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Case Report

Use of a long-term continuous glucose monitor for predicting sulfonylurea dose in patients with neonatal diabetes mellitus: a case series

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Highlights

- Integration of continuous glucose monitoring (CGM) during the neonatal period.
- Long-term use of CGM aids dose and frequency adjustments for glibenclamide.
- Cases of neonatal diabetes mellitus were transitioned to oral sulfonylureas.

Abstract. Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes that presents with uncontrolled hyperglycemia during the first 6 months of life. NDM is a rare disease in which gene variants mainly cause β-cell loss or dysfunction (6q24 duplication, *KCNJ11*, and *ABCC8*). Although NDM is primarily treated through insulin therapy, it is highly challenging to manage blood glucose levels using insulin therapy during infancy. In contrast, *KCNJ11* and *ABCC8* mutant patients received oral sulfonylureas (SU) instead of insulin injections; however, the dose and frequency differ among individuals. Continuous glucose monitoring (CGM) is useful in patients with type 1 diabetes; but reports on patients with NDM are lacking. Herein, we report two cases of NDM with the *KCNJ11* variant. We used CGM not only during insulin injection therapy but also after switching to oral SU therapy. The CGM data can also be used to determine the dose and frequency of SU. Furthermore, long-term CGM may be useful for adjusting SU dose and frequency, and maintaining good glycemic control not only during insulin injection but also during oral SU therapy.

Key words: neonatal diabetes, sulfonylurea, glycemic control, continuous glucose monitoring (CGM)

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Introduction

Neonatal diabetes mellitus (NDM) is a type of diabetes characterized by uncontrolled hyperglycemia during the first 6 months of life (1, 2). NDM is a rare disease with an incidence of one per 300,000–400,000 live births (3). Over 80% of patients with diabetes under 6 months of age have a monogenic cause, with the most common one being β cell/potassium channel variant (2, 4–6). Autoimmune NDM is extremely rare (type 1 diabetes mellitus) (4, 7).

NDM is divided into 2 types: transient NDM (TNDM) and permanent NDM (PNDM) (1, 2). In a Japanese cohort, 52% of NDM cases were TNDM, required insulin therapy, and spontaneously resolved within 18 mo (6, 8). Most cases of TNDM are caused by abnormalities in chromosome 6, 6q24 duplication in the paternal allele, or loss of methylation at 6q24 in the maternal allele (8). Conversely, PNDM is caused by variants of the *KCNJ11* and *ABCC8* genes, which encode the ATP-dependent potassium channel (Kir6.2/SUR1) of the β-cells of the pancreas (8). Suzuki *et al.* reported that 35% of Japanese patients with NDM and other molecular defects had *KCNJ11* or *ABCC8* variants (6).

NDM is primarily treated with insulin therapy. However, administering insulin therapy in infants is challenging because of the very low dose of insulin, small body surface area, and unpredictable feeding patterns (9); nevertheless, very little data are available on the methods of insulin delivery in NDM (3). In contrast, patients with *KCNJ11* and *ABCC8* mutants are treated with oral sulfonylurea (SU) rather than insulin injection (3). Some studies have reported the effectiveness of continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) in patients with NDM receiving insulin therapy (10–17). However, few studies have reported the effectiveness of CGM in patients with NDM during and after switching to oral SU (18, 19).

Here, we report two cases of NDM that were initially treated with insulin infusion using CSII and a sensor-augmented pump (SAP); however, their treatment was switched to oral SU with CGM during the neonatal period.

Case Presentation

Case 1

A 37-d-old male baby was brought to the local doctor because of fever (39°C). His mother had gestational diabetes, but othere was no family history of diabetes. The patient was born at 38 wk and 5 d of gestation with a weight of 2428 g and presented with polydipsia (breastfeeding every hour) and polyurea for several days. The local doctor checked his urine and determined his urinary glucose level. The patient was then transferred to another hospital wherein blood gas analysis revealed moderate diabetic ketoacidosis (**Table 1**); the patient was then transferred to our hospital on the same day. The patient showed signs of dehydration (capillary refill time of 4 s and loss of skin turgor). Details of the post-hospitalization events and outcomes are shown in **Fig. 1**. Rehydration and continuous venous insulin infusion (CVII) were administered. Ketoacidosis improved the next morning, and the insulin infusion was changed to CSII with SAP (MiniMed 640G system, Medtronic plc, Dublin, Ireland). The patient experienced burst seizures on the same day. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) were performed. EEG revealed 2–3 Hz spike waves in the left frontal head region, whereas MRI revealed no remarkable changes. We considered his condition to be similar to that of patients with developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome. Because of the possibility of developmental delay while continuing insulin therapy, we decided to switch to oral glibenclamide at 1.0 mg/kg/d instead of CSII, but continued to monitor the glucose trends. Antiepileptic drugs (AEDs) were not administered. The patient developed hypoglycemia, and we discontinued CSII, 3 days after the administration of glibenclamide. **Figure 2** shows the results of CGM data the next day after insulin infusion was discontinued (**Fig. 2A**). His glucose level decreased rapidly after taking glibenclamide, but increased gradually after 3 h, and was hyperglycemic 5–6 h after taking glibenclamide. The amount and interval of glibenclamide administration were adjusted using CGM. The glucose level of the patient stabilized when he consumed glucose (3.0 mg/kg/d) every time he sucked; however, this was difficult for his parents (**Fig. 2B**, 11 d after admission). We again adjusted the amount of glucose and interval, following which the glucose level became increasingly stable even when the amount and interval of glibenclamide administration decreased. The patient showed no seizure. MRI findings were normal, and EEG showed no signs of epilepsy without AEDs. The patient was discharged on day 35 of hospitalization.

Table 1. Results of blood test on admission

	Case 1	Case 2
Venous blood gas		
pH	7.280	6.820
pCO_2 (mmHg)	18.5	26.2
pO_2 (mmHg)	40.8	46.0
HCO_3 (mmol/L)	8.4	4.0
B.E. (mmol/L)	–16.9	–29.5
Biochemical examination		
Glu (mg/dL)	534	919
C-peptide (ng/mL)	0.02	0.08
Total ketone body (μmol/L)	12230	17360
3-HB (μmol/L)	8741	13860
Glycoalbumin (%)	48.9	46.9
Antibody		
GAD antibody (U/mL)	< 5.0	< 5.0
IA-2 antibody (U/mL)	< 0.6	< 0.6

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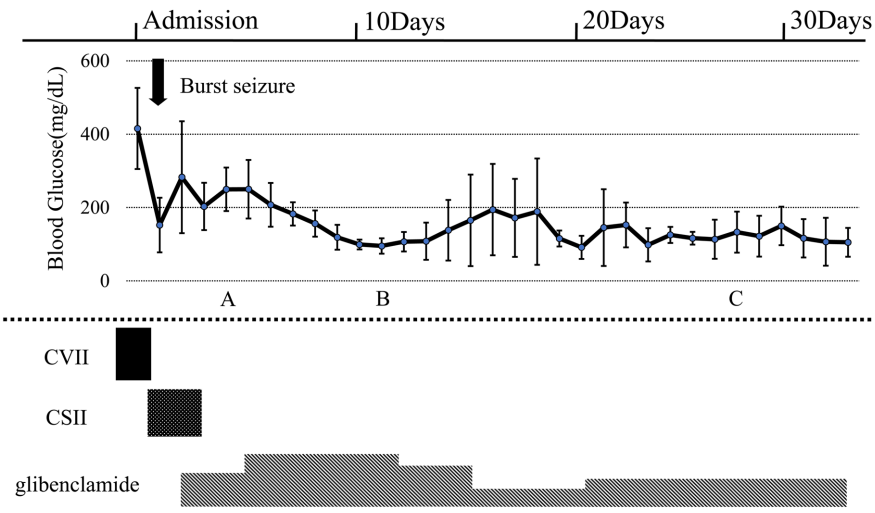

Fig. 1. Progress of case 1 after hospitalization. Changes in blood glucose level are shown using a line curve. This patient had a burst seizure on day 2 after admission (arrow). We switched the therapy from insulin injections to glibenclamide.

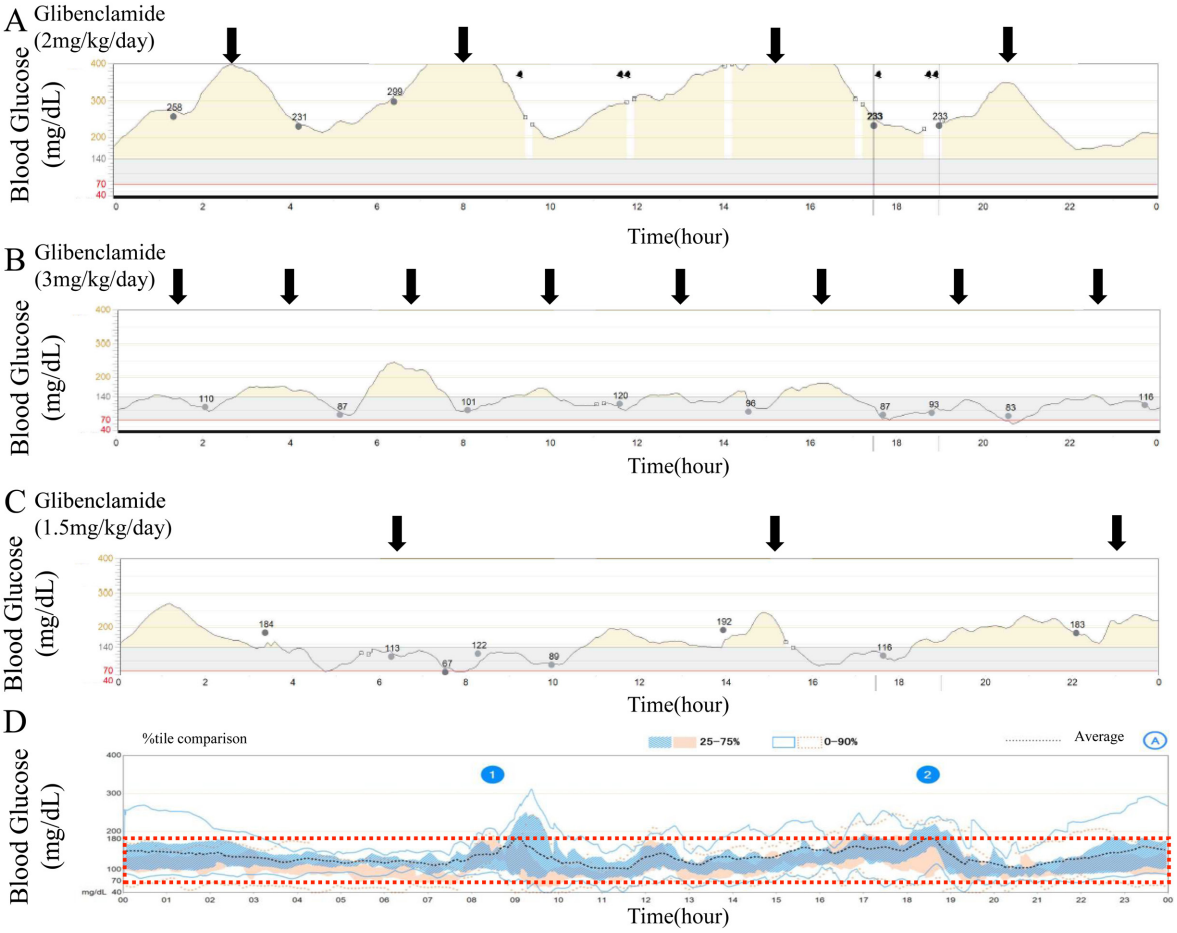

Fig. 2. Results of continuous glucose monitoring (CGM) for case 1 during hospitalization. Figure A shows the results of CGM on day 5 (glibenclamide, 2 mg/kg/d, q4). We adjusted the amount and interval of glibenclamide administration using CGM. **Fig. 2B** shows the results of CGM on day 11 (glibenclamide, 3 mg/kg/d, q8). The glucose level stabilized when the patient took the drug every time while sucking, but this was challenging for his parents. We adjusted the amount and interval of glibenclamide administration using CGM. **Fig. 2C** shows the results of CGM on day 28 (glibenclamide, 1.5 mg/kg/d, q3). The blood glucose levels continued to stabilize. **Fig. 2D** shows the results of CGM 2 yr after admission. His blood glucose level mostly remained within the normal range (70–180 mg/dL, surrounded by a square dotted line), and the change in blood glucose level was not significant.

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Upon discharge, the patient's glucose levels improved without insulin infusion (**Fig. 2C**). Written informed consent was obtained from his parents for genetic examination, which revealed a heterogeneous missense variant (c.510 G>T, p. K170N) in *KCNJ11* on target sequencing. This variant has been previously reported in patients with PNDM (20, 21); thus, we diagnosed the patient with DEND syndrome. After 2 yr, his glycemic control remained within the normal range (**Fig. 2D**), with good neurological development and no seizures with glibenclamide (0.4 mg/kg/d; 3 or 4 times daily). The patient continued to receive real-time CGM (Guardian Connect, Medtronic plc), and the dose and frequency of glibenclamide were adjusted.

Case 2

A 56-d-old male baby was brought to a local doctor because of frequent vomiting and poor sucking in the morning. There was no family history of diabetes. He was born at 41 wk and 3 d of gestation and weighed 2665 g. The patient exhibited Kussmaul breathing and signs of dehydration (capillary refill time of 4 sec and loss of skin turgor). Blood gas analysis revealed severe diabetic ketoacidosis, and the patient was transferred to our hospital on the same day (**Table 1**). Details of the post-hospitalization events and outcomes are shown in **Fig. 3**. Rehydration and CVII therapy were initiated. Ketoacidosis improved the following morning, and the patient was switched to CSII with SAP. His condition was subsequently stable. Therefore, insulin therapy was initiated. We suggested genetic testing for the patient's family and obtained their consent. He was discharged with the SAP; however, glycemic control was very difficult, and his glucose levels remained high (**Fig. 4A**). Three months after admission, written informed consent for genetic examination was obtained from the patient's parents. Next-generation sequencing

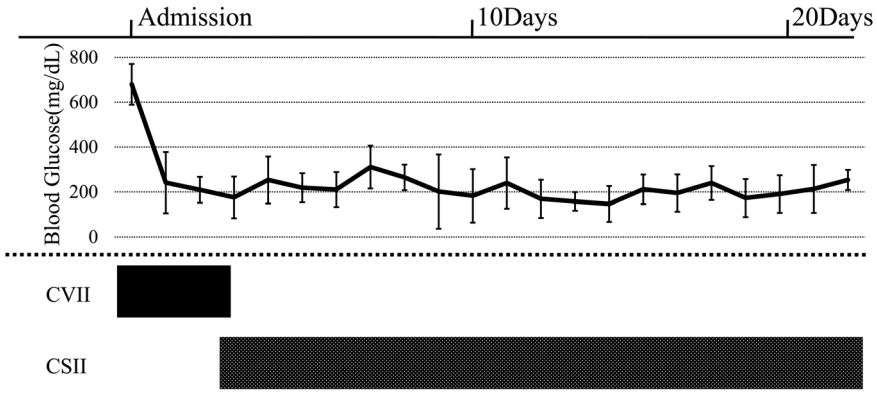

Fig. 3. Progress of the patient after the first hospitalization. Changes in blood glucose level are shown using a line curve. Seizures were not observed. We continued to control the patient's blood glucose levels using a sensor-augmented pump (SAP).

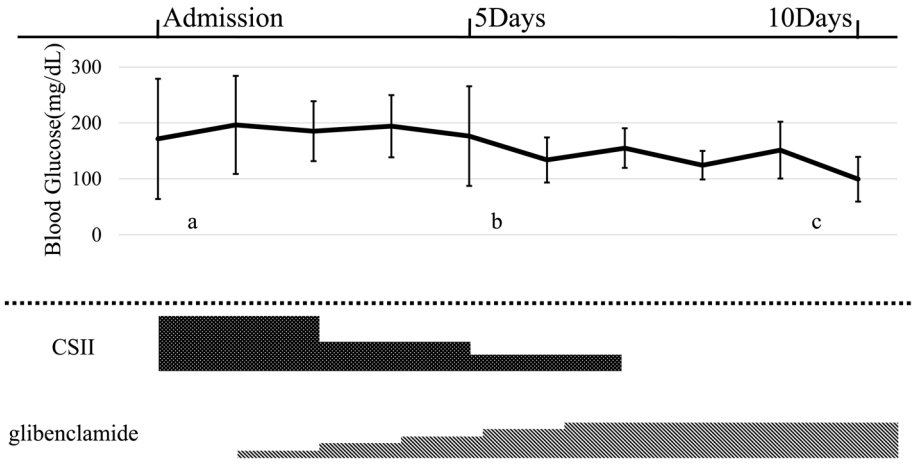

Fig. 4. Results of continuous glucose monitoring (CGM) for case 2. **Fig. 4A** shows the results of CGM, 3 mo after the first hospitalization (insulin injection using SAP). We switched treatment from insulin injection to oral sulfonylurea (SU) after detecting a missense variant in *KCNJ11*. **Fig. 4B** shows the results of CGM during the second hospitalization. **Fig. 4C** shows the results of CGM, 2 mo after switching to SU (glibenclamide, 1 mg/kg/d, q12). The patient's glucose level continued to stabilize and mostly remained within the normal range (70–180 mg/dL, surrounded by a square dotted line); the change in blood glucose level was not significant.

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revealed a novel heterogeneous missense variant (c.988 T>G, p. Y330D) in *KCNJ11*. Based on the prediction by Mutation Taster and Polyphen2 software, this variant was regarded as disease-causing. The other variants (p.Y330C and p.Y330H) were registered as pathogenic in ClinVar; thus, the patient was diagnosed with neonatal diabetes. Consequently, we changed the therapy to oral glibenclamide, according to Pearson *et al.* (22). The patient was readmitted and switched to oral glibenclamide. The details of this process are shown in **Fig. 5**. We started glibenclamide at 0.2 mg/kg/d and increased by 0.2 mg/kg/d every day for 5 d after admission (1.0 mg/kg/d). His glycemic control improved, and CSII was terminated 6 d after admission. The CGM data for days 1, 6, and 10 are shown in **Fig. 4B**. A comparison with glucose controls is shown in **Fig. 4C**. After 1 yr and 6 mo, we adjusted the dosage and frequency of glibenclamide based on lifestyle changes (increase in momentum) and CGM data. After 2 yr, his glycemic control remained within the normal range (**Fig. 5D**), with good neurological development and no seizures, and glibenclamide intake twice a day (0.2 mg/kg/d).

Discussion

Genetic testing was performed immediately in both the patients because of extreme hyperglycemia. Furthermore, we switched to SU therapy immediately after burst seizures or after we the *KCNJ11* variant. Both patients showed improved glycemic control and no neurological problems such as epilepsy. Lemelman *et al.* (23) suggested that genetic testing should be considered immediately in patients presenting with extreme acute hyperglycemia. Li *et al.* (24) recommended early transition from insulin to SU therapy in patients with NDM. Patients with NDM having *KCNJ11* and *ABCC8* variants who switched to SU therapy, especially before 4 yr of age, showed global improvement in neurological outcomes and alleviated epilepsy earlier (25, 26). Moreover, patients with intermediate DEND syndrome who switched to SU therapy within 1 yr of age maintained their developmental scores, whereas those who switched to SU therapy after 1 yr of age had a reduced developmental score (27). Early genetic testing may be beneficial for neonates with extreme hyperglycemia. Moreover, for patients with NDM harboring K_{ATP} channel variants, SU therapy should be initiated early to improve glycemic control and neurological symptoms.

Our patients were successfully switched to SU therapy before 1 yr of age. In previous studies, approximately 90% of patients with diabetes and the *KCNJ11* variant were successfully switched to SU and discontinued insulin therapy (22, 26, 28, 29). Babiker *et*

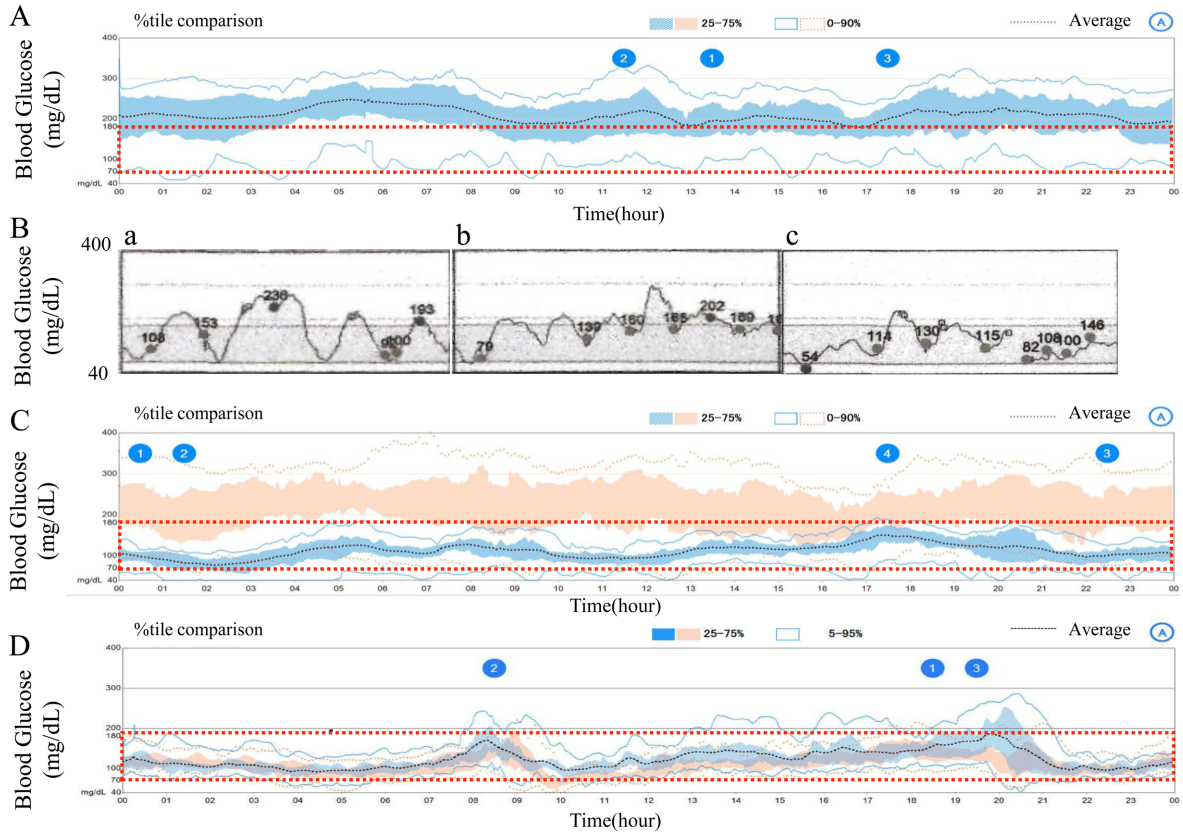

Fig. 5. Progress of case 2 during hospitalization after switching from insulin injection to oral SU therapy. Changes in blood glucose level are shown using a line curve. Seizures were not observed. We continued to control the patient's blood glucose levels using CGM.

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al. reported that the younger the patient, the greater the likelihood of a successful switch to SU (29). Moreover, some patients with neurological symptoms improved after SU administration, particularly before 4 yr of age (25, 26, 30). When *KCNJ11* or *ABCC8* variants are detected in patients with NDM, the goal is to switch to SU as soon as possible.

In case 1, the seizure ceased, and EEG signal improved after the administration of glibenclamide without any AED. K_{ATP} channels (Kir6.2/SUR1), which are encoded by *KCNJ11* and *ABCC8* genes, are found not only on pancreatic β-cells but also in other tissues, including muscles and the brain (31). This accounts for the fact that approximately 20% of patients with NDM have neurological deficits, including developmental delays and seizures (31). The efficacy of SU therapy in improving neurological and psychomotor function in patients with *KCNJ11* or *ABCC8* variants has been reported (27, 32); however, there are no reports on the control of epilepsy without AEDs. Hashimoto *et al.* (26) and Shimomura *et al.* (33) evaluated the clinical course of DEND syndrome in patients with therapy-resistant epilepsy and reported controlled seizures and improved EEG findings after glibenclamide therapy. These findings suggest that SU therapy may help control epilepsy. In cases of DEND syndrome, administering SU therapy may be effective not only for improving glycemic control but also for seizure control.

We adjusted the doses of insulin and SU while monitoring blood glucose levels using CGM. SAP therapy is effective in patients with type 1 diabetes, regardless of age (34). Some studies have reported the benefits of CSII and CGM in patients with NDM (10, 15, 17, 19, 35). Three previous studies have shown that CGM is useful not only for insulin therapy, but also for switching to oral SU in patients with NDM with the *KCNJ11* variant (19, 35, 36). Li *et al.* reported the feasibility of switching to oral SU therapy before genetic testing (24). Some patients are resistant to oral SU therapy; thus, insulin and glibenclamide with frequent blood glucose monitoring is necessary when switching therapy (22). CGM is helpful not only for judging the effectiveness of oral SU therapy, but also for administering oral SU doses.

The dose and frequency of glibenclamide administration differed between the two cases. The primary and maintenance doses of SU differ individually, depending mainly on the genetic variant (22, 24, 26, 29). Some clinical reports have indicated differences in the frequency (2–6 times a day) and dose (0.18–3.0 mg/kg/d at response dose) of glibenclamide (19, 26, 35, 36). These studies used CGM to adjust the dose and frequency of glibenclamide (19, 35, 36) but did not apply long-term CGM monitoring. We adjusted the dose of glibenclamide by referring to the CGM data on a long-term basis, and the glycemic control remained within the normal range for a long time without insulin injection. Long-term CGM may be useful for adjusting the dose and frequency of glibenclamide and maintaining good glycemic control.

Conclusion

Here, we report two cases of NDM that were controlled using CGM before and after switching to SU therapy. CGM is useful for adjusting not only insulin doses, but also oral SU doses and frequencies, and long-term use of CGM should be considered for treating infants and children with NDM.

Conflict of interests: The authors declare no conflicts of interest associated with this article.

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