Successful sulfonylurea treatment in a patient with permanent neonatal diabetes mellitus with a novel KCNJ11 mutation

Sung Yeon Ahn, MD, PhD1, Gu-Hwan Kim, PhD2, Han-Wook Yoo, MD, PhD2,3

1Department of Pediatrics, Ulsan University Hospital, Ulsan, 2Medical Genetics Center, 3Department of Pediatrics, Asan Medical Center Children’s Hospital, University of Ulsan College of Medicine, Seoul, Korea

Permanent neonatal diabetes mellitus refers to diabetes that occurs before the age of 6 months and persists through life. It is a rare disorder affecting one in 0.2–0.5 million live births. Mutations in the gene KCNJ11, encoding the subunit Kir6.2, and ABCC8, encoding SUR1 of the ATP-sensitive potassium (KATP) channel, are the most common causes of permanent neonatal diabetes mellitus. Sulfonylureas close the KATP channel and increase insulin secretion. KCNJ11 and ABCC8 mutations have important therapeutic implications because sulfonylurea therapy can be effective in treating patients with mutations in the potassium channel subunits. The mutation type, the presence of neurological features, and the duration of diabetes are known to be the major factors affecting the treatment outcome after switching to sulfonylurea therapy. More than 30 mutations in the KCNJ11 gene have been identified. Here, we present our experience with a patient carrying a novel p.H186D heterozygous mutation in the KCNJ11 gene who was successfully treated with oral sulfonylurea.

Key words: Permanent neonatal diabetes mellitus, KCNJ11, Sulfonylurea compounds

Introduction

Neonatal diabetes mellitus (NDM) presenting within the first 6 months of life includes permanent neonatal diabetes mellitus (PNDM), which require lifelong therapy, and transient neonatal diabetes mellitus (TNDM) where the condition shows remission during infancy but relapses in adolescence. Almost all cases of neonatal diabetes have monogenic etiology in contrast to the autoimmune diabetes presenting in children beyond 6 months of age. PNDM is associated with defects in pancreatic beta cell development and function. Activating mutations in the KCNJ11 gene, encoding the subunit Kir6.2, and ABCC8 gene, encoding the sulfonylurea receptor 1 (SUR1) of ATP-sensitive potassium (KATP) channel, which has a key role in insulin secretion in glucose metabolism, are the most common causes and account for approximately 40% of all cases of PNDM. More than 30 mutations in the KCNJ11 gene have been identified. Mutations in the glucokinase (GCK) and insulin (INS) genes have also been reported in patients with PNDM.

Sulfonylureas close the KATP channel by an ATP-independent route, leading to increase insulin secretion. Therefore, in many patients with PNDM with Kir6.2 and SUR1 mutations, insulin therapy can be replaced by oral sulfonylureas which offer more improvement in glycemic control and better quality of life.

We report a case of PNDM caused by a novel p.H186D heterozygous mutation in the KCNJ11 gene whose treatment was successfully transitioned from insulin to oral sulfonylurea.
sulfonylurea.

**Case report**

A female child was born at 38-week age of gestation with intrauterine growth retardation. She was delivered by cesarean section with a birth weight of 2.5 kg. She was diagnosed with neonatal diabetes at 2 months of age. She was the first child of two siblings. Her parents were unrelated, and her family was healthy and had no history of diabetes. Laboratory results at diagnosis were: blood glucose, 1,041 mg/dL; pH, 7.025; HCO$_3^-$, 5.1 mmol/L; pCO$_2$, 19.8 mmHg; sodium, 147 mmol/L; potassium, 5.6 mmol/L; chloride, 113 mmol/L; blood urea nitrogen, 31 mg/dL; creatinine, 1.2 mg/dL; urine ketone, +++; glycosylated hemoglobin (HbA1c), 7.7%; and C-peptide, 0.2 ng/mL. After recovery from diabetic ketoacidosis, she had injections of neutral protamine Hagedorn (NPH) insulin two times a day and regular insulin (RI) four times a day. Her maximal daily insulin dose was at 1.5 U/kg. Her insulin requirement was gradually decreased to 0.44 U/kg/day by 4 months of age. She took NPH and RI injection twice a day from 10 months of age. Although there were several hypoglycemic events, insulin injection for glucose control after the infancy period could not be stopped.

Genetic study for neonatal diabetes using genomic DNA extracted from peripheral lymphocyte was done at 4.5 years of age, and a novel heterozygous mutation of the KCNJ11 gene located on chromosome 11p15.1 and encoding Kir6.2, c.556C>G (p.His186Asp), was found (Fig. 1). Genetic study for her parents could not be done.

Transition of treatment from insulin to sulfonylurea was attempted at the age of 4.8. Before the trial, her daily insulin requirement was at 0.44 U/kg. Laboratory findings were as follows: HbA1c, 6.9%; fasting glucose, 205 mg/dL; C-peptide, 0.84 ng/mL; 24-hour urine C-peptide, 2.2 μg; negative for islet cell antibody; anti-insulin antibody; and anti-GAD antibody. She was 103.2 cm in height (25th–50th percentile), 17 kg in weight (50th–75th percentile) and did not have any specific neurological deficit. Oral sulfonylurea (glibenclamide) was initiated at a dose of 0.1 mg/kg/day divided into two equal doses. The glibenclamide dose was gradually increased to 0.4 mg/kg/day over 1 week and the insulin was stopped. Oral glucose tolerance test (glucose, 1.75 g/kg) was done at 6 months and 1 year after completion of the sulfonylurea transition. The results demonstrate improvement of insulin and C-peptide secretory response during treatment. Insulinogenic index [Δinsulin (30 min–0 min)/ΔGlucose (30 min–0 min)], a marker of beta cell function, became increased from 0.10 to 0.18, and acute C-peptide response [ΔC-peptide (30 min–0 min)×1,000/Glucose (30 min–0 min)] became increased from 6.48 to 8.29 (Table 1). The patient is now 7.5 years of age with a height of 121.4 cm (50th percentile) and weight of 23.4 kg (50th percentile). Recent glibenclamide dose is 0.3 mg/kg/day and HbA1c is 6.2%. Blood glucose was well controlled without episodes of hypoglycemia and the HbA1c has been lower than during insulin

| Table 1. Oral glucose tolerance test at 6 months and 1 year after oral sulfonylurea treatment |
|---------------------------------------------------------------|
| Hormone          | Basal | 30 min | 60 min | 120 min |
| 6 Months after SU |       |        |        |         |
| Glucose (mg/dL)  | 121   | 175    | 144    | 156     |
| Insulin (μIU/mL) | 3.12  | 8.47   | 3.87   | 8.41    |
| C-peptide (ng/mL)| 0.56  | 0.91   | 0.97   | 1.23    |
| 12 Months after SU|      |        |        |         |
| Glucose (mg/dL)  | 85    | 173    | 161    | 165     |
| Insulin (μIU/mL) | 3.32  | 19.38  | 14.46  | 16.67   |
| C-peptide (ng/mL)| 0.62  | 1.35   | 1.24   | 1.70    |

SU, sulfonylureas.

**Partial seq. of KCNJ11 gene**

**Fig. 1.** DNA sequence analysis of the patient revealed a novel heterozygous mutation of the KCNJ11 gene encoding Kir6.2.
Closure of KATP channels that lead to insulin secretion by pancrea-
also found in some cases. Account for nearly half of all cases of PNDM. Therefore, molecular diag-
expected in patients with mutations in other genes, such as
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Sulfonylureas (SU) can close the KATP channel and increase insulin secretion. Many cases with KCNJ11 and ABCC8 mutation can be treated with oral sulfonylureas. Treatment response is not expected in patients with mutations in other genes, such as glucokinase gene, FOXP3, and IPF1. Therefore, molecular diagnosis in neonatal diabetes may help identify patients that are likely to respond to oral sulfonylureas.

Pearson et al. reported the responses to sulfonylurea according to mutation types in diabetic patients caused by KCNJ11 mutation. Switching from insulin to SU was successful in 90% of patients. There were no differences in blood insulin, C-peptide level, and insulin injection dose between the successful group and unsuccessful group. R201H mutation was the most common and all patients responded well to sulfonylurea. V59M, R201C, F35V, H46Y, R50Q, G53R, R201L, E322K, Y330S, F333I mutations also belong to the successful group. Switching to SU was unsuccessful in patients with Q52R, I296L, and L164P mutations. In addition, failure of switching to SU was more related with the presence of neurologic features (14% in successful group and 80% in unsuccessful group) and older age at initiation of SU. Median age was 6 years old (intraquartile range, 3–12 years) in the successful group and 18 years old (intraquartile range, 6–35 years) in the unsuccessful group. The report about a mother and daughter carrying the same KCNJ11 mutation showed that the daughter could be switched from insulin to SU at age 8.5 years, but her mother had an incomplete response. The trial of SU switching in a poorly controlled diabetic 19 years old patient with R201H mutation, a mutation type expected to respond successfully, failed. These observations suggest that factors that can affect the success of switching to SU include; mutation type, severity of mutation, and duration of the diabetes. A long-standing diabetes may lead to islet beta cell exhaustion resulting in nonresponse to SU.

NDM is a monogenic form of diabetes that presents within the first 6 months of life. Heterozygous activating mutations in the KCNJ11 and ABCC8 gene encoding the subunits Kir6.2 and SUR1 of KATP channel in pancreatic beta cells are the most common and account for nearly half of all cases of PNDM. Mutations in the glucokinase (GCK), insulin (INS) genes have also been reported in patients with PNDM. The causes of rare syndromic PNDM includes recessive mutations in several genes, such as PDX1, EIF2AK3, GCK, PTF1A, FOXP3, NEUROG3, NEUROD1, RFX6, IER3IP1, HNF1B, GLIS3, PAX6, SLC19A2, SLC2A2, and WFS1. In TNDM, imprinted locus at chromosome 6q24 seen in more than half of cases, and KCNJ11 and ABCC8 gene mutations are also found in some cases.

Glucose increases intracellular ATP level and it induces the closure of KATP channels that lead to insulin secretion by pancreatic beta cells. Activating mutations in the KCNJ11 or ABCC8 gene of KATP channel lead to KATP channels remaining open despite the presence of glucose, thus, insulin secretion cannot be increased. On the contrary, loss of function mutations cause congenital hyperinsulinemia due to the closure of the KATP channel and lead to increased insulin secretion.

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effect on neurodevelopmental outcome and glycemic control, empiric trial of SU before genetic testing in neonatal diabetes patients can be considered\textsuperscript{15}.

In conclusion, as the mutation type, severity of mutation, and duration of the diabetes are the major factors affecting the success of switching to SU, early genetic analysis and trial of sulfonylurea is important in the management of neonatal diabetes. Further studies looking at the result of SU treatment and long term follow up in PNDM patients are needed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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