Case Report

MODY3 AND PANCREATIC TRANSPLANT: MAKING A CASE FOR UNIVERSAL MODY SCREENING BEFORE TRANSPLANT

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ABSTRACT

Objective: Maturity onset diabetes of the young (MODY) comprise a group of autosomal dominant forms of diabetes and account for approximately 1 to 2% of diabetes. Of these, MODY3 is the most common form, and patients are often misdiagnosed as having type 1 diabetes mellitus (T1D). Moreover, many of these patients develop end-stage renal disease. Because of this, there is frequent clinical discussion as to whether simultaneous pancreas and kidney transplantation is warranted. Although MODY3 can often be treated with sulfonylureas, many of these patients have never received this class of drugs. This raises an important clinical question: should sulfonylurea-naïve MODY3 patients undergo pancreas transplants?

Methods: We present the case of a 31-year-old female with a history of T1D and end-stage renal disease.

Results: After receiving a living-donor kidney transplant, the patient's C-peptide level was detectable during evaluation for a pancreas transplant. Genetic testing was performed due to an extensive family history of T1D. She was positive for a mutation in the hepatocyte nuclear factor-1α (*HNF1A*) gene (R272H), which was consistent with MODY3. Initiation of sulfonylurea treatment allowed her to transition off insulin and be managed with only a sulfonylurea. Thanks to her diagnosis, 2 family members were subsequently diagnosed with MODY3 and transitioned off insulin.

Conclusions: This clinical scenario prompted us to suggest that sulfonylurea-naïve MODY3 patients should be treated with sulfonylureas prior to consideration for a pancreas transplant. Moreover, it may also be warranted to screen for MODY in patients with presumed T1D who are being considered for pancreas transplant. **(AACE Clinical Case Rep. 2015;1:e123-e126)**

Abbreviations:
HNF1A = hepatocyte nuclear factor-1α; **MODY** = maturity onset diabetes of the young; **T1D** = type 1 diabetes mellitus

INTRODUCTION

Maturity onset diabetes of the young (MODY) are a group of autosomal dominant forms of diabetes caused by single gene mutations and account for 1 to 2% of diabetes (1). MODY is characterized by young age at disease onset and an absence of islet antibodies (2). Several forms of MODY have been characterized, with MODY3 being the most common in adults (3,4). MODY3 is caused by mutations in the gene encoding for hepatocyte nuclear factor-1α (*HNF1A*) (5). Metabolic abnormalities in MODY3 include elevated glucose and low circulating insulin levels (6). Carriers of *HNF1A* mutations have glycosuria and β-cell dysfunction prior to the development of diabetes (7). Additionally, MODY3 patients have complications from chronic hyperglycemia at similar rates to those seen in type 2 diabetes (8,9). Interestingly, some individuals with *HNF1A* mutations have developmental malformations of

Submitted for publication July 12, 2014
Accepted for publication September 22, 2014
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DOI: 10.4158/EP14336.CR

the kidney (10,11). Finally, of pertinence to this report, these individuals are often misdiagnosed with type 1 diabetes (T1D); however, after proper identification, they can frequently be transitioned to sulfonylureas alone (12,13).

Simultaneous pancreas and kidney transplant has shown to be effective in a small number of patients with MODY3 and end-stage renal disease (14,15). It is unclear if treatment with sulfonylureas is warranted in newly diagnosed MODY3 patients who have already received a kidney transplant. In this report, we present a patient who presented to the Endocrinology clinic at Northwestern University after a kidney transplant due to the unexpected finding of elevated C-peptide levels. While her initial diagnosis was T1D, we subsequently diagnosed her with MODY3 based on the results of genetic studies. Although she was being considered for a pancreatic transplant, we started sulfonylurea therapy and were able to transition her off insulin completely. With her new diagnosis, we tested and subsequently diagnosed her brother and mother with MODY3, and they were also transitioned off insulin.

CASE REPORT

The patient was a 31-year-old Caucasian female who had been diagnosed with T1D at the age of 5 and treated with insulin thereafter. Her T1D was complicated by retinopathy and nephropathy, and she developed end-stage renal disease in her 20s. She did not report any hypoglycemic unawareness. She was initially recommended for a simultaneous pancreas and kidney transplant at age 29. During the evaluation, her C-peptide level was found to be 7.32 ng/mL (normal range, 0.8-3.9). In the meantime, she received a living-donor kidney transplant from her paternal aunt. Her repeat C-peptide level after kidney transplantation was 4.21 ng/mL. Due to the detectable C-peptide level, she was referred to the Endocrinology clinic at Northwestern University for consultation prior to undergoing a pancreas transplant.

On interview, her family history was significant for T1D in her brother and mother, as well as multiple members on the maternal side of her family (Fig. 1). Other significant medical history included hypertension. At the time of her visit, her body mass index was 26 kg/m^2, glycated hemoglobin A1c was 8.4%, and total daily insulin dose was ~15 units. Because it was unclear how she was diagnosed with T1D 25 years earlier, islet cell, glutamic acid decarboxylase, and insulin autoantibodies were measured in our clinic and were all negative. The combination of history and clinical factors (e.g., family history, autosomal dominant inheritance, detectable C-peptide, and negative antibodies) led us to initiate genetic testing for MODY. Testing was positive for a mutation in *HNF1A* (801 G>A, Arg272His) (Athena Diagnostics, Worchester, MA), consistent with MODY3 (16). Her insulin treatment was halted, and she was transitioned to glyburide with good control of her diabetes as determined by fingerstick glucose levels.

With the genetic diagnosis of *HNF1A*-associated diabetes, we also confirmed the same mutation in her brother. At the time of patient's new diagnosis, her brother was 25 years old. He had been diagnosed with T1D at age 11, and his clinical course was complicated by retinopathy, neuropathy, and gastroparesis. He reported taking large doses of insulin (~60-70 U daily) with poor control. After his sister's diagnosis of MODY3, he underwent genetic testing and was found to have same *HNF1A* R272H mutation

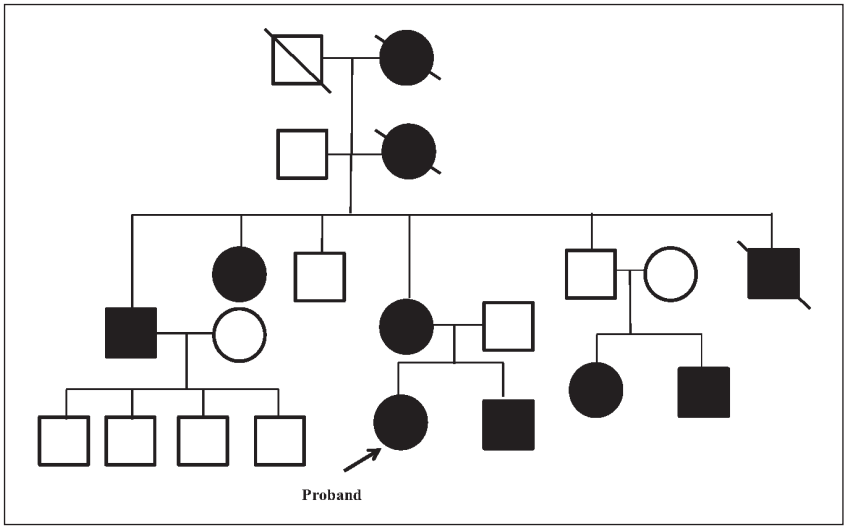

Fig. 1. Patient's pedigree. The diagram shows the proband (*closed circle with arrow*), female family members with diabetes (*closed circles*), female family members without diabetes (*open circles*), male family members with diabetes (*closed squares*), and male family members without diabetes (*open squares*). Circles or squares with a line indicate deceased family members.

as his sister. He was started on glyburide and immediately reported better control of his glucose levels and was transitioned off insulin as the glyburide dose was increased.

At the time of patient's diagnosis, her mother was 55 years old. She had been diagnosed with T1D at age 7. She was initially treated with oral medications and transitioned to insulin at age 10. It is unclear how she was diagnosed with T1D, which was well controlled with a glycated hemoglobin A1c of ~7.0% on a total daily insulin dose of ~25 U, and her only complication was neuropathy. Her family history was significant for diabetes in 3 of her 5 siblings (Fig. 1). Because of the MODY diagnoses in both her children, she was also started on glyburide.

DISCUSSION

We present a patient who was diagnosed with MODY3/*HNF1A* diabetes after renal transplant. While no specific genotype-phenotype correlations have been described in MODY3/*HNF1A* with regard to who can be transitioned off insulin, it is interesting to note that our proband and her family members have been very responsive to sulfonylurea treatment. Our patient's course suggests that sulfonylurea-naïve patients with MODY3 under consideration for simultaneous pancreas and kidney transplantation may benefit from a trial of sulfonylurea treatment, even after kidney transplant. Even though we do not yet know the long-term outcome of renal transplant alone and sulfonylurea treatment in our patient, patients with MODY3 can remain responsive to sulfonylureas for many years (12,13). However, many patients have to restart insulin, and this may be especially true if they were treated with insulin for a long period prior to the diagnosis of MODY3 (17). In the case of *HNF1A* R272H mutations, the onset of diabetes seems to be particularly early for MODY and would otherwise be considered as antibody-negative type 1 (type 1b following Eisenbarth classification) (1). This certainly argues for autoantibody testing in early onset diabetes. Moreover, because patients with MODY are often diagnosed well after the first presentation of diabetes, clinical guidelines will be useful for when and how to transition the subjects to oral medications under different situations. For instance, if a patient with MODY can be transitioned to oral medication and avoid an additional organ transplant, it seems reasonable that oral medications should be favored over an additional transplant.

This patient's clinical scenario also raises the question if patients listed for simultaneous pancreas and kidney or pancreas after kidney transplant should be screened for MODY. At this point, we would recommend that patients being considered for simultaneous pancreas and kidney transplant or pancreas after kidney transplant should be screened for MODY, at least through initial assessment of C-peptide, anti-islet antibodies, and family history. If any evidence of familial inheritance exists, genetic assessment should be performed. Supporting this position, in a single center in France, 50 out of 150 patients were suspected to have a type of MODY by history alone (14). Of the 50 screened, 12 patients were found to have known mutations in the MODY3 or MODY5 genes. As an additional point of interest, patients with MODY5 have renal malformations that may lead to early onset renal failure; thus, these individual may have increased need for pancreas and renal transplantation.

CONCLUSION

Overall, our patient's case illustrates the point that reassessment of the etiology of diabetes is important throughout the clinical course, especially when a major surgery such as pancreatic transplant is being considered. If their family history is equivocal, reassessment of the etiology of diabetes, especially for a monogenic form of the disease, may be warranted in patients with previously diagnosed T1D with detectable C-peptide levels and negative autoantibody status. However, C-peptide levels may be elevated in end-stage renal disease (18), so attention to the variable of kidney function is needed when interpreting C-peptide levels.

It is possible that among the 27,156 pancreas transplantations performed in the United States (19) and the 1 to 2% of patients with MODY, there may be a significant number of patients with undiagnosed MODY who may benefit from sulfonylurea treatment. Such benefits could include improved control of diabetes, decreased complications, and avoidance of additional surgical risk.

DISCLOSURE

The University of Chicago receives royalties from Athena Diagnostics for genetic testing for mutations in *GCK*, *HNF1A*, *HNF4A*, and *HNF1B*. Dr. Priyathama Vellanki is supported in part by NIH T32 DK007169. Dr. Brian T. Layden. is supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Career Development Grant#1IK2BX001587-01. Dr. Louis H. Philipson is partially supported by P30 DK20595 and the American Diabetes Association grant 1-11-CT-41.

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