


Neonatal diabetes caused by the heterozygous Pro1198Leu mutation in the *ABCC8* gene in a male infant: 6-year clinical course

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Keywords

ABCC8 gene, Neonatal diabetes, Sulfonylurea receptor 1

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J Diabetes Investig 2020; 11: 502–505

doi: 10.1111/jdi.13127

ABSTRACT

Neonatal diabetes is a rare disease, often caused by a monogenic abnormality. A male infant patient developed diabetic ketoacidosis at 2 months-of-age due to the heterozygous *ABCC8* gene mutation (p.Pro1198Leu). After genetic diagnosis, insulin therapy was successfully transitioned to oral sulfonylurea therapy. For >6 years, oral sulfonylurea therapy has been safe and effective, and the required amount of sulfonylureas has progressively decreased. The mutation was transmitted in an autosomal-dominant fashion across three generations of his family, but the severity of diabetes varied among members from neonatal diabetes to mild diabetes. One family member had normal glucose tolerance despite having the mutation. This case presentation could help in the understanding of neonatal diabetes caused by the *ABCC8* gene mutation.

INTRODUCTION

Diabetes with onset <6 months-of-age that is autoantibody-negative for type 1 diabetes is called “neonatal diabetes.” Neonatal diabetes is often caused by a monogenic abnormality, and >20 genes have been reported as the causal gene^{1,2}. The adenosine triphosphate-sensitive K⁺ channel of pancreatic β-cells consists of the regulatory subunit by sulfonylurea receptor 1 encoded by the *ABCC8* gene, and the pore-forming subunit by Kir6.2, encoded by the *KCNJ11* gene³. Activating mutations of these genes, which leads to impairment of the closing of the adenosine triphosphate-sensitive K⁺ channel, causes neonatal diabetes^{1,2}. Here, we report the 6-year clinical course of a male infant with neonatal diabetes caused by an *ABCC8* gene mutation.

CASE REPORT

The male infant patient (Figure 1, III-1) was born in the 39th week of gestation with a birthweight of 3410 g (83.3rd percentile). At 2 months-of-age, he was admitted to the

Wakayama Medical University Hospital, Wakayama, Japan, due to diabetic ketoacidosis. Ketonuria, hyperglycemia (plasma glucose 557 mg/dL [69.6 mmol/mL], glycated hemoglobin 7.8%), metabolic acidosis (pH 7.19, pO₂ 128 mmHg, pCO₂ 13.6 mmHg, HCO₃ 8.8 mmol/L) and low serum C-peptide level (<0.2 ng/mL [<0.066 nmol/L]) were detected and insulin therapy was started. The autoantibodies to glutamic acid decarboxylase and islet antigen 2 were negative. Neurological abnormalities, such as developmental delay or epilepsy, were not observed.

After admission, we learned that the patient’s paternal female cousin (III-3) had also developed neonatal diabetes. As previously reported, the heterozygous p.Pro1198Leu mutation (NM_000352: c.3593 C>T) in the *ABCC8* gene, which was functionally an activating mutation, was associated with the development of her diabetes. Her treatment was successfully transitioned from insulin injection to oral sulfonylurea therapy after genetic diagnosis at 12 years-of-age⁴. We therefore carried out genetic analysis of the *ABCC8* gene in our current patient and found the same mutation. After genetic diagnosis, the patient began to receive 0.10 mg/kg/day glibenclamide as the

Received 29 May 2019; revised 1 August 2019; accepted 5 August 2019

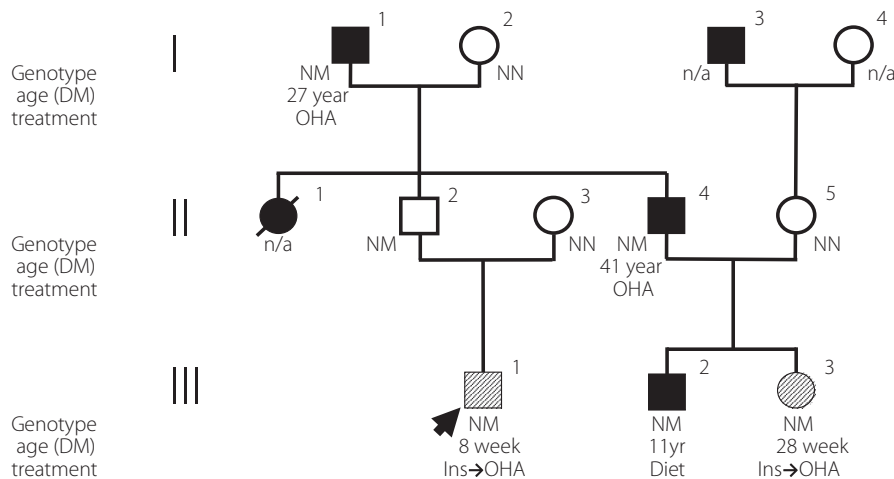


Figure 1 | Pedigree of a family with the p.Pro1198Leu mutation in the *ABCC8* gene. Circles represent females and squares indicate males. A slash mark through the circle indicates individuals who have died. An arrow indicates the proband. Black filling denotes diabetes mellitus (DM) and vertical hatching denotes neonatal diabetes. The genotype is given below each symbol. Age (DM), age at diagnosis of diabetes mellitus; INS, insulin; M, p.Pro1198Leu mutation in the *ABCC8* gene; N, normal genotype; n/a, data not available; OHA, oral hypoglycemic agent.

initial dose, which was progressively increased to 0.43 mg/kg/day (Figure 2). After starting oral sulfonylurea therapy, his blood glucose control dramatically improved and insulin therapy was stopped. Since then, we have followed up the patient for 6 years. His glycated hemoglobin levels have been controlled at approximately 5.5% during this period, and the required amount of glibenclamide has progressively decreased to 0.13 mg/kg/day (Figure 3). His growth has been satisfactory (bodyweight 22.5 kg [+0.1 standard deviation], height 120.2 cm [+0.5 standard deviation] at 6 years of age) and adverse events, such as hypoglycemia and obesity, have not been observed.

Furthermore, known manifestations of neonatal diabetes, such as epilepsy and change in dental color, were not observed in the affected members of this family⁵.

Within the family, the mutation was transmitted in an autosomal-dominant fashion across three generations, but the severity of diabetes varied between members (Figure 1). The present patient's grandfather (I-1) was diagnosed with diabetes at 27 years-of-age, and had been treated with oral hypoglycemic agents, including sulfonylureas, as early-onset common type 2 diabetes. The patient's uncle (II-4) was diagnosed with diabetes at 41 years-of-age. Although asymptomatic, his diabetes was

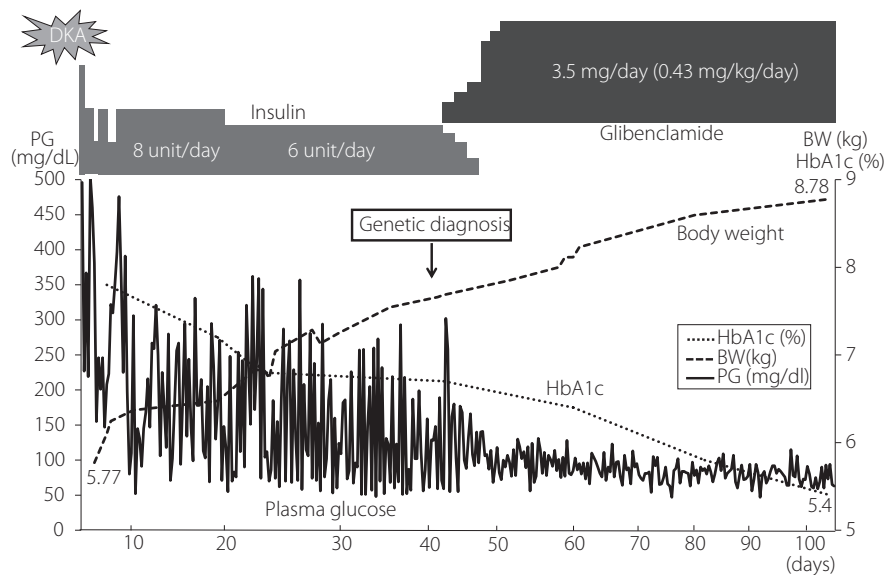


Figure 2 | Clinical course of plasma glucose levels, bodyweight and glycated hemoglobin (HbA1c) levels after admission. Blood glucose control was very unstable during insulin injection therapy. After starting oral sulfonylurea therapy, however, the patient's blood glucose control was dramatically improved and insulin therapy was stopped. BW, bodyweight; DKA, diabetic ketoacidosis; PG, plasma glucose level.

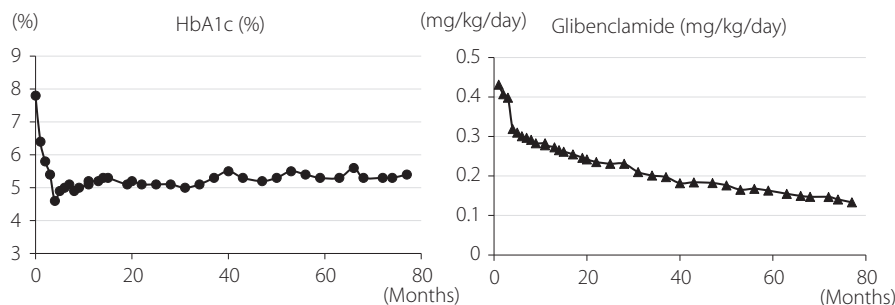


Figure 3 | Clinical progress of glycated hemoglobin (HbA1c) levels and the required amount of glibenclamide for 6 years. The required amount of glibenclamide progressively decreased from 0.43 to 0.13 mg/kg/day, and the patient's HbA1c levels have been controlled at approximately 5.5% over a period of approximately 6 years.

discovered by a medical check carried out when his daughter's neonatal diabetes was revealed to be due to the *ABCC8* gene mutation. Oral sulfonylurea therapy was also effective for the uncle. The present patient's paternal male cousin (III-2) also had the same mutation, but his diabetes was well controlled without medication. Furthermore, although the present patient's father (II-2) also had the same mutation, the result of his 75-g oral glucose tolerance test was normal glucose tolerance (Table S1). The clinical information of the family members with the *ABCC8* gene mutation is shown in Table S2. The phenotypic variability in diabetes among affected members was difficult to explain from their clinical information, so we examined for mutations in other known maturity-onset diabetes of the young genes (*HNF4A*, *GCK*, *HNF1A*, *PDX1*, *HNF1B*, *NEUROD1*, *KLF11*, *CEL*, *PAX4*, *INS*, *BLK*, *KCNJ11*, *APPL1*) with exome sequencing in III-1, III-2 and III-3. Although we did not find rare mutations that were thought to be associated with monogenic diabetes, we detected three missense mutations (*HNF1A*: p.Ile27Leu, rs1169288, *KCNJ11*: p.Lys23Glu, rs5219, p.Val337Ile, rs5215), which have been reported to be associated with type 2 diabetes in the genome-wide association study (Type 2 Diabetes Genetics Portal: <http://www.type2diabetesgenetics.org/home/portalHome>). We checked these missense mutations among affected members, but neither mutation was associated with the severity of diabetes (Table S3).

This research was carried out following the Declaration of Helsinki, and approved by Wakayama Medical University ethics committee (approval numbers 30 and 83). Written informed consent was obtained from all participants.

DISCUSSION

Oral sulfonylurea therapy is reportedly responsive in patients with diabetes caused by the *ABCC8* gene mutation⁶. Furthermore, the treatment has been reported as safe and effective until 13 months in one study⁷, and 3.5 years in another study⁸ after the start. The long-term clinical course of such patients, however, has not been detailed. In the present patient, insulin therapy was successfully transitioned to oral sulfonylurea therapy after genetic diagnosis. After that, oral sulfonylurea therapy

was safe and effective for >6 years, and the required amount of sulfonylureas progressively decreased. Furthermore, diabetes in the present patient's paternal grandfather (I-1) with the same mutation was well controlled with oral hypoglycemic agents, including sulfonylurea at 75 years-of-age (Table S2). These findings suggest that the treatment effect of oral sulfonylurea therapy is stable for a relatively long-term period.

In the present patient's family, the mutation was transmitted in an autosomal-dominant fashion across three generations, but the severity of diabetes varied from mild diabetes to neonatal diabetes. Furthermore, one member had normal glucose tolerance, despite having the mutation. Such phenotype variability for diabetes has also been reported in other families, where it was caused by dominantly inherited mutations^{9,10}. Furthermore, in one of the families reported, a member did not have diabetes, despite having the mutation, which was found in his son with neonatal diabetes and in his mother with adult-onset diabetes¹⁰. Other genetic factors might be involved in the phenotypic variability for diabetes due to the *ABCC8* gene mutation. To explain the phenotype variability for diabetes in the present family, we investigated mutations in other known maturity-onset diabetes of the young genes with exome sequencing, but no mutation identified had an association with the severity of diabetes in the present family.

In this family group, because the present patient's father (II-2) had not been diagnosed with diabetes, he had not been informed about the genetic risk for neonatal diabetes. If he was aware of his genetic risk and the possibility of heritability to his child, his son might have been able to receive treatment with sulfonylurea from an earlier stage. The present case suggests that during genetic counseling with a family with neonatal diabetes caused by the *ABCC8* gene mutation, it is necessary to consider phenotypic variability for diabetes.

ACKNOWLEDGMENTS

This work was supported by Japan Society for the Promotion of Science JSPS KAKENHI Grant Number JP17K09842. We acknowledge proofreading and editing by Benjamin Phillis at the Clinical Study Support Center, Wakayama Medical University.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | The result of a 75-g oral glucose tolerance test in the father of the proband (II-2).

Table S2 | Clinical characteristics of patients with the heterozygous P1198L mutation in the *ABCC8* gene.

Table S3 | Missense mutations in known genes of maturity-onset diabetes of the young identified in the family, and the relationships to the risk of type 2 diabetes reported in the genome-wide association study.