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# Effectiveness of Medium-Chain Triglyceride Oil Therapy in Two Japanese Citrin-Deficient Siblings: Evaluation Using Oral Glucose Tolerance Tests

**Hiroki Otsuka,[1,2] Hideo Sasai,[1,2] Elsayed Abdelkreem,[1,3] Norio Kawamoto,[1] Minako Kawamoto,[1] Toshiya Kamiya,[4] Yasuo Tanimoto,[4] Atsuo Kikuchi,[5] Shigeo Kure,[5] Chikahiko Numakura,[6] Kiyoshi Hayasaka[6] and Toshiyuki Fukao[1,2]**

[1]Department of Pediatrics, Graduate School of Medicine, Gifu University, Gifu, Gifu, Japan
[2]Division of Clinical Genetics, Gifu University Hospital, Gifu, Gifu, Japan
[3]Department of Pediatrics, Faculty of Medicine, Sohag University, Nasser, Sohag, Egypt
[4]Department of Pediatrics, JA Mie Kouseiren Matsusaka Central General Hospital, Matsusaka, Mie, Japan
[5]Department of Pediatrics, Tohoku University School of Medicine, Sendai, Miyagi, Japan
[6]Department of Pediatrics, Yamagata University School of Medicine, Yamagata, Yamagata, Japan

Citrin deficiency, an inherited defect of the liver-type mitochondrial aspartate/glutamate carrier isoform (citrin), may cause impairment of glycolysis because of an increase in the cytosolic NADH/$NAD^+$ ratio. We report a Japanese boy whose main complaint was recurrent hypoglycemic episodes. He was suspected as having citrin deficiency because of his peculiar preference for protein- and fat-rich food. His young sister also had a similar food preference. Both siblings were diagnosed with citrin deficiency by genetic analysis. The brother and sister underwent an oral glucose tolerance test (OGTT) at 10 and 7 yr of age, respectively. Blood glucose, ammonia, lactic acid, pyruvic acid, and insulin levels were monitored before starting the test, and then every 30 min. During this test, they maintained blood glucose levels until 180 min. At 210 min, they experienced vomiting, feeling ill, and decreased blood glucose levels (2.9 and 2.8 mmol/l in the brother and sister, respectively). The sister and brother recovered uneventfully by intravenous glucose injection. In a second OGTT, 4 months after medium-chain triglyceride (MCT) oil supplementation, they had no major symptoms and normal glucose levels were maintained, even after 240 min. Additionally, after MCT oil therapy, their food preference slightly changed as they started eating more carbohydrates. Our OGTT data suggest excess carbohydrate intake has adverse consequences in patients with citrin deficiency, including hypoglycemia after a few hours. MCT oil therapy may be effective in preventing such hypoglycemia and improving metabolic derangement, even during the so-called apparently healthy period.

**Keywords:** citrin deficiency; food preference; hypoglycemia; medium-chain triglyceride; oral glucose tolerance test
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## Introduction

Citrin is the liver-type mitochondrial aspartate/glutamate carrier isoform. It mediates the transfer of NADH-reducing equivalent from cytosol to mitochondria as part of the malate-aspartate shuttle in the liver. Citrin plays a role in various metabolic pathways, including glycolysis, gluconeogenesis, and ureagenesis. Citrin deficiency is an autosomal recessive disease caused by *SLC25A13* mutations. This disease was first described in Japan, where it has a high prevalence, but it has also been recognized in several countries worldwide (Kobayashi et al. 1999). The two well-defined clinical phenotypes of citrin deficiency are neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD: Online Mendelian Inheritance in Man [OMIM] 605814) and adult-onset type II citrullinemia (CTLN2: OMIM 603471). Nearly all patients with NICCD outgrow their symptoms within the first year of life. A small proportion of patients develops hyperammonemic encephalopathy (CTLN2), usually between 20 and 40 yr of age (Saheki et al. 2010). However, some patients suffer from various manifestations during the so-called apparently healthy period; some children are diagnosed with citrin deficiency without an apparent history of NICCD. The most striking symptom during the apparently healthy period is a peculiar preference for protein- and fat-rich food with an aversion to

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Correspondence: Toshiyuki Fukao, Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1 Gifu, Gifu 501-1194, Japan.
e-mail: toshi-gif@umin.net

carbohydrate-rich food (Saheki et al. 2008). Ketotic hypoglycemia is also relatively common during this period (Kure et al. unpublished observation).

In this study, we report two Japanese siblings with citrin deficiency who were diagnosed during the apparently healthy period. We also performed an oral glucose tolerance test (OGTT) before and after medium-chain triglyceride (MCT) oil supplementation. Our findings will lead to a better understanding of the biochemical consequences of citrin deficiency and the effect of MCT oil therapy.

## Case Presentation

The proband, a male child, was referred to Gifu University Hospital at the age of 8 yr because he experienced recurrent hypoglycemic convulsions. He was born to non-consanguineous Japanese parents at 39 weeks of gestation with a birth weight of 2,740 g. Results of newborn screening, including galactose, methionine and phenylalanine, were normal. He had a history of hypoglycemia and apnea during his neonatal period, but no apparent NICCD symptoms (e.g., cholestasis, hepatomegaly, liver dysfunction). He was breastfed and had poor weight gain until 5 months of age. Thereafter, he was well until 5 yr of age when he developed morning hypoglycemic convulsions. Further details are not available. Morning hypoglycemic convulsions recurred at the age of 7 yr after skipping dinner. His blood glucose level was 1.7 mmol/l (normal range, 3.8-6.1), insulin level was 0.2 $\mu$U/dl (normal range, 1.84-12.2), C-peptide level was 0.1 ng/ml (normal range, 0.61-2.09), and total ketone body (TKB) level was 1.8 mmol/l (normal range, < 0.13). Morning hypoglycemic convulsions recurred again at 8 yr of age after a small dinner. His blood glucose level was 1.7 mmol/l, insulin level was < 0.1 $\mu$U/dl, C-peptide level was 0.1 ng/ml, ammonia level was 20 $\mu$mol/l (normal range, 14.8-41.3), adrenocorticotropic hormone level was 153.7 pg/ml (normal range, 7.2-63.3), antidiuretic hormone level was 100 ng/ml (normal range, 300-4,200), TKB level was 1.6 mmol/l, and free fatty acid level was 2.2 mmol/l (normal range, 0.14-0.85). He recovered uneventfully in both episodes using 20 ml of 20% glucose.

A physical examination in Gifu University Hospital at 8 yr of age showed that the patient's height was 122.5 cm (−1.3 SD) and his weight was 23.2 kg (−0.9 SD). He had no hepatomegaly or other remarkable clinical findings. Mild defects in ketogenesis or glycogen synthase deficiency were initially suspected because hypoglycemic events recurred at an older age than with so-called ketotic hypoglycemia. Additionally, TKB levels were low relative to simultaneously measured glucose levels (blood glucose X TKB [both in mmol/l] were 3.1 and 2.6; normal range, 8-12) (Bonnefont et al. 1990). However, we did not identify such defects by molecular analysis. A careful history taking revealed peculiar feeding habits. He disliked rice and sweets but liked beans, fried chicken, and meat. An *SLC25A13* mutational analysis demonstrated that he was a compound heterozygote for two pathogenic mutations: c.851_854delGTAT (p.Arg284fs) and c.1019_1177del (p.340_392del) (Kikuchi et al. 2012). He was finally diagnosed with citrin deficiency at 10 yr of age.

The parents noted that the younger sister also had a similar characteristic food preference. A genetic analysis demonstrated that she had the same mutations as her elder brother. We permitted their characteristic feeding after a definite diagnosis. However, at 7 yr of age, the sister suffered from morning hypoglycemic convulsions, even after having enough dinner. These convulsions occurred just after the diagnosis had been confirmed. Both patients sometimes complained of general fatigue without hypoglycemia.

MCT oil supplementation was reported to be effective in patients with NICCD and CTLN2 (Hayasaka et al. 2012, 2014). Therefore, we thought that MCT oil might also be effective for the siblings' symptoms. Both siblings were given MCT oil supplementation (5 ml twice a day). We performed OGTT to investigate the cause behind the recurrent hypoglycemic episodes in the siblings. An OGTT and self-reported questionnaire for food preference were provided before and after MCT oil therapy in the brother and sister at 10 and 7 yr of age, respectively. The elder brother started to eat more steamed rice and other carbohydrate-rich food after MCT oil supplementation.

*Ethical considerations*

MCT oil therapy for citrin-deficient patients was approved by the Ethical Committee of the Graduate School of Medicine, Gifu University, Japan. The research was carried out in accordance with the principles contained within the Declaration of Helsinki. The parents provided informed consent to participate in the study.

*First OGTT (before MCT oil supplementation)*

On the day before OGTT, the two siblings had a normal dinner with their food preference. The next morning, after fasting for 12 h, they received 1.75 g/kg glucose orally; both siblings readily took the glucose solution within a short time. Careful monitoring of blood glucose, ammonia, lactic acid, pyruvic acid, and insulin levels was undertaken before starting this test, and then every 30 min for 180 min. The siblings tolerated the test well and had no complaints until 180 min. However, at 210 min, they suffered from abdominal pain, fatigue, and vomiting. At that time, their blood glucose levels were 2.9 and 2.8 mmol/l in the brother and sister, respectively (Fig. 1, Table 1). They were treated with an intravenous slow injection of 20 ml of 20% glucose followed by a maintenance glucose infusion. They recovered uneventfully within 30 min.

*Second OGTT (after MCT oil supplementation)*

The OGTT was repeated 4 months after starting MCT oil supplementation. In the morning of the test, the siblings received 5 ml of MCT oil as usual. In contrast to the first

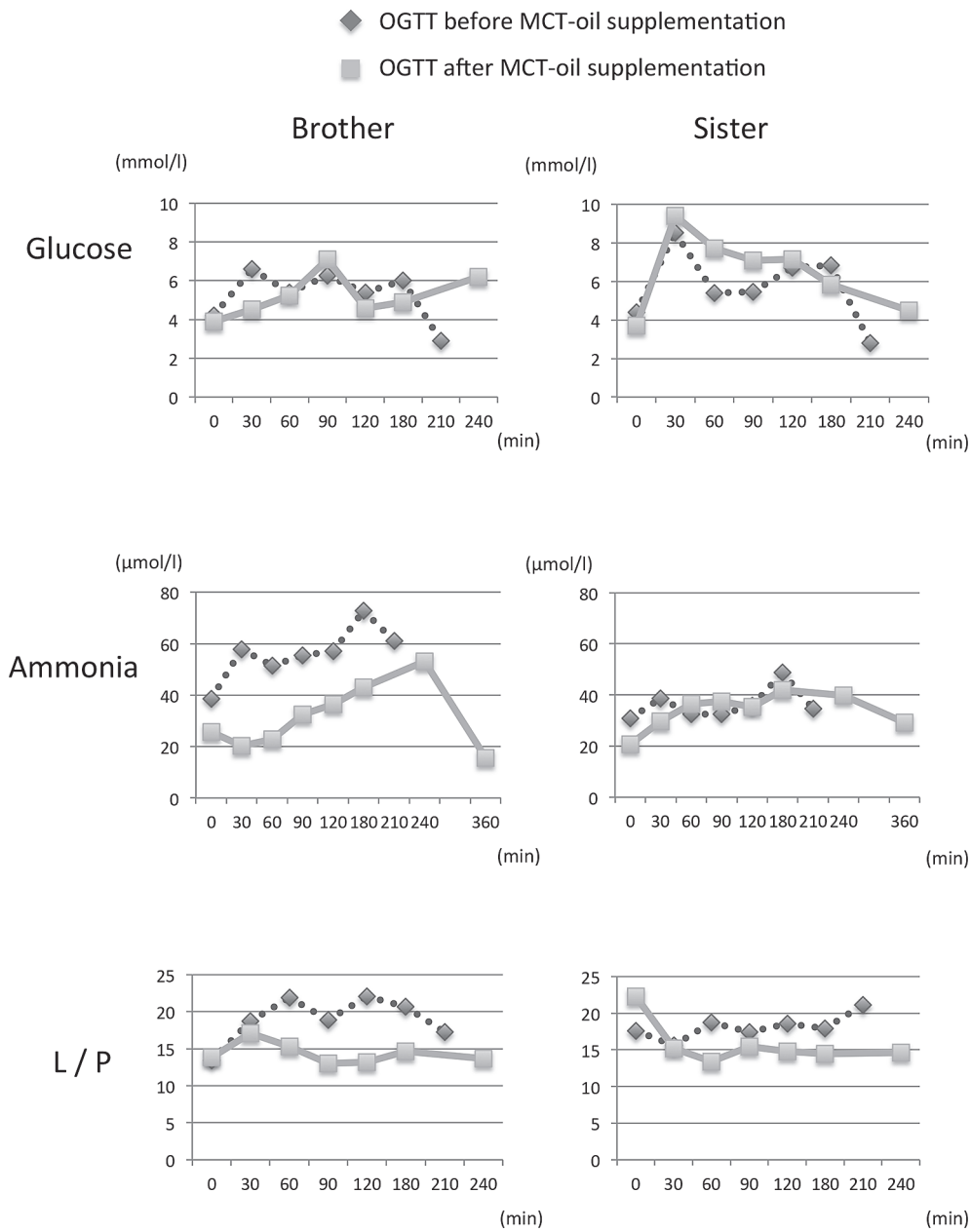


Fig. 1. OGTT in two siblings with citrin deficiency.
An OGTT test was performed before and 4 months after starting MCT oil therapy. Both siblings suffered from abdominal pain, fatigue, and vomiting at 210 min in the first test (before MCT oil supplementation). There were no major clinical symptoms, even after 240 min in the second test (after MCT oil supplementation). MCT, medium-chain triglycerides; L/P, lactate to pyruvate ratio; OGTT, oral glucose tolerance test.

test, they had no major symptoms and their normal glucose levels were maintained, even at 240 min. They were able to eat after 240 min. In the elder brother, the lactate to pyruvate (L/P) ratio and the ammonia levels during the first test were higher than those during the second test, although this elevation was less evident in the young sister (Fig. 1).

*Self-reported questionnaire for food preference*

The siblings ranked many types of food using a five-point scale (1, favorite; 2, like; 3, neutral; 4, dislike; 5, hate) before and 4 and 9 months after MCT oil therapy. Their food preference changed after MCT oil therapy (Table 2). Although they still preferred protein- and fat-rich food, they started to tolerate some carbohydrates. Additionally, the complaints of general fatigue became less frequent.

## Discussion

In addition to the two classic clinical phenotypes (NICCD and CTLN2), some patients with citrin deficiency present with several manifestations during the so-called apparently healthy period. These manifestations include a peculiar food preference, anorexia, failure to thrive, dyslip-

Table 1. OGTT data.

**Brother**

*OGTT before MCT-oil supplementation*

| | 0 | 30 | 60 | 90 | 120 | 180 | 210 | (min) |
|---|---|---|---|---|---|---|---|---|
| Glucose (mmol/l) | 4.2 | 6.6 | 5.4 | 6.3 | 5.4 | 6.0 | 2.9 | |
| IRI (μU/ml) | 1.6 | 23.3 | 8.2 | 18.2 | 7.5 | 18.9 | 2.7 | |
| Ammonia (μmol/l) | 38.6 | 57.7 | 51.5 | 55.4 | 57.1 | 72.8 | 61.0 | |
| Lactic Acid (mmol/l) | 0.67 | 1.11 | 1.16 | 1.08 | 1.41 | 1.02 | 0.81 | |
| Pyruvic Acid (mmol/l) | 0.050 | 0.059 | 0.053 | 0.057 | 0.064 | 0.050 | 0.047 | |
| L/P | 13.4 | 18.7 | 21.9 | 18.8 | 22.1 | 20.7 | 17.2 | |

*OGTT after MCT-oil supplementation*

| | 0 | 30 | 60 | 90 | 120 | 180 | 240 | 360 | 720 | (min) |
|---|---|---|---|---|---|---|---|---|---|---|
| Glucose (mmol/l) | 3.9 | 4.5 | 5.2 | 7.1 | 4.6 | 4.9 | 6.2 | | | |
| IRI (μU/ml) | 1.5 | 12.3 | 9.7 | 34.9 | 5.2 | 9.6 | 17.5 | | | |
| Ammonia (μmol/l) | 25.8 | 20.2 | 23.0 | 32.5 | 36.4 | 43.1 | 53.2 | 15.7 | 23.0 | |
| Lactic Acid (mmol/l) | 0.69 | 0.96 | 0.99 | 0.81 | 0.77 | 0.87 | 0.69 | | | |
| Pyruvic Acid (mmol/l) | 0.050 | 0.056 | 0.065 | 0.063 | 0.058 | 0.059 | 0.051 | | | |
| L/P | 13.8 | 17.1 | 15.3 | 13.0 | 13.2 | 14.6 | 13.7 | | | |

**Sister**

*OGTT before MCT-oil supplementation*

| | 0 | 30 | 60 | 90 | 120 | 180 | 210 | (min) |
|---|---|---|---|---|---|---|---|---|
| Glucose (mmol/l) | 4.4 | 8.5 | 5.4 | 5.4 | 6.7 | 6.8 | 2.8 | |
| IRI (μU/ml) | 8 | 56.6 | 11.8 | 17.1 | 27 | 37 | 1.1 | |
| Ammonia (μmol/l) | 30.8 | 38.6 | 32.5 | 32.5 | 35.8 | 48.7 | 34.7 | |
| Lactic Acid (mmol/l) | 1.20 | 1.05 | 1.30 | 1.19 | 1.31 | 1.14 | 1.49 | |
| Pyruvic Acid (mmol/l) | 0.068 | 0.067 | 0.069 | 0.068 | 0.070 | 0.064 | 0.070 | |
| L/P | 17.6 | 15.6 | 18.7 | 17.4 | 18.6 | 17.9 | 21.1 | |

*OGTT after MCT-oil supplementation*

| | 0 | 30 | 60 | 90 | 120 | 180 | 240 | 360 | 720 | (min) |
|---|---|---|---|---|---|---|---|---|---|---|
| Glucose (mmol/l) | 3.7 | 9.4 | 7.7 | 7.1 | 7.2 | 5.8 | 4.5 | | | |
| IRI (μU/ml) | 1.8 | 42.2 | 23.7 | 33.1 | 37.4 | 34.5 | 5 | | | |
| Ammonia (μmol/l) | 20.7 | 29.7 | 36.4 | 37.5 | 35.3 | 42.0 | 39.8 | 29.1 | 29.7 | |
| Lactic Acid (mmol/l) | 1.78 | 1.62 | 1.43 | 1.34 | 1.33 | 1.14 | 1.01 | | | |
| Pyruvic Acid (mmol/l) | 0.080 | 0.107 | 0.107 | 0.087 | 0.090 | 0.079 | 0.069 | | | |
| L/P | 22.3 | 15.2 | 13.4 | 15.4 | 14.8 | 14.4 | 14.6 | | | |

Table 2. Changes in food preference by a self-reported questionnaire.

| | *Brother* | | | *Sister* | | |
|---|---|---|---|---|---|---|
| Foods | MCT-oil Start | After 4 Months | After 9 Months | MCT-oil Start | After 4 Months | After 9 Months |
| Fish | 1 | 1 | 1 | 2 | 1 | 2 |
| Hamburg | 2 | 3 | 2 | 2 | 2 | 1 |
| Salami | 2 | 3 | 3 | 1 | 1 | 1 |
| Green Soybean | 2.5 | 3 | 2 | 1 | 1 | 1 |
| Peanat/Almond | 1 | – | 1 | 2 | 1 | 1 |
| Boiled Egg | 1 | 3 | 2 | 1 | 1 | 2 |
| Cheeze | 1.5 | 2 | 1 | 2 | 1 | 2 |
| Wheat Noodle | 3 | 3 | 4 | 2 | 2 | 2 |
| Rice | 3 | 2 | 2 | 1 | 1 | 2 |
| Corn | 2.5 | 2 | 3 | 1 | 2 | 2 |
| Banana | 4 | 3 | 3 | 4 | 2 | 2 |
| Juice | 3 | 3 | 3 | 1 | 2 | 2 |
| Candy/Gummi | 4 | 2.5 | 1.5 | 3 | 1 | 1.5 |
| Japanese Traditional Sweets (Sugar Rich) | 4.5 | 4 | 4 | 4 | – | 1 |

1, favorite; 2, like; 3, neutral; 4, dislike; 5, hate.

idemia, hypoglycemia, gastroenteropathy, fatigue, and impaired quality of life (Nagasaka et al. 2009). The clinical and laboratory features of this period are not completely defined. Notably, some patients are diagnosed with citrin deficiency during their older childhood without an apparent history of NICCD. A peculiar food preference may be, if typical, a pathognomonic feature for citrin deficiency, as found in our siblings.

Ketotic hypoglycemia is a relatively common clinical condition. This condition may result from mild defects in glucose and its related metabolism, such as glycogen storage diseases or defects in gluconeogenesis (Brown et al. 2015). Among 18 Japanese citrin-deficient patients who were diagnosed during the apparently healthy period, hypoglycemia was the diagnostic clue in seven patients (Kure et al. unpublished observation). Therefore, citrin deficiency should be considered a genetic cause of ketotic hypoglycemia. We considered OGTT may be useful for evaluating glucose metabolism in citrin deficiency.

During the first OGTT, both siblings developed hypoglycemia after 210 min, and this was unexpected. Because both siblings had the same presentation, the hypoglycemic event was not just a coincidence. After MCT oil supplementation, both siblings did not have hypoglycemia, even after 240 min. The reason why they developed hypoglycemia after the first OGTT is unclear. We speculate the following reasons might be involved. Fasting for 12 h before OGTT depletes glycogen stores. During an OGTT, insulin promotes glycogenesis, and suppresses gluconeogenesis and fatty acid oxidation. In healthy children, hepatic glycogenolysis and gluconeogenesis may play a major role in maintaining blood glucose at 180 min and longer after an OGTT. However, citrin deficiency is expected to impair glycolysis and gluconeogenesis because of an increased $NADH/NAD^+$ ratio. Moreover, citrin deficiency may impair glycogenesis. In support of this possibility, a glucagon test showed no rise in blood glucose levels in the fasting and postprandial states in an infant with citrin deficiency who showed two episodes of ketotic hypoglycemia (Hachisu et al. 2005). Impaired glycogenesis, with subsequent defective glycogenolysis, may contribute to hypoglycemia 180 min after an OGTT; the mechanism may mimic prolonged fasting for longer than 15 h. Therefore, defective glycogenesis and gluconeogenesis could explain a hypoglycemic event during the first OGTT. MCT oil travels through the portal vein to the liver where it provides mitochondrial NADH by beta-oxidation and enhances lipogenesis. This leads to a decrease in the cytosolic $NADH/NAD^+$ ratio. MCT oil supplementation might improve glycogen storage, incurring more tolerance against hypoglycemia in the second OGTT. Whether the effect of MCT oil on our patients was due to long (4 months) or short supplementation is unclear.

In a previously reported case, blood lactate levels decreased from 37.7 mg/dl to 10.6 mg/dl during an OGTT in a citrin-deficient infant who had ketotic hypoglycemia (Hachisu et al. 2005). In our patients, lactate levels did not decrease during the OGTT, but the L/P ratio was elevated in both siblings. This finding may indicate an increased $NADH/NAD^+$ ratio in the cytosol during an OGTT, reflecting impairment of glycolysis. Notably, the L/P ratio did not increase during the second OGTT (after MCT oil supplementation). Moreover, especially in the elder brother, an increased blood ammonia level was more evident in the first than in the second OGTT. In another report, a citrin-deficient girl at the age of 10 yr had a more elevated ammonia level that was measured after a carbohydrate-rich hospital breakfast than after her favorite fat- and protein-rich breakfast. Plasma ammonia levels, which were measured at 1-2 h after taking various types of breakfast, were positively correlated with simultaneously-drawn glucose levels. They considered that the cause of elevation in ammonia levels was insufficient urea cycle function due to a cytosolic shortage of aspartic acid. This shortage could have been caused by NADH accumulation in the cytosol as a consequence of citrin deficiency (Saheki et al. 2010). We also consider that elevated ammonia levels may be due to a shortage of hepatic ATP in citrin deficiency because of NADH accumulation. MCT-oil supplementation may improve hepatic ATP shortage, and in turn, improve blood ammonia levels.

As discussed above, MCT oil supplementation was effective in preventing hypoglycemia and improving metabolic derangement during the OGTT in our patients. MCT oil supplementation changed the siblings' food preferences, although the changes in the young sister were not so apparent (Table 2). The young sister considered steamed rice as her favorite, but she only ate a small amount. This finding indicates a limitation of self-reported questionnaires that are provided to young children, such as our patient (7 yr of age). The parents recorded more apparent changes in siblings' food preferences. MCT oil supplementation may be beneficial, not only for patients with NICCD and CTLN2 (Hayasaka et al. 2012, 2014), but also for citrin-deficient patients, even during the apparently healthy period. However, a cohort study with more patients is required to validate the effect of MCT oil on citrin-deficient patients during the apparently healthy period.

## Conclusion

Our experience with two siblings suggests that we should consider citrin deficiency in patients with hypoglycemic episodes. Checking food preferences in these patients is imperative. Our OGTT data suggest that excess carbohydrate intake has adverse consequences and may cause hypoglycemia after a few hours. MCT oil supplementation may be useful for patients with citrin deficiency, even during the apparently healthy period.

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## Conflict of Interest

The authors declare no conflict of interest.

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