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Relationship between Blood Ammonia and Plasma free Amino Acids Concentration in Adult-Onset Citrullinemia Type 2: A Case Report

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1. Abstract

1.1. Aim: Elevated plasma citrulline (Cit) concentration is a characteristic finding in adult-onset type II citrullinemia (CTLN2). However, the plasma free amino acids (PFAA) profile associated with ammonia detoxification has not been fully analyzed.

1.2. Methods: We evaluated the relationship between blood ammonia (B-NH_3) and the PFAA concentrations through a 50-year-old man with CTLN2 following for over 8 years without liver transplantation.

1.3. Results: Plasma Cit, arginine, total aromatic amino acids (phenylalanine and tyrosine) and methionine concentrations showed significant positive correlation with B-NH_3 concentration, while the molar ratio of branched-chain amino acids versus aromatic amino acids showed significantly negative correlation with B-NH_3 concentration. The other hand, plasma glutamine (Gln) concentration was nearly within normal range and did not show significant correlation with B-NH_3 concentration.

1.3. Conclusion: Several PFAA including Cit dynamically changed and significantly correlated with B-NH_3 concentration, while plasma Gln concentration showed nearly normal range and do not correlated with B-NH_3 concentration in CTLN2. Further study is necessary to clarify the mechanism of the impaired Gln synthesis for ammonia detoxification in CTLN2.

2. Introduction

Adult-onset type II citrullinemia (CTLN2) is an inherited urea cycle disorder caused by a mutation in the *SLC25A13* gene, which encodes the liver-specific isoform of the mitochondrial aspartate-glutamate carrier (AGC2; known as citrin) [1-3]. CTLN2 is clinically characterized by a high plasma citrulline (Cit) concentration and acute hyperammonemic encephalopathy (AHE), ultimately leading to death due to brain edema [1,2,5]. The geographic prevalence of CTLN2 is relatively high in South Asia, including Japan, where its prevalence is approximately 1/100,000-230,000 persons as reported by [3]. Although the patients with CTLN2

require liver transplantation to recover completely [4], dietary management based on low carbohydrates and high protein and fat with medium-chain triglyceride (MCT) oil and medical treatments for hyperammonemia have been developed, resulting in a long-term maintenance of the quality of life before liver transplantation [5-8]. Regarding the plasma free amino acid (PFAA) profile in patients with CTLN2, the plasma Cit concentration is extremely higher and has diagnostic value [2,5,9,10]. On the other hand, the plasma glutamine (Gln) concentration, which is closely associated with the detoxification of ammonia in the liver, muscle, kidney and brain, is not elevated in most patients with CTLN2. However, the precise mechanisms underlying the change of plasma Gln concentration in CTLN2 have not been fully clarified. Moreover, there is no reliable data for the serial changes of PFAA concentrations in the CTLN2 patients during the long term period. Therefore, we evaluated the relationship between blood ammonia (B-NH_3) and PFAA concentrations through a man with CTLN2 following for over eight years without liver transplantation.

3. Case Report

A 41-year-old Japanese man visited our hospital for the first time on January, 2013, because his elder brother had been diagnosed with CTLN2 in 2012 [5]. Although he had a history of neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD), he had never experienced any serious events caused by hyperammonemia and never undergone a checkup until 41 years old. Regarding his eating habits, he had preferred protein and fat-rich foods, such as peanuts and sweets, from early childhood. His consciousness was completely clear, and no abnormal neuropsychiatric signs were seen on a physical examination. The liver function test findings were almost normal. The B-NH_3 (baseline range using enzyme method in our hospital; 15-70 μg/dL) and plasma glucose concentrations were 64 μg/dL and 92 mg/dL, respectively. The PFAA profile showed characteristic changes (high Cit and normal Gln concentrations) and molecular analysis showed a compound heterozygous mutation of *SLC25A13*. Imaging tests (abdominal sonography and computed tomography [CT]) showed slight fatty liver without splenomegaly or liver tumors. Histological examination of the liver could not be performed, as he did not consent to undergo a liver biopsy. Although he initially received the nutritional management with a low-carbohydrate diet with MCT oil (Macton® 45 ml/day; Kissei Pharmaceutical Co., Ltd., Matsumoto, Japan) and medical treatments using sodium pyruvate and lactulose to prevent the onset of AHE since 2013 [5], he has admitted to our hospital totally 6 times until April, 2022, because of AHE due to his self-discontinuing medication during the follow-up. Table 1 shows the laboratory data from the fourth to sixth admission due to AHE since 2020. Liver function tests showed almost stable results over three admissions; the platelet count gradually decreased, but the lipid and renal functions showed no marked changes. Although the fibrosis index based on four factors (FIB-4 index), which is a reliable marker for liver fibrosis, gradually increased, the stiffness of the liver measured using shear-wave elastography was within the normal range (4.67 kPa on March 4, 2022). Figure 1 shows the findings of abdominal CT and brain MRI obtained on March 2 and 4, 2020, respectively. The findings of abdominal contrast-enhanced CT showed multiple regenerative nodules in the right hepatic lobes and mild undulation of the hepatic surface, suggesting mild progression of liver fibrosis. MRI showed the effects of hyperammonemia on brain, i.e. transverse T2-weighted fast fluid-attenuated inversion recovery (FLAIR) imaging showed symmetric areas of increased signal intensity along the cortex and insula in both cerebral hemispheres. Figure 2 shows the medical treatments and serial changes in B-NH_3, plasma Cit and Gln concentrations during the same period. The B-NH_3 concentration dynamically fluctuated during the first three to four days after admission but rapidly decreased and stabilized since then. The plasma Cit concentration remained constantly high, regardless of the presence of hyperammonemia, and increased further starting in 2022. The plasma Gln concentration was nearly within the normal range, regardless of the presence of hyperammonemia. Nutritional management with MCT oil had been continuously performed by a dietitian [total calories/day are 1600 kcal + 200 kcal (MCT oil), protein 75 g, fat 75 g and carbohydrate 175 g (PFC % ratio 20:40:40)] (Max 540).

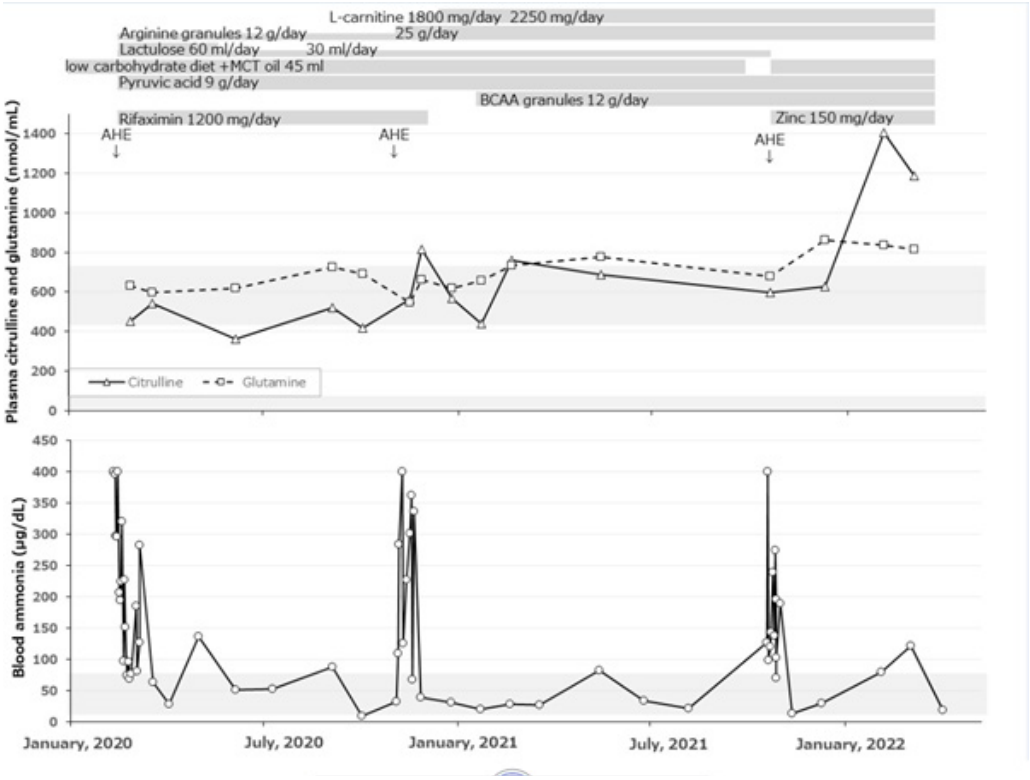

Figure 1: Medical treatments and changes in the levels of plasma citrulline, glutamine and blood ammonia since 2020. Reference ranges: glutamine, 422-703 nmol/L, citrulline 17.1-42.6 nmol/L, and blood ammonia, 15-70 μg/dL. AHE: Acute hyperammonemic encephalopathy, BCAA: branched-chain amino acids, MCT: Medium-chain triglyceride.

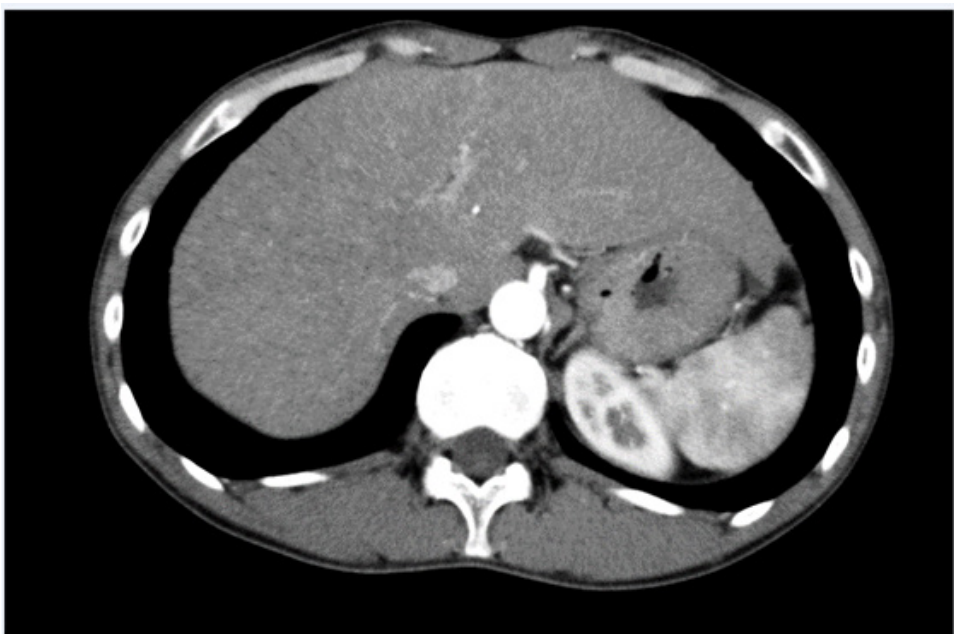

Figure 2a: The findings of abdominal CT and brain MRI. (a) The findings of contrast-enhanced CT show multiple regenerative nodules in the right hepatic lobes and mild undulation of the hepatic surface.

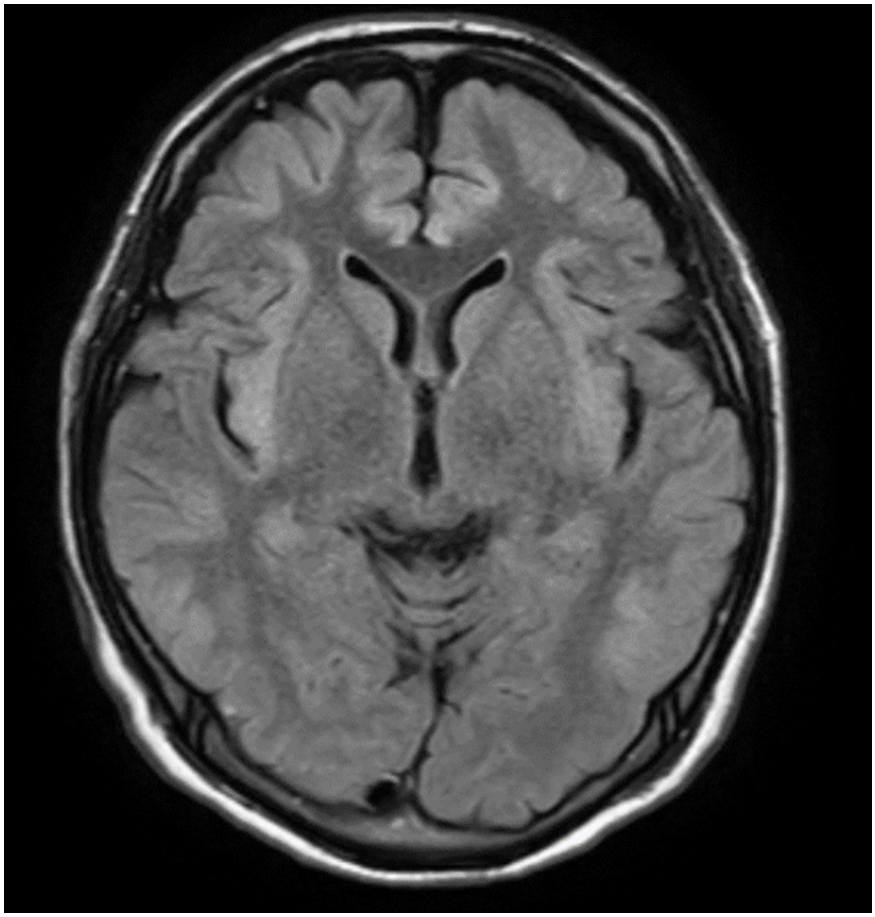

Figure 2b: The findings of abdominal CT and brain MRI. (b) Transverse T2-weighted fast FLAIR imaging shows symmetric areas of increased signal intensity along the cortex and insula in both cerebral hemispheres.

Table 1: Coma grade and laboratory data on acute hyperammonemic encephalopathy since

	February, 2020	November, 2020	October, 2021
Age (years old)	48	49	50
Coma grade (JCS)	3	2	3
Peripheral blood tests			
RBC (x 10^4μL*)	509	521	567
Hemoglobin (g/dL)	15.7	16.3	17.4
Hematocrit (%)	44.6	46.2	50.1
WBC (μL)	9300	7900	6500
Platelet (x 10^3μL)	184	140	101
Liver function tests			
T-Bil (mg/dL)	0.8	1.2	1.5
AST (IU/L)	26	31	27
ALT (IU/L)	33	38	37
γGTP (IU/L)	63	70	58
Albumin (g/dL)	4.1	n.t	3.3
PT-INR	1.1	n.t	1.0
FIB-4 index (<1.3)	1.19	1.77	2.20
Lipids			
Triglyceride (mg/dL)	69	55	41
HDL-cholesterol (mg/dL)	122	100	83
LDL-cholesterol (mg/dL)	84	79	62
Renal function			
Urea nitrogen (mg/dL)	20.0	20.0	16.0
Creatinine (md/dL)	0.58	0.76	0.70
eGFR (ml/min)	115.9	85.7	93.3
Blood glucose (mg/dL)	124	98	125
Blood ammonia (μg/dL)	>400	109→>400*	127→>400*

JCS, Japan coma scale; RBC, red blood cells; WBC, white blood cells; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, gamma glutamyl transferase; PT-INR, prothrombin time international ratio; FIB-4 index; fibrosis index based on 4 factors.
*data of next day morning

4. Evaluation of PFAAs

We collected data on PFAAs and B-NH_3, which were simultaneously measured between February 2013 and March 2022. Blood samples were basically obtained from the peripheral vein in the fasting condition in the morning at the outpatient clinic or on admission. Plasma PFAA was measured by high performance liquid chromatography in outside institution (SRL Co., Ltd. Tokyo, Japan). We mainly focused PFAA related to ammonia detoxification, gluconeogenesis and ketogenesis, and examined the relationship with PFAA and B-NH_3 concentration. Statistical analyses were performed using the SPSS 17.0 software program (SPSS, Chicago, IL, USA). Correlation analysis was performed using Spearman's rank test. $P<0.05$ was considered significantly. The correlation between B-NH_3 and PFAA and several parameters for amino acids status was showed in the Table 2. Plasma Cit, Arg, phenylalanine (Phe), Tyrosine (Tyr), methionine (Met) and threonine (Thr) showed a significantly positive correlation with the B-NH_3 concentration. Furthermore, the total aromatic amino acid (AAA; Phe + Tyr) and threonine (Thr)/serine (Thr/Ser) ratio, total amino acid (total AA) and total nonessential AA (NEAA) also showed a significantly positive correlation with the B-NH_3 concentration. Although valine (Val) and leucine (Leu)—except for isoleucine (Ile)—were significantly correlated with the B-NH_3 concentration, the branched-chain AA (BCAA; Val + Leu +Ile) to AAA molar ratio (Fischer ratio) showed a significantly negative correlation. In contrast, the plasma Gln concentration showed no significant correlation with the B-NH_3 concentration. Among the PFAAs related to gluconeogenesis and/or ketogenesis, the Ile, alanine (Ala) and Ser concentrations were below the reference range.

Table 2: Correlations between blood ammonia concentration and plasma free amino acids concentration and several parameters for amino acids imbalance.

Variants	*r*	*P-value*
Cit	**0.524**	**0.001**
Arg	**0.429**	**0.007**
Orn	0.074	0.653
Gln	0.066	0.690
Glu	0.068	0.682
Tau	0.166	0.311
Asp	-0.213	0.192
Asn	0.179	0.273
Ala	-0.153	0.352
Gln/Ala	0.246	0.126
Thr	**0.407**	**0.011**
Ser	0.004	0.982
Thr/Ser	**0.499**	**0.001**
Val	-0.206	0.207
Leu	-0.244	0.134
Ile	0.058	0.725
BCAA	-0.182	0.266
Phe	**0.487**	**0.002**
Tyr	**0.629**	**<0.0001**
AAA	**0.430**	**0.007**
Fischer ratio	**-0.343**	**0.033**
Met	**0.494**	**0.002**
total AA	**0.422**	**0.008**
NEAA	**0.404**	**0.011**
EAA	0.104	0.527

Statistical analysis was performed using the Spearman's rank test.

$P<0.05$ was considered significant.

Cit, citrulline; Arg, arginine; Orn, ornithine; Gln, glutamine; Glu, glutamic acid; Tau, taurine; Asp, aspartate; Asn, asparagine; Ala, alanine; Thr, threonine; Ser, serine; Val, valine; Leu; Ile, isoleucine; BCAA, branched chain amino acids (Val + Leu + Ile); Phe, phenylalanine; Tyr, tyrosine; AAA, aromatic amino acid (Phe + Tyr); Met, methionine; total AA, total amino acids; NEAA, nonessential amino acid; EAA, essential amino acids.

5. Discussion

The diagnostic algorithm for urea cycle disorders with hyperammonemia indicates that the plasma Gln concentration is a first-step indicator and that the plasma Cit concentration is a second indicator [9]. A high Cit concentration and a normal Gln concentration have been observed in the majority of patients with CTLN2 [5-7,9,11]. However, long-term data on the PFAA dynamics and on the relationship between B-NH_3 and PFAA concentrations in CTLN2 are lacking. Therefore, in the present study, we focused the relationship between B-NH_3 and PFAAs in a patient with CTLN2 who was followed for over eight years without liver transplantation. The following results were obtained in the present study: 1) plasma Cit and Arg concentrations, but not the Orn concentrations, increased and were significantly correlated with the B-NH_3 concentration; 2) the plasma Gln concentration was nearly within the normal range and showed no significant correlation with the B-NH_3 concentration; 3) the plasma BCAA concentration decreased despite the oral administration of BCAA granules, but no significant correlation with the B-NH_3 concentration was observed, 4) the plasma AAA and Met concentrations were within the normal range but were significantly correlated with the B-NH_3 concentration; 5) the Fischer ratio significantly decreased due to the decrease in the plasma BCAA concentration and showed a negative correlation with the B-NH_3 concentration; 6) the plasma Ala concentration decreased but was not correlated with the B-NH_3 concentration; 7) the plasma Thr/Ser ratio was higher than in the controls (1.17 ± 0.13; mean value ± standard deviation according to reference 5) but did not show a significant correlation with the B-NH_3 concentration; and 8) the total AA and NEAA values showed a significantly positive correlation with the B-NH_3 concentration. Although these findings were similar to those previously reported in CTLN2, we indicated, for the first time that several PFAAs, including Cit, Arg and AAA, were significantly correlated with the B-NH_3 concentration. Because AAA are metabolized in the liver, the plasma AAA concentration increases according to the severity of liver dysfunction [12], indicating that the elevation of the plasma AAA concentration is related to the severity of hepatocellular damage with fibrosis, such as in liver cirrhosis (LC). Interestingly, our data showed that the plasma AAA concentrations were within the normal range, whereas the values of serum fibrosis markers, such as hyaluronate and type IV collagen, were slightly increased. Moreover, the values denoting liver stiffness were normal and the mild progression of liver fibrosis was also suggested by the abdominal CT findings. Therefore, a liver biopsy will be necessary to clarify this discrepancy. The high plasma Cit concentration was attributed to the decrease in argininosuccinate synthase 1 (ASS1) activity, which is critical for converting Cit to Orn in the urea cycle of the liver and gradually decreases with the progression of liver injury due to fibrosis [2,10,13]. The plasma Arg concentration was also high in CTLN2, in which causes in part the synthesis of Arg in the kidney [10,14,15]. L-arginine activates N-acetylglutamate, which induces the activation of carbamoyl phosphate synthetase I (CPSI), the rate-limiting enzyme of the urea cycle [11,16]. Therefore, the oral administration of L-arginine may ameliorate urea cycle dysfunction due to activation of CPSI and the supply of Arg to the urea cycle. Conversely, the plasma Orn concentration in our case was within the normal range and not correlated with the B-NH_3 concentration. The plasma Gln concentration is usually high under conditions of chronic hyperammonemia, such as in LC with portal-systemic shunt, and is considered an indicator of brain edema in acute or chronic liver failure [17,18]. However, the plasma Gln concentration reportedly shows no elevation in the majority of patients with CTLN2 [5-7,10,16]. In our case, the plasma Gln concentration also was almost within normal range and did not change dynamically, regardless of the presence of hyperammonemia (Figure 1). Regarding why the plasma Gln concentration is increased in CTLN2 despite a hyperammonemic state, Wilson et al. proposed that elevated Cit itself inhibits glutamine synthetase (GS) activity [11]. Suggested that although numbers of GS-positive hepatocytes are not decreased in CTL2 patients, the function of GS in catalyzing the ATP-dependent synthesis of Gln from Glu for ammonia detoxification is impaired [6]. However, since MCT oil supplemental therapy can supply ATP and/or substrates for hepatic GS [5-7], the plasma Gln concentration increases following appropriate dietary therapy with MCT oil [6]. On observing Figure 1 in detail, although the plasma Gln concentration showed an increasing trend after appropriate guidance for dietary management with MCT oil from the beginning of 2022. As a possible mechanism underlying the lack of elevation of plasma Gln concentrations in CTLN2, we suggest that the duration of hyperammonemia may be closely associated with the elevation of the plasma Gln concentration, as the continuous hyperammonemic state due to LC with portal-systemic shunt induces a high plasma Gln concentration [17,18]. Notably, AHE in our case suddenly occurred once or twice per year, with a duration of three to four days. After achieving complete remission of AHE, the B-NH_3 concentration rapidly improved and remained nearly normal. Clarifying the precise mechanism underlying the changes in the plasma Gln concentration in CTLN2 will require examining the enzyme activities, including ASS1 and GS activities, in the liver of patients with CTLN2. The plasma BCAA concentration decreased despite the oral administration of BCAA granules. This result suggests that the utilization of BCAA for ammonia detoxication in the skeletal muscle may have been increased. Recently, Miyazaki et al. indicated that the PFAA profile of citrin-deficient children during the healthy stage differed from those of NICCD and CTLN2 patients, suggesting that the impaired function of both the urea cycle and energy metabolism might be compensated by AA metabolism [19]. In CTLN2, changes in the dietary habits, including overdose of dietary carbohydrate and alcohol intake, are mainly considered to

be precipitating factors for onset of AHE [7-9,20]. Actually, Kitaoka et al. have reported that AHE was triggered in a 72-year-old man with CTLN2 after the patient stopped consuming pulse-based snacks, such as soybeans and peanuts, due to dental problems [21]. In our case, self-interruption and/or incorrect MCT oil intake were considered potential precipitating factors of AHE. Several limitations associated with the present study warrant mention. First, the PFAA data were obtained from a single CTLN2 patient. Second, the influence of oral administration such as for L-arginine and BCAA granules could not be ruled out. Thirdly, the total calorie intake volume and each % component of protein, fat and carbohydrate per day were not equal during the follow-up period. In conclusion, the concentrations of several PFAAs, including Cit, Arg and AAA, were significantly correlated with the B-NH_3 concentration. However, the plasma Gln concentration was nearly within the normal range, regardless of the presence of hyperammonemia, and showed no significant correlation with the B-NH_3 concentration. Further studies involving the regulation of Gln synthesis in extrahepatic organs will be required to clarify the reason for the impaired Gln synthesis in CTLN2.

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6. Authorship

Contribution: Y. Fujiwara supported the medical care of this patient and wrote part of the manuscript; K. Suzuki mainly supported the medical care of this patient in the outpatient clinic, designed the study and wrote part of the manuscript; M. Miura supported the medical care of this patient; H. Kuroda performed the statistical analysis; C. Abe and S. Segawa performed nutritional guidance; H. Takahashi supervised and read the final draft of this paper. All authors reviewed and approved the final version of the manuscript.

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