Clin Pediatr Endocrinol 2017; 26(3), 165–169

Case Report

Sulfonylurea treatment in an infant with transient neonatal diabetes mellitus caused by an adenosine triphosphate binding cassette subfamily C member 8 gene mutation

Masayo Yamazaki[1], Hideo Sugie[2], Makiko Oguma[1, 3], Tohru Yorifuji[4], Toshihiro Tajima[1], and Takanori Yamagata[1]

[1]*Department of Pediatrics, Jichi Medical University, Tochigi, Japan*

[2]*Faculty of Health and Medical Sciences, Tokoha University, Shizuoka, Japan*

[3]*Department of Pediatrics, Japan Community Health care Organization Utsunomiya Hospital, Tochigi, Japan*

[4]*Department of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, Osaka, Japan*

Abstract. Neonatal diabetes mellitus (NDM) is an insulin-requiring monogenic form of diabetes that generally presents before six months of age. The following two types of NDM are known: transient NDM (TNDM) and permanent NDM (PNDM). Here we report on an infant with TNDM caused by a mutation (p.Gly832Cys) of the gene for the ATP binding cassette subfamily C member 8 (ABCC8). The patient exhibited hyperglycemia (600 mg/dL) at five weeks of age and insulin treatment was initiated. As genetic analysis identified a missense mutation within *ABCC8*, the insulin was replaced by glibenclamide at five months of age. Thereafter, the insulin was successfully withdrawn and his glycemic condition was well controlled at a dose of 0.0375 mg/kg/d. Since the patient's blood glucose was under control and serum C-peptide levels were measurable, glibenclamide was stopped at 1 yr, 10 mo of age. The lack of DM relapsed to date confirms the TNDM diagnosis. In conclusion, when insulin is replaced with a sulfonylurea-class medication (SU) in NDM patients, serum C-peptide levels should be closely monitored and fine adjustment of SU dose is recommended.

Key words: transient neonatal diabetes mellitus (TNDM), *ABCC8*, sulfonylurea

Introduction

Neonatal diabetes mellitus (NDM) is defined as an insulin-requiring monogenic form of diabetes presenting before six months of age (1, 2). It is a rare disease, affecting approximately 1 in 300,000–500,000 newborns (1). NDM is categorized into two types: permanent NDM (PNDM) and transient NDM (TNDM) (1). Most cases of TNDM are caused by genetic or

Received: October 27, 2016
Accepted: February 21, 2017
Corresponding author: Masayo Yamazaki, MD, Department of Pediatrics, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan
E-mail: r0845mh@jichi.ac.jp

epigenetic defects on chromosome 6q24 (70%) (1, 2). The development of function mutations in potassium voltage-gated channel subfamily J member 11 (*KCNJ11*) or ATP binding cassette subfamily C member 8 (*ABCC8*) that encode the Kir6.2 and SUR1 protein subunits accounts for 31% and 10% of cases of TNDM, respectively (1, 2).

NDM caused by mutations in *KCNJ11* and *ABCC8* may respond to sulfonylureas (SU) (1, 2). Therefore, the identification of the underlying genetic causes of NDM is important for patient care.

Here we report on an infant with TNDM caused by an *ABCC8* mutation. In this patient, a low dose of SU was effective for the control of blood glucose levels.

Case Report

A boy was delivered at term via spontaneous vaginal delivery, following an uneventful pregnancy, with a birth weight of 2,800 g. He was not dysmorphic. At 5 wk of age, he presented to a local hospital with a two-day history of frequent vomiting without diarrhea. At this time, marked hyperglycemia (blood glucose 600 mg/dL) and glucosuria were observed. Therefore, he was referred to our hospital (Jichi Children's Medical Center Tochigi) for further evaluation.

He was inactive and with decreased skin turgor. His body weight was 4,176 g (–0.2 SD for a normal Japanese boy of this age) and his body length was 52.0 cm (–0.6 SD for a normal Japanese boy of this age). There was no family history of DM. The blood analyses 1 h after feeding were as follows: blood glucose, 258 mg/dL; serum insulin, 1.9 μU/mL; and serum C-peptide, 0.6 ng/mL; glycated hemoglobin (HbA1c), 4.3%; and glycoalbumin (GA), 31.1% (3). Venous blood gas analysis revealed a pH of 7.459, pCO_2 of 32.5 mmHg, HCO_3 of 22.5 mmol/L, and a base excess of –0.4 mmol/L. Glutamic acid decarboxylase (GAD) antibodies were not detected and the patient was negative for urine ketones. Ultrasonography showed a normal pancreas. Based on these findings he was diagnosed with NDM and intravenous insulin injection and fluid therapy were initiated. Thereafter, twice-daily injections of mixed insulin analog (NovoRapid 30 Mix®, Insulin Aspart) in the morning (1 unit) and evening (1 unit) commenced (total daily dose of insulin 0.5 U/kg).

As a mutation of *ABCC8* was identified in this patient, oral glibenclamide was initiated at a dose of 0.2 mg/kg/d in two doses at 5 mo of age in accordance with a previous report (4). The clinical course of blood glucose levels and of the insulin and glibenclamide doses in the hospital are summarized in Fig. 1A. Three days after initiation, the glibenclamide dose was increased to 0.4 mg/kg/d in two doses since his blood glucose levels ranged between 73 and 324 mg/dL. Four days after the initiation of glibenclamide, the insulin dose was decreased to 0.5 U (0.075 U/kg) in the morning and stopped in the evening due to the development of hypoglycemia two hours after the insulin injection. The insulin was stopped 4 d after the initiation of glibenclamide. At this point, the dose of glibenclamide was 0.4 mg/kg/d. As shown in Fig. 1A, due to the frequency with which the patient exhibited hypoglycemia, the dose of glibenclamide was gradually decreased to 0.0375 mg/kg/d (0.27 mg/d) in two doses. Figure 1B shows the changes of serum C-peptide and GA levels. His serum C-peptide was 1.9 ng/mL when he was discharged. The patient's serum C-peptide and GA levels were as follows: 1.2 ng/mL and 13.3%, respectively, at 6 mo of age, 1.7 ng/mL and 11.9% at 8 mo of age, and 2.6 ng/mL and 10.9% at 1 yr and 4 mo of age (Fig. 1B). Because the DM was very well controlled at 0.27 mg/d of glibenclamide, the dose was not changed. At 1 yr and 10 mo of age, the patient's body weight was 11.3 kg and the dose of glibenclamide was 0.27 mg/d (0.024 mg/kg/d). At this time, his serum C-peptide and GA levels were 1.0 ng/mL and 12.5%, respectively. Due to the good control of DM and measurable C-peptide levels, glibenclamide was discontinued. Since that time, the patient

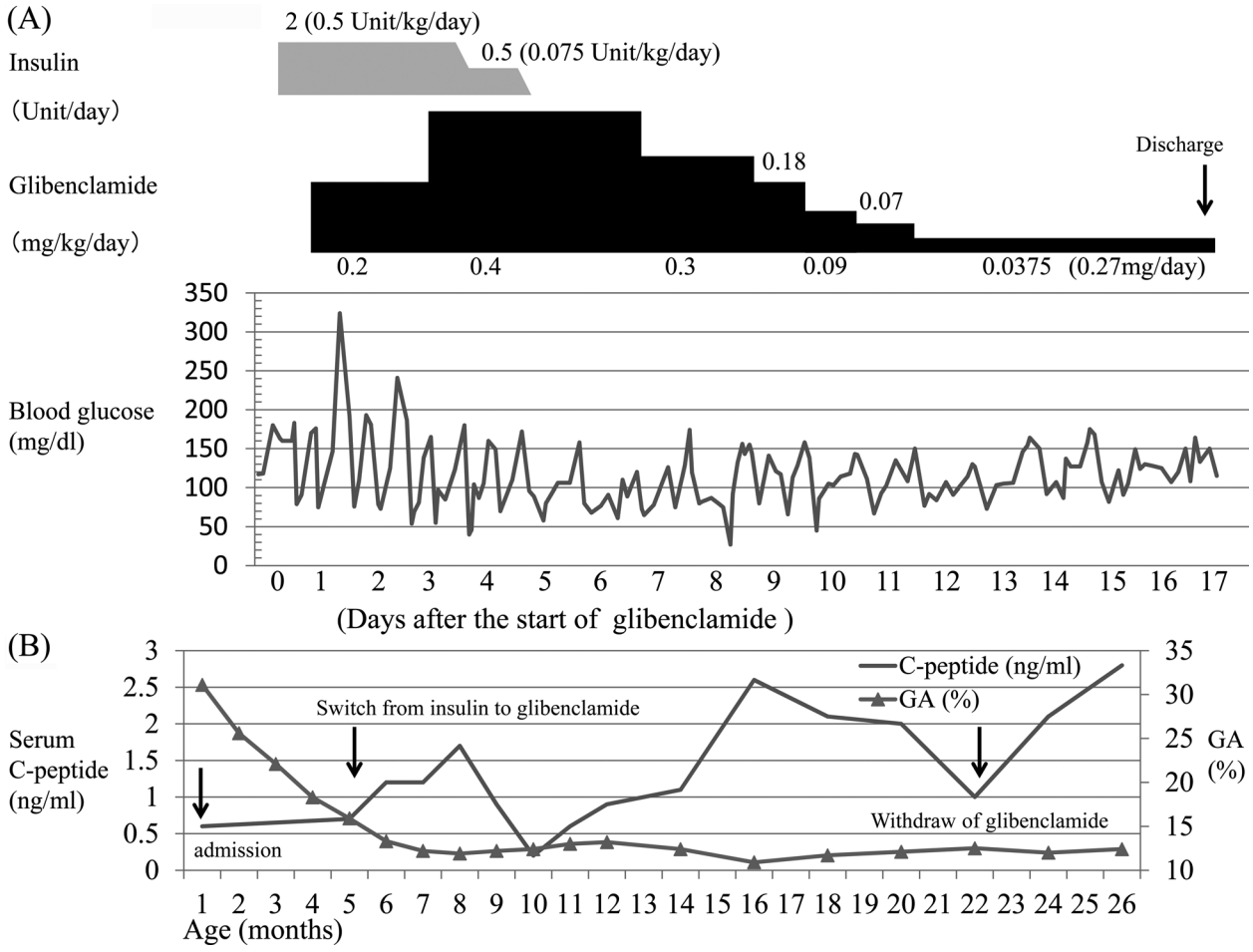

Fig. 1. (A) Patient clinical course while switching from insulin to glibenclamide. Oral glibenclamide was initiated at a dose of 0.2 mg/kg/d. Insulin therapy was stopped when the glibenclamide reached a dose of 0.4 mg/kg/d. As hypoglycemic episodes were frequent, glibenclamide was gradually decreased to 0.0375 mg/kg/d. (B) Changes in serum C-peptide and GA levels after discharge

has not exhibited hyperglycemia. The patient is currently 3 yr of age and his HbA1c level is 5.7% without medication. Therefore, the diagnosis of TNDM is confirmed. His developmental milestones are normal.

Genetic analysis

After receiving approval from the institutional review board and obtaining written informed consent, *KCNJ11* and *ABCC8* genetic analyses were performed. Genomic DNA was obtained from lymphocytes. All nearby exons and introns were amplified by PCR and the PCR products were subjected to Sanger sequencing. As a result, a recently reported *ABCC8* mutation (p.Gly832Cys) (6) was identified in this patient sample (Fig. 2A). *In silico* analysis using sorting intolerant from tolerant (SIFT) and polymorphism phenotyping (PolyPhen) II suggested that this amino acid substitution might be pathogenic. The patient's parents did not have this mutation (Fig. 2B, C), indicating a *de novo* mutation.

Discussion

We encountered a Japanese boy with TNDM caused by an *ABCC8* mutation. DM

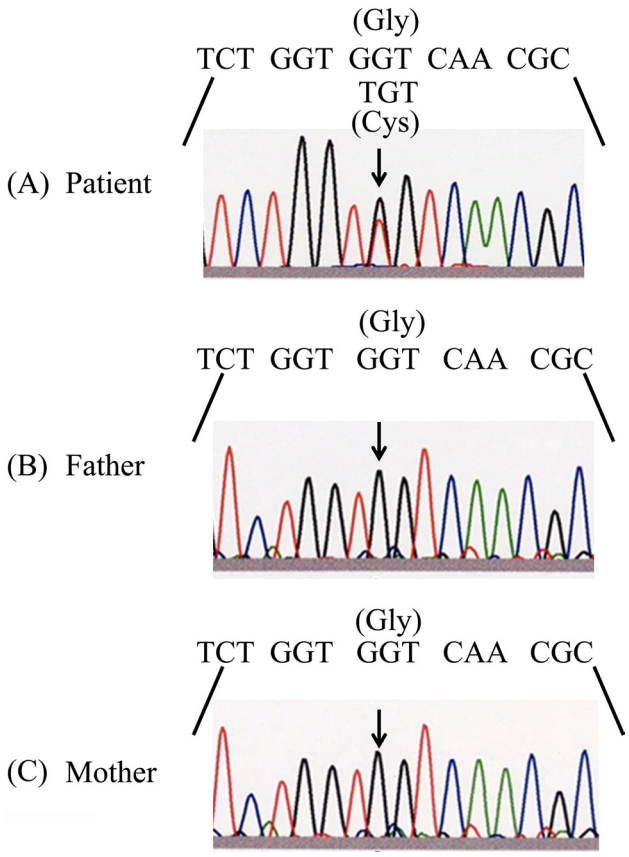

Fig. 2. *ABCC8* mutation. (A) The patient had a G→T nucleotide change at position 2494 (arrow). This nucleotide change results in a cysteine for glycine substitution at codon 832 (p.Gly832Cys). (B) The father does not have a nucleotide change (arrow). (C) The mother does not have a nucleotide change (arrow).

caused by *ABCC8* mutations may respond to SUs (1, 2). In previous reports, the average dosage of glibenclamide for patients with *ABCC8* mutations was 0.07–2.80 mg/kg/d (1, 5). In the present case study, when treatment was switched from insulin to glibenclamide, the maintenance dose was 0.0375 mg/kg/d, which is lower than the average dosage. This low dose was sufficient due to the patient's intrinsic capacity for insulin secretion. Indeed, his serum C-peptide levels were measurable during the follow-up examinations. Rafiq *et al.* (5) reported that the dose of SU required for DM with *ABCC8* mutations depends on the degree of intrinsic insulin secretion. According to their study, a very low dose of SU (< 0.1mg/kg/d) is effective for patients with measurable serum C-peptide levels. Therefore, when a patient with NDM is treated with SU, serum C-peptide levels should be closely monitored. If serum C-peptide is measurable, a low dose of SU (< 0.1 mg/kg/d) is recommended.

A genotype-phenotype correlation has been observed to some extent for *ABCC8* mutations (1). As p.Gly832Cys was also identified in a patient with TNDM similar to our own case (6), this mutation may be a cause of TNDM, and not PNDM.

The development of a function mutation in *ABCC8* occurs in approximately 10% of patients with TNDM (1, 2). These patients are usually diagnosed before six months of age and the remission of DM occurs between six and 12 mo of age (1, 2). DM may relapse in adolescence (1, 2); therefore, careful patient follow-up of the patient is necessary.

Our patient manifested DM at 5 wk of age; however, his glycemic control gradually improved and the medication was stopped at one year and 10 mo of age, confirming the diagnosis of TNDM. To date, a precise explanation for the biphasic course of remission and relapse has not been elucidated. In a study using a mouse model of *KCNJ11*-induced NDM, mice cured of NDM had higher insulin sensitivities relative to control mice (7). In a human study, the E23K polymorphism of KCNJ11 was related to type2 diabetes (8). In that study, although nondiabetic individuals with E23K genotype had reduced insulin secretion, they had higher insulin sensitivity than normal controls. This evidence suggests that the difference between TNDM and PNDM may depend on an individual's insulin sensitivity even in individuals with high insulin sensitivity, as insulin resistance increases during adolescence, their high insulin sensitivity may not be sufficient to compensate for reduced insulin secretion; thus, DM subsequently relapses. However, this theory requires further study.

Acknowledgements

We thank Dr. Sian Ellard (Royal Devon & Exeter NHS Hospital) for her useful advice.

References

1. Aguilar-Bryan L, Bryan J. Neonatal diabetes mellitus. Endocr Rev 2008;29: 265–91. [Medline] [CrossRef]
2. Greeley SAW, Tucker SE, Naylor RN, Bell GI, Philipson LH. Neonatal diabetes mellitus: a model for personalized medicine. Trends Endocrinol Metab 2010;21: 464–72. [Medline] [CrossRef]
3. Suzuki S, Koga M, Amamiya S, Nakao A, Wada K, Okuhara K, *et al*. Glycated albumin but not HbA1c reflects glycaemic control in patients with neonatal diabetes mellitus. Diabetologia 2011;54: 2247–53. [Medline] [CrossRef]
4. Hattersley A. Transferring patients with diabetes due to a Kir6.2 mutation from insulin to sulphonylureas in patients who are aged under 1 year. http://www.diabetesgenes.org/content/transferring-patients-diabetes-due-kir62-mutation-insulin-sulphonylureas.
5. Rafiq M, Flanagan SE, Patch AM, Shields BM, Ellard S, Hattersley AT, Neonatal Diabetes International Collaborative Group. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. Diabetes Care 2008;31: 204–9. [Medline] [CrossRef]
6. Hashimoto Y, Dateki S, Hirose M, Satomura K, Sawada H, Mizuno H, *et al*. Molecular and clinical features of K_{ATP} -channel neonatal diabetes mellitus in Japan. Pediatr Diabetes 2016; [Epub ahead of print]. [Medline] [CrossRef]
7. Remedi MS, Agapova SE, Vyas AK, Hruz PW, Nichols CG. Acute sulfonylurea therapy at disease onset can cause permanent remission of K_{ATP}-induced diabetes. Diabetes 2011;60: 2515–22. [Medline] [CrossRef]
8. Villareal DT, Koster JC, Robertson H, Akrouh A, Miyake K, Bell GI, *et al*. Kir6.2 variant E23K increases ATP-sensitive K^+ channel activity and is associated with impaired insulin release and enhanced insulin sensitivity in adults with normal glucose tolerance. Diabetes 2009;58: 1869–78. [Medline] [CrossRef]