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[Case Report]

## Serial investigation of continuous glucose monitoring in a very low birth weight infant with transient late-onset hyperglycemia

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### Abstract

Transient late-onset hyperglycemia was detected in a very low birth weight (VLBW) infant (gestational age 28 weeks, birth weight 1,082 g) by routine point-of-care glucose monitoring. The infant had no clinical symptom. Serial continuous glucose monitoring (CGM) was conducted for 3 days at 31, 35, and 39 weeks' post conceptual age. The difference values between the maximum and minimum blood glucose levels during the interval from one enteral feeding to the next enteral feeding were  $32.3 \pm 14.3$  mg/dL,  $47.5 \pm 22.9$  mg/dL, and  $27.5 \pm 12.9$  mg/dL for the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> CGM, respectively. The serial change in the values was statistically significant ( $p < 0.01$ ). CGM is widely used as a routine clinical practice, which is true even in VLBW infants. Hyperglycemic events detected by only once of CGM in otherwise healthy preterm infants have already been reported on larger numbers of patients. To our knowledge, this is the first report that the change of glucose intolerance in a VLBW infant with transient late-onset hyperglycemia was investigated by serial CGM.

**Key words :** continuous glucose monitoring, serial, very low birth weight infants, late-onset hyperglycemia, glucose intolerance

### Introduction

Continuous glucose monitoring (CGM) is used safely and reliably in neonates, including very low birth weight (VLBW) infants, in whom it detects many more episodes of both low and high glucose concentrations than intermittent blood glucose measurements<sup>1)</sup>. Most previous studies have been conducted in newborns with hypoglycemia, and a few studies have reported blood glucose variability in VLBW infants with transient neonatal hyperglycemia yet<sup>2-4)</sup>. We performed serial CGM in a VLBW infant with late-onset hyperglycemia detected by routine screening.

### Case

A 1,082 g (+0.08 SD) female infant was born at 28 weeks of gestation by normal vaginal delivery.

Her clinical course was unremarkable, and total parenteral nutrition was started on day 1 of life. The maximum intravenous glucose infusion rate was 7.3 mg/kg/min on day 3. She received fortified mother's milk (HMS-1®, Morinaga Milk Ind. Tokyo, Japan) via gastric tube every 2 hour and no intravenous glucose on day 17 (31 weeks' post conceptual age : PCA). After her admission, her blood glucose level was checked at least twice a day by point-of-care testing (Radiometer ABL835). As the treatment for apnea of prematurity, aminophylline, which may be potentially affecting blood glucose levels, was administered from day 0 to day 74 of life. Other drugs such as steroids used for prevention of chronic lung disease were not given.

On day 20 of life, a high fasting blood glucose level of 206 mg/dL was measured. Since then, her blood glucose level remained high. However, there was no dehydration or body weight loss, and labora-

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tory tests revealed negative findings for urine ketones and occasional positive finding of glucosuria. Except for hyperglycemia, there were no signs of stress such as infection or intracranial hemorrhage. The patient met the diagnostic definition of late-onset neonatal hyperglycemia rather than neonatal diabetes mellitus (Table 1.<sup>5)</sup>). Thus, we conducted the 1<sup>st</sup> CGM starting on day 24 (31 weeks' PCA) for three continuous days. The 2<sup>nd</sup> and 3<sup>rd</sup> CGM episodes subsequently performed from 35 and 39 weeks' PCA, respectively, showed relatively stable glycemic patterns. We used fortified mother's milk or preterm infant formula that has a higher concentration of protein and carbohydrate. During the 1<sup>st</sup> CGM period, full enteral nutrition was provided at 120–130 ml/kg/day by slow injection for about 1 hour through a syringe every 2 hours. On the first day of the 2<sup>nd</sup> CGM period, feeding interval was changed 2 to 3 hourly. During the 3<sup>rd</sup> CGM period, she was

fed on demand with 20–25 ml/kg/feeding approximately every 3 to 4 hourly. Her blood glucose level was in the normal range from 35 weeks' PCA, and she had no hyperglycemic episodes. The hospital course of her fasting blood glucose levels and body weights is illustrated in Fig. 1. During follow-up at 3, 6, 9, 12, and 18 months of age, she presented with normal growth and development. From this clinical course, we have had the final diagnosis as transient late-onset neonatal hyperglycemia.

#### Materials and Methods

The Japanese Red Cross Musashino Hospital ethics committee approved this study, and informed consent was obtained from the child's parents.

The CGM system (iPro®2 Professional CGM; Medtronic MiniMed, Northridge, CA, USA) uses a disposable glucose oxidase-based platinum electrode

Table 1. Criteria for neonatal transient late-onset hyperglycemia

- On full enteral feeding without any i.v. glucose supply
- A whole blood glucose level >180 mg/dL just before feeding
- Hyperglycemia for at least 7 days
- A trace amount of glucose in the urine or the urinary glucose level is ± to +1
- Otherwise clinically stable (no osmotic diuresis, and subsequent dehydration and body weight loss)
- Transient and no need for treatment

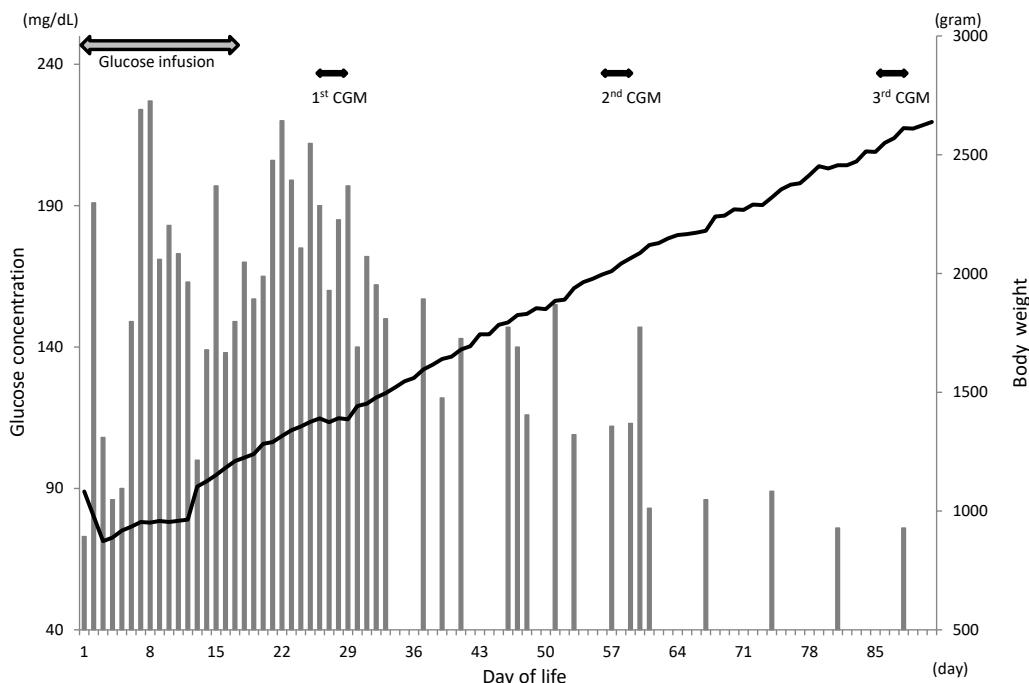


Fig. 1. The hospital course of her blood glucose levels and body weights.

The black line represents serial body weight and the bar represents the fasting blood glucose level.

Interestingly, regardless of the fasting glucose level, the body weight gain is almost constant during the hospital course.

sensor called the Sofsensor<sup>®</sup>, which was manually inserted into the subcutaneous tissue in the patient's lateral thigh. The sensor catalyzes interstitial glucose, thereby generating an electrical current that is recorded on a monitor every 5 min as an averaged glucose value. To calibrate this monitor, capillary blood samples were intermittently analyzed with a point-of-care hand-held glucometer (the Nova StatStrip; Nova Biomedical, Waltham, MA, USA) at least four times daily<sup>6,7)</sup>. For accuracy of CGM data for high glucose levels, calibration was performed at postprandial timing several times during each CGM. The patient underwent each CGM for 3 days in our hospital. There was no evidence

of local edema, inflammation, or infection at the sensor site in the baby. The CGM system was well tolerated. The baby did not make any attention to put at either the sensor or the lead.

Statistical analyses were performed using one-way analysis of variance (ANOVA) to compare the difference in the measurements between groups. We performed statistical analysis with SPSS 11.5 software (SPSS Inc., Cary, NC). Differences were considered significant at  $p < 0.05$ .

### Results (Fig. 2)

The 1<sup>st</sup> CGM results showed almost the same

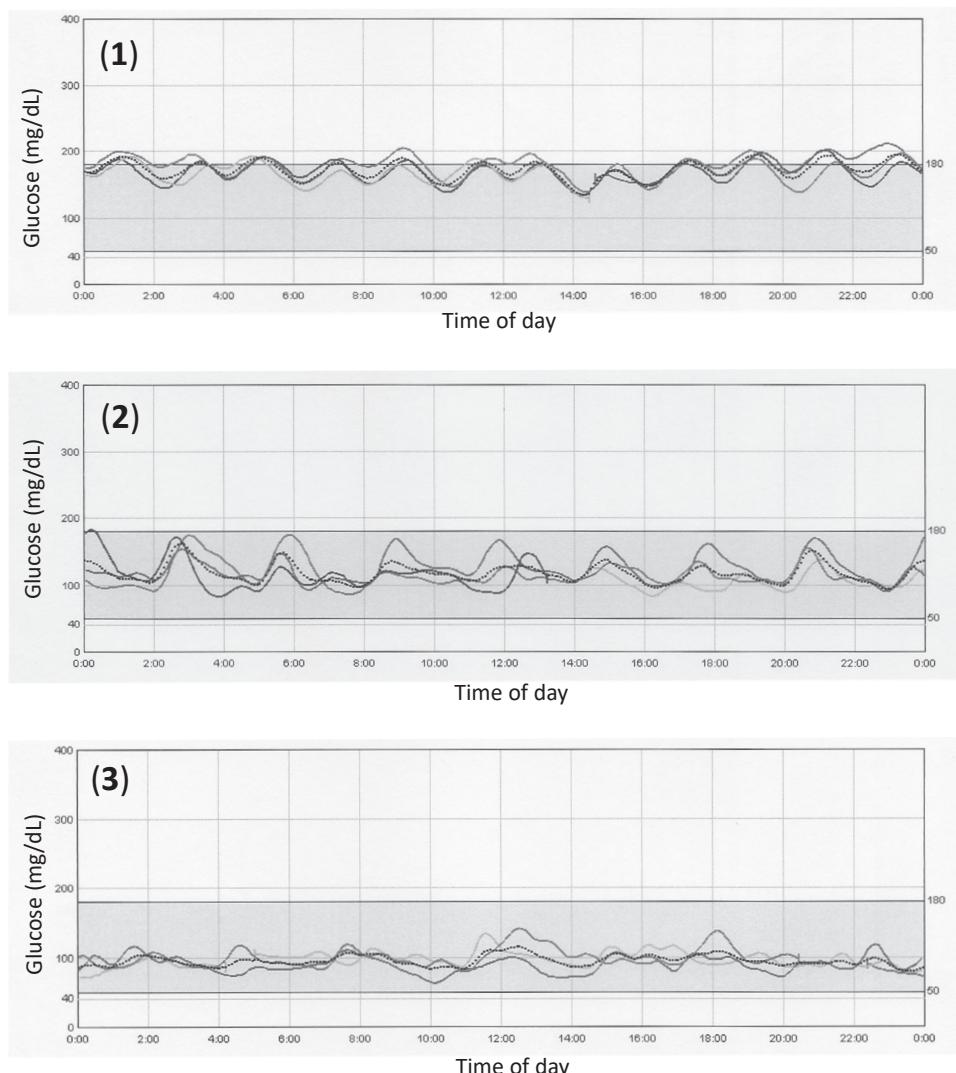


Fig. 2. Continuous glucose monitoring (CGM) data over 3 days in this patient.

Each panel has time (representing a 24-hour period) on the horizontal axis and glucose level (mg/dL) recorded on the vertical axis. The dotted line indicates the serial change of the average value of the data for the 3 days. (1) The patient at 31 weeks' postconceptional age (PCA) undergoing tube feeding every 2 h ( $>150$  mg/dL : 89%, mean 172 mg/dL). (2) The patient at 35 weeks' PCA undergoing tube feeding from every 2 to 3 h on the first day of CGM ( $>150$  mg/dL : 10%, mean 117 mg/dL). (3) The patient at 39 weeks' PCA undergoing oral self-feeding every 3 to 4 h ( $>150$  mg/dL : 0%, mean 95 mg/dL).

pattern of daily glycemic change over the 3 days. Even the lowest blood glucose level exceeds 150 mg/dL on the 1<sup>st</sup> day during initial CGM.

We calculated the differences between the maximum and minimum blood glucose levels during the interval from one enteral feeding to the next enteral feeding and named it “glucose variability between feedings”<sup>7)</sup>. The respective values were  $32.33 \pm 14.3$  mg/dL,  $47.5 \pm 22.9$  mg/dL, and  $27.5 \pm 12.9$  mg/dL for the first, second, and third CGM periods. The serial change in the values was statistically significant ( $p < 0.01$ ).

### Discussion

Hyperglycemia in VLBW infants has been studied mainly in the first week of life using CGM<sup>2,3)</sup>. To date, there are few reports of CGM in stable preterm infants<sup>4,6-8)</sup>. These reports were considerations of the cases by which only several % will be hyperglycemic levels throughout the day. But in this case, even the lowest blood glucose level exceeds 150 mg/dL on the 1<sup>st</sup> day during initial CGM. Therefore a differential diagnosis with neonatal diabetes was required. The present study uniquely using repeated CGM results to demonstrate the clinical course of late-onset hyperglycemia in a stable VLBW infant. The etiology of late-onset neonatal hyperglycemia is while being still unclear<sup>5)</sup>.

The first CGM results showed almost the same pattern of daily glycemic change over the 3 days. Based on the fact that the blood glucose level fluctuates regularly in accordance with the time of feeding, the following factors may be implicated in hyperglycemia : 1) inadequate endogenous insulin secretion in response to blood glucose level and 2) lack of sufficient insulin-dependent tissues (fat and muscle)<sup>9)</sup>. The second CGM period showed that glucose variability between feedings was higher than that of the first CGM period. On the first day of this CGM period, the interval of tube feeding was changed from every 2 hours to 3 hours, which might have revealed remarkable glycemic variability but showed only a 10% incidence of hyperglycemia. The last CGM period during self-feeding (maximum 200 ml/kg/day, orally every 3 to 4 hourly) revealed the glucose variability between feedings was lower than that of the second CGM period. The patient had no episodes of abnormal glucose level.

The maturation of glucose tolerance in VLBW infants with late-onset transient neonatal hyperglycemia as well as transient neonatal hyperinsulinemic hypoglycemia<sup>10)</sup> may be able to be confirmed based on

the range of fluctuation of serial CGM measurements. If hyperglycemia is detected in a stable, fully enteral-fed VLBW infant with point-of-care glucose monitoring, CGM is a safe and great clinical diagnostic tool which avoidance of extremely high glucose level.

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