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Correspondence

Lactulose: A treatment for hyperammonemia in a lysinuric protein–intolerant patient with dynamic blood amino acid concentrations

To the Editor,

Lysinuric protein intolerance (LPI) is a rare autosomal recessive disorder caused by variants in the *SLC7A7* gene, which encodes a component of the dibasic amino acid transporter in the intestinal epithelia and renal tubular cells [1]. Dysfunction in the transporter interrupts the absorption and reabsorption of dibasic amino acids (lysine, arginine, and ornithine), leading to an imbalance in blood amino acid levels and to hyperammonemia arising from a dysfunctional urea cycle. In LPI patients with hyperammonemia, lactulose is the first choice of treatment [1,2]. However, the means by which lactulose affects the maldistribution of amino acids in LPI remain unclear, while a low lysine level is presumed to be associated with the pathophysiology of LPI complications [3].

A 16-year-old male was referred to our institution for disturbance of consciousness and insufficient food intake arising from hyperammonemia. After 20 mL of lactulose three times a day was started on day 10, the patient's blood ammonia level improved from 114 μg/dL at day 0 to 69 at day 40, 38 at day 220, and 70 at day 580 (Fig. 1), and his consciousness level recovered. Protein restriction was started around day 60 to further investigate the patient's condition. The urinary and blood amino acid profiles obtained via LC/MS were typical of LPI. The genetic diagnosis of LPI was established with a variant in the *SLC7A7* gene (c.1228C > T; p.Arg410Ter). The genetic variant was homozygous.

The changes in the distribution of blood amino acids were determined based on the relative changes in amino acid levels at 40, 220, and 580 days after the patient's presentation at our institution (base line: 0 day) (Table 1); these changes were expressed as values relative to the baseline calculated by k-means clustering (JMP pro16, SAS). Because there was a broad range of blood levels of total amino acids during the observation period, and chronological changes in the blood level of amino acids with low levels would be hard to evaluate, we evaluated the changes as a relative value. Following lactulose administration, ornithine, arginine, and glutamic acid levels increased along with changes in ammonia levels (Fig. 1). The blood levels of several essential amino acids, such as valine, isoleucine, leucine, phenylalanine, and methionine decreased after the introduction of lactulose (Table 1 and Fig. 1). However, the concentrations of these amino acids at 580 days were within the reference range. Therefore, we concluded that the administration of lactulose improved the patient's amino acid metabolism due to a reduction in hyperammonemia. Although protein restriction was started after lactulose administration, the patient's total blood amino acid level did not change significantly during the observation period. Therefore, we thought that the patient's blood level of ammonia improved mainly due to lactulose induction. The normalization of blood ammonia levels through the administration of lactulose resulted in several amino acids related to ammonia metabolism once again participating in other metabolic pathways [4,5]. Indeed, the blood level of lysine decreased during treatment. In contrast, the blood levels of arginine and ornithine increased for two reasons. First, these amino acids are not essential; thus, these amino acids can be provided via metabolites from other amino acids. Second, lactulose decreases the blood level of ammonia which is metabolized in the urea cycle. Thus, arginine and ornithine were not consumed in the urea cycle. In contrast, the patient's blood levels of lysine, arginine, and ornithine were still under the reference range at day 580, probably because of the nature of LPI. Intriguingly, the blood level of glutamine was significantly high during the observation period, which reflects the presence of excessive blood ammonia [6]. This finding may indicate the need for further investigation of hyperammonemia in the patient. Our case suggests that lactulose unveils the imbalance of amino acids in LPI by reducing the burden of ammonia metabolism. Although the effect of long-term lactulose administration in LPI remains unclear, lysine levels seem to be the primary target of lactulose treatment in the disease.

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Author contributions

KK and TS: Drafting of the manuscript and final approval of the article.

YW and MA: Interpretation of the data and final approval of the article.

AI, HE, HA, JK, KY, YK, KE, YY, TO, HK, and AK: Acquisition of the data, medical care of the patient, and final approval of the article.

TM: Interpretation of the data, revision of the draft, and final approval of the article.

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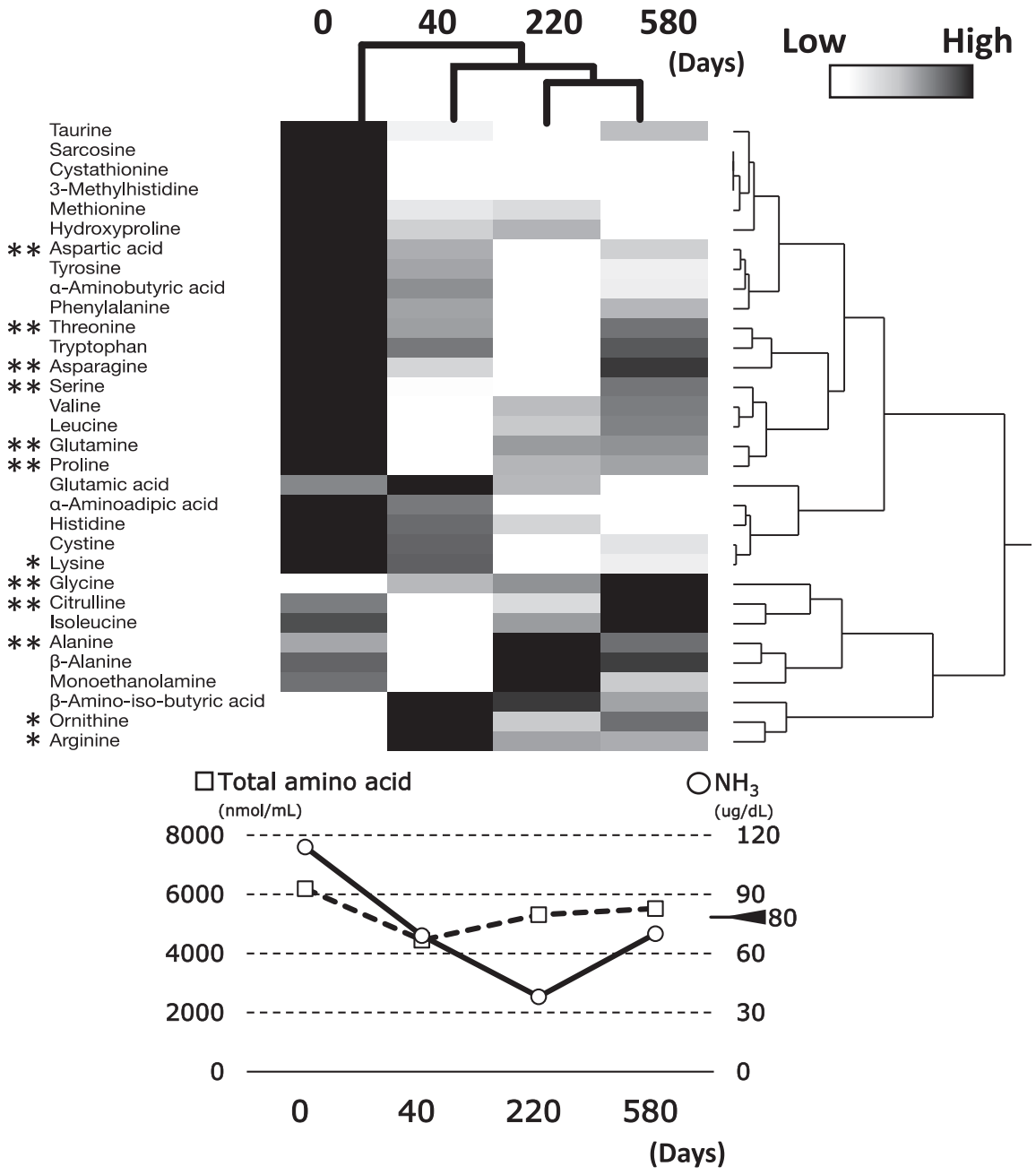

Fig. 1. Relative changes in the patient's blood amino acid levels during lactulose treatment were evaluated using k-means clustering. The patient's total blood amino acid and ammonia levels are shown in the lower panel.
*, amino acid level at 580 days was lower than the reference range.
**, amino acid level at 580 days was higher than the reference range.

Table 1.
Concentration and relative vaule of plasma amino acids in the patient during observation periods.

		Concentration					Relative change			
		Reference range		40	220	580	0	40	220	580
Taurine	nmol/mL	39.5–93.2	148.4	36.9	33.1	54	1.00	0.35	0.26	0.41
Aspartic acid	nmol/mL	<2.4	8.1	4.6	3.3	4	1.00	0.79	0.48	0.55
Hydroxyproline	nmol/mL	<21.6	19.9	16.4	16.8	15.8	1.00	1.15	0.98	0.89
Threonine	nmol/mL	66.5–188.9	279.5	231	183.6	251.4	1.00	1.15	0.77	1.01
Serine	nmol/mL	72.4–164.5	335.9	243.6	243.1	298.5	1.00	1.01	0.84	1.00
Asparagine	nmol/mL	44.7–96.8	134.1	102	94.3	131	1.00	1.06	0.82	1.10
Glutamic acid	nmol/mL	12.6–62.5	69	80.4	63.1	55.8	1.00	1.62	1.07	0.91
Glutamine	nmol/mL	422.1–703.8	1814.2	1402.9	1593.8	1612.9	1.00	1.08	1.02	1.00
Sarcosine	nmol/mL	Trace	5.1	0	0	0	1.00	0.00	0.00	0.00
α-Aminoadipic acid	nmol/mL	No detectable	6.9	3.9	0	0	1.00	0.79	0.00	0.00
Proline	nmol/mL	77.8–272.7	497.7	304.5	358.5	372.8	1.00	0.85	0.84	0.84
Glycine	nmol/mL	151.0–351.0	447.4	474.1	489.9	542.4	1.00	1.47	1.28	1.36
Alanine	nmol/mL	208.7–522.7	1022.9	678.6	1455.3	1237.1	1.00	0.92	1.66	1.36
Citrulline	nmol/mL	17.1–42.6	102.5	55.1	66.6	138.9	1.00	0.75	0.76	1.52
α-Aminobutyric acid	nmol/mL	7.9–26.6	89.1	48	20.5	24.3	1.00	0.75	0.27	0.31
Valine	nmol/mL	147.8–307.0	280.6	154.5	191	231	1.00	0.77	0.79	0.92
Cystine	nmol/mL	13.7–28.3	46.7	40.3	23.4	25.9	1.00	1.20	0.58	0.62
Cystathionine	nmol/mL	Trace	1.5	0	0	0	1.00	0.00	0.00	0.00
Methionine	nmol/mL	18.9–40.5	66.3	40.5	41.4	38.9	1.00	0.85	0.73	0.66
Isoleucine	nmol/mL	43.0–112.8	81.9	44.5	68.8	87.2	1.00	0.76	0.98	1.19
Leucine	nmol/mL	76.6–171.3	143	92.1	103.1	120.2	1.00	0.90	0.84	0.94
Tyrosine	nmol/mL	40.4–90.3	148.5	68.2	36.8	41.6	1.00	0.64	0.29	0.31
Phenylalanine	nmol/mL	42.6–75.7	61.1	44.7	35.9	42.7	1.00	1.02	0.69	0.78
γ-Amino β-hydroxy butyric acid	nmol/mL	No detectable	0	0	0	0	–	–	–	–
β-Alanine	nmol/mL	Trace	2.7	0	3.2	3	1.00	0.00	1.38	1.25
β-Amino-isobutyric acid	nmol/mL	Trace	2.2	3.7	3.6	3	1.00	2.34	1.91	1.53
γ-Aminobutyric acid	nmol/mL	No detectable	0	0	0	0	–	–	–	–
Monoethanolamine	nmol/mL	<10.4	6.4	5.8	6.7	6	1.00	1.26	1.22	1.05
Homocystine	nmol/mL	No detectable	0	0	0	0	–	–	–	–
Histidine	nmol/mL	59.0–92.0	127.8	117.9	101.1	95.2	1.00	1.28	0.92	0.84
3-Methylhistidine	nmol/mL	<5.0	2.8	0	0	0	1.00	0.00	0.00	0.00
1-Methylhistidine	nmol/mL	<18.5	0	0	0	0	–	–	–	–
Carnosine	nmol/mL	No detectable	0	0	0	0	–	–	–	–
Anserine	nmol/mL	No detectable	0	0	0	0	–	–	–	–
Tryptophan	nmol/mL	37.0–74.9	43.8	42.6	38.9	43.1	1.00	1.35	1.04	1.10
Hydroxylysine	nmol/mL	No detectable	0	0	0	0	–	–	–	–
Ornithine	nmol/mL	31.3–104.7	11.8	18.4	13.3	16.3	1.00	2.17	1.31	1.55
Lysine	nmol/mL	108.7–242.2	167.6	136.7	48.5	56.2	1.00	1.14	0.34	0.38
Arginine	nmol/mL	53.6–133.6	13.8	33.5	20.9	20.2	1.00	3.38	1.77	1.64
Total amino acids	nmol/mL	2068.2–3510.3	6189.2	4447.6	5307.7	5517.3				

Data availability

Data will be made available on request.

References

[1] A. Noguchi, T. Takahashi, Overview of symptoms and treatment for lysinuric protein intolerance, J. Hum. Genet. 64 (2019) 849–858.

[2] H. Yoshiji, S. Nagoshi, T. Akahane, Y. Asaoka, Y. Ueno, K. Ogawa, T. Kawaguchi, M. Kurosaki, I. Sakaida, M. Shimizu, M. Taniai, S. Terai, H. Nishikawa, Y. Hiasa, H. Hidaka, H. Miwa, K. Chayama, N. Enomoto, T. Shimosegawa, T. Takehara, K. Koike, Evidence-based clinical practice guidelines for liver cirrhosis 2020, Hepatol. Res. 51 (2021) 725–749.

[3] W. Mauhin, F. Habarou, S. Gobin, A. Servais, A. Brassier, C. Grisel, C. Roda, G. Pinto, D. Moshous, F. Ghalim, P. Krug, N. Deltour, C. Pontoizeau, S. Dubois, M. Assoun, L. Galmiche, J.P. Bonnefont, C. Ottolenghi, J. de Blic, J.B. Arnoux, P. de Lonlay, Update on Lysinuric protein intolerance, a multi-faceted disease retrospective cohort analysis from birth to adulthood, Orphanet J. Rare Dis. 12 (2017) 3.

[4] B. Siri, G. Olivieri, A. Angeloni, S. Cairoli, C. Carducci, G. Cotugno, S. Di Michele, T. Giovanniello, G. La Marca, F.R. Lepri, A. Novelli, C. Rossi, M. Semeraro, C. Dionisi-Vici, The diagnostic challenge of mild citrulline elevation at newborn screening, Mol. Genet. Metab. 135 (2022) 327–332.

[5] F. Ingoglia, J.L. Chong, M. Pasquali, N. Longo, Creatine metabolism in patients with urea cycle disorders, Mol. Genet. Metab. Rep. 29 (2021), 100791.

[6] L.R. Soria, M. Nitzahn, A. De Angelis, S. Khoja, S. Attanasio, P. Annunziata, D. J. Palmer, P. Ng, G.S. Lipshutz, N. Brunetti-Pierri, Hepatic glutamine synthetase augmentation enhances ammonia detoxification, J. Inherit. Metab. Dis. 42 (2019) 1128–1135.

Keisuke Kakisaka[a,*], Takuro Sato[a], Yasunori Wada[b], Ai Ito[b], Hisashi Eto[a], Hiroaki Abe[a], Jo Kanazawa[a], Kenji Yusa[a], Yohei Kooka[a], Kei Endo[a], Yuichi Yoshida[a], Takayoshi Oikawa[a], Hidekatsu Kuroda[a], Akio Miyasaka[a], Manami Akasaka[b], Takayuki Matsumoto[a]

[a] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Iwate Medical University, Yahaba, Japan*

[b] *Department of Pediatrics, School of Medicine, Iwate Medical University, Yahaba, Japan*

[*] Corresponding author at: Division of Gastroenterology and Hepatology, School of Medicine, Iwate Medical University, 1-1-1 Idaidori, Yahaba-cho, Iwate 0283694, Japan.
E-mail address: keikaki@iwate-med.ac.jp (K. Kakisaka).