OBSERVATIONS

Successful Transition From Insulin to Sulfonylurea Therapy in a Patient With Monogenic Neonatal Diabetes Owing to a KCNJ11 P333L Mutation

Although monogenic neonatal diabetes may be caused by mutations in >20 different genes, the most common are activating heterozygous mutations in KCNJ11, encoding the Kir6.2 subunit of the ATP-sensitive K^+ channel (K_{ATP} channel), which is highly expressed in pancreatic β-cells and brain (1). Mutated K_{ATP} channels typically have decreased sensitivity to ATP inhibition, hampering insulin secretion even during hyperglycemia. Oral sulfonylureas (SUs) have been demonstrated to be an effective treatment in the majority of cases, given that they close the K_{ATP} channels by an ATP-independent mechanism (2). However, the likelihood of success is largely predicted by the particular mutation. Previous reports of the P333L mutation indicated insensitivity to SU therapy. We report a case representing a novel response to SU therapy in this same mutation.

A 13-month old Hispanic male presented to our facility for continued management of diabetes. His diabetes was diagnosed at 3 months of age after presenting in severe diabetic ketoacidosis. He was treated with insulin and subsequently placed on an insulin pump. His insulin dosage at the time of presentation to our facility was 0.4 units/kg/day, and his hemoglobin A_{1c} was 9.6% (81 mmol/mol). He was otherwise healthy and growing and developing normally. However, his parents remained challenged with the care of diabetes in a young toddler. Given his young age at diabetes onset, genetic testing for monogenic diabetes was sent and revealed a dominant heterozygous KCNJ11 mutation of P333L. Review of the literature revealed an unsuccessful transition of a previous patient with the same P333L mutation. After discussion with the family, an established SU protocol (3) was modified and inpatient transition from insulin to SU therapy was attempted. Glyburide (glibenclamide) was titrated from a starting dose of 0.2 mg/kg/day to 1 mg/kg/day, which resulted in a complete discontinuation of insulin after 6 days. Pre-SU fasting C-peptide was <0.1 mg/mL, increased to 0.47 ng/mL after 3 days of therapy, and normalized at 1.86 ng/mL by 3 months of outpatient follow-up. Hemoglobin A_{1c} decreased to 6.7% (50 mmol/mol) at the 7-month follow-up. There were no adverse events observed: no hypoglycemia, diarrhea, or feeding intolerance, and complete blood count and complete metabolic panel remained normal for age throughout treatment. The patient is now 27 months old and has sustained improved glycemic control on a glyburide dose of 0.4 mg/kg/day. He continues to achieve normal, age-appropriate neurodevelopmental milestones. The family regularly voices satisfaction with the decreased intensity of care required on the new oral regimen.

This case demonstrates a novel response to oral SU therapy in a patient with a KCNJ11 mutation that has been previously been reported to be resistant to transition from insulin therapy. Further study of these important rare cases will help to clarify the factors that influence the likelihood of successful SU treatment and neurodevelopmental outcome. Finally, the case highlights the variability of predicted response based exclusively on genotype and reemphasizes the importance, and potential life-altering impact, of genetic screening for patients suspected of having monogenic forms of diabetes.

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K.Q.P., with the assistance of A.J.B. and S.A.W.G. and utilization of references (Ewan R. Pearson, Neonatal Diabetes International Collaborative Group), drafted inpatient transition protocol implemented for this patient and participated in direct inpatient and outpatient care of this patient. A.J.B. provided oversight of patient care and protocol drafting. K.S.V. provided revision of case report and ongoing oversight of outpatient care of patient. S.A.W.G. provided protocol oversight and feedback, along with inpatient/outpatient feedback throughout this patient's course. K.Q.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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