

HNF1B-MODY Masquerading as Type 1 Diabetes: A Pitfall in the Etiological Diagnosis of Diabetes

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Abstract

Hepatocyte nuclear factor-1B (HNF1B) maturity-onset diabetes of the young (MODY), also referred to as “renal cysts and diabetes syndrome” or MODY-5, is a rare form of monogenic diabetes that is caused by a deletion or a point mutation in the HNF1B gene, a developmental gene that plays a key role in regulating urogenital and pancreatic development. HNF1B-MODY has been characterized by its association with renal, hepatic and other extrapancreatic features.

We present the case of a 39-year-old female patient who was first diagnosed with type 1 diabetes, but then, owing to the absence of anti-islet autoantibodies and to the disease’s progression, was labeled later on as having atypical type 2 diabetes. She was finally recognized as having HNF1B-MODY, a diagnosis that had been suggested by the lack of metabolic syndrome and by the presence of unexplained chronically disturbed liver function tests and hypomagnesemia. There was a 10-year delay between the onset of diabetes and the molecular diagnosis. An atypical form of diabetes, especially in patients with multisystem involvement, should raise suspicion for an alternative etiology. A timely diagnosis of HNF1B-MODY is of utmost importance since it can greatly impact diabetes management and disease progression as well as family history.

Key Words: HNF1B, HNF1B-MODY, MODY-5, monogenic diabetes, type 1 diabetes, diabetes classification

Precision medicine, defined as providing the right therapy for the right patient at the right time, has gained much attention in the past 10 years, particularly in the field of diabetes. Classifying diabetes is the first step of this process, one that is not always straightforward. Indeed, there is a considerable overlap in the phenotypes of patients with type 1 diabetes (T1D), type 2 diabetes (T2D), and monogenic diabetes. As a consequence, monogenic diabetes is misdiagnosed in about 80% of cases [1]. Current guidelines recommend considering the diagnosis of monogenic diabetes in children and young adults who lack the typical features of T1D and T2D. In other words, monogenic diabetes should be considered in patients with negative diabetes-associated autoantibodies (which are not routinely searched for despite being listed in the recommendations) [2], preserved beta cell function more than 3 to 5 years after diabetes diagnosis, and lack of obesity/metabolic syndrome, especially when a strong family history is present [3]. Moreover, the differential diagnosis of hepatocyte nuclear factor-1B (HNF1B) maturity-onset diabetes of the young (MODY) or mitochondrial diabetes should be raised whenever the diabetes is associated with multiorgan involvement.

Case Report

A 39-year-old Moroccan female patient presented to the emergency department in March 2007 with polyuria, polydipsia, and an 8-kg weight loss within a few weeks prior to her presentation [usual weight: 54 kg, body mass index (BMI)

24 kg/m²]. Blood glucose was 340 mg/dL (18.6 mmol/L), and hemoglobin A1c (HbA1c) was 12.4% (112 mmol/mol). She was not ketotic. Although an aunt had T2D, neither of her parents nor her 3 siblings had been previously diagnosed with diabetes.

Her past medical history included gastric ulcer disease and 4 miscarriages. She had 1 daughter who was born prematurely with a birth weight of 1.9 kg and who was being treated for vesicoureteral reflux.

On admission, biological testing revealed a thyroid-stimulating hormone of 0.01 (lab reference range: 0.3–4 mU/L), deranged liver function tests (LFTs) with aspartate aminotransferase 114 [3× the upper limit of normal (ULN)], alanine aminotransferase 117 (3× ULN), gamma-glutamyl transferase 445 (13× ULN), and alkaline phosphatase 420 (3.5× ULN).

Hyperthyroidism workup revealed elevated free triiodothyronine and free thyroxine levels (8.8 pg/mL and 33 pg/mL, respectively) and strongly positive thyrotropin receptor autoantibodies and antithyroid peroxidase antibodies, with a heterogeneous hypervascular parenchyma on thyroid ultrasound in favor of Graves’ disease. She was thus started on 60 mg of carbimazole per day and 20 mg of propranolol 3× day.

As part of the workup of deranged LFTs, an abdominal ultrasound was performed and was unremarkable. Viral and autoimmune hepatitis, Wilson’s disease, hemochromatosis, and coeliac disease were all ruled out. Liver elastography showed a score of A0F0. The biochemical liver abnormalities

were attributed to either hyperthyroidism or to a seronegative autoimmune hepatitis.

The patient was considered as having T1D, taking into account her age at the time of diagnosis, her normal BMI, the signs of catabolism, and the presence of an autoimmune thyroid disease, and was started on basal bolus insulin therapy. There were no microvascular complications of diabetes at that time.

In the following months, she gained her weight back, and HbA1c decreased to 5.7% (65 mmol/mol) with many hypoglycemic episodes. These episodes occurred once daily, were mainly of grade 2 as per the Ademolous classification [4], and were attributed to the honeymoon phase, which led to the decrease of the insulin doses to half. Antigliutamate decarboxylase and anti-islet antigen 2 antibodies came back negative.

In November 2008, 18 months after starting treatment, the diagnosis of T1D was in doubt in view of the tight glycemic control under very low insulin doses (0.15 U/kg/day). Antigliutamate decarboxylase D, anti-islet antigen 2, and anti-Zinc transporter 8 autoantibodies were negative once again, and human leukocyte antigen (HLA) typing revealed the presence of the protective HLA DRB1*15-DQB1*0602 haplotype. Therefore, she was considered to have T2D, albeit of atypical presentation, since she lacked several features of the metabolic syndrome: high-density lipoprotein-cholesterol was 0.72 g/L (1.86 mmol/L); triglycerides, 0.56 g/L (0.63 mmol/L); and BMI, 24 kg/m². She was weaned off insulin and started on a sulfonylurea, with hyperglycemia occurring predominantly in the postprandial state. Thyroid hormones levels were normal, thyrotropin receptor antibodies were negative, and carbimazole was stopped.

Thereafter, the patient's diabetes remained well controlled, with HbA1c between 6.7% and 7.9% (50-63 mmol/mol) on glimepiride 1 to 3 mg/day, with frequent hypoglycemia (5/week, mainly of grade 2, with 1 episode of grade 3). Although thyroid hormones remained within the normal range, the cholestatic and hepatocellular patterns worsened, ruling out hyperthyroidism as the cause of the disturbed LFTs. The workup of autoimmune hepatitis and coeliac disease was once again negative in 2016. Biliary magnetic resonance imaging showed an unremarkable liver and biliary tree and a 4-mm hemorrhagic cyst at the upper pole of the left kidney. The patient underwent a liver biopsy, which was normal, ruling out fatty liver. She was started empirically on ursodeoxycholic acid.

In February 2017, 10 years after her diabetes diagnosis, insulin glargine was resumed because of an acute worsening of glycemic control with HbA1c reaching 12.4% (112 mmol/mol), due in part to many dietary errors. HbA1c decreased to 7.7% (61 mmol/mol) 6 months later.

Taking into account the patient's atypical presentation and disease progression, the etiology of diabetes was questioned again: in view of the unexplained chronically disturbed liver function tests and of a newly found hypomagnesemia (0.62 mmol/L), the hypothesis of an HNF1B-MODY diagnosis was raised, despite having normal renal morphology and function. The diagnosis was confirmed a few months later by genetic testing, showing a complete heterozygous deletion of the HNF1B gene.

In May 2020, diabetes was once again poorly controlled, HbA1c was 9.2% (77 mmol/mol) on glargine 14 units and glimepiride 4 mg, due to many dietary errors secondary to personal stress.

Renal assessment revealed a serum creatinine of 54 μ mol/L, microalbuminuria in the physiological range, and normal renal morphology on ultrasound.

A test meal revealed significant residual insulin secretion, 13 years after the diagnosis of diabetes, with C peptide levels of 0.181 nmol/L and 0.654 nmol/L, fasting and at 2 hours, respectively (lab reference range in the fasting state: 0.27-1.27 nmol/L).

Normal fecal chymotrypsin and elastase levels ruled out pancreatic insufficiency, and pancreatic magnetic resonance imaging was unremarkable. Pelvic ultrasonography was normal. Liver function tests showed persistent cholestasis and cytolysis (gamma-glutamyl transferase, 8 \times ULN; alkaline phosphatase, 2 \times ULN; alkaline phosphatase, 2 \times ULN; alanine aminotransferase, 2.5 \times ULN).

The patient was started on liraglutide at the weight of 52 kg, in combination with repaglinide (4-1-2 mg). One month later, HbA1c had decreased to 6.7% (81 mmol/mol) at the expense of recurrent hypoglycemia, prompting a decrease of the repaglinide dosage to half. In December 2020, HbA1c was 6.6% (49 mmol/mol) on liraglutide 1.2 mg and repaglinide (1-0-1 mg), and body weight was 45 kg (Table 1).

Discussion

Hepatocyte nuclear factor-1B (*HNF1B*) is a developmental gene located on chromosome 17q12 that plays an important role in regulating urogenital and pancreatic development. *HNF1B* may undergo deletion or point mutations, leading to dominantly inherited diseases with diverse phenotypes ranging from MODY to renal, pancreatic, hepatic, genito-urinary, and even neurologic manifestations [5, 6].

An Atypical Form of Diabetes

Our patient was eventually found to have a complete heterozygous deletion of the *HNF1B* gene, confirming the diagnosis of HNF1B-MODY. There was a significant delay in the diagnosis because her initial clinical presentation was highly suggestive of T1D: she was young and lean, lacked a significant family history of diabetes mellitus, and was diagnosed with an autoimmune thyroid disease. The absence of islet autoantibodies was a rather unexpected finding. However, 2% to 4% of T1D are antibody-negative at the time of diagnosis [7], a finding that has been attributed to an immune response to yet undiscovered islet antigens or to the lack of a humoral response in some patients [8]. HLA typing was decisive in this setting since the presence of the protective HLA DQB1*0602 allele ultimately ruled out the diagnosis of autoimmune T1D [9]. Thereafter, the patient was considered to have an atypical form of T2D, given that she had no features of the metabolic syndrome, and was successfully started on low doses of sulfonylurea. Hence, distinguishing between monogenic and T1D or T2D can be particularly challenging, and many MODY patients end up misdiagnosed as having T1D or T2D [7]. What also did not make the diagnosis of MODY straightforward in our patient was the absence of a dominantly inherited transmission of diabetes. HNF1B-MODY may escape from such a mode of inheritance since molecular defects of *HNF1B* occur de novo in 50% of cases. Thus, the lack of a medical history in ascendants should not deter from considering HNF1B-MODY [5, 6] in patients with atypical forms of diabetes.

Table 1. Diabetes treatment and laboratory trends from 2007 to 2020

	HbA1c, %	Weight, kg	Treatment of diabetes	LFTs (UI/L)	TFTs and Ab
March 2007	12.4	46	None	ASAT:114 ALAT: 117 GGT: 445 ALP: 420	TSH: 0.01 mU/L FT4: 33 pg/mL FT3: 8.8 pg/mL TRAb: 4.3 UI/L Anti-TPO: 2365 U/mL
November 2008	6.2	54	Glargine 5 units Novorapid 1-2-2 units	ASAT:26 ALAT:38 GGT:127 ALP:139	TSH: 1.4 mU/L TRAb < 1 U/mL
June 2012	7.3	51	Glimepiride 1 mg	ASAT: 38 ALAT:37 GGT:174 ALP: 191	TSH: 3.16mU/L
July 2014	7.1	52	Glimepiride 1 mg	ASAT: 54 ALAT: 55 GGT: 215	TSH: 3 mU/L TRAb: 1.446 UI/L
February 2017	12.4	54	Glimepiride 1 mg		TSH: 1.1 mU/L Anti-TPO > 600 U/mL
July 2017	7.7	54	Glimepiride 3 mg Glargine 12 units	ASAT: 44 ALAT: 44 GGT: 283 ALP: 362	
May 2020	9.2	52	Glimepiride 4 mg Glargine 14 units	ASAT: 90 ALAT: 88 GGT: 297 ALP: 278	TSH: 1.6 mU/L Anti-TPO: >600 U/mL TRAb: negative
December 2020	6.6	45	Repaglinide 1-0-1 mg Liraglutide 1.2 mg/day	ASAT: 37 ALAT: 38 GGT: 250 ALP: 242	TSH: 4.070 mU/L

Normal reference ranges: TSH, 0.3-4 mU/L; FT4, 9.8-19 pg/mL; FT3, 2.3-4.2 pg/mL; TRAb, 0-1 UI/L; anti-TPO, 0-65 U/mL; ASAT, <35 UI/L; ALAT, <40 UI/L; GGT, <35 UI/L; ALP, <120 UI/L; HbA1c, <6.5%.

Abbreviations: Ab, antibodies; ALAT, alanine aminotransferase; ALP, alkaline phosphatase; anti-TPO, anti-thyroid peroxidase antibodies; ASAT, aspartate aminotransferase; FT3, free triiodothyronine; FT4, free thyroxine; GGT, gamma-glutamyl transferase; HbA1c, hemoglobin A1c; LFTs, liver function tests; TFTs, thyroid function tests; TRAb, thyrotropin receptor antibodies; TSH, thyroid-stimulating hormone.

The diabetes presentation of our patient was concordant with what has been depicted in a large series of patients with *HNF1B* mutations/deletions [6]. Indeed, *HNF1B*-MODY occurs after the age of 25 in nearly 60% of cases, in lean patients in 80% of cases, and with symptoms of insulin deficiency at diagnosis in half the cases, leading to insulin as the initial treatment, all of which applied to our patient. Compared to patients with an *HNF1B* mutation, those with an *HNF1B* deletion have a clinical presentation that resembles more T1D, which applied to our patient as well. The blood glucose profiles in *HNF1B*-MODY have not been fully described, in contrast to glucokinase-MODY and *HNF1A*/*HNF4A*-MODY, in which hyperglycemia has been shown to occur in the fasting and postprandial states, respectively [10]. In our patient, hyperglycemia was predominant after meals, a finding consistent with the primary defect in insulin secretion in *HNF1B*-MODY.

It is also worth mentioning that our patient's diabetes was well controlled with a sulfonylurea/glinide over the course of several years, similarly to what has been previously described in *HNF1B*-MODY patients. This is consistent with the residual insulin secretion demonstrated during the test meal. In the present case, because of the patient's compulsive eating behavior, liraglutide was eventually used as an add-on therapy, leading to excellent metabolic control. The efficiency of

glucagon-like peptide 1 receptor agonists has been reported in some patients with *HNF1A*-MODY and *HNF4A*-MODY but has yet to be described in *HNF1B*-MODY patients [11].

The prognosis of *HNF1B*-MODY observed after 12 years of diabetes is quite similar to that of *HNF1A*-MODY and T1D with regards to the prevalence of retinopathy (27%), neuropathy (40%), and macrovascular complications (10%) [6, 12]. On the other hand, renal impairment is much more prevalent in *HNF1B*-MODY patients, with 21% suffering from end-stage renal disease and 44% from stages 3 and 4 chronic kidney disease [5], due to the major role played by *HNF1B* in renal development. It is also worth noting that our patient remained free of complications 13 years after diabetes onset.

An Unusual Presentation of the *HNF1B* Syndrome

HNF1B-MODY, sometimes referred to as “renal cysts and diabetes syndrome” is characterized by the presence of multiple kidney cysts, with only a minority of patients having few or no cysts at all [5, 6]. Functional renal features are frequently encountered in the form of chronic/end-stage kidney disease not imputable to diabetes (44% of cases), hypomagnesemia (75% of cases), hypokalemia, or hyperuricemia. What was striking in our case was the lack of morphological kidney abnormality, which could have hinted at the diagnosis. The sole

renal abnormality consisted of a low level of serum magnesium, which, however, is a common finding in the context of poorly controlled diabetes, as was the case in our patient at the time of the dosage [13].

HNF1B syndrome may include other features, such as exocrine pancreatic insufficiency (70% of cases), partial or total pancreatic atrophy (62% of cases), genital tract abnormalities (50% of cases) such as bicornuate uterus or Mayer-Rokitansky-Kuster-Hauser syndrome, and intellectual disabilities, none of which were present in our patient. Of note, HNF1B-MODY patients may present more frequently than previously described with a more restricted phenotype, as suggested by a recent study using gene panel sequencing (next-generation sequencing) for the molecular diagnosis of monogenic diabetes [14].

Finally, it was the abnormal liver function tests that posed the greatest diagnostic challenge, as they had been successively attributed to hyperthyroidism, to a seronegative autoimmune hepatitis in the context of T1D and Grave's disease, and to nonalcoholic steatohepatitis, all of which were eventually ruled out. Chronic liver cytolysis and/or cholestasis have been described in 70% of cases of HNF1B-MODY patients, with no or minor morphological and histological abnormalities [6]. It was the unexplained chronically disturbed LFTs, along with the atypical diabetes presentation, that provided the clue leading to our patient's HNF1B-MODY diagnosis.

Consequences of the Genetic Diagnosis

A timely diagnosis of HNF1B-MODY is of utmost importance since it can greatly affect diabetes management and disease progression. It can help improve the patient's quality of life by substituting insulin treatment with a sulfonylurea, at least during the first few years of diabetes [6], and should lead to the screening of all the organ systems that may be involved in the HNF1B syndrome to establish an appropriate treatment plan. Furthermore, familial genetic testing should ensue since it can detect relatives with the same variant/deletion, greatly impacting their prognosis. This is of particular importance to our patient's daughter who was diagnosed with vesicoureteral reflux, a feature that might be part of the HNF1B disease spectrum.

Conclusion

The search for islet antibodies should be the first step in the etiological diagnosis of diabetes, even if the clinical presentation is strongly suggestive of T1D. In the absence of islet antibodies, one should reconsider the diagnosis of autoimmune diabetes, particularly when a protective HLA allele is present or when residual insulin secretion is maintained years after the diagnosis. In such a context, a dominantly inherited transmission of diabetes is highly suggestive of MODY. When extrapancreatic features coexist, especially kidney morphological abnormalities or unexplained chronically disturbed liver function tests, the diagnosis of HNF1B-MODY must be raised, regardless of family history, since *HNF1B* molecular defects occur de novo in half of the cases.

Disclosures

The authors have nothing to disclose.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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