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Case Report

Management of a case of transient neonatal diabetes mellitus using continuous glucose monitoring

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Abstract. Neonatal diabetes mellitus (NDM) is a very rare disorder and its diagnosis can be challenging especially in mild and transient cases. Herein, we describe a 2.4-kg female infant born at 38 wk of gestation who showed hyperglycemia (388 mg/dL) on Day 1. Intermittent blood sampling showed glucose concentrations of 100–150 mg/dL on Day 2–5. However, continuous glucose monitoring (CGM) from Day 7 revealed hyperglycemia (> 200 mg/dL) after every feeding. The patient required low-dose (0.1–0.2 U/kg/d) insulin therapy for a short period (7 d). During the treatment, hypoglycemic (< 50 mg/dL) events were not detected by real- time CGM. Follow-up CGM from Day 32 showed normoglycemia for 3 full days; therefore, we ascertained that the diabetes had been transient. Later genetic analysis revealed an abnormal methylation pattern on chromosome 6q24, which is the most frequent cause of transient NDM. Most cases of 6q24-related NDM relapse after puberty, implying that long term follow up is required. We speculate that the NDM in this case might not have been diagnosed without CGM. This report highlights the usefulness of CGM for the initial diagnosis, monitoring during insulin therapy, and confirmation of improvement in patients with transient NDM.

Key words: continuous glucose monitoring, hyperglycemia, 6q24-related diabetes, neonatal diabetes mellitus

Introduction

Continuous glucose monitoring (CGM) has recently become established in neonatal intensive care units. A CGM device, which measures subcutaneous glucose concentrations at 5-min intervals, is a more informative and less invasive method than repeated blood glucose measurement. Therefore, there is increasing interest in its clinical use, particularly in very low birth weight (VLBW) infants and in term neonates that have some risk factors for hypoglycemia (1–5). However, the usefulness of CGM for identifying possible cases of neonatal diabetes mellitus (NDM) has not been established.

Case Report

A female baby was delivered by emergency cesarean section at 38 wk of gestation, because of partial placental abruption. Her birth weight was 2.4 kg (−1.0 standard deviation) and her Apgar scores were 8 and 8 at 1 and 5 min, respectively. She was the first child of healthy, unrelated parents and there was no remarkable family history, including diabetes. On the day after delivery, she was transferred to the Neonatal Intensive Care Unit because of frequent vomiting and constipation. This study was approved by the institutional review board (ID: P191201000).

Her vital signs were stable; she had a heart rate of 128/min, a respiratory rate of 30/min, a blood pressure of 67/48 mmHg, and an oxygen saturation level of 100% in room air. Physical examination revealed abdominal distension, but no other abnormalities. However, the initial laboratory examination revealed a blood glucose of 388 mg/dL without severe metabolic acidosis (base deficit of 4.0 mEq/L); therefore, we initiated intravenous insulin therapy at a dose of 0.5 U/kg/d, and her blood glucose fell below 70 mg/dL, when we stopped insulin administration for the day. From Day 2, she was fed formula every 3 h and administered 1–3 mg/kg/min glucose by intravenous infusion. We checked her blood glucose concentration just before feeding four times a day, and this was in the range of 100–150 mg/dL. The abdominal distension was suspected to be due to Hirschsprung's disease, and the symptom was controlled effectively by frequent administration of an enema.

To permit close monitoring of glucose status, we started real-time CGM (Guardian™ Connect CGM system, Medtronic, Japan) from Day 7. This system is approved for use in patients with type 1 or type 2 unstable diabetes (no limitation to patients' age). We

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obtained informed consent from the patient's parents to use CGM for possible diagnosis of diabetes. The CGM revealed a high level of variability in interstitial glucose concentration between feeds, with repeated episodes of hyperglycemia (> 200 mg/dL) (**Fig. 1A**). We then resumed intravenous insulin at a low dose (0.1–0.2 U/kg/d), which was adjusted according to the blood glucose measurements at the time of sensor calibration. We set the lower alarm at 60 mg/dL in order to detect possible hypoglycemia. The use of CGM allowed us to avoid both hyper- (> 200 mg/dL) and hypoglycemic (<50 mg/dL) events (**Fig. 1B**). We stopped insulin administration from Day 15, and the infant gained weight adequately thereafter. We repeated CGM from Day 32, when the infant was consuming formula every 3 h and not receiving intravenous glucose. This 72-h analysis revealed a range of glucose concentrations from 56 to 186 mg/dL, with no episodes of hyperglycemia (> 200 mg/dL) (**Fig. 2**). On the basis of these results, we ascertained that this was a case of transient diabetes.

After obtaining written informed consent from the child's parents, a genetic work-up was performed for NDM. Sequencing of the coding exons of *ABCC8* and *KCNJ11* revealed no variants. Methylation-specific polymerase chain reaction amplification of the 6q24 imprinted locus showed an abnormal pattern, suggestive of paternal disomy or hypomethylation of the maternal allele. Consequently, the child was diagnosed with 6q24-

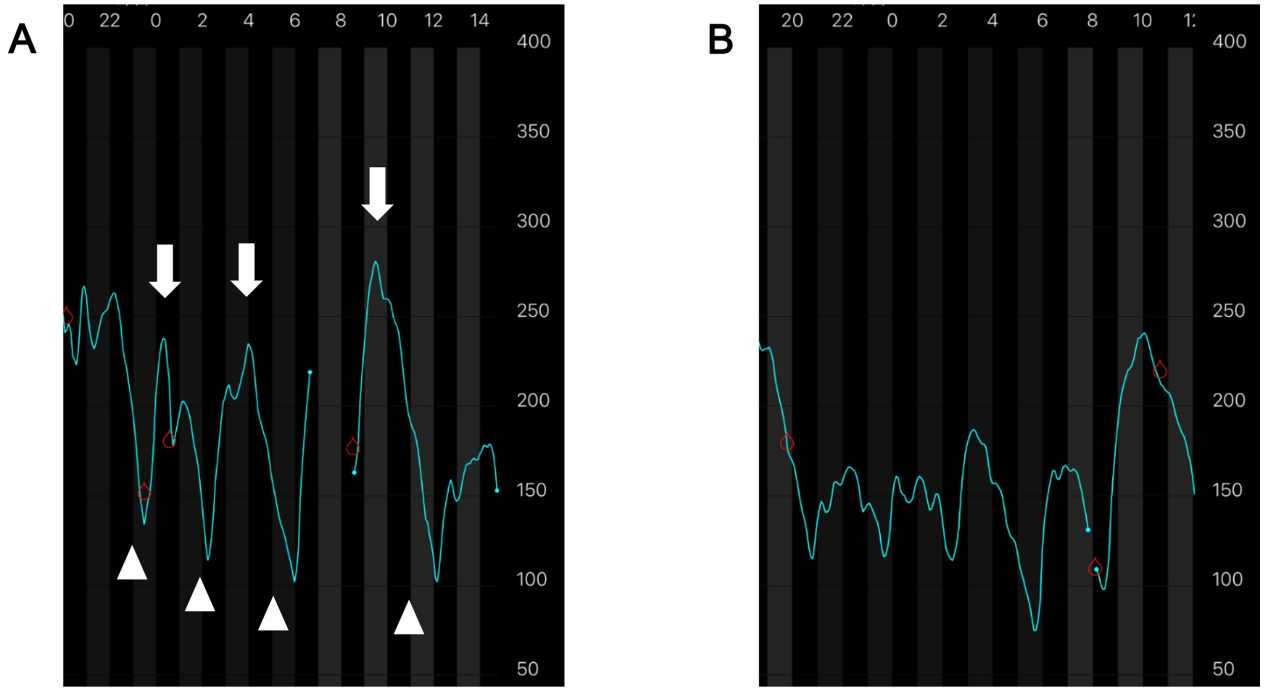

Fig. 1. Screen captures from the continuous glucose monitoring system. (A) Day 7, 2000 h–Day 8 1400 h (data missed Day 8 between 0600 and 0800 h). At each feed, the triangles show that the interstitial glucose concentration was 100–150 mg/dL, and the arrows show that this was increased to > 200 mg/dL. (B) Day 8, 1800 h–Day 9, 1200 h. Regular administration of insulin prevented hyperglycemia (> 200 mg/dL) after four of the five feedings, and hypoglycemia (< 50 mg/dL) did not occur.

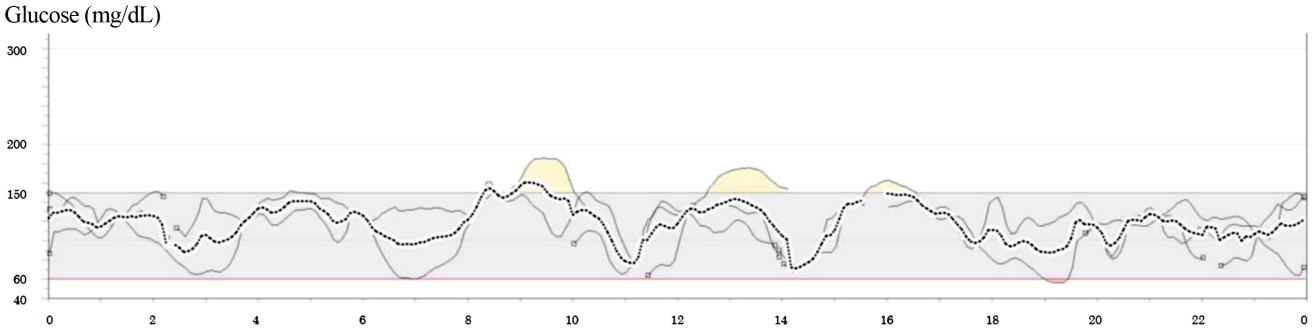

Fig. 2. Seventy-two-hour continuous glucose monitoring trace. The mean glucose concentration was 118 ± 27 (standard deviation) mg/dL. The percentages of time during which hyperglycemia (> 200 mg/dL) and hypoglycemia (< 50 mg/dL) were identified were 0% and 0%, respectively.

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related transient NDM. We explained to the family about the possibility of future relapse and that the risk of a subsequent child also having NDM would be low.

Discussion

CGM is well established in the management of adult diabetes mellitus and has also provided important insights regarding neonatal glucose metabolism. In some prospective cohort studies of VLBW infants, CGM has shown that the prevalence of hypo- and hyperglycemia in the first week of life is very high (1). In other studies, CGM has revealed that clinically stable preterm infants are still at risk of abnormal glycemia, even after the establishment of full enteral nutrition (2). In addition, in studies involving term or near-term neonates possessing risk factors (maternal diabetes, gestational age of 35–36 weeks, low birth weight [< 10^{th} percentile or < 2500 g], or high birth weight [> 90^{th} percentile or > 4500 g]), CGM showed that many neonates experience prolonged periods of low interstitial glucose, despite regular blood glucose testing and a clinical management protocol designed to maintain normoglycemia (3). Recently, a real-time CGM system has been reported to help maintain the blood glucose concentrations of VLBW infants within the euglycemic range (4, 5).

NDM is considered to be a rare disorder, with an estimated incidence of 1/89,000 in Japan (6). Although diagnostic criteria have been proposed (**Table 1**) (7), the diagnosis of NDM can be challenging because the symptoms may be subtle and non-specific. Furthermore, the glycemic variation may be missed if blood sampling is infrequent. Glycated hemoglobin (HbA1c), a marker of the glycemic status of the preceding months, cannot be used for blood glucose monitoring in neonates because of the presence of fetal hemoglobin, and glucose tolerance testing has not been standardized for newborns. It is reported that glycated albumin may reflect recent glycemic status and can be helpful for diagnosing NDM (8). The case reported herein highlights the usefulness of CGM for the management of NDM. In neonates, blood glucose concentrations are usually measured just before feeding and it is difficult to estimate when blood glucose concentration will peak after each feed. As shown in the present report, there may be substantial variation in glucose concentration; therefore, a single measurement is unlikely to reveal hyperglycemia. By contrast, CGM is capable of identifying the peak in blood glucose concentration, the number of hyperglycemic episodes, and the positive interstitial increment (the area under the interstitial glucose concentration curve above a particular value). Once NDM is suspected, the treatment goals are to achieve glycemic control and prevent both hyper- and hypoglycemia. During insulin therapy, real-time CGM can be a useful way of maintaining safe glycemic control. With an appropriate alarm setting, it is possible to perform blood sampling before hypoglycemic events may occur. It must be mentioned that real-time CGM only suggests the timings to check blood glucose level. In addition, the insulin dosage should be adjusted by blood glucose measurements, not solely by CGM results. CGM is useful for confirming that infants are not having abnormal interstitial glucose levels over a long period of time.

NDM has two clinical variants: a transient form (TNDM) and a permanent form (PNDM). These variants differ in the duration of insulin dependence early in the disease: insulin secretion recovers spontaneously within several months of birth in TNDM but not in PNDM. In Japan, TNDM and PNDM have been reported to account for 45.8% and 54.2% of the total cases, respectively (1). Abnormalities on the imprinted locus of chromosome 6q24 are the most common cause, accounting for two-thirds of all TNDM cases. Most patients with 6q24-TNDM are born small-for-gestational-age, which likely reflects insulin deficiency *in utero*. At its onset, many patients experience hyperglycemic dehydration, and they often have several associated conditions, including macroglossia, umbilical hernia or organ anomalies (9). However, the present case showed none of these, meaning that a diagnosis relied on the assessment of glucose status alone. Remission usually occurs by 18 mo of age (median: 3 mo); however, a notable proportion of the patients relapse after puberty (median: 14 yr). This relapsed diabetes is permanent and characterized by diminished insulin secretion but not obesity or

Table 1. Proposed diagnostic criteria of neonatal diabetes mellitus (NDM) (Inagaki)

A diagnosis of NDM is based on (1) the time of onset, (2) persistent hyperglycemia, and (3) specific symptoms of NDM.

(1) + (2) or (1) + (3) are diagnostic markers for NDM.

(1) The onset before 6 mon of age
* The onset is defined as the day of the first insulin treatment.
* Can be beyond 6 mon in cases with insulin gene mutations.

(2) Persistent hyperglycemia of ≥ 200 mg/dL
* Hyperglycemia due to prematurity or excessive glucose infusion should be excluded.
* Two or more episodes of hyperglycemia must be confirmed on different days. However, caution should be taken for the rapid deterioration due to ketoacidosis.

(3) Specific symptoms of NDM
* Feeding difficulty, dehydration and failure to thrive without insulin treatment.

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autoantibodies. Interestingly, there have been several reports of patients with 6q24-related diabetes who do not have a history of TNDM (10). It is not clear whether these patients did not have TNDM or whether they had relatively mild diabetes that went unrecognized during the neonatal period. We speculate that mild TNDM, such as in the present case, is underdiagnosed where clinicians rely solely on the recognition of symptoms or take blood samples infrequently. Because of this, CGM may represent one of the most sensitive screening tools for TNDM.

Conflict of Interests: None of the authors have any potential conflicts of interest associated with this report.

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References

1. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, Ong K, *et al*. Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of the NIRTURE study. J Pediatr 2010;157: 715–9.e1, 3. [Medline] [CrossRef]
2. Mola-Schenzle E, Staffler A, Klemme M, Pellegrini F, Molinaro G, Parhofer KG, *et al*. Clinically stable very low birthweight infants are at risk for recurrent tissue glucose fluctuations even after fully established enteral nutrition. Arch Dis Child Fetal Neonatal Ed 2015;100: F126–31. [Medline] [CrossRef]
3. Harris DL, Battin MR, Weston PJ, Harding JE. Continuous glucose monitoring in newborn babies at risk of hypoglycemia. J Pediatr 2010;157: 198–202.e1. [Medline] [CrossRef]
4. Uettwiller F, Chemin A, Bonnemaison E, Favrais G, Saliba E, Labarthe F. Real-time continuous glucose monitoring reduces the duration of hypoglycemia episodes: a randomized trial in very low birth weight neonates. PLoS One 2015;10: e0116255. [Medline] [CrossRef]
5. Galderisi A, Facchinetti A, Steil GM, Ortiz-Rubio P, Cavallin F, Tamborlane WV, *et al*. Continuous glucose monitoring in very preterm infants: A randomized controlled trial. Pediatrics 2017;140: e20171162. [Medline] [CrossRef]
6. Nagashima K, Tanaka D, Inagaki N. Epidemiology, clinical characteristics, and genetic etiology of neonatal diabetes in Japan. Pediatr Int 2017;59: 129–33. [Medline] [CrossRef]
7. Kawai M. Neonatal diabetes mellitus. Nihon Rinsho 2016;74(Suppl 2): 485–9 (In Japanese). [Medline]
8. 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]
9. Docherty LE, Kabwama S, Lehmann A, Hawke E, Harrison L, Flanagan SE, *et al*. Clinical presentation of 6q24 transient neonatal diabetes mellitus (6q24 TNDM) and genotype-phenotype correlation in an international cohort of patients. Diabetologia 2013;56: 758–62. [Medline] [CrossRef]
10. Yorifuji T, Matsubara K, Sakakibara A, Hashimoto Y, Kawakita R, Hosokawa Y, *et al*. Abnormalities in chromosome 6q24 as a cause of early-onset, non-obese, non-autoimmune diabetes mellitus without history of neonatal diabetes. Diabet Med 2015;32: 963–7. [Medline] [CrossRef]