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Case Report

ABCC8-Related Monogenic Diabetes Presenting Like Type 1 Diabetes in an Adolescent

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ABSTRACT

Background: Identifying cases of diabetes caused by single gene mutations between the more common type 1 diabetes (T1D) and type 2 diabetes (T2D) is a difficult but important task. We report the diagnosis of ATP-binding cassette transporter sub-family C member 8 (ABCC8)-related monogenic diabetes in a 35-year-old woman with a protective human leukocyte antigen (HLA) allele who was originally diagnosed with T1D at 18 years of age.
Case Report: Patient A presented with polyuria, polydipsia, and hypertension at the age of 18 years and was found to have a blood glucose > 500 mg/dL (70-199 mg/dL) and an HbA1C (hemoglobin A1C) >14% (4%-5.6%). She had an unmeasurable C-peptide but no urine ketones. She was diagnosed with T1D and started on insulin therapy. Antibody testing was negative. She required low doses of insulin and later had persistence of low but detectable C-peptide. At the age of 35 years, she was found to have a protective HLA allele, and genetic testing revealed a pathogenic mutation in the ABCC8 gene. The patient was then successfully transitioned to sulfonylurea therapy.
Discussion: Monogenic diabetes diagnosed in adolescence typically presents with mild to moderate hyperglycemia, positive family history and, in some cases, other organ findings or dysfunction. The patient in this report presented with very high blood glucose, prompting the diagnosis of T1D. When she was found to have a protective HLA allele, further investigation revealed the mutation in the sulfonylurea receptor gene, ABCC8.
Conclusion: Patients suspected of having T1D but with atypical clinical characteristics such as negative autoantibodies, low insulin requirements, and persistence of C-peptide should undergo genetic testing for monogenic diabetes.

Introduction

Monogenic diabetes is an umbrella term encompassing all forms of diabetes caused by single mutations in genes responsible for glucose homeostasis. It is currently thought that these monogenic forms of diabetes are responsible for up to 2% of all diabetes cases[1] and up to 3.5% diagnosed before 30 years of age,[2] but most of these patients are misdiagnosed as having either type 1 diabetes (T1D) or type 2 diabetes (T2D). Accurately diagnosing these patients often allows for treatment with oral medications rather than insulin,

Abbreviations: ABCC8, ATP-binding cassette transporter sub-family C member 8; ATP, Adenosine triphosphate; HbA1C, Hemoglobin A1C; HLA, Human leukocyte antigen; IA-2, Islet cell antigen 2; IAA, Insulin autoantibodies; KATP, adenosine triphosphate (ATP) sensitive potassium; MODY, Maturity onset diabetes of the young; SD, Standard deviation; SUR1, Sulfonylurea receptor 1; T1D, Type 1 diabetes; T2D, Type 2 diabetes.

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improved glucose control, diagnosis and treatment of related conditions, testing of relatives, and increased knowledge for family planning.

We present the case of a 35-year-old woman, patient A, presumed to have T1D who was successfully transitioned from insulin to sulfonylurea therapy after the discovery that she had a pathogenic mutation in the sulfonylurea receptor 1 (SUR1) protein encoded by the ATP Binding Cassette Subfamily C Member 8 (ABCC8) gene.

Case Report

Patient A has provided written informed consent for this case report. She was presented in 2002 at the age of 18 years after having symptoms of polyuria, polydipsia, and hypertension for at least a year. She was found to have a random blood glucose of 584 mg/dL, an HbA1c (hemoglobin A1C) of > 14%, and undetectable C-peptide. Ketones were negative. Autoantibodies were not checked at the initial diagnosis. Her body mass index at the time was 20 kg/m^2. She was diagnosed with T1D and treated with insulin, soon transitioning to an insulin pump. While on the insulin pump, it was noted that she required only about 0.3 units/kg of rapid acting insulin daily.

In addition to her relatively low insulin needs, lengthy symptomatic onset, and lack of ketones, there were several other features of patient A's disease that cast doubt on the diagnosis of T1D. Her C-peptide rebounded to the low normal range (0.41-0.63 ng/mL [0.5-3.0 ng/mL]) and remained stable until at least 15 years after the diagnosis of T1D. Her autoantibodies were measured multiple times, albeit not until ~10 years after diagnosis, and she was found to have autoantibodies to IAA (insulin autoantibodies) but not GAD65 (glutamic acid decarboxylase65) or IA-2 (Islet cell antigen 2). Through her participation in an institutional review board-approved research study after informed consent, she was found to be heterozygous for HLA-DQB1*0602. This human leukocyte antigen (HLA) allele is thought to be protective against T1D.[3,4] As part of a study exploring the development of diabetes in those with this protective allele, sequencing of a panel of genes known to be associated with monogenic diabetes was then performed.

Patient A was found to have a heterozygous pathogenic variant, c.3067C>T (p.His1023Tyr), in ABCC8, consistent with autosomal dominant ABCC8-related diabetes. Patient A has 1 sibling who is healthy and genetic sequencing revealed that he does not harbor the c.3067C>T (p.His1023Tyr) mutation in ABCC8. Patient A's parents have not undergone sequencing of ABCC8. They are in their late 70s with no evidence of hyperglycemia.

After discovery of this mutation, patient A was successfully transitioned from insulin therapy to sulfonylurea therapy with 0.1 mg/kg glyburide daily (Fig.). The patient was on a hybrid closed-loop pump system at the time the sulfonylurea was started. The sulfonylurea was titrated up over 5 days, while bolus insulin was reduced by 50% and then eliminated, and basal insulin was adjusted by the automated basal feature. This allowed the patient to make the transition from insulin to sulfonylurea safely in the outpatient setting, and to our knowledge, this is the first case report to capture hybrid closed-loop data while transitioning to sulfonylurea therapy. The patient has now been receiving glyburide for 3 years, with an A1c of 4.5% to 6.5% (similar to her A1c on insulin therapy). Based on her continuous glucose monitor, she is currently "in range" (70-180 mg/dL) >75% of the time. At the age of 29 years, shortly before her diabetes diagnosis was clarified, patient A developed rheumatoid arthritis which has required ongoing treatment.

Highlights

- Monogenic diabetes accounts for 2-3% of diabetes cases, though this is likely an underestimate.
- ABCC8 mutations comprise a rare type of MODY (maturity-onset diabetes of the young).
- Negative antibodies, low insulin doses, lack of ketosis and persistence of C-peptide suggest MODY.

Clinical Relevance

Patients suspected of having type 1 diabetes but with atypical clinical characteristics such as negative autoantibodies, low insulin requirements, and persistence of C-peptide should undergo genetic testing for monogenic diabetes.

Discussion

Monogenic diabetes is a rare subset of diabetes caused by a single gene mutation in one of >20 genes associated with pancreatic development, glucose sensing, insulin production, or insulin release. It is currently thought to account for 2% to 3% of all diabetes cases, though these estimates likely underrepresent the true prevalence.[1,2] Indicators of monogenic diabetes include family history that suggests autosomal dominance, mild to moderate hyperglycemia often in the absence of obesity, and other organ manifestations such as pancreatic defects or congenital anomalies of the kidney or urogenital tract.[5]

ABCC8 is located on chromosome 11p and has 39 exons encoding the SUR1, a subunit of the ATP-sensitive potassium channel expressed in beta cells in the pancreas. Mutation of ABCC8 can lead to either deactivation or overactivation of the KATP (a subunit of the ATP-sensitive potassium channel) channel, causing increased or decreased secretion of insulin, respectively. Numerous variants in the ABCC8 gene have been reported, but most present as either hyperglycemia or hypoglycemia in the neonatal period.[6] Neonatal diabetes due to ABCC8 mutations can be either permanent or transient. Although listed as a type of maturity-onset diabetes of the young (MODY), diabetes onset after the neonatal period, while described, is rare.[7-11]

Here we report the second known case of monogenic diabetes due to a His1023Tyr mutation in ABCC8. Experimental studies have demonstrated that the p.His1023Tyr change has an activating effect on these channels, which means that the channel would remain open and not allow for insulin to be released.[12] This variant has not been observed in control populations,[13] but has been previously reported as pathogenic in an individual with transient neonatal diabetes, who relapsed at the age of 16 years.[12] Interestingly, the 2 patients had quite different clinical courses. While patient A developed diabetes at 18 years of age, the first reported patient developed diabetic ketoacidosis and was started on insulin at 3 weeks of age, went into remission 10 months later, then relapsed at 16 years of age, and is now maintained on glipizide.[12] The mechanisms underlying these differences remain to be elucidated.

Patients with classical T1D and monogenic diabetes can present very similarly; however, the presence of another autoimmune disease in a patient presenting with more severe hyperglycemia and without a family history would support the diagnosis of T1D.[14] Autoimmune thyroid disease and systemic rheumatologic diseases are common in women with later onset T1D, and the development of rheumatoid arthritis in this patient supported the initial diagnosis of T1D in this patient.[14,15]

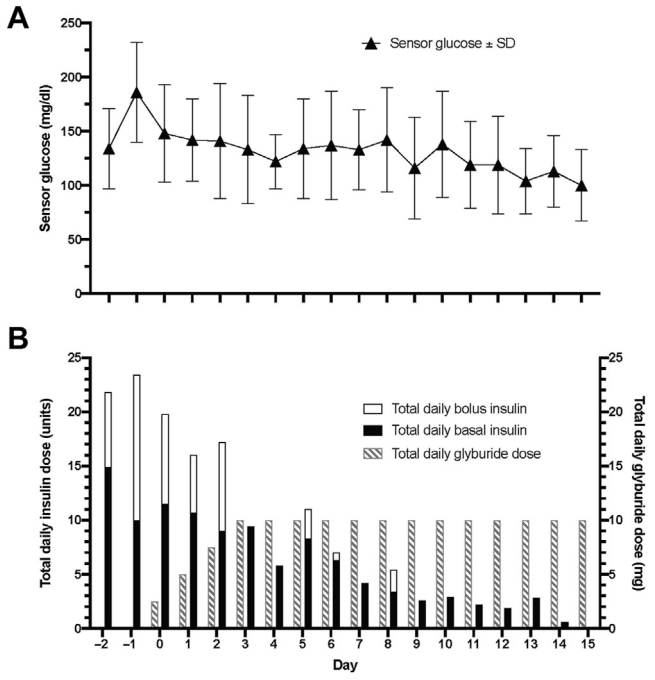

Fig. Glyburide dose, basal and bolus insulin doses, and average glucose during transition from insulin to sulfonylurea therapy. *A*, Average sensor glucose ± SD for 2 days before and during the 15-day transition period. *B*, Daily glyburide and basal/bolus insulin doses 2 days before and during the 15 day transition period. Glyburide dosing was titrated up over days 0 to 3. Basal insulin was controlled by a hybrid closed loop system in auto mode throughout the transition period. Bolus insulin was reduced to 50% of the suggested bolus wizard dose on day 0 and eliminated on day 3.

The combination of negative autoantibodies, a somewhat atypical clinical course and a high index of clinical suspicion led researchers to test for and identify the gene defect that led to the diagnosis of monogenic diabetes in patient A. While calculators and algorithms have been developed to help determine who to test for monogenic diabetes, these are still imperfect tools. Patient A was predicted to have <1% chance of having MODY from the Exeter Diabetes MODY probability calculator (https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator),[16] but turned out to harbor a pathogenic ABCC8 mutation that is responsive to sulfonylureas. The low risk of MODY is in part due to the lack of family history of diabetes, which would be expected in a dominantly inherited condition. The patient's parents were not tested given their lack of diabetes and dramatic hyperglycemia presentation in ABCC8 mutation carriers. This case highlights the importance of obtaining genetic sequencing to determine the proper diagnosis and treatment in patients with diabetes and atypical features. HLA typing is much less specific than genetic testing, and risk versus protective alleles are only relevant for T1D, not T2D, thus the authors recommend genetic testing in cases of diabetes with atypical features.

Disclosure

J.B.M. reports consulting for Bayer, Boehringer Ingelheim, Mannkind, and Thermo Fisher and grant funding from Novo Nordisk and JDRF. M.S.A. owns stock in Medtronic and Merck and is a consultant for Imcyse and Sana. The other authors have no multiplicity of interest to disclose.

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