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Case Report

Clinical management of diazoxide-unresponsive congenital hyperinsulinism: A single-center experience

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Highlights

- Despite clinical advances in the management of CHI, treatment options remain limited.
- A maximum dose of octreotide (25 μg/kg/d) can safely replace lanreotide 60 mg.
- Home-based CGM is useful for determining therapeutic strategy and management.

Abstract. The most common cause of persistent hypoglycemia in newborns and children is congenital hyperinsulinism (CHI). Remarkable advancements in diagnostic tools and treatments, including novel imaging and genetic techniques, and continuous subcutaneous octreotide administration, have improved the prognosis of diazoxide-unresponsive CHI; however, in clinical practice, some issues remain. Here, we report a case series consisting of four adenosine triphosphate-sensitive potassium-associated CHI cases, discuss the practical use of new international guidelines published in 2023, and suggest clinical issues associated with CHI management. Based on the clinical experience of two diffuse and two focal CHI cases, we employed an updated treatment strategy, including genetic diagnosis to determine treatment plans, careful catheter management, switching from octreotide to long-acting somatostatin, effective utilization of a continuous glucose monitoring (CGM) device, measures for feeding problems, and individualized and systematic developmental follow-up. Particularly, our cases suggest a safe method of switching from octreotide to lanreotide, elucidate the efficacy of home-based CGM monitoring, and indicate need for personalized support for feeding problems. Severe CHI is a rare and challenging disorder; thus, further accumulation of experience according to new treatment strategies is essential in generating high-quality evidence for the development and approval of new treatment options.

Key words: congenital hyperinsulinism, lanreotide, continuous glucose monitoring, ABCC8, KCNJ11

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Introduction

In newborns and children, congenital hyperinsulinism (CHI) is the most common cause of severe and persistent hypoglycemia. CHI exists in two forms: a transient form that develops soon after birth and generally resolves by 3–4 mo of age and a persistent form with a more protracted duration (1). The incidence of transient CHI was estimated to be 1 in 13,600 births and that of persistent CHI was 1 in 31,600 births according to the 2017–2018 National Survey in Japan (2).

This field has significantly advanced since the first case of CHI was described in the 1950s. Dramatic advances have been made in the diagnostic tools, including novel radiological imaging techniques for focal CHI and new genetic techniques that enhance our understanding of the pathophysiology of transient and persistent forms of neonatal hyperinsulinism. Diazoxide (DZX), an adenosine triphosphate-sensitive potassium (KATP) channel opener, is a first-line drug for controlling hypoglycemia in children with CHI and has been reported to be effective in > 70% of these cases (3).

In clinical practice, CHI can be classified according to its response to DZX. Up to 90% of cases with DZX-unresponsive CHI have pathogenic inactivating variant(s) in one of the two genes that encode the two subunits of the β-cell plasma membrane KATP channel, KCNJ11 and ABCC8 (4), with diffuse or focal pancreatic histopathology. Recessive biallelic variants or dominant monoallelic *ABCC8* or *KCNJ11* pathogenic variants (s) cause diffuse CHI, whereas paternally inherited recessive *ABCC8* or *KCNJ11* pathogenic variants may cause focal CHI, which could be addressed via lesionectomy. Continuous subcutaneous octreotide (OCT), a somatostatin analog infusion using commercial pumps intended for insulin administration, is commonly utilized as a second-line treatment for DZX-unresponsive CHI to avoid the need for subtotal pancreatectomy. Thus, determining the precise etiology of CHI early is important as the diagnosis may direct the selection of therapy and the need for long-term follow-up.

Clinical guidelines (1) and a nationwide survey (2) of CHI were published in Japan in 2017 and 2019, respectively. Moreover, following a prospective, open-label clinical trial of subcutaneous OCT for DZX-unresponsive CHI (the SCORCH study) (5) in 2020, OCT for CHI was approved in Japan. Herein, we report our single-center experience with DZX-unresponsive CHI after the regulatory approval of OCT. In this case series, we elucidate the practical use of new international guidelines for diagnosing and managing hyperinsulinism published in 2023 (6) and suggest clinical issues for CHI management.

Patients and Methods

We report four patients referred to Tokyo Medical and Dental University Hospital with refractory hypoglycemia due to DZX-unresponsive CHI between 2020 and 2023. None of the patients had a family history of gestational diabetes or diabetes mellitus in first-or second-degree relatives. Patient 1's older sister had an ABCC8-associated CHI (7); however, patients 1 and 2 were unrelated. The clinical courses of all four patients are illustrated in Supplementary Fig. 1.

Genetic analysis

All patients underwent a next-generation sequencing-based panel sequencing of genes known to cause CHI, including *ABCC8, KCNJ11, GLUD1, GCK, HNF4A, HNF1A,* and *HADH* (Kazusa DNA Research Institute, Japan), followed by Sanger sequencing for family analysis.

Ethics of experimentation

The use of lanreotide (LRT), an unapproved and off-label drug, and the unapproved use of continuous glucose monitoring (CGM), including the Medtronic MiniMed system and the Dexcom G6 system for patients with CHI, were approved by the Institutional Review Board of Tokyo Medical and Dental University (article No. 2023-027 on Aug 30, 2023). The 18F-DOPA PET study protocol was approved by the Central Japan International Medical Center Review Board (article No. 23-02 on Dec 26th, 2011), and the 18F-DOPA PET study was conducted at Chubu Medical Center for Prolonged Traumatic Brain Dysfunction. All procedures were performed in accordance with the ethical standards of the institutional and national research committees and the Declaration of Helsinki, as revised in 2013.

Informed consent

Written informed consent to publish the patients' data, imaging results, and genetic testing results was obtained from the parents of all patients.

Results

The clinical, genetic, and therapeutic characteristics and prognoses of all four patients (three males) with CHI due to *KATP* gene variants are demonstrated in **Table 1**.

Patient 1

A large for gestational age (birth weight, 4,380 g + 3.7 SD; height, 52.5 cm + 2.2 SD at 38 wk 4 d of gestation) male neonate born to consanguineous Kurdish parents presented with hypoglycemia (blood glucose: BG, 1 mg/dL; immunoreactive insulin: IRI, 8.6 μIU/mL) at 3 h of age (7). He required an infusion of high-concentration glucose (glucose infusion rate, GIR, 13.6 mg/kg/min), continuous intravenous infusion of glucagon (30 μg/kg/h), DZX (15 mg/kg/d), and continuous tube feeding of breast milk to maintain BG above 3.5 mmol/L. Based on genetic analysis revealing biallelic mutations in

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Table 1. Clinical characteristics of patients 1–4

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Female	Male	Male
Age of onset	At birth	At birth	At birth	23 d
Gestational age	38 wk 4 d	36 wk 4 d	39 wk 6 d	38 wk 4 d
Birth weight [SDS]	4,380 g [+3.7]	4,666 g [+6.6]	3,772 g [+2.0]	3,970 g [+3.2]
Birth length [SDS]	52.5 cm [+2.2]	50 cm [+1.6]	51 cm [+0.9]	54 cm [+3.2]
Age of transfer	23 d	6 d	45 d	43 d
Disease type	Diffuse suspected	Diffuse suspected	Focal	Focal
Genetics				
Gene	*ABCC8*	*ABCC8*	*ABCC8*	*KCNJ11*
Variant	p.H1401TfsTer59 Homozygous	p.H1401TfsTer59 Homozygous	p.R836Ter Paternal heterozygous	p.R136AfsTer5 Paternal heterozygous
Age of genetic diagnosis [d of age]	18	53	67	70
Treatment				
DZX [duration]	Y [3 d–7 m]	Y [2 d–1 y 4 m]	Y [2 d–45 d]	Y [27 d–4 m]
Glucagon [duration]	Y [1 d–3 m]	Y [0 d–57 d]	N	Y [24 d–52 d]
OCT [duration]	Y [25 d–]	Y [9 d–]	Y [45 d–56 d]* Intermittent: 19 d–45 d	Y [48 d–4 m]
LRT [duration]	N	N	Y [56 d–6 m]	Y[4 m–]
Nutrition				
GSD-N [duration]	N	Y [19 d–10 m]	Y [59 d–6 m]	Y [2 m 20 d–6 m]
Cornstarch [duration]	Y [47 d–7 m]	Y [1 y 1 m–2 y]	Y [17 d–2 m 2 d]	N
Tube feeding [duration]	Continuous [15 d–99 d]	Continuous [3 d–2 y]	Oral and tube [15 d–6 m]	Oral and tube [24 d–]
Gastrostomy [duration]	N	Y [1 y 4 m–3 y 3 m]	N	N
CV catheterization				
TCVC	Y	Y	N	N
PICC	Y	Y	Y	Y
CGM	Medtronic paradigm	Medtronic paradigm	Dexcom G6	Dexcom G6
Comorbidities				
GERD	N	Y	N	Y
Sucking problem	Y	Y	N	Y
Intestinal malrotation	N	N	Y	N
Comorbidities for LGA	Clubfoot	N	N	Clavicular fracture at birth
Complications				
Catheter-associated infection	Y	Y	N	Y
Early catheter obstruction	Y	Y	N	Y
Biliary debris	Y	Y	Y	Y
Outcome [age]	[4 y 2 m]	[3 y 4 m]	[1 y]	[6 m]
Height SDS	+1.4	+0.2	–0.6	–0.6
Body weight SDS	+1.5	+2.7	+0.3	–1.4
Development	DQ: 119	DQ: 104	No developmental delay	No developmental delay
Food difficulty	N	N	N	Need of tube feeding

SDS, standard deviation score; DZX, diazoxide; OCT, octreotide; LRT, lanreotide; GSD-N, GSD formula N; TCVC, tunneled central venous catheterization; PICC, peripherally inserted central venous catheter; CGM, continuous glucose monitoring; GERD, gastroesophageal reflux disease; LGA, large for gestational age; DQ, developmental quotient; Y, yes; N, no.

ABCC8 (homozygous p.H1401TfsTer59), we assumed that the patient had diffuse CHI and transferred to our hospital for continuous subcutaneous OCT injection at 23 d of age. A Medtronic MiniMed system was utilized for continuous subcutaneous OCT injections and real-time CGM. Introduction and dose increments of OCT, up to 25 μg/kg, led to a well-controlled BG level that was monitored by CGM; however, glucagon could not be tapered directly because of multiple catheter obstructions in a peripherally inserted central venous catheter (PICC) and tunneled central venous catheterization (TCVC) and catheter-related bloodstream infection. Continuous IV glucagon infusion and tube feeding were discontinued at 93 and 99 d of age, respectively. The patient was transferred to another medical institution at 107 d of age and discharged at 137 d of age. DZX administration was discontinued at 7 mo of age. At the age of three, the patient was able to fast for 6 to 8 h without a hypoglycemic episode with 10 μg/kg/d OCT treatment and did not show apparent growth or developmental deficiency (weight, 19.4 kg: + 1.5 SD; height, 106.7 cm: + 1.4 SD; developmental quotient [DQ], 104 at 4 yr and 2 mo of age).

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Patient 2

A premature large for gestational age (birth weight, 4,666 g + 6.6 SD; height, 50.0 cm + 1.6 SD at 36 wk, 4 d gestation) female neonate born to consanguineous Kurdish parents presented with hypoglycemia (BG, 13 mg/dL; IRI, 11.2 μIU/mL) at birth (7). Despite multimodality treatment, including an infusion of high-concentration glucose (GIR, 15 mg/kg/min), continuous intravenous infusion of glucagon (40 μg/kg/h) through PICC, DZX (10 mg/kg/d), and continuous tube feeding of breast milk, a BG above 3.5 mmol/L could not be maintained. The patient was transferred to our hospital at 6 d of age. Owing to the unresponsiveness to dose increments of DZX up to 15 mg/kg/d, continuous subcutaneous OCT injection and CGM using a Medtronic MiniMed system were initiated at 9 d of age. Dose increments of OCT, up to 25 μg/kg at 19 d of age, led to well-controlled BG levels. TCVC implantation was performed, and nutritional status was calculated using the GSD formula N (Meiji Co., Ltd. Tokyo, Japan), which is a high-carbohydrate (86.4 g/100 g) and fat-free milk-based formula for glycogen storage disease, was started at 13 and 19 d of age, respectively. Genetic analysis revealed biallelic mutations in *ABCC8* (homozygous p.His1401hrfsTer59). Therefore, the patient was diagnosed with diffuse CHI. GIR and glucagon levels gradually decreased, and glucagon levels ceased at 57 d of age. After being transferred back to the introduced medical institution at 91 d of age because of a persistent sucking problem and gastroesophageal reflux, continuous tube feeding was maintained and gastrostomy with cardioplasty was conducted at 10 mo of age, leading to more stable control of BG levels. The patient was discharged at 1 yr and 4 mo of age and gastrostomy closure was performed at 3 yr and 3 mo. At the age of three, the patient was able to fast for 6 to 8 h without a hypoglycemic episode by 7 μg/kg/d OCT treatment with cornstarch nutrition, 3 g/kg/d, and did not show apparent growth or developmental delay (weight, 19.7 kg: + 2.7 SD; height, 95.4 cm: + 0.2 SD; DQ, 119 at 3 yr and 4 mo of age).

Patient 3

A large for gestational age (birth weight, 3,772 g + 2.0 SD; height, 51.0 cm + 0.9 SD at 39 wk 6 d of gestation) male neonate born to nonconsanguineous Chinese parents presented with hypoglycemia (BG, 37 mg/dL; IRI, 17.8 μIU/mL) at 22 h of age. To maintain BG above 3.5 mmol/L, the patient required an infusion of high-concentration glucose (GIR, 15 mg/kg/min), DZX (15 mg/kg/d), and intermittent subcutaneous administration of OCT. At 45 d old, the patient was transferred to our institution for continuous subcutaneous OCT injection. Introduction (15 μg/kg) and dose increments of OCT, up to 25 μg/kg, and infusion of high concentration glucose were tapered using CGM by a Dexcom G6 system and ceased at 58 d of age. At 56 d of age, OCT was replaced with a long-acting somatostatin analog, LRT (60 mg), administered monthly via deep subcutaneous injection. Genetic analysis revealed a paternally inherited heterogeneous variant in *ABCC8* (p.Arg836Ter). For insufficient suckling and occasional vomiting, tube feeding with GSD formula N was continued. After confirming the stability of the BG control for 1 month (Supplementary Fig. 2A), the patient underwent a second round of LRT and was discharged at 87 d of age. A 6-fluoro-(18F)-L-3,4-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET) scan performed at 5 mo of age revealed increased uptake in the focal region of the pancreatic uncinate process, which appeared resectable (Supplementary Fig. 2B). After restarting continuous subcutaneous OCT injections using an insulin pump, partial pancreatectomy was performed at 7 mo of age. The extent of resection was determined by CGM monitoring and multiple intraoperative pathological diagnoses (Supplementary Fig. 2C). Intestinal malrotation was incidentally detected during surgery and Ladd's procedure was performed. Postoperatively, OCT was tapered without a hypoglycemic episode (Supplementary Fig. 2D), and the insufficient suckling was resolved. At 10 mo of age, the patient could fast for 4 to 6 h without treatment and did not show apparent growth or developmental deficiency (weight, 9.695 kg: + 0.3 SD; height, 73.5 cm: –0.6 SD at 1 yr of age).

Patient 4

A 23-d-old male neonate with coronavirus disease 2019 developed fever and was hospitalized for hypoglycemia (BG, 22 mg/dL; IRI, 19.1 μIU/mL). The patient was born large for gestational age (birth weight, 3,970 g + 3.2 SD; height, 54 cm + 3.2 SD at 38 wk 4 d of gestation) to non-consanguineous Vietnamese parents and had no apparent hypoglycemic episodes before hospitalization. Even after the fever subsided, he required an infusion of high-concentration glucose (GIR, 8.7 mg/kg/min) to maintain BG above 3.5 mmol/L; therefore, DZX (up to 15 mg/kg/d) and continuous intravenous infusion of glucagon (10 μg/kg/h) through PICC were initiated. The patient was transferred to our hospital for continuous subcutaneous OCT injections and continuous subcutaneous OCT injection with CGM using the Dexcom G6 system which was initiated at 46 d of age. Continuous subcutaneous OCT injections was initiated at 48 d of age with dose increments of OCT, up to 25 μg/kg, led to a well-controlled BG level monitored by CGM, and glucagon was tapered at 50 d of age. Because of frequent vomiting due to severe gastroesophageal reflux, a combination of oral and tube feeding of milk and oral glucose gel was utilized to prevent hypoglycemia and stabilize the BG. Genetic analysis demonstrated a paternally inherited heterogeneous variant of *KCNJ11* (p.R136AfsTer5), and contrast-enhanced computed tomography (CT) revealed an enhancing nodule in the body of the pancreas (Supplementary Fig. 3A). Therefore, the patient was suspected to have focal CHI. After

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discharge at 89 d of age, OCT was replaced with LRT 60 mg with stable BC (Supplementary Fig. 3B) at 137 d of age. At 6 mo of age, the patient could fast for 3 h without a hypoglycemic episode, as assessed by home monitoring with CGM and did not show apparent growth or developmental deficiency (weight, 6.705 kg: –1.4 SD; height, 66.5 cm: –0.6 SD).

Genetic analysis was performed immediately after transfer in all patients, resulting in a genetic diagnoses at 52 ± 24 [18–70] d of age. In all four patients, all variants detected were previously reported to be pathogenic (7–10).

All patients were treated with DZX but were unresponsive. Continuous intravenous infusion of glucagon was effective for refractory and severe hypoglycemia, especially in patients 1 and 2; however, early and recurrent catheter obstruction and catheter-related bloodstream infection occurred during glucagon administration despite the use of PICC and TCVC. After introducing a continuous subcutaneous OCT injection via an insulin pump device, the Medtronic MiniMed System, glucagon, and high-concentration glucose infusions were tapered in all patients. The average duration from the introduction of continuous subcutaneous OCT to the end of glucagon (patients 1–3) and continuous glucose infusion (all patients) was 40 ± 32 [5–68] d and 43 ± 30 [15–70] d, respectively. Biliary debris developed after the introduction of OCT in all patients but improved after the administration of ursodeoxycholic acid (10 mg/kg). Patients 3 and 4 were switched from OCT to a long-acting somatostatin analog, LRT, administered monthly as a deep subcutaneous injection. The use of LRT resulted in the simplification of treatment regimens and stabilization of BG control (Supplementary Figs. 2A, 3B) without significant side effects, except for temporary tubercles at injection sites and transient elevation of liver function enzymes (< 2 times the upper limit of normal).

To maintain euglycemia, carbohydrate supplementation was employed using the GSD formula N for patients 2–4 and uncooked corn starch for patients 1 and 2 after late infancy. Although nutritional stability is essential for a safe and stable BG management, all patients had comorbidities that could influence nutrition. Continuous or intermittent intragastric infusion of the formula was administered via a nasogastric tube or gastrostomy using portable pumps. Feeding problems (i.e., GERD and feeding difficulty) gradually improved with age, and patients 1 and 2 discontinued tube feeding at 3 and 21 mo of age, respectively.

All patients were managed with the support of real-time CGM and two different devices: a Medtronic MiniMed system and a Dexcom G6 system, especially in the acute phase and during the changing and tapering of treatments. CGM was used not only to support the avoidance of hypoglycemia but also to help identify glycemic trends, evaluate treatment effects, and determine the fasting time in each patient. In patients 3 and 4, it was confirmed that the therapeutic effect of LRT persisted for 28 d; subsequently, the next administration was performed.

None of the patients demonstrated abnormal magnetic resonance imaging findings indicating brain damage. The auxological outcomes of unoperated diffuse-type CHI (patients 1 and 2) indicated no shortness of stature at 3 yr of age (+ 0.9 and + 0.2 SD, respectively). The neurological and developmental outcomes of all the patients were within the normal range for each age group.

Discussion

Based on the experiences of these four DZX-unresponsive and KATP-associated CHI cases, we discuss updated treatment strategies, from recent to new guidelines, and the remaining clinical issues in CHI management (Supplementary Table 1).

Diagnosis

Early genetic diagnosis of focal CHI due to a paternally inherited recessive *ABCC8* or *KCNJ11* pathogenic variant may lead to cure via lesionectomy and become treatment-free, as in patient 3. Heavy birth weight for gestational age and DZX unresponsiveness were the most discriminative, independent, and additive factors for identifying children with KATP-associated CHI (11). Thus, individuals with DZX-unresponsive CHI born at a normal or large gestational age should be prioritized for earlier testing of KATP-associated genes.

Although the presence of a single paternally inherited *ABCC8* or *KCNJ11* variant offers a positive predictive value of approximately 60–90% for focal CHI (4, 12, 13), not all patients with a paternal variant have focal lesions (14, 15). Interpreting these results in Japanese patients is often difficult because a focal lesion may resemble a diffuse or multifocal lesion (16). Therefore, a combination of genetic and imaging analyses was necessary. Although molecular diagnostic services are readily available on a research or commercial basis, 18F-DOPA PET for infants and children with CHI is currently offered only at one facility in Japan, on a research basis (17, 18). A new candidate tracer, 68 gallium-NOGADA-exendin-4 (19), should be further evaluated in clinical trials before being recommended as an additional option. As only 10–20 cases of DZX-unresponsive severe CHI are expected to occur in Japan annually (18, 20), domestic and international collaborations for further accumulation and evaluation of cases are necessary to establish a better diagnostic strategy.

Treatment

Reconstituted glucagon is not approved for use in CHI but may be a "key drug" for preventing severe hypoglycemia in patients with severe CHI (21), especially when critical and uncontrolled hypoglycemia develops at birth, as seen in patients 1 and 2. However, the intravenous infusion of glucagon is generally limited

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to short-term use because of its side effects and technical issues, including catheter management. In addition to high-dose intravenous glucose administration, glucagon and hyperinsulinemia may be associated with problematic catheter occlusion (22–25). Indeed, our patients treated with glucagon required (multiple) re-insertions of a central venous catheter for catheter obstruction and infection, even with TCVC. Thus, more careful management of central venous catheters, including flow management and heparinization, may be required in patients with severe CHI to prevent occlusion and infection. Recently, the efficacy of dasiglucagon, a soluble glucagon analog delivered via continuous subcutaneous infusion, was reported in infants and children with CHI (26). In clinical practice, the severity of CHI can be assessed based on the prolonged need for glucagon administration, despite GIR > 10 mg/kg/min, to maintain euglycemia before the introduction of OCT.

OCT has been used since the late 1980s as a long-term therapy for patients with DZX-unresponsive CHI to avoid the need for pancreatectomy and was approved as a second-line treatment in Japan in 2020. However, continuous subcutaneous OCT with a pump carries the risk of pump disconnection and failure, causing radical and severe hypoglycemia. LRT and octreotide LAR have also been used in children with hyperinsulinism and have the advantage of being administered once a month (27–29). In our patients, biliary debris was found after initiation of OCT but resolved after the administration of ursodeoxycholic acid without relapse after LRT. To decrease the risk of severe side effects, including necrotizing enterocolitis (30), we introduced low-dose OCT, and after confirming the efficiency and appropriate dose of OCT, OCT was carefully switched to LRT. Based on our experience, we suggest that a maximum dosage of OCT (25 μg/kg/d) could safely replace LRT 60 mg.

Although surgical treatment is recommended for patients suspected of having a resectable focal lesion (1, 5), approximately 70% of patients with focal CHI in Japan have a lesion in the head of the pancreas (13). In some cases, removal of lesions in the pancreatic head may require a Roux-en-Y pancreatojejunostomy with a higher risk of injury to the common bile duct (31). This may be one way to maintain medical treatment with subcutaneous OCT or LRT until remission in patients with CHI with a large focal lesion or a lesion in the pancreatic head adjacent to the common bile duct. These Japanese patients have a milder phenotype, greater effectiveness of OCT, and a higher potential for remission than patients with biallelic diffuse CHI (16, 17, 32).

Management

Despite the remaining challenges, including discrepancies and time lags with self-monitoring of BG (SMBG), CGM in conjunction with SMBG has been reported in several studies as useful for preventing hypoglycemia in infants and children with CHI (33–37); however, it has not been approved for use in CHI management. Owing to the possibility of gradual improvement and spontaneous remission (17, 38), CGM may also be useful when determining safe feeding intervals and tapering or discontinuing OCT in patients with DZX-unresponsive CHI. The time in and below this range could be new parameters for evaluating blood glucose control in patients with CHI. Furthermore, real-time CGM can be used for home-based monitoring to avoid hypoglycemia and to share CGM data with a clinician via an application or website. Indeed, patient 4 safely switched from OCT to LRT without hospitalization through home-based CGM monitoring.

Some reports have suggested the efficacy of uncooked cornstarch and a high-carbohydrate formula (GSD-N) in infants with CHI (1, 39–41); however, there is no evidence from controlled studies. Based on our experience, the introduction of cornstarch during early infancy may exacerbate GERD owing to bloating or constipation. Feeding problems, including vomiting, GERD, difficulty in sucking or swallowing, and food refusal, occur frequently in patients with CHI and may be associated with persistent hyperinsulinism (42). Although most of these issues resolve over time (42, 43), some feeding problems, such as food aversion, are slow to resolve and may persist for more than 3 yr (42). Therefore, patients with severe and diffuse CHI accompanied by serious feeding problems, as in patient 2, should be considered for early gastrostomy intervention to reduce the hospitalization stay.

Abnormal neurodevelopmental outcomes have been observed in up to 48% of children with severe CHI (44, 45). Even in the absence of neurodevelopmental difficulties or brain imaging features, as in our patient, periodic developmental follow-up is required to facilitate early referral to community services. Additionally, some cases of KATP-associated CHI that develop diabetes despite absence of pancreatic surgery have been reported (38, 46, 47), indicating the need for long-term follow-up and transition to adult care, regardless of whether continuing treatment for CHI is warranted. Therefore, the establishment of comprehensive continuous support systems with careful follow-up and individualized approaches for each child and family is required to ensure optimal patient experiences and outcomes.

Conclusion

Despite scientific and clinical advances, diagnostic tools and treatment options remain limited, and have not been approved for use in most children with CHI. Additionally, high-quality evidence for new tools and medications is often lacking. As severe CHI is a rare and challenging disorder, consolidation of patients in the acute phase into centers specializing in CHI, multidisciplinary team care for all stages of CHI, and multilateral assessment based on a national registry are essential for the standardization and improvement of treatment strategies. Our cases indicate a safe method of switching from OCT to LRT, the efficacy of home-

based CGM monitoring, and the need for personalized support for feeding problems. Further accumulation of experience based on new treatment strategies, including assessment of the effectiveness of long-acting OCT or the effect of CGM-based control on long-term neurological prognosis, is required to generate high-quality novel evidence for the development and approval of new treatment options in the future.

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