Two Cases of Diabetic Ketoacidosis in HNF1A-MODY Linked to Severe Dehydration

Is it time to change the diagnostic criteria for MODY?

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OBJECTIVE—Hepatocyte nuclear factor-1A maturity-onset diabetes of the young (HNF1A-MODY) is a monogenic form of diabetes caused by heterozygous mutations in *HNF1A*. Currently, a history of diabetic ketoacidosis (DKA) is an exclusion criterion for genetic testing for MODY.

HISTORY AND EXAMINATION—In this article, we describe two unrelated patients aged 17 and 24 years with severe DKA developed several years after the diagnosis of HNF1A-MODY.

INVESTIGATION—Both patients were treated with insulin, but their metabolic control was poor (HbA_{1c} 15%, 140 mmol/mol and 13%, 119 mmol/mol, respectively) due to noncompliance and missed insulin injections. In both patients, DKA followed a course of recurrent vomiting with dehydration and prerenal acute kidney injury. Their glycemia, blood pH, and base excess at admission were 97 mmol/L [1,748 mg/dL], 6.80, and −33 mmol/L (patient 1) and 34 mmol/L [613 mg/dL], 7.03, and −14 mmol/L (patient 2).

CONCLUSIONS—This anecdotal observation supports the notion that a history of DKA does not exclude MODY.

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Hepatocyte nuclear factor-1A maturity-onset diabetes of the young (HNF1A-MODY) is a monogenic form of non-insulin-dependent diabetes caused by heterozygous mutations in the *HNF1A* gene (1). Diabetic ketoacidosis (DKA) is presumably lacking in these patients because they do not have absolute insulinopenia (2). Here, we describe two patients with genetically confirmed HNF1A-MODY negative for pancreatic autoantibodies who developed severe DKA several years after the diagnosis of diabetes.

A girl (now 17 years old; BMI, 20.1 kg/m^2) had diabetes presenting with moderate hyperglycemia without DKA diagnosed at the age of 4 years. After insulin therapy for 1 year, followed by 2 years of excellent glycemic control through diet only, insulin was reintroduced at the age of 7 years. Since then, her metabolic control has been very poor because of noncompliance and skipped insulin injections (HbA_{1c} 15%, 140 mmol/mol). The evening before admission for DKA she attended a night club and consumed alcohol. Later that night, she had recurrent vomiting. At admission, she was lethargic and had signs of severe ketoacidosis and dehydration. Her glycemia was 97 mmol/L (1,748 mg/dL), blood pH was 6.80, and base excess was −33 mmol/L. She was hyperosmotic and had acute renal failure with hyperpotassemia and hyponatremia. The C-reactive protein remained low (0.2 mg/L). Because of a positive family history of diabetes and absence of pancreatic autoantibodies, we performed genetic testing and found a previously published heterozygous mutation p.Arg272His in the *HNF1A* gene.

A man (now 24 years old; BMI 29.4 kg/m^2) had diabetes diagnosed at age 13 years. Insulin treatment was initiated and genetic investigation based on a positive family history of diabetes and negative pancreatic autoantibodies detected the heterozygous mutation p.Ser142Phe in the *HNF1A* gene. After the genetic diagnosis, he was treated with gliclazide monotherapy for 2 years. Insulin treatment was then resumed due to worsening metabolic control (HbA_{1c} 8.9%, 73.7 mmol/mol), which continued because of lack of treatment compliance (HbA_{1c} 13%, 119 mmol/mol). At age 23 years, recurrent vomiting developed because of acute gastritis that gradually led to admission for DKA. At admission, he was unconscious, seriously dehydrated, and had prerenal acute kidney injury and tachycardia (heart rate 160 bpm) caused by atrial flutter. His glycemia was 34 mmol/L (613 mg/dL), blood pH was 7.03, and base excess was −14 mmol/L.

According to the current diagnostic recommendations, the presence of DKA is considered an exclusion criterion for MODY (1). This statement is based on the observations that even noncompliant HNF1A-MODY patients never develop DKA because of residual insulin production that suppresses ketogenesis (2). However, as demonstrated in our two cases, the fragile balance can be broken by serious dehydration. Additional precipitating factors may include gastrointestinal illness with diarrhea and vomiting or alcohol intoxication (3).

The two demonstrated cases of DKA in poorly controlled HNF1A-MODY may have implications for the need of adequate

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patient education and for individual assessment of the indication criteria for genetic testing because, although the molecular genetic diagnosis of MODY diabetes has direct implications for patient treatment (4), most cases of MODY remain misclassified (5).

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