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Relationship between BloodAmmonia and Plasma freeAminoAcids Concentration inAdult-Onset Citrullinemia Type 2:ACase Report

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1. Abstract

Aim: Elevatedplasmacitrulline(Cit)concentrationisacharacteristic 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.

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

Results: PlasmaCit,arginine,totalaromaticaminoacids(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 aminoacidsshowedsignificantlynegativecorrelationwithB-NH_3 concentration.Theotherhand,plasmaglutamine(Gln)concentrationwasnearlywithinnormalrangeanddidnotshowsignificant

1.3. Conclusion: Several PFAA including Cit dynamically changed and significantly correlated with B-NH_3concentration, while plasma Gln concentration showed nearly normal range and do not correlated with B-NH_3concentration in CTLN2. Further study is necessary to clarify the mechanism of the impaired Gln synthesis for ammonia detoxification in CTLN2.

2. Introduction

Adult-onsettypeIIcitrullinemia(CTLN2)isaninheritedureacycle 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), ultimatelyleadingtodeathduetobrainedema[1,2,5].Thegeographic prevalence of CTLN2 is relatively high in South Asia, including Japan,whereitsprevalenceisapproximately1/100,000-230,000 personsasreportedby[3].AlthoughthepatientswithCTLN2 correlationwithB-NH_3 concentration.

require liver transplantation to recover completely [4], dietary managementbasedonlowcarbohydratesandhighproteinandfat withmedium-chaintriglyceride(MCT)oilandmedicaltreatments for hyperammonemia have been developed, resulting in a long- term maintenance of the quality of life before liver transplanta- tion [5-8]. Regarding the plasma free amino acid (PFAA) profile inpatientswithCTLN2,theplasmaCitconcentrationisextremely higher and has diagnostic value [2,5,9,10]. On the other hand, the plasmaglutamine(Gln)concentration,whichisscloselyassociated withthedetoxificationofammoniaintheliver,muscle,kidneyand brain, isnot elevated in most patientswith CTLN2. However, the precisemechanismsunderlyingthechangeofplasmaGlnconcentrationinCTLN2havenotbeenfullyclarified.Moreover,thereis no reliable data for the serial changes of PFAAconcentrations 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

A41-year-old Japanese man visited our hospital for the first time on January, 2013, because his elder brother had been diagnosed withCTLN2in2012[5].Althoughhehadahistoryofneonatalintrahepaticcholestasiscausedbycitrindeficiency(NICCD),hehad never experienced any serious events caused by hyperammonemiaandneverundergoneacheckupuntil41yearsold.Regarding hiseatinghabits,hehadpreferredproteinandfat-richfoods,such as peanuts and sweets, from early childhood. His consciousness was completely clear, and no abnormal neuropsychiatric signs wereseenonaphysicalexamination.Theliverfunctiontestfind- ings were almost normal. The B-NH_3 (baseline range using en- zyme method in our hospital; 15-70 μg/dL) and plasma glucose concentrations were 64 μg/dL and 92 mg/dL, respectively.The PFAAprofileshowedcharacteristicchanges(highCitandnormal Gln concentrations) and molecular analysis showed a compound heterozygous mutation of *SLC25A13*. Imaging tests (abdominal sonography and computed tomography [CT]) showed slight fatty liverwithoutsplenomegalyorlivertumors.Histologicalexamination 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®45ml/day;KisseiPharmaceuticalCo.,Ltd.,Matsumoto, Japan) and medical treatments using sodium pyruvate and lactulosetopreventtheonsetofAHEsince2013[5],hehasadmittedto ourhospitaltotally6timesuntilApril,2022,becauseofAHEdue tohisself-discontinuingmedicationduringthefollow-up.Table1 showsthelaboratorydatafromthefourthtosixthadmissiondueto AHEsince2020.Liverfunctiontestsshowedalmoststableresults over three admissions; the platelet count gradually decreased, but thelipidandrenalfunctionsshowednomarkedchanges.Although the fibrosis index based on four factors (FIB-4 index), which is a reliablemarkerforliverfibrosis,graduallyincreased,thestiffness of the liver measured using shear-wave elastography was within the normal range (4.67 kPa on March 4, 2022). Figure 1 shows thefindingsofabdominalCTandbrainMRIobtainedonMarch2 and 4, 2020, respectively.The findings of abdominal contrast-enhanced CT showed multiple regenerative nodules in the right hepatic lobes and mild undulationof the hepatic surface, suggesting mild progression of liver fibrosis. MRI showed the effects of hyperammonemiaonbrain,i.e.transverseT2-weightedfastfluid-attenuatedinversionrecovery(FLAIR)imagingshowedsymmetric areas of increased signal intensity along the cortex and insula in bothcerebralhemispheres.Figure2showsthemedicaltreatments 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 presenceof hyperammonemia, and increased further starting in 2022. The plasmaGlnconcentrationwasnearlywithinthenormalrange,regardlessofthepresenceofhyperammonemia.Nutritionalmanagementwith MCToilhadbeencontinuouslyperformedbyadietitian [totalcalories/dayare1600kcal+200kcal(MCToil),protein75 g, fat 75 g and carbohydrate 175 g (PFC % ratio 20:40:40)] (Max 540).

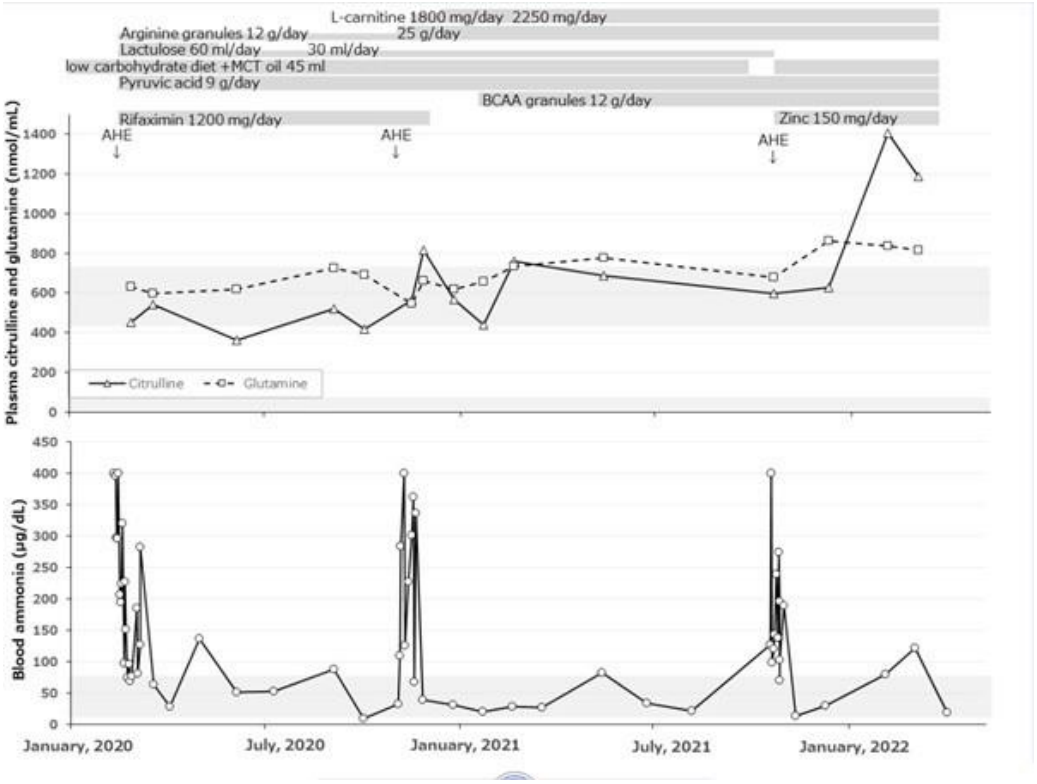

Figure 1: Medical treatments and changes in the levels of plasma citrulline, glutamine and blood ammonia since 2020. Reference ranges: glutamine, 422-703 nmol/L, citrulline 17.1-42.6 nmol/L, and blood ammonia, 15-70 μg/dL.AHE:Acute hyperammonemic encephalopathy, BCAA: branched-chain amino acids, MCT: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

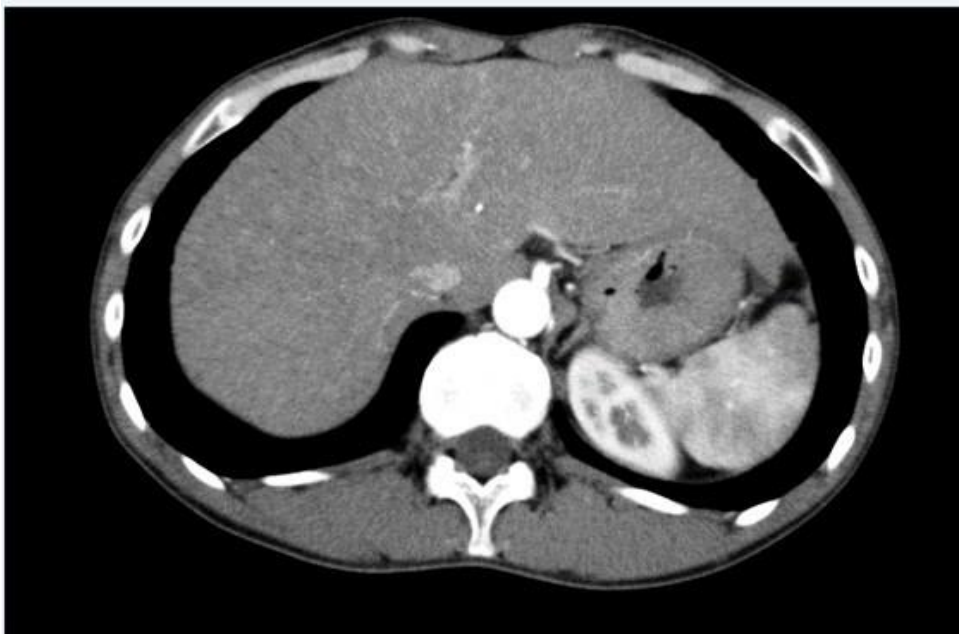

Figure2a:ThefindingsofabdominalCTandbrainMRI.(a)Thefindingsofcontrast-enhancedCTshowmultipleregenerativenodulesintheright hepaticlobesandmild undulationof thehepatic surface.

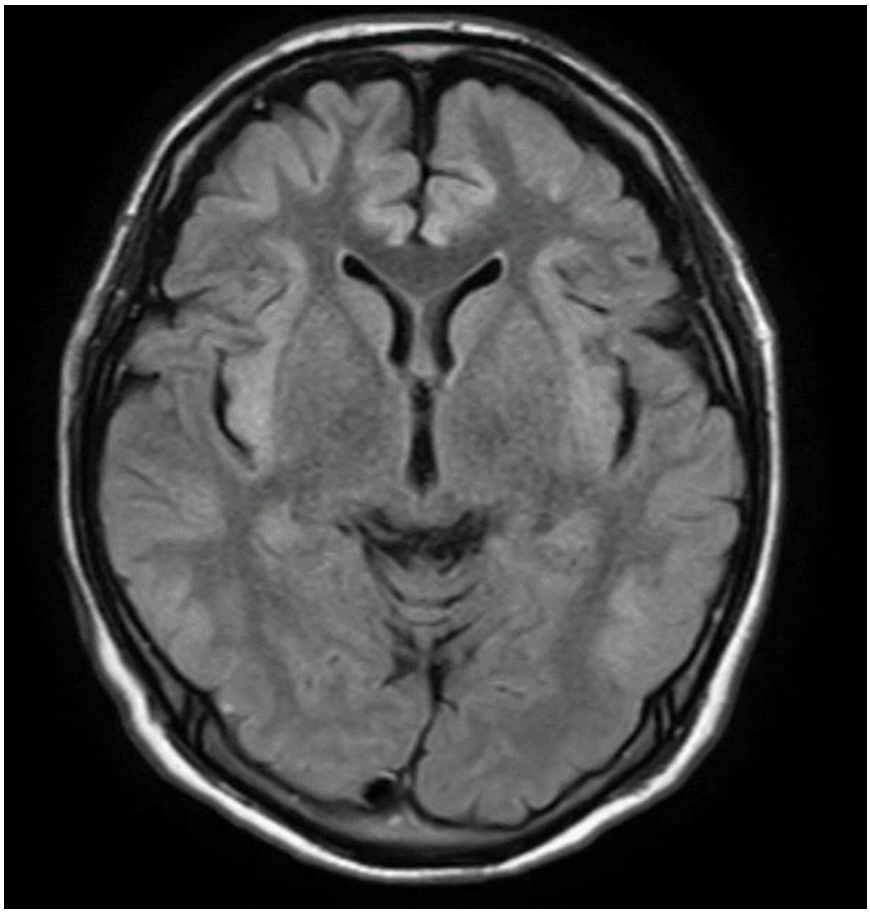

Figure 2b: The findings of abdominal CT and brain MRI. (b) Transverse T2-weighted fast FLAIR imaging shows symmetric areas of increased signal intensity along the cortex and insula in both cerebral hemispheres.

Table1: Comagradeandlaboratorydataonacutehyperammonemicencephalopathysince

	February,2020	November,2020	October,2021
Age(yearsold)	48	49	50
Coma grade (JCS)	3	2	3
Peripheralbloodtests 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
Liverfunctiontests			
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-4index(<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			
Ureanitrogen(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,Japancomascale;RBC,redbloodcells;WBC,whitebloodcells;T-Bil,totalbilirubin;AST,aspartateaminotransferase;ALT,alanineaminotransferase;γGTP,gammaglutamyltransferase;PT-INR,prothrombintimeinternationalratio;FIB-4index;fibrosisindexbasedon4factors.
*data of next day morning

4. Evaluationof 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.PlasmaPFAAwasmeasuredbyhighperformanceliquid chromatography in outside institution (SRL Co., Ltd. Tokyo, Japan).We mainly focused PFAArelated 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'sranktest.*P*<0.05wasconsideredsignificantly.Thecorrelationbetween B-NH_3 andPFAAandseveralparametersforamino 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)andtotalnonessential AA (NEAA)alsoshowed a significantly positive correlation with the B-NH_3 concentration. Although valine (Val) and leucine (Leu)—except for isoleucine (Ile)—weresignificantlycorrelatedwiththeB-NH_3concentration, the branched-chain AA (BCAA; Val + Leu +Ile) to AAA molar ratio(Fischerratio)showedasignificantlynegativecorrelation.In contrast,theplasmaGlnconcentrationshowednosignificantcorrelationwiththeB-NH_3concentration.Among thePFAAs 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**
totalAA	**0.422**	**0.008**
NEAA	**0.404**	**0.011**
EAA	0.104	0.527

StatisticalanalysiswasperformedusingtheSpearman'srank test.

P<0.05wasconsidered 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; totalAA, total amino acids; NEAA, nonessential amino acid; EAA, essential amino acids.

5. Discussion

The diagnostic algorithm for urea cycle disorders with hyperammonemiaindicatesthattheplasmaGlnconcentrationisafirst-step indicatorandthattheplasmaCitconcentrationisasecondindicator [9].AhighCitconcentrationandanormalGlnconcentrationhave been observed in the majority of patients with CTLN2 [5-7,9,11]. However, long-term data on the PFAAdynamics and on the relationship between B-NH_3 and PFAAconcentrations in CTLN2 are lacking. Therefore, in the present study, we focused the relationshipbetweenB-NH_3andPFAAsinapatientwithCTLN2whowas followed for over eight years without liver transplantation. The followingresultswereobtainedinthepresentstudy:1)plasmaCit andArg concentrations, but not the Orn concentrations, increased andweresignificantlycorrelatedwiththeB-NH_3concentration;2) the plasma Gln concentration was nearly within the normal range and showed no significant correlation with the B-NH_3 concentration;3)theplasmaBCAAconcentrationdecreaseddespitetheoral administration of BCAA granules, but no significant correlation with the B-NH_3 concentration was observed, 4) the plasmaAAA and Met concentrations were within the normal range but were significantly correlated with the B-NH_3concentration; 5) the Fischerratiosignificantlydecreasedduetothedecreaseintheplasma BCAAconcentrationandshowedanegativecorrelationwiththe B-NH_3 concentration; 6) the plasmaAla concentration decreased but was not correlated with the B-NH_3 concentration; 7) the plasmaThr/Serratiowashigherthaninthecontrols(1.17±0.13;mean value ± standard deviation according to reference 5) but did not showasignificantcorrelationwiththeB-NH_3concentration;and 8) the totalAAand NEAAvalues showed a significantly positive correlationwiththeB-NH_3concentration.Althoughthesefindings were similar to those previously reported in CTLN2, we indicated, for the first time that several PFAAs, including Cit, Arg and AAA,weresignificantlycorrelatedwiththeB-NH_3concentration. BecauseAAAare metabolized in the liver, the plasmaAAAconcentration increases according to the severity of liver dysfunction [12], indicating that the elevation of the plasma AAA concentrationisrelatedtotheseverityofhepatocellulardamagewithfibrosis, such as in liver cirrhosis (LC). Interestingly, our data showed thattheplasmaAAAconcentrationswerewithinthenormalrange, whereasthevaluesofserumfibrosismarkers,suchashyaluronate and type IV collagen, were slightly increased. Moreover, the values denotingliverstiffness were normal and the mildprogression ofliverfibrosiswasalsosuggestedbytheabdominalCTfindings. 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,inwhichcausesinpartthesynthesisofArginthekidney[10,14,15].L-arginineactivatesN-acetylglutamate,whichinduces 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-systemicshunt,andisconsideredanindicatorofbrainede- ma 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 changedynamically,regardlessofthepresenceofhyperammone- mia (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 ofGSincatalyzingtheATP-dependentsynthesisofGlnfromGlu for ammonia detoxification is impaired [6]. However, since MCT oilsupplementaltherapycansupplyATPand/orsubstratesforhepatic GS [5-7], the plasma Gln concentration increases following appropriatedietarytherapywithMCToil[6].OnobservingFigure 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 onceortwiceperyear,withadurationofthreetofourdays.After achieving complete remission of AHE, the B-NH_3 concentration rapidlyimprovedandremainednearlynormal.Clarifyingthepre- cise mechanism underlying the changes in the plasma Gln concentration in CTLN2 will require examining the enzyme activities,includingASS1andGSactivities,intheliverofpatientswith CTLN2. The plasma BCAA concentration decreased despite the oral administration of BCAA granules. This result suggests that the utilization of BCAAfor ammonia detoxication in the skeletal muscle may have been increased. Recently, Miyazaki et al. indicated that the PFAAprofile of citrin-deficient children during the healthystagedifferedfromthoseofNICCDandCTLN2patients, suggesting that the impaired function of both the urea cycle and energymetabolism might be compensated byAAmetabolism [19]. In CTLN2, changes in the dietary habits, including overdose of dietarycarbohydrateandalcoholintake,aremainlyconsideredto

beprecipitatingfactorsforonsetofAHE[7-9,20].Actually,Kita- oka et al. have reported thatAHE was triggered in a 72-year-old manwithCTLN2afterthepatientstoppedconsumingpulse-based snacks,suchassoybeansandpeanuts,duetodentalproblems[21]. Inourcase,self-interruptionand/orincorrectMCToilintakewere considered potential precipitating factors ofAHE. Several limitationsassociatedwiththepresentstudywarrantmention.First,the PFAAdata 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 intakevolumeandeach%componentofprotein,fatandcarbohy- drate 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,theplasmaGlnconcentrationwasnearlywithin thenormalrange,regardlessofthepresenceofhyperammonemia, and showed no significant correlation with the B-NH_3 concentra- tion. 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 patientandwrotepartofthemanuscript;K.Suzukimainlysupported the medical care of this patient in the outpatient clinic, designed thestudyandwrotepartofthemanuscript;M.Miurasupportedthe medical care of this patient; H. Kuroda performed the statistical analysis;C.AbeandS.Segawaperformednutritionalguidance; H.Takahashi supervised and read the final draft of this paper.All authorsreviewedandapprovedthefinalversionofthemanuscript.

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