Patient With iDEND Syndrome–Related Mutation

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Mutations on the ATP-sensitive K^+ (K_{ATP}) channel are the most common cause of permanent neonatal diabetes. Heterozygous gain-of-function mutations in KCNJ11 and ABCC8, encoding respectively for the Kir6.2 and sulfonylurea receptor 1 (SUR1) subunit of the K_{ATP} channel, account for the majority of cases of permanent neonatal diabetes (1). Kir6.2 is expressed in the pancreatic β-cell, but also in skeletal muscle, peripheral nerves, and especially in the brain. Specific KCNJ11 mutations also are associated with developmental delay and epilepsy, known as developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome, or in milder forms, intermediate DEND (iDEND). Sulfonylureas improve K_{ATP} channel function in the pancreatic β-cell and also in neuronal and muscle cells, and could potentially play a role in the treatment and/or prevention of such neurologic manifestations.

Our patient has a KCNJ11 mutation associated with iDEND syndrome and was successfully switched to glyburide early. The patient was a female born at 34.4 weeks' gestation, with appropriate weight and length, from nonconsanguineous, healthy, Caucasian parents. Nonketotic hyperglycemia was noted on the first day, needing continuous intravenous insulin therapy (0.005–0.03 UI/kg/h). Pancreatic autoantibodies were negative. At 3 weeks, she was switched to continuous subcutaneous insulin infusion (CSII), using only basal rate at 0.075 UI/kg/h. At the start of CSII therapy, C-peptide was 0.04 nmol/L (normal range 0.29–1.30) and A1C was 6.1% (43 mmol/mol). Results of genetic study revealed a de novo heterozygous mutation c.175G>A (p.Val59Met) in the KCNJ11 gene. This mutation has been described as a cause of a sulfonylurea-responsive form of neonatal diabetes and sometimes iDEND.

At 44 days, glyburide was started at 0.1 mg/kg every 12 h and increased gradually to 0.3 mg/kg every 12 h while decreasing insulin requirements. Only two asymptomatic hypoglycemic episodes were recorded and both quickly resolved with oral glucose. No other side effects were reported. After 1 week on glyburide, C-peptide levels rose to the normal range (0.49 nmol/L) and A1C decreased to 5.6% (38 mmol/mol), with glycemic values in the range of 3.6–10.7 mmol/L. At 13 months old, A1C was 7.6% (52 mmol/mol) without hypoglycemic episodes, the neurologic examination was normal, and all appropriate milestones had been achieved.

To the best of our knowledge, this is the youngest reported case of neonatal diabetes due to p.Val59Met treated with sulfonylureas. Similar metabolic outcomes with sulfonylureas have been reported in older patients (2–4). The initiation of glyburide at such a young age provided a simple and successful way of treatment compared with insulin. Furthermore, glyburide may improve the neurologic prognosis, by decreasing not only the number of hypoglycemia events, but also by restoring K_{ATP} channel function in neuronal cells. As sulfonylurea-responsive forms are not clinically distinguishable from other forms of neonatal diabetes, early genetic testing should be advised. KCNJ11 is proposed as the first gene to be studied as it is a single exon gene and accounts for 55% of permanent cases (5). The genetic confirmation of a sulfonylurea-responsive form of neonatal diabetes would lead to an early-targeted treatment that improves metabolic control and could improve the neurologic outcome.

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and wrote the manuscript. S.M. and M.N. researched data and reviewed and edited the manuscript. R.C.-H. contributed to the discussion and reviewed and edited the manuscript. J.O. performed the genetic test and reviewed and edited the manuscript. M.R.-K. contributed to the discussion and wrote, reviewed, and edited the manuscript. M.R.-K. is the guarantor of this work and, as such, had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Rubio-Cabezas O, Flanagan SE, Damhuis A, Hattersley AT, Ellard S. KATP channel mutations in infants with permanent diabetes diagnosed after 6 months of life. Pediatr Diabetes 2012;13:322–325
2. Ješić MD, Ješić MM, Sajić S, Zdravković V, Maglajlić S. Transition from insulin to glibenclamide in a one-month-old infant with neonatal diabetes mellitus caused by a new mutation in KCNJ11 (Abstract). Pediatr Diabetes 2012;13(Suppl. 17):73
3. Pearson ER, Flechtner I, Njølstad PR, et al.; Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006;355:467–477
4. Chan YM, Laffel LMB. Transition from insulin to glyburide in a 4-month-old girl with neonatal diabetes mellitus caused by a mutation in KCNJ11. Pediatr Diabetes 2007;8:235–238
5. Sperling MA. ATP-sensitive potassium channels—neonatal diabetes mellitus and beyond. N Engl J Med 2006;355:507–510