

HNF1 β Diabetes or Maturity-Onset Diabetes of the Young Type 5 With Rare HNF1 β Mutation: A Case Report

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Case Presentation

A 7-year-old girl presented to the endocrinology office for a second opinion regarding her recent diabetes diagnosis. Four months before arriving in our office, she had been to an urgent care facility for nausea and vomiting with much of her family, who had been experiencing the same symptoms, presumed to be viral gastroenteritis. Testing revealed that the patient had ketones and glucose in her urine, and her blood glucose was 240 mg/dL (13.32 mmol/L).

The patient's family followed up with her pediatrician and were referred to a pediatric endocrinology clinic, where she was given a 2-hour 75-g oral glucose tolerance test, causing her blood glucose to rise to >200 mg/dL (>11 mmol/L). According to her mother, the pediatric facility tested for type 1 diabetes antibodies, which were negative. The patient's blood glucose readings were high after eating and came back down without treatment, so the pediatric endocrinologist ordered testing for maturity-onset diabetes of the young (MODY). The mother reported that the sample was insufficient to complete the MODY test. Because of the way her blood glucose levels reacted to meals and the MODY suspicion, the family was advised to control the patient's diabetes with her diet, so her mother had been restricting her carbohydrate intake to <65 g per meal and monitoring her blood glucose. Her mother was uncomfortable with

this plan and felt like no one was listening to them.

The patient's mother reported a family history of type 2 diabetes in the patient's maternal grandmother. The patient denied any change in her weight in the last year. On physical examination, her weight was 24.4 kg, her height was 1.4 m, and her BMI was 12.4 kg/m², which was in the 1st percentile (healthy weight is 5th to 85th percentile). Her A1C was 5.2%.

Initially, the patient was thought to have type 1 diabetes type b (i.e., negative for insulin autoantibodies and with low C-peptide), with gradual onset based on the history provided. Laboratory tests including C-peptide and insulin antibodies were ordered to help confirm her diagnosis. She was prescribed insulin aspart with meals, with an insulin-to-carbohydrate ratio of 1 unit of insulin for every 50 g of carbohydrates. She was also instructed to correct for high blood glucose with 0.5 units of insulin per 50 mg/dL (2.8 mmol/L) above 150 mg/dL (8.3 mmol/L).

She followed up in 1 month. Her meter download showed only two blood glucose readings >80 mg/dL (>4.4 mmol/L), and her mother was no longer restricting her carbohydrate intake. At her next follow-up 3 months later, she was seen by a different provider in the practice who still had concerns about type 1 diabetes versus MODY; the provider expressed concern regarding her risk of diabetic ketoacidosis (DKA) and started insulin glargine 1 unit daily. MODY

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testing was prescribed at this visit, but not performed.

When she followed up again, she saw another provider, the third one in the same practice, who reviewed everything and felt that she was in the honeymoon phase of her type 1 diabetes and continued insulin glargine 1 unit daily, as well as the 0.5 units of insulin aspart per 50 g of carbohydrate plus a correction dose of 0.5 units per 50 mg/dL (2.8 mmol/L) over 150 mg/dL (8.3 mmol/L). She remained on this regimen for a few months and stopped the insulin glargine on her own because her mother felt the insulin aspart was helping her more.

Two years after diagnosis, her insulin requirements had not increased, she continued to have postprandial hyperglycemia, and she did not develop DKA. At this time, insulin autoantibody tests were ordered again. Again, MODY testing was ordered but not performed by the patient.

Another year passed, and the patient started to have hypoglycemia, so she was placed on a continuous glucose monitoring (CGM) system. Five months after starting CGM, the family requested that MODY testing be ordered again, and this time, the test was performed. The laboratory evaluations showed a C-peptide level of 6.8 ng/mL, and repeat testing for the GAD65 and insulin antibodies was negative. MODY had been suspected early on, and since the patient continued to require low amounts of insulin and antibodies for autoimmune diabetes were negative, MODY was still in the differential. A MODY panel had been ordered three times, but 4 years had passed by the time it was completed. A MODY panel using Ambry Genetics Next-Generation (Ambry Genetics, Aliso Viejo, Calif.) sequencing (sensitivity 99%) was performed. It tested for MODY type 1–5, specifically looking for known variants of the genes glucokinase (GCK), hepatocyte nuclear factor-1-alpha (HNF1 α), hepatocyte nuclear factor-4-alpha (HNF4 α), hepatocyte

nuclear factor-1-beta (HNF1 β), and insulin promoter factor-1 (PDX1). The patient's results revealed a mutation of the HNF1 β gene, which correlates with a diagnosis of HNF1 β diabetes or MODY5. This patient had a p.T376I variant located in coding exon 5 of the HNF1 β gene. The patient's MODY panel was negative for known genetic mutations associated with GCK, HNF1A, HNF4A, and PDX-1.

Due to the close association of MODY5 with renal anomalies, the diabetologist collected more history. The patient's mother reported that, as a baby, the patient had a kidney issue that resolved; she could not recall what it was. After the results of the genetic testing, the patient had a renal ultrasound, which showed kidney asymmetry, but this asymmetry was within normal limits. Menarche occurred for this patient around the age of 11 years. Family history revealed that the patient's father has kidney issues and hyperglycemia, and her paternal grandfather was currently on dialysis and denied his diabetes diagnosis.

This patient, now 13 years old, continues to maintain well-controlled blood glucose levels. Her most recent A1C was 5.5%. She uses a CGM system and continues to use insulin aspart before meals. The patient and her mother have become well-educated on diabetes management, and the patient feels special to have such a unique form of diabetes.

Questions

1. When should MODY be suspected?
2. What additional manifestations can be found in patients with HNF1 β diabetes?
3. How should HNF1 β diabetes be managed?
4. What are the implications of the p.T376I variant in HNF1 β diabetes?

Commentary

MODY is a type of diabetes characterized by early onset before the age

of 25 years in nonobese individuals with an absence of pancreatic β -cell antibodies (1). There are currently 13 genes associated with this disorder and 13 types of MODY for each of these genes (2). Inheritance is autosomal dominant with 85–95% penetrance, and patients are usually heterozygous for these mutations (1,3).

Our patient had a mutation in the HNF1 β gene on chromosome 17q12, which caused her to develop HNF1 β diabetes, formerly known as MODY5 (4). It has also been reported that there are de novo mutations, with one study citing that 26 out of 201 adults with HNF1 β did not inherit the gene mutation (5). Since most cases of MODY are autosomal dominant with respect to inheritance, we suspected that our patient's mother or father might have the same mutation. When asked about symptoms of hyperglycemia, the patient's mother stated that the patient's father had experienced high blood glucose in a pattern similar to our patient, but he declined to seek medical treatment. The patient's paternal grandfather also has diabetes and is on dialysis.

The HNF1 β gene is expressed in the liver, kidney, intestine, stomach, lung, ovary, and pancreatic islet cells (6). Mutations in this gene can result in pancreatic atrophy leading to insufficient insulin production and a diagnosis of HNF1 β diabetes or MODY5, but because the HNF1 β gene is expressed outside of the pancreas as well, other manifestations can arise (7,8). Renal anomalies such as renal dysplasia, renal cysts, glomerulocystic disease, and renal insufficiency have been well documented in HNF1 β diabetes (7,8). We plan to monitor our patient with annual kidney function testing to watch for these possible manifestations.

Other abnormalities that have been seen with HNF1 β gene mutations include hypomagnesemia, elevated serum aminotransferases, and genital abnormalities (7,8). Documented associated genital

abnormalities consist of Mullerian or Wolffian duct malformations such as bicornate uterus, atresia of the vas deferens, or epididymal cysts (8). In our case, the patient has had normal menstrual cycles thus far, but if she were to have problems with infertility in the future, then further work-up should be done to look for genital abnormalities.

Management of HNF1 β diabetes can include oral hypoglycemic agents or insulin therapy, depending on how much islet cell function a patient retains (3). A retrospective chart review reported that only 10 of the 201 adults reviewed had been tried on a secretagogue, and of those 10, only 3 had success with its use for their diabetes treatment (5). It is possible that our patient's condition could be managed with oral hypoglycemic agents instead of short-acting insulin. This possibility was proposed to the patient, but she preferred to continue short-acting insulin therapy.

The significance of the p.T376I variant is not well known. According to the patient's results report from Ambry Genetics, the mutation is located on coding exon 5 of the HNF1 β gene and results from a cytosine to thymine substitution at nucleotide position 1127. The threonine at codon 376 is replaced by isoleucine, an amino acid with similar properties.

Literature searches using multiple search engines revealed only one other case of this variant in the presence of

another mutation. In a cohort of 54 Polish MODY patients, one patient was heterozygous for this HNF1 β , p.T376I variant as well as an alteration in her HNF4 α gene, which is associated with HNF4 α diabetes or MODY1. Her mother, who also had diabetes, was also heterozygous for both alterations, whereas her brother and sister, both with diabetes, were heterozygous for only the HNF4 α alteration (9). No case of a patient with only the p.T376I mutation of HNF1 β has been found.

Clinical Pearls

- MODY forms of diabetes should be considered in young patients with signs and symptoms of diabetes, low insulin requirements, and negative diabetes antibodies.
- HNF1 β diabetes should be contemplated in patients with renal or genital abnormalities presenting with symptoms of hyperglycemia, polyuria, or polydipsia.
- More research needs to be done to understand the implications of the p.T376I variant in HNF1 β diabetes.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

AL.H. performed a literature review and wrote the manuscript. A.M.H. saw the case, contributed to the manuscript, and reviewed/edited the manuscript. A.M.H. is the guarantor of this work and, as such,

ensures the veracity of case study and the details of the presented case.

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