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Diabetes mellitus exacerbates citrin deficiency via glucose toxicity

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ABSTRACT

Aims: Citrin is an aspartate/glutamate carrier that composes the malate-aspartate reduced nicotinamide adenine dinucleotide (NADH) shuttle in the liver. Citrin deficiency causes neonatal intrahepatic cholestasis (NICCD), failure to thrive and dyslipidemia (FTTDCD) and adult–onset type II citrullinemia (CTLN2). Hepatic glycolysis is essentially impaired in citrin deficiency and a low-carbohydrate diet was recommended. The lethal effect of infusion of glycerol- and fructose-containing osmotic agents was reported in these patients. Hyperalimentation was also reported to exacerbate CTLN2; however, glucose toxicity was unclear in citrin deficiency.

Methods: We studied two CTLN2 patients complicated with type 2 diabetes mellitus (DM), Case 1 presented with hyperammonemic encephalopathy accompanied with DM, while Case 2 presented with hyperammonemic encephalopathy relapse upon the onset of DM after several years' remission following supplementation with medium-chain triglycerides (MCT) and adherence to a low-carbohydrate diet.

Results: Insulin therapy with MCT supplementation and a low-carbohydrate diet improved hyperammonemia and liver function in Case 1. Additional insulin therapy improved hyperammonemia in Case 2.

Abbreviations: MCT, medium-chain triglycerides; AST, aspartate aminotransferase; ALT., alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, gamma-glutamyltranspeptidase; ChE, cholinesterase; TG, triglycerides.

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Conclusion: Glucose is not toxic for citrin deficiency in normoglycemia because glucose uptake and metabolism by hepatocytes are limited in normoglycemia. However, glucose becomes toxic during persistent hyperglycemia and antidiabetic therapy is indispensable for CTLN2 patients with DM.

1. Introduction

Citrin, which is encoded by the *SLC25A13* gene, is a Ca^{2+}-binding aspartate/glutamate carrier that transfers cytosolic reducing equivalents produced during glycolysis to the mitochondria as part of the malate-aspartate reduced nicotinamide adenine dinucleotide (NADH) shuttle in the liver [1] (Fig. 1). Citrin deficiency is a recessively inherited metabolic disorder characterized by age-dependent clinical manifestations that include neonatal intrahepatic cholestasis (NICCD: OMIM 605814), failure to thrive and dyslipidemia (FTTDCD), and adult-onset type II citrullinemia (CTLN2: OMIM 603471) [1,2].

Hepatic glycolysis is coupled with de novo lipogenesis and is essentially impaired in citrin deficiency due to a defect in the NADH shuttle (Figs. 1, 2). Hepatocytes use fatty acids and glucose as energy sources during fasting and postprandial states, respectively. Down-regulation of peroxisome proliferator-activated receptor α (PPARα) was reported in the liver of CTLN2 patients [3]. In citrin deficiency, hepatocytes cannot use glucose and fatty acids resulting in energy deficit. Supplementation with medium-chain triglycerides (MCT) can provide energy to the hepatocytes, and it is a reasonable therapy for NICCD and CTLN2 [4–7].

On the other hand, the infusion of glycerol- and fructose-containing osmotic agents has been reported to produce a lethal effect in CTLN2 patients [8] (Fig. 2). In addition, a high-carbohydrate diet is unfavorable for citrin deficiency, and it sometimes becomes triggers the onset of CTLN2 [1,2]. There was also a report of a CTLN2 patient, who received hyperalimentation and developed hyperammonemic encephalopathy accompanied with hyperglycemia; however, glucose toxicity was unclear [9]. Hepatic glucose uptake and metabolism are limited in normoglycemia owing to the low glucose affinity of glucose transporter 2 (GLUT2) [10]. In contrast, persistent hyperglycemia was predicted to increase glucose uptake and metabolism and cause glucose toxicity in hepatocytes.

We present two CTLN2 patients complicated with type 2 diabetes mellitus (DM) and confirmed glucose toxicity during persistent hyperglycemia. One case presented with hyperammonemic encephalopathy accompanied with DM, while the other presented with hyperammonemic encephalopathy relapse upon the onset of DM after several years of remission

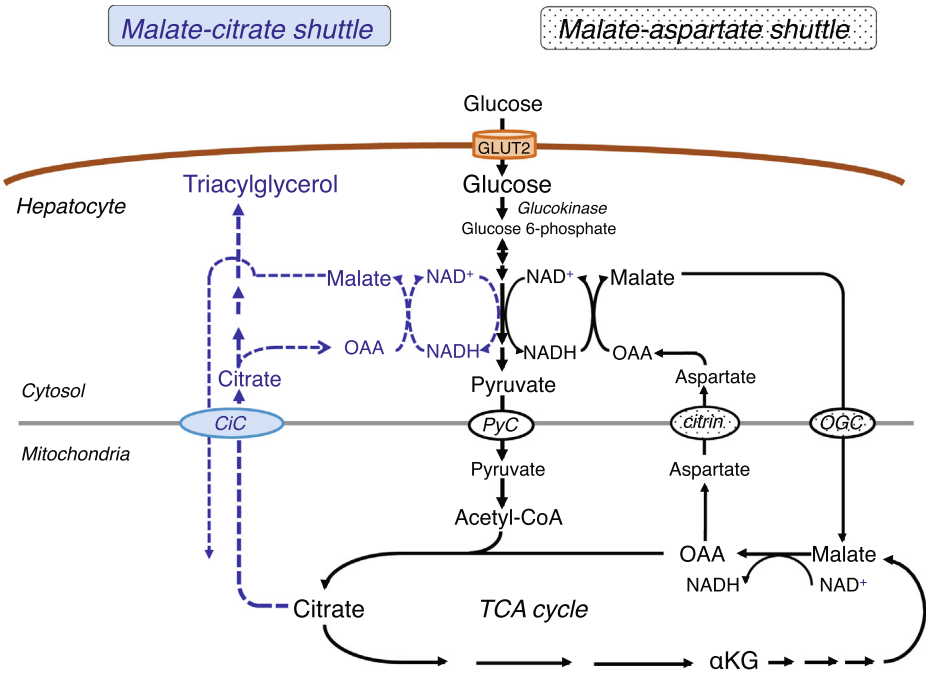

Fig. 1 – Glycolysis and lipogenesis in the liver. Acetyl-CoA, acetyl coenzyme A; αKG, α-ketoglutarate; CiC, citrate carrier; GLUT2, glucose transporter 2; NADH, nicotinamide adenine dinucleotide hydrogen; NAD^+, nicotinamide adenine dinucleotide-oxidized; OAA, oxaloacetate; OGC, 2-oxoglutarate carrier; PyC, pyruvate carrier; TCA, tricarboxylic acid.

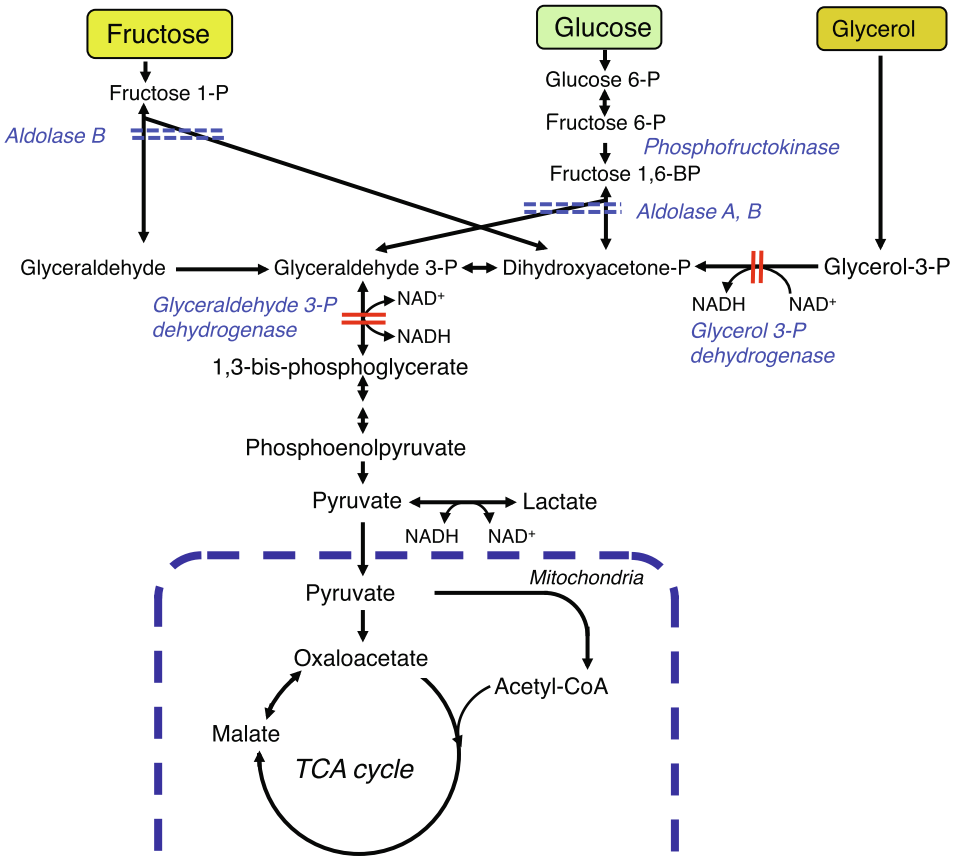

Fig. 2 – Glucose, fructose and glycerol metabolism in the liver. Glyceralaldehyde 3-phosphate dehydrogenase and glycerol 3-phosphate dehydrogenase (red double solid lines) are impaired in citrin deficiency. Aldolase B (blue double dotted lines) is impaired in hereditary fructose intolerance. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

following MCT supplement therapy [6]. Both exhibited favorable results upon using antidiabetic and MCT supplement therapies.

2. Materials and Methods

2.1. *Case reports*

2.1.1. *Case 1*

A male aged 61 years and 11 months was admitted to Hospital A because of recurrent episodes of hyperammonemic encephalopathy during the preceding two weeks. He had no apparent NICCD symptom, but he preferred high-protein and high-fat foods and disliked carbohydrates since childhood. He had recurrent acute pancreatitis at 19 years of age, received a blood transfusion, and experienced a hepatitis C infection. At 60 years of age, he complained of edema in the lower extremities, and multiple tumorous lesions were detected in the liver through abdominal echography and magnetic resonance imaging. Abdominal echography also demonstrated pancreatic atrophy and calcification. A liver biopsy specimen revealed mild fibrosis with mononuclear cell infiltration, moderate to severe deposits of iron and lipofuscin, and macro- and microvesicular fat droplets in<10% of hepatocytes. Biochemical analysis revealed liver dysfunction, mild anemia, hyperglycemia (151–260 mg/dL), and increased glycated hemoglobin A1c (HbA1c) levels (6.4–6.5%: 46–47 mmol/mol). Nateglinide (30 mg/day) was being administered for hyperglycemia in the month prior to the present hospital admission.

On admission, he weighed 52.6 kg and he was 172.9 cm tall. His body mass index was 17.8 kg/m^2. He had mild anemia and venous ulcers on the lower left leg. There was no hepatosplenomegaly or abnormal neurological findings. The laboratory data revealed mild hyperammonemia, citrullinemia, hypoalbuminemia, mild liver dysfunction, mild anemia and thrombocytopenia, and mild hypothyroidism (Table 1). Other remarkable findings (normal levels given in parentheses) were fasting plasma glucose 127 mg/dL (<110 mg/dL), prandial plasma glucose 236 mg/dL (<140 mg/dL), fasting immunoreactive insulin (IRI) 3.0 μU/mL (2–10 μU/mL), fasting C-peptide 0.72 ng/mL (1.0–2.0 ng/mL), HbA1c 6.2% (4.4–5.8%), hyaluronic acid 427 ng/dL (<50 ng/dL), type IV collagen 368.0 ng/mL (<150 ng/mL), and ferritin 998 ng/ml (15–160 ng/mL). Assessment of the fasting C-peptide-to-glucose ratio and homeostatic model assessment of beta cell function (HOMA-β) indicated decreased insulin secretion, and homeostatic model assessment of insulin resistance (HOMA-IR) analysis

Table 1 – Summary of laboratory data of patients.

Patient	Case 1						Case 2						
Days after MCT therapy	−75	330	940	1180	1357		0	435	879	1385	2050	2234	
Body Weight (kg)	52.6		60.0	59.6	60.0		37.0	42.0	36.7	39.2	38.5	37.8	
Laboratory data	reference ranges												
Citrulline (μmol/L)	17.1–42.6	197.8	227.9	54.2	57.5	49.9	839	256.2	121.5	347	–	273.4	
Glutamine (μmol/L)	422.1–703.8	357.8	464.8	648.0	576.1	498.4	448.1	490.7	542.5	430.8	–	490.2	
Fischer ratio	2.43–4.40	2.43	1.12	1.56	1.86	2.69	1.77	2.1	2.43	1.88	–	2.18	
Albumin (g/dL)	3.8–5.3	2.7	2.3	4.0	4.2	4.3	3.2	4.6	4.4	4.2	–	4.2	
AST (IU/L)	13–33	54	49	38	29	28	49	24	34	21	36	28	
ALT (IU/L)	8–42	42	34	29	22	20	64	36	56	29	43	33	
ALP (IU/L)	115–359	707	609	448	407	329	302	181	326	267	243	278	
γ-GTP (IU/L)	13–64	163	199	92	72	61	110	49	52	28	–	31	
ChE (IU/L)	185–501	48	65	137	136	159	233	324	248	264	–	214	
TG (mg/dL)	30–149	–	79	66	125	–	1889	346	273	206	–	87	
Ammonia (μg/dL)	40–80	95	217	98	49	24	120	29	170	208	85	28	
HbA1c (%)	4.9–5.8	6.2	6.1	5.7	5.6	5.4	5.9	6.4	6.2	6.4	6.6	6.0	

showed no insulin resistance. He was a compound heterozygote with c.1311 + 1G > A (p.Val411_Cys437del) and c.1751-5_1751-4ins[TTTTTTTTTTTTTTTTT;NM_138459.2:c.-194_*1573inv;C;1751-21_1751-5] (p.?) mutations in *SLC25A13*. He was diagnosed with CTLN2 accompanied with DM and hypothyroidism. He was treated with insulin supplement therapy (11–16 IU of insulin/day) and levothyroxine sodium hydrate (25 μg/day) and small amounts of MCT (5–15 mL of Macton oil per day; Macton oil is composed of 85% MCT and 5% long-chain triglycerides). He also received one pack of branched amino acid-rich enteral nutrition supplement (Aminoleban EN, Otsuka Pharmaceutical) in addition to his diet, with a total of 2000 kcal a day (protein:fat:carbohydrate (PFC) ratio 14:31:55). He had sudden sensorineural hearing loss in his left ear, which was treated with steroid pulse therapy at the age of 62 years and 3 months. He passed a tarry stool and received red blood cell transfusion at the age of 62 years and 4 months. At the age of 62 years and 5 months, he received two packs of Aminoleban EN with his diet, with a total of 1600 kcal a day (PFC ratio 22:24:54)

The level of plasma citrulline, serum ferritin, and serum choline esterase (ChE) gradually improved, accompanied with decreased HbA1c level (Fig. 3, Table 1). He experienced occasional hyperammonemia but no episodes of encephalopathy. After three years (at 64 years of age), the administration of Aminoleban EN was stopped. The administration of Macton oil was increased to 45 mL/day with his diet (total 2500–3000 calories a day; PFC ratio 17–20:48–49:32–34); the levels of blood ammonia, ChE, gamma-glutamyltranspeptidase (γ-GTP), and alkaline phosphatase (ALP) and the Fischer ratio were normalized after 6 months (Table 1).

2.1.2. *Case 2*

A 48-year-old female presented with the first episode of hyperammonemic encephalopathy. She had no episode of NICCD, but she had experienced acute pancreatitis at 18 years of age and episodes of unconsciousness at 44 years of age. Following the diagnosis of citrin deficiency, she was treated with an MCT supplement (30 mL of Macton oil/day) with a low-carbohydrate formula (1800 kcal a day; PFC ratio 15:50:35), as previously reported (case 2 in reference 6). After the treatment, she sometimes experienced postprandial-hyperammonemia (91–97 μg/dL), with no episode of hyperammonemic encephalopathy (Fig. 4, Table 1). The HbA1c level was initially 5.8–5.9%, and it increased to >6.0% after 49 years of age. She experienced a second episode of mild hyperammonemic encephalopathy at 50 years of age, when she had anorexia and lost weight (from 41.8 kg to 36.7 kg) due to work-related stress. Her condition improved after changing jobs. However, the frequency of hyperammonemia (>100 μg/dL) gradually increased, accompanied with increased HbA1c level from 6.0 (41 mmol/mol) to 6.4% (46 mmol/mol) at 51 years of age to 6.3 to 7.1% at 52 years of age. She had a third episode of hyperammonemic encephalopathy at 53 years of age, and she began receiving insulin regimen (4.5 IU insulin daily). The blood ammonia level decreased, accompanied with a decreased level of HbA1c (Fig. 4).

3. Results and discussion

We report two CTLN2 patients affected with diabetic mellitus. One patient received insulin therapy with an MCT supplement and a low-carbohydrate diet for DM and CTLN2, which improved hyperammonemia accompanied with a decrease in the level of HbA1c. The other patient developed DM during MCT supplement therapy for CTLN2 [6]. The MCT supplement therapy had improved the hyperammonemia and maintained her health for a few years. However, a relapse of hyperammonemic encephalopathy occurred, accompanied with an increase in the level of HbA1c. Antidiabetic therapy improved the level of HbA1c and blood ammonia. These findings indicate that glucose toxicity becomes apparent during persistent hyperglycemia, and antidiabetic therapy is indispensable for patients with citrin deficiency and DM.

Glycolysis is essentially impaired in the liver of the patients with citrin deficiency due to a defect in the NADH shuttle. Carbohydrate toxicity was proposed by Saheki et al. [11] A lactose (galactose)-restricted and MCT-supplemented formula is recommended for NICCD patients [4]. Galactose metabolism is inhibited at the step involving UDP-glucose 4-epimerase-mediated catalysis in hepatocytes because of increased cytosolic NADH, and toxic metabolites would accumulate and damage the hepatocytes. Infusion of glycerol- and fructose-containing osmotic agents is lethal for patients with CTLN2 [8]. This is similar to the lethality that can arise due to parenteral fructose loading for patients with hereditary fructose intolerance (aldolase B deficiency) (Fig. 2) [12]. Fructose is rapidly taken up and metabolized in hepatocytes quite different from glucose. Parenteral fructose administration, even to healthy controls, results in the consumption of ATP, an accumulation of metabolites (fructose 1-phosphate), trapping of inorganic phosphate (Pi), and a decrease of ATP in hepatocytes [12]. Parenteral administration of fructose-based solutions to patients with hereditary fructose intolerance results in the depletion of Pi and ATP in the hepatocytes, which causes acute hepatocyte necrosis and profound metabolic acidosis. At least 15 fatal cases have been reported [13]. Additionally, a lethal response to the infusion of glycerol- and fructose-containing solution occurs in patients with citrin deficiency, because they have defects in fructose and glycerol metabolism at the step involving catalysis by glyceraldehyde 3-phosphate dehydrogenase and glycerol 3-phosphate dehydrogenase, respectively, due to a defect in the NADH shuttle.

A carbohydrate-rich diet is not recommended for patients with citrin deficiency [2,4–6]. Two possibilities can be considered. One is that carbohydrates are harmful (toxic) for the hepatocytes of these patients. The other possibility is that a carbohydrate-rich diet (low-protein and low-fat diet) cannot provide enough energy to the hepatocytes of the patients. The latter possibility is quite likely, because the hepatocytes of individuals with citrin deficiency cannot use glucose due to a defect in the NADH shuttle but can use protein and fat as energy sources [7].

Regarding the mechanisms of glucose toxicity, hepatocytes ordinarily take up and metabolize glucose only during the fed state (in hyperglycemia) because GLUT2 is a low-affinity glucose transporter of hepatocytes, with a Km of 15 to 20 mM [10] (Fig. 1). However, if the individuals have persistent hyperglycemia, large amounts of glucose can be incorporated into hepatocytes. Increase in cytosolic glucose enhances the activity of glucokinase (GK) via activation of the GK regulatory protein. Activated GK facilitates phosphorylation of glucose to glucose 6-phosphate. Cytosolic glucose 6-phosphate can be subsequently metabolized for glycogen

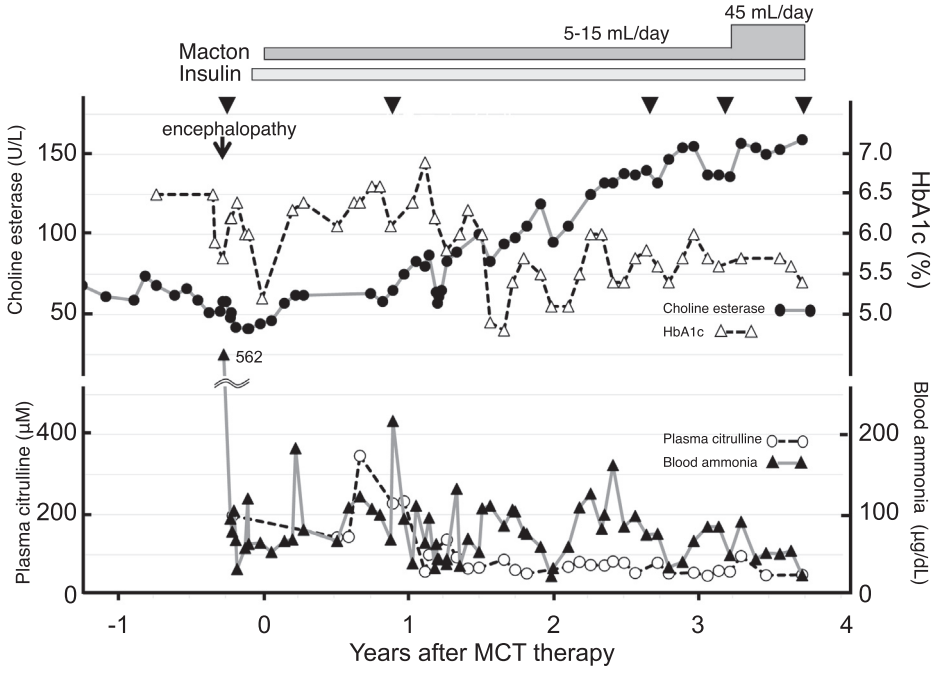

Fig. 3 – Changes in the levels of blood ammonia, plasma citrulline, choline esterase, and HbA1c in Case 1. Arrowheads indicate the ages of the patient at the time of testing described in Table 1.

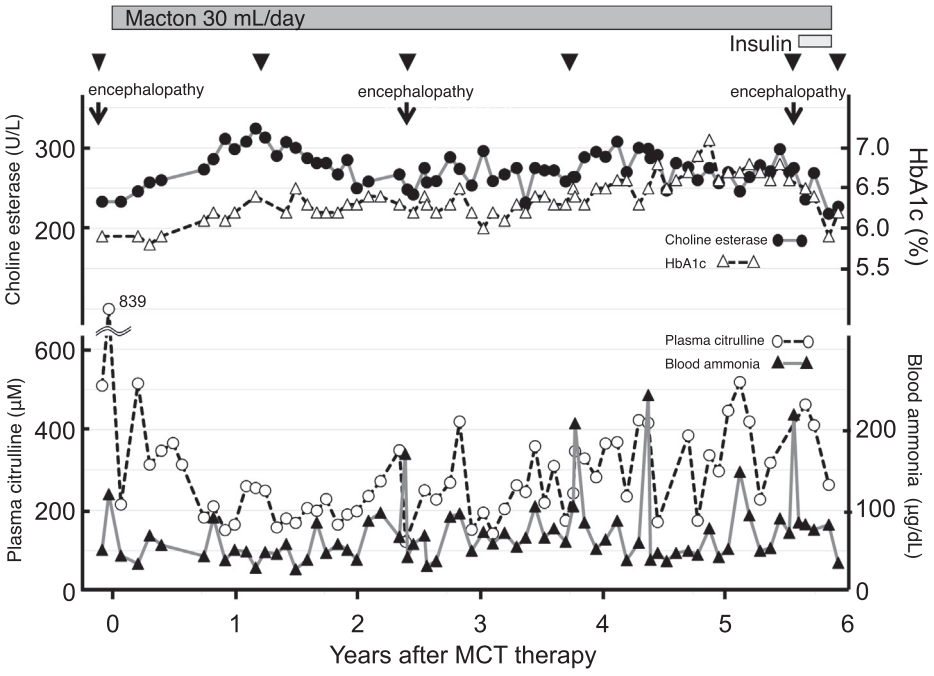

Fig. 4 – Changes in the levels of blood ammonia, plasma citrulline, choline esterase, and HbA1c in Case 2. Arrowheads indicate the ages of the patient at the time of testing described in Table 1.

synthesis and gluconeogenesis, and/or via glycolysis. However, glycogen synthesis and gluconeogenesis would be suppressed in diabetic patients due to a defective insulin action. As a result, glucose 6-phosphate may be metabolized via glycolysis and glucose metabolites subsequently may accumulate, decrease Pi and ATP, and damage hepatocytes in CTLN2 patients due to a defect in the NADH shuttle. Tamakawa et al. [9] described a 52-year-old female with CTLN2 who underwent appendectomy at the age of 18 years, cholecystectomy at the age 29 years, and a radical mastectomy for breast cancer and subtotal gastrectomy due to peptic ulcer at age 46. At the age of 52 years, she experienced anorexia and weight loss (from 36 kg to 27.5 kg). She received hyperalimentation and developed hyperammonemic encephalopathy (blood ammonia 721 μg/L) accompanied with hyperglycemia (214 mg/dL). Hyperalimentation fluids were changed to low-glucose solution and the levels of blood ammonia and glucose were normalized. She received hyperalimentation again, developed hyperammonemic encephalopathy, and recovered again following a low-glucose infusion. This indicates that glucose becomes toxic during persistent hyperglycemia, which supports our findings. It is also very important to notice that glucose can be administered to the patients safely, if the level of blood glucose is controlled within the normal range.

The difference between the toxic effects of parenteral fructose administration or persistent hyperglycemia and the unfavorable effect of a carbohydrate-rich diet (a low-protein and low-fat diet) is an important aspect to consider when planning treatment. The daily requirement of carbohydrate in the formula is important especially for children. Hypoglycemia has been reported in children with citrin deficiency who receive an extremely low carbohydrate diet [14–16]. Numakura et al. [17] also reported that 18 children among 126 children with citrin deficiency had episodes of hypoglycemia. The recommended dietary allowance for carbohydrate (130 g/day for adults and children based on the average minimum amount of glucose utilized by the brain) should be administered, especially to children, to avoid hypoglycemia, because patients with citrin deficiency have a defect in gluconeogenesis [18].

Regarding the relationship between citrin deficiency and DM, complications associated with DM are not frequent in patients with citrin deficiency, and aralar (isoform of citrin) is expressed in the islet beta cells, indicating that there is no direct relationship between citrin deficiency and DM [19].

4. Conclusion

Avoiding persistent hyperglycemia is very important for patients with citrin deficiency in addition to the contraindication of administration of glycerol- and fructose-containing solutions. Antidiabetic therapy is indispensable for patients with citrin deficiency and DM.

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Declaration of competing interest

The authors had no potential conflicts of interest (COI) associated with this work.

Ethical approval

The ethics committee of the Yamagata University School of Medicine approved our research project (reference number 116/2018). All procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all patients for molecular analysis and their involvement in the clinical trials of MCT therapy.

Author contributions

Design of the study: Y. W., C. N., and K. H. Recruitment of patients into the study, as well as providing clinical data: Y. W., T. T., K. F., T. T., Y. H., and K. T. Pathological analysis: M. Y. Wrote the manuscript: K. H. All authors participated in interpretation of data and provided critical revisions to the manuscript drafts. All authors read and approved the final manuscript.

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