The patient returned in one week with finger-stick assessments demonstrating fasting blood sugars of 80 to 90s and preprandial blood sugars of 140s. She did not have any blood sugars greater than 160. She was placed on multiple injection daily therapy with a discussion regarding future insulin pump therapy. Genetic testing for maturity-onset diabetes of the young (MODY) was discussed given the atypical presentation of her diabetes and lack of positive antibodies.

The patient returned in one month with excellent glycemic control on 4-6 units of basal insulin and 15:1 carbohydrate to insulin ratio for her meals with fasting blood sugar of 70-120 and preprandial and bedtime blood sugars less than 130 with rare occasions as high as 170. She had no hypoglycemia. She and her family contemplated the recommendation for genetic testing for MODY due to high cost and lack of insurance coverage for genetic testing.

The patient elected to pay for genetic testing, which returned positive for hepatocyte nuclear factor-1 alpha (HNF1A) heterozygous missense mutation consistent with MODY3. Subsequently, the patient's insulin was discontinued, and she was placed on sulfonylurea therapy with oral glimepiride 1 mg daily. She returned for follow up three months later with blood sugars ranging in the 90 to 130s without hypoglycemia.

Discussion

Monogenic diabetes, accounting for approximately 2-6% of all diabetes cases, is caused by single gene mutations.[1,2] At least eleven different genes causing MODY have been identified.[3] MODY is characterized by an autosomal dominant inheritance, early of onset (<25 years of age) and a primary defect in beta-cell function. Mutations in the glucokinase (MODY2) and HNF1A/4A (MODY 3 and 1) genes are the most common causes of MODY.[4] The majority of MODY cases go undiagnosed due to misclassification as type 1 or type 2 diabetes.[5] Misdiagnosis may lead to unnecessary treatment with insulin.

MODY3 is the most common form and the phenotype is characterized by non-ketotic, insulin-sensitive diabetes and insulin secretion defect.[6] These patients have low renal threshold with normal blood glucose levels leading to glycosuria.[7] Due to lean body habitus and somewhat similar presentation at onset this form of MODY is often misdiagnosed as type 1 diabetes.[8,9] Linkage analysis has localized MODY3 mutations to the transcription factor 1 (TCF1) gene encoding HNF1A, localized on chromosome 12.[10] HNF1A is a transcription factor important to pancreatic development and beta cell differentiation and function.[11] The resultant insulin secretory defect is significant enough to cause severe hyperglycemia that leads to microvascular complications.[12] MODY3 may be responsive to oral sulfonylureas as the sulfonylurea receptor is downstream from the beta-cell defect.[13] In fact, HNF1A diabetes has marked sulfonylurea sensitivity even when compared to type 2 diabetes.[13,14] However, this responsiveness depends on the length of disease as the HNF1A mutation causes a progressive defect in beta-cell function with resultant increasing hyperglycemia and treatment requirements.[15]

MODY may be considered in any individual carrying a diagnosis of either type 1 or type 2 diabetes with atypical features for these polygenic disorders. Correctly identifying cases of monogenic diabetes is important as diagnosis can help

predict the clinical course of the patient, explain other associated features and most importantly determine proper clinical treatment and management. Furthermore, proper diagnosis in one individual will have implications for other family members with diabetes and also allow appropriate genetic counseling. Diabetes places an enormous burden on society in terms of economic resources and reduced quality of life.[16] Many diabetics including type 2 diabetic require insulin as part of their medication regime, which has become increasingly expensive.[17] Transfer of insulin therapy to sulfonylureas following identification of patients with MODY3 with genetic testing following an initial misdiagnosis of type 1 diabetes has been shown to be successful in 71% of selected patients up to a median of 39 months without deterioration of glycemic control.[18] However, the cost saving benefit of this transition in therapy must be weighed against the cost of genetic testing. Therefore, genetic testing must be reserved for individuals with suspicious characteristics and presentations for MODY when genetic testing will change clinical management.

Clinical suspicion of monogenic diabetes should first be followed by a limited laboratory evaluation to ensure appropriate genetic testing in selected patients.[4] A diagnosis of type 1 diabetes may be considered incorrect in individuals with history of diabetes diagnosed before the age of 6 months,[19] family history of diabetes with an affected parent,[20] evidence of endogenous insulin production outside the honeymoon phase (after 3 years of diabetes) and/or absent pancreatic islet autoantibodies.[21,22] Endogenous insulin production is generally considered with a presence of a detectable c-peptide (> 0.6 ng/mL) when glucose is > 144 mg/dL. Pancreatic autoantibodies include GAD 65, IA-2 and islet cell antibodies. Insulin antibodies may also be assessed in insulin naïve patients. Positive antibodies nearly always indicate type 1 diabetes. However, negative antibodies do not exclude a diagnosis of type 1 diabetes as antibodies may wane with duration of disease. Furthermore, up to an additional 4% of type 1 diabetes may have no detectable autoantibodies time of diagnosis.[21] Suspicion for MODY in a patient with a diagnosis of type 2 diabetes may be considered when patients do not match the typical phenotype characterized by type 2 diabetes. These individuals will less often have marked obesity and/or have family members with diabetes who are normal weight, will not have signs of insulin resistance on examination such as acanthosis nigricans, and may come from ethnic backgrounds that have a low prevalence of type 2 diabetes.[23] Furthermore, laboratory evaluation will be negative for insulin resistance with fasting c-peptide levels within the normal range.[24] The best practice guidelines produced in 2008 helped define clinical criteria for testing babies, children and adults for GCK, HNF1A, and HNF4A mutations including both diagnostic and predictive genetic tests.[25]

The above case is an excellent example of high clinical suspicion leading to an early diagnosis of a rare form of an otherwise common diagnosis. The patient's presentation of diabetes was neither typical for type 1 nor 2 diabetes leading to further evaluation. Proper laboratory evaluation prior to genetic testing increased the pretest probability of this expensive testing. Most importantly, in this patient's case, an identifiable genetic cause of her disease altered her disease treatment and potentially saved thousands of dollars in the cost of therapy over the course of her lifetime.

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