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Case Report

A case of diffuse congenital hyperinsulinism in which continuous glucose monitoring contributed to the choice of a treatment strategy following a subtotal pancreatectomy

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Highlights

- Elevated blood glucose trends in CGM indicate a decay in insulin secretion.
- CGM can help in choosing a treatment strategy.

Abstract. Patients with diffuse congenital hyperinsulinism (CHI) refractory to drug therapy require subtotal or near-total pancreatectomy. Although almost all patients develop diabetes postoperatively, the clinical course and timing of insulin therapy remain unclear. A 7-yr-old girl presented with recurrent hypoglycemia shortly after birth and a relatively elevated insulin level, which confirmed the diagnosis of CHI. Genetic analysis revealed compound heterozygous ATP-binding cassette, Subfamily C, Member 8 pathogenic variants and diffuse CHI was suspected. Because her condition was refractory to diazoxide and octreotide, she underwent a subtotal pancreatectomy at the age of 4 mo. The drug therapy was discontinued. Although an oral glucose tolerance test at the age of 2 yr showed hyperglycemia after loading, continuous glucose monitoring (CGM) revealed that her daily glucose trends were almost within the 70–180 mg/dL range, and mild hypoglycemia appeared during the daytime. After the age of 6 yr, CGM showed an elevation in glucose trends from midnight to early morning, suggesting that insulin secretion was attenuated and hepatic glucose production was insufficiently suppressed. Insulin therapy was initiated at the age of 7 yr. These results indicate that CGM can be useful for making treatment decisions.

Key words: congenital hyperinsulinism**,** pancreatectomy, hypoglycemia, continuous glucose monitoring

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Introduction

Congenital hyperinsulinism (CHI) leads to hypoglycemia due to inappropriately elevated insulin secretion. CHI can be classified clinically into transient and persistent forms. Transient CHI is commonly associated with maternal gestational diabetes, intrauterine growth retardation, and perinatal stress and resolves within days or months. Persistent CHI continues for a longer period than the transient form. The incidence of persistent CHI in Japan is one in 35,400 neonates (1, 2). Underlying genetic causes are identifiable in 45–79% of children with persistent CHI (3, 4). Approximately 80% of the pathogenic variants occur in ATP-binding cassette, Subfamily C, Member 8 (*ABCC8*) (MIM: 600509), and potassium channel, inwardly rectifying, Subfamily J, Member 11 (*KCNJ11*) (MIM: 600937). These genes encode the sulfonylurea receptor (SUR) and inward rectifier potassium (Kir) channels, respectively. Together, these proteins form an octamer of four SUR1 and four Kir6.2, which constitute the ATP-sensitive potassium (KATP) channel on the β-cell plasma membrane (3, 4). Histologically, persistent CHI is classified as focal or diffuse. In focal CHI, the abnormality is confined to limited regions of the pancreas. Focal lesions stem from paternally inherited pathogenic variants of *ABCC8* and *KCNJ11,* along with embryonic somatic deletion of the maternal alleles of the imprinted chromosomal region 11p15.1–11p15.5 (5). Diffuse CHI involves the entire endocrine pancreas and is typically caused by homozygous or compound heterozygous pathogenic variants of *ABCC8* and *KCNJ11* (1).

Therapeutic approaches differ between focal and diffuse varieties of CHI. The former can be completely cured after resection of the focal lesion and does not require frequent follow-up (6). However, the latter usually requires long-term drug therapy or surgical intervention. Although advances in drug therapy have reduced the number of patients requiring surgery, those refractory to drug therapy still require subtotal (80–94% resection) or near-total pancreatectomy (> 95% resection) (1, 7). The surgical outcomes were less satisfactory in these patients. Hypoglycemia persisted at a rate as high as 60% postoperatively. Furthermore, pancreatic β-cell function declines postoperatively, with 91–96% of patients having diabetes development requiring insulin therapy 11–14 yr postoperatively (8, 9). However, to the best of our knowledge, no study has reported the details of the postoperative clinical course. Herein, we report the case of a female patient with diffuse CHI who underwent subtotal pancreatectomy and developed diabetes mellitus 5 yr postoperatively. Her glucose trends were monitored using an oral glucose tolerance test (OGTT) and continuous glucose monitoring (CGM).

Case Report

The present study was approved by the ethics committee of Tokyo Metropolitan Children's Medical Center (H26–4) and was performed after obtaining written informed consent from the parents of the patient. **Table 1** summarizes the clinical findings of the patient. The patient, a female neonate born as the first child of non-consanguineous healthy Japanese parents, had no congenital malformations. Two hours postpartum, her blood glucose level was 26 mg/dL, and she was transferred to our hospital. Recurrent hypoglycemia requiring intravenous dextrose at a high glucose infusion ratio (GIR) and relatively high insulin levels led to the diagnosis of CHI. The maximum GIR was 17.0 mg/kg/min. Immunoreactive insulin at blood glucose 36 and 19 mg/dL was 26.9 and 23.5 μU/mL, respectively. Diazoxide was begun at the age of 6 d but was ineffective, even at 12 mg/kg/d.

Genomic DNA samples from the patient and her parents were analyzed by Sanger sequencing, which confirmed the presence of compound heterozygous *ABCC8* variants (c.[2311T>G];[2992C>T]) (**Figs. 1A and 1B**). The c.2922C>T (p.Arg998*) variant was previously identified in patients with CHI (10). The c.2311T>G (p.Tyr771Asp) variant is not included in the Genome Aggregation Database (https://gnomad.broadinstitute.org) or the Integrative Japanese Genome Variation Database (http://jmorp.megabank.tohoku.ac.jp/ijgvd/). This missense variant was assessed as damaging by Sorting Intolerant From Tolerant (http://sift.bii.a-star.edu.sg/), probably damaging by Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/), and possibly pathogenic by Mendelian Clinically Applicable Pathogenicity (http://bejerano.stanford.edu/mcap/). The tyrosine residue at codon 771 is conserved among species

Table 1. Clinical characteristics

At birth	
Birth weight (kg)	3.6 (+2.3 SD)
Birth length (cm)	49.9 (+0.7 SD)
Gestational weeks	38
Congenital malformation	None
At the age of 1 day	
Blood glucose (mg/dL)	36
Immunoreactive insulin (μU/mL)	26.9
Free fatty acid (mmol/L)	0.085
Ammonia [a] (μg/dL)	71
At the age of 2 days	
Blood glucose (mg/dL)	19
Immunoreactive insulin (μU/mL)	23.5
3-Hydroxybutyric acid (μmol/L)	< 2.0
Maximum glucose infusion rate (mg/kg/min)	17.0
Diazoxide treatment	
Maximum dosage (mg/kg/d)	12
Duration (wk)	7
Octreotide treatment	
Maximum dosage (μg/kg/d)	24
Duration (wk)	19

[a] Reference range: < 140 μg/dL.

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(**Fig. 1C**). Altogether, p.Tyr771Asp was assessed as "likely pathogenic" in accordance with the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) (PM2, PM3, PP3, and PP4) (11). Genetic analysis raised the index of suspicion of diffuse CHI. The genetic characteristics of the patient are shown in **Table 2**.

Treatment with octreotide was initiated via

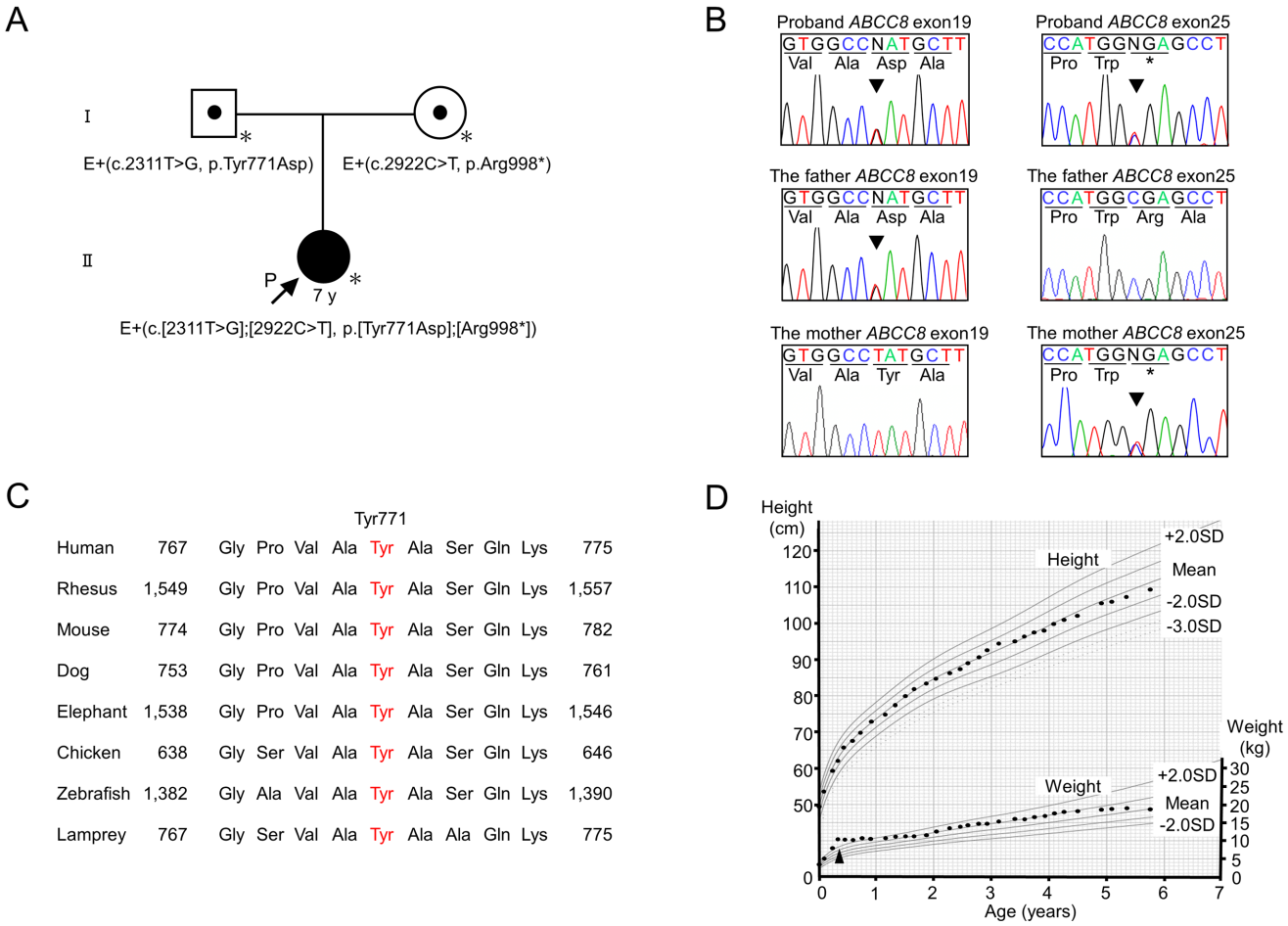

Fig. 1. (A) Family pedigree. The arrow indicates the patient. E+ indicates *ABCC8* variant positive. (B) Chromatograms of the *ABCC8* variants identified in the family (c.2311 T>G, c.2992 C>T). Arrowheads indicate the mutated nucleotides. (C) The panel shows the sequence conservation of the 771 residue. (D) Patient's growth chart. The upper and lower charts show height and weight, respectively. The arrowhead indicates the timing of the subtotal pancreatectomy.

Table 2. Genetic characteristics

	c.2922C>T	c.2311T>G
Amino acid change	p.Arg998*	p.Tyr771Asp
Previously reported in patients with CHI	Suchi M *et al*., 2003 (10)	None
Allele frequency		
gnomAD	0	0
jMorp	0	0
Funcional prediction		
M-CAP	-	0.925
PolyPhen-2	-	1.000
SIFT	-	0.000
Classified by ACMG/AMP guidelines	-	Likely pathogenic
Inheritance	Maternal	Paternal

ACMG/AMP, American College of Medical Genetics and Genomics and the Association for Molecular Pathology; CHI, congenital hyperinsulinism; gnomAD, Genome Aggregation Database; jMorp, Japanese Multi Omics Reference Panel; M-CAP, Mendelian Clinically Applicable Pathogenicity; SIFT, Sorting Intolerant From Tolerant.

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continuous subcutaneous injection at the age of 18 d, and diazoxide was tapered. Although the octreotide dosage was increased to 24 μg/kg/d and continued for ten weeks, the patient required intravenous dextrose with GIR 10 mg/kg/min to prevent hypoglycemia. Furthermore, she repeatedly experienced catheter-related cutaneous infections and was at risk of airway obstruction due to obesity (**Fig. 1D**). Therefore, she underwent a 90% pancreatectomy at the age of 4 mo.

Histopathological examination revealed large islet cell nuclei in specimens from the pancreatic tail, body, and head, corresponding to the features of diffuse CHI. At postoperative week 2, her blood glucose level increased to 200–300 mg/dL, and intravenous dextrose and octreotide were discontinued. Her blood glucose level was almost within the 60–130 mg/dL range two weeks after the cessation of medication. The patient was discharged at the age of 6 mo.

Her blood glucose level was measured using self-monitoring blood glucose (SMBG), and the glucose trends were monitored regularly using CGM (Medtronic iPro®2 and FreeStyle LibrePro®). The CGM results at the age of 1 yr and 2 mo (**Fig. 2A**) demonstrated that her glucose trends tended to be low between noon and evening, when her activity level was high, and became elevated around or after midnight due to the ingestion of a pre-bedtime dietary supplement. Her daytime blood glucose levels increased over time in the absence of treatment. **Fig. 2B** shows the results of the OGTT at the age of 2 yr and 11 mo. Hyperglycemia was observed 30 min after glucose loading and the patient's blood glucose levels decreased to the normal range 3 h after loading. Her insulinogenic index was 0.04 (μU/mL per mg/dL), indicating decreased insulin secretion after glucose loading (12). In contrast, the results of CGM and SMBG during the same period demonstrated that her glucose level was almost within the 70–180 mg/dL range (**Figs. 2C and 2D**), which is the standard range used as a control marker for CGM (13), and her hemoglobin A1c (HbA1c) was 6.1% (NGSP). Moreover, hypoglycemia was occasionally detected using SMBG during the daytime when the activity level was high. Therefore, glucose monitoring continued.

After the patient entered nursery school at the age of 2 yr, her blood glucose level during the daytime tended

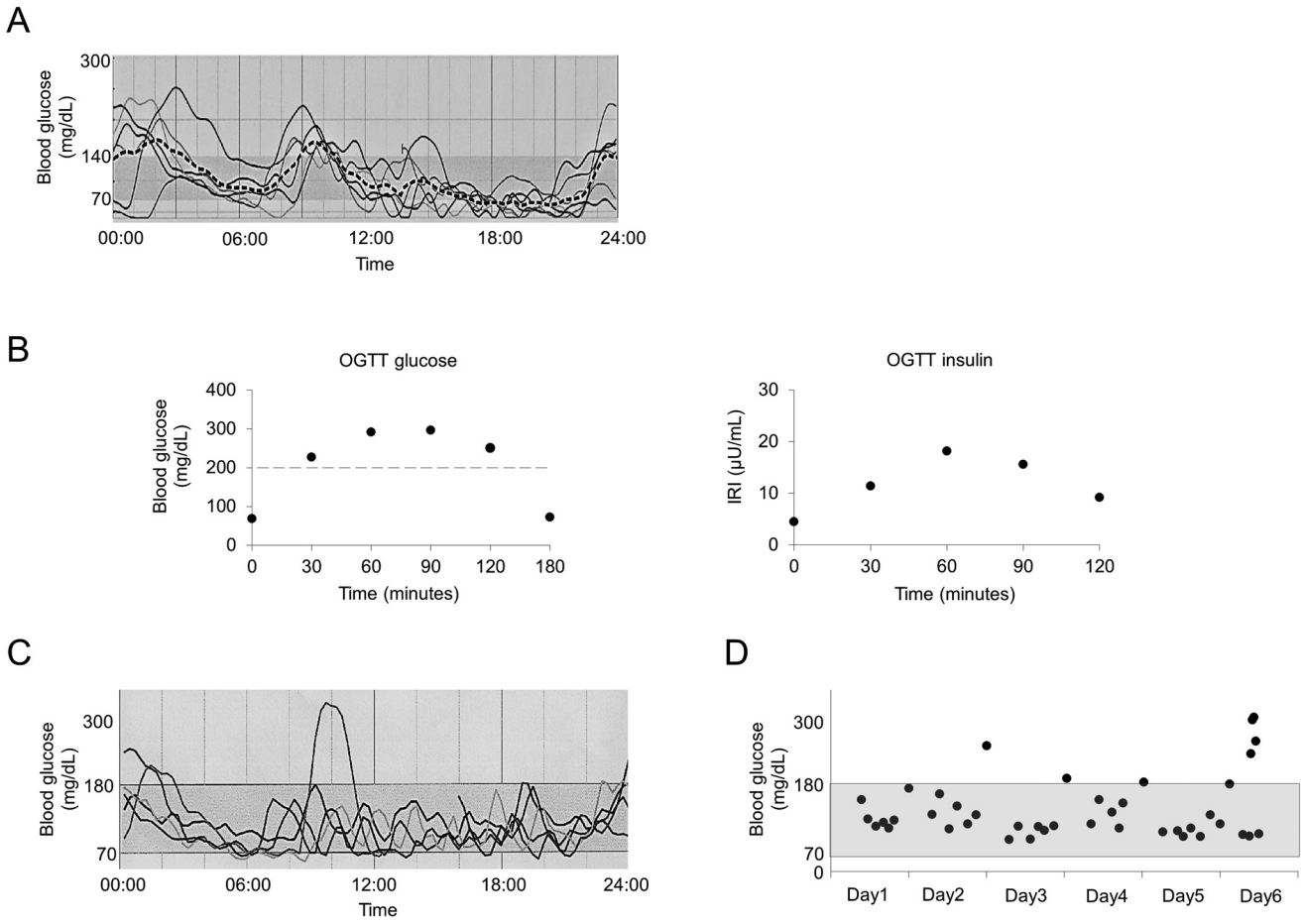

Fig. 2. (A) Result of CGM for 6 days at the age of 1 yr 2 mo (Medtronic iPro®2). The glucose trends were calibrated by SMBG values. The dotted line shows the average blood glucose level over the 6 days. (B) Result of OGTT at the age of 2 yr 11 mo. The dotted line indicates 200 mg/dL. (C) The result of CGM over 5 days at the age of 2 yr 11 mo (FreeStyle LibrePro®). The glucose trends were not calibrated by the SMBG value. (D) Blood glucose level as assessed using SMBG for the same period as in (C). SMBG detected a spike in the blood glucose level exceeding 180 mg/dL during OGTT on day 6.

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to remain high because of the dietary supplements she was given to prevent hypoglycemia. From 2 to 5 yr, her blood glucose level showed no marked change, and her HbA1c level remained at approximately 6.0%. At the age of 5 yr and 4 mo, her HbA1c level increased to 6.8%, and diabetes was diagnosed. FreeStyle Libre®, an intermittently scanned CGM (isCGM), was then begun. The pre-bedtime supplementary diet was no longer necessary because her glucose trends on CGM no longer demonstrated hypoglycemia during sleep. In contrast, her fasting blood glucose level before breakfast on the SMBG gradually increased from approximately 5 yr (**Figs. 3A and 3B**). Furthermore, her glucose trends on CGM from midnight to early morning, when blood glucose levels were less affected by activity and diet, increased over time (**Fig. 3C**). **Fig. 3D** shows the results of the OGTT at the age of 6 yr and 11 mo. Compared to the OGTT results at the age of 2 yr and 11 mo, her insulinogenic index was unchanged (0.06), but her blood glucose level remained above 300 mg/dL 3 h after loading, suggesting that her insulin secretion after glucose loading had deteriorated further. Her HbA1c level worsened from 6.8% at the age of 6 yr and 1 mo to 8.2% at the age of 7 yr and 3 mo. However, hypoglycemia was occasionally detected on SMBG during the daytime, depending on diet and activity. To improve her CGM hyperglycemia findings around or after midnight, she began receiving insulin detemir (Levemir®), a basal insulin analog, before bedtime (0.2–0.3 units/kg).

Discussion

We report the case of a patient with diffuse CHI who underwent pancreatectomy and developed diabetes 5 yr after surgery. The patient had compound heterozygous *ABCC8* variants. None of the public databases contained

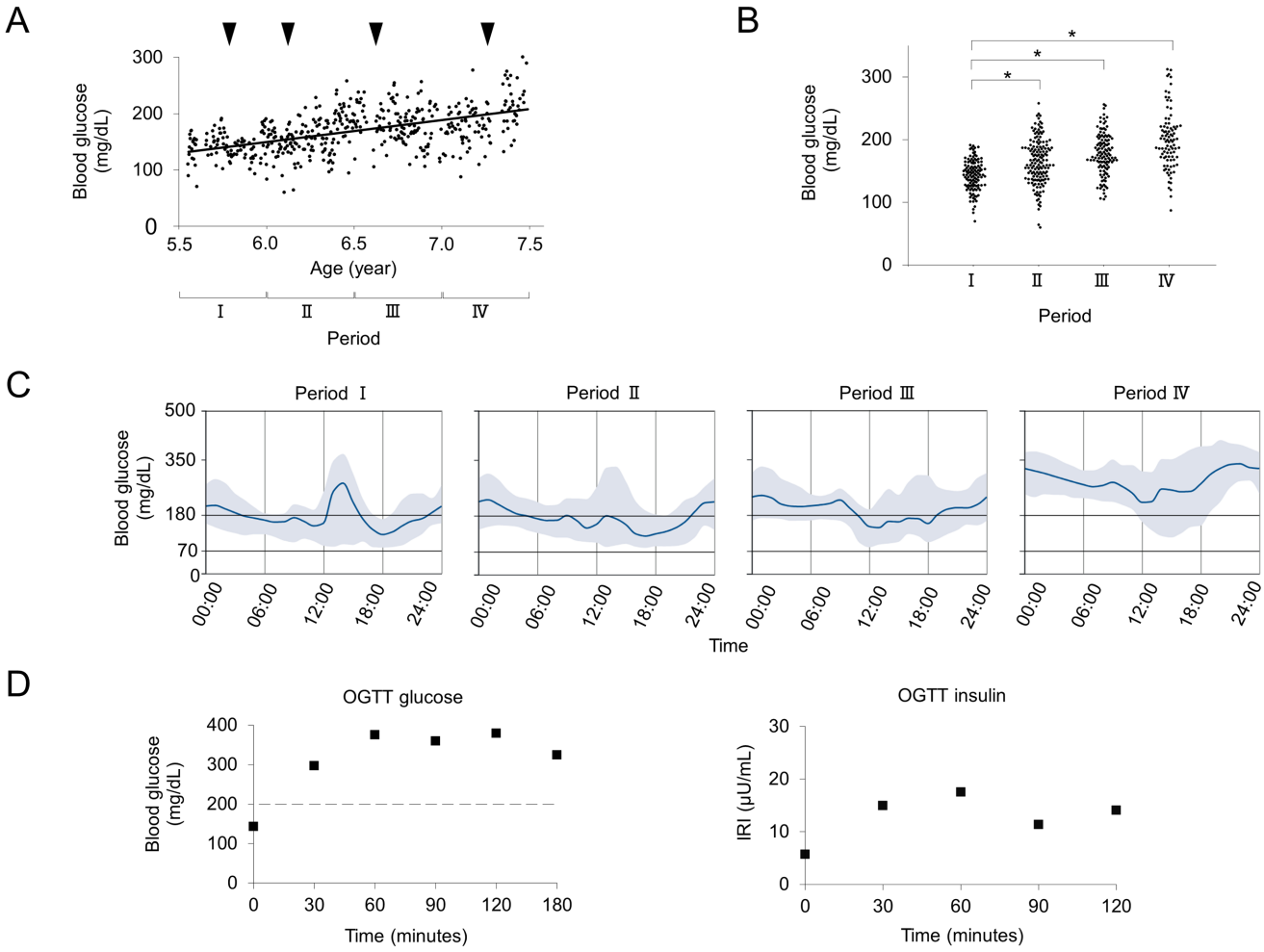

Fig. 3. (A) Fasting blood glucose levels before breakfast from the age of 5 yr 6 mo to 7 yr 6 mo. The 2 yr were divided into four periods of 6 mo each (period I to IV). The solid line indicates the regression line. The arrowheads indicate the timing of the measurement of HbA1c. HbA1c at periods I, II, III, and IV was 6.8%, 6.8%, 8.1%, and 8.2%, respectively. (B) A swarm plot of fasting blood glucose levels for each period. Groups conjoined with an asterisk differed statistically ($P < 0.01$) according to the Bonferroni multiple comparisons test. (C) Representative results of CGM for 2 weeks included per period. The solid line indicates the median blood glucose level. The shaded area indicates the 5–95th percentile of the blood glucose level. (D) The result of OGTT at the age of 6 yr 11 mo. The dotted line indicates 200 mg/dL.

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the p.Tyr771Asp variant, which was assessed as "likely pathogenic" according to ACMG/AMP guidelines. Based on the clinical course, this variant was considered pathogenic.

Although the OGTT is recommended for detecting abnormal glucose tolerance in patients with CHI after surgery (8), the results did not contribute to choosing the treatment strategy in our case. Although the OGTT at the age of 2 yr and 11 mo detected decreased insulin secretion, the glucose trends detected by CGM were almost within the 70–180 mg/dL range, and mild hypoglycemia was observed during the daytime when the activity level was high. Approximately 35% of patients with CHI who underwent near-total pancreatectomy reportedly demonstrated an association of fasting hypoglycemia with postprandial hyperglycemia (8). Presumably, insulin secretion decreased after glucose loading in these patients; however, the accompanying hypoglycemia made it difficult to determine when to initiate therapy.

In the present case, insulin therapy was initiated after CGM detected elevated glucose trends between midnight and early morning. Fasting blood glucose levels are maintained via hepatic glucose production, which is regulated by insulin (14). As insulin levels decrease, hepatic glucose production is no longer suppressed, and fasting blood glucose levels increase (15). In our case, CGM detected attenuation of insulin secretion postoperatively through changes in the glucose trend from midnight to early morning. In patients with CHI who develop diabetes, night glucose trends may be useful in choosing the treatment strategy, and CGM can detect glucose trends more easily than SMBG.

One limitation of the present study was the use of isCGM. Although isCGM readily detects blood glucose fluctuations without calibration, differences between values obtained by the system and actual blood glucose levels have been reported (16). Therefore, the fasting blood glucose levels were confirmed by SMBG while using isCGM.

Conclusion

CGM can detect attenuation in insulin secretion over time through elevations in blood glucose trends from midnight to early morning, which can be useful for making treatment decisions.

Conflicts of interests: Y. H. received seminar speaker fees from Novo Nordisk..

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References

1. Banerjee I, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Dunne MJ. Therapies and outcomes of congenital hyperinsulinism-induced hypoglycaemia. Diabet Med 2019;36: 9–21. [Medline] [CrossRef]
2. Yorifuji T, Horikawa R, Hasegawa T, Adachi M, Soneda S, Minagawa M, *et al*. (on behalf of The Japanese Society for Pediatric Endocrinology and The Japanese Society of Pediatric Surgeons). Clinical practice guidelines for congenital hyperinsulinism. Clin Pediatr Endocrinol 2017;26: 127–52. [Medline] [CrossRef]
3. Snider KE, Becker S, Boyajian L, Shyng SL, MacMullen C, Hughes N, *et al*. Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. J Clin Endocrinol Metab 2013;98: E355–63. [Medline] [CrossRef]
4. Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. Eur J Endocrinol 2013;168: 557–64. [Medline] [CrossRef]
5. de Lonlay P, Fournet JC, Rahier J, Gross-Morand MS, Poggi-Travert F, Foussier V, *et al*. Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. J Clin Invest 1997;100: 802–7. [Medline] [CrossRef]
6. Arya VB, Mohammed Z, Blankenstein O, De Lonlay P, Hussain K. Hyperinsulinaemic hypoglycaemia. Horm Metab Res 2014;46: 157–70. [Medline] [CrossRef]
7. Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E. Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur J Endocrinol 2003;149: 43–51. [Medline] [CrossRef]
8. Beltrand J, Caquard M, Arnoux JB, Laborde K, Velho G, Verkarre V, *et al*. Glucose metabolism in 105 children and adolescents after pancreatectomy for congenital hyperinsulinism. Diabetes Care 2012;35: 198–203. [Medline] [CrossRef]
9. Arya VB, Senniappan S, Demirbilek H, Alam S, Flanagan SE, Ellard S, *et al*. Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. PLoS One 2014;9: e98054. [Medline] [CrossRef]
10. Suchi M, MacMullen C, Thornton PS, Ganguly A, Stanley CA, Ruchelli ED. Histopathology of congenital hyperinsulinism: retrospective study with genotype correlations. Pediatr Dev Pathol 2003;6: 322–33. [Medline] [CrossRef]
11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al*. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17: 405–24. [Medline] [CrossRef]
12. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, *et al*. Committee of the Japan Diabetes Society on the

Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 2010;1: 212–28. [Medline] [CrossRef]
13. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, *et al*. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42: 1593–603. [Medline] [CrossRef]
14. Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. Nat Rev Endocrinol 2017;13: 572–87. [Medline] [CrossRef]
15. Rizza RA, Mandarino LJ, Gerich JE. Dose-response characteristics for effects of insulin on production and utilization of glucose in man. Am J Physiol 1981;240: E630–9. [Medline]
16. Fokkert MJ, van Dijk PR, Edens MA, Abbes S, de Jong D, Slingerland RJ, *et al*. Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. BMJ Open Diabetes Res Care 2017;5: e000320. [Medline] [CrossRef]