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CASE REPORT

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Plasma amino acids in patients with essential tremor

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Abstract

Essential tremor (ET) is one of the most common movement disorders. However, there are currently no accepted biomarkers for ET. This report suggested that concentration of plasma glutamic acid, aspartic acid, and taurine could be biomarkers for ET.

KEYWORDS

amino acid, aspartic acid, essential tremor, glutamic acid, taurine

1 | INTRODUCTION

The plasma concentrations of 39 amino acids were compared between 7 patients with essential tremor (ET) and 7 healthy controls to establish a plasma amino acid profile for patients with ET. Concentrations of plasma glutamic acid, aspartic acid, and taurine could be helpful in the diagnosis of ET.

Essential tremor (ET) is one of the most common movement disorders, characterized by an isolated action tremor of the bilateral upper limb with or without a tremor in other locations.[1] ET prevalence in population-based studies has been reported as 3.1% in the population ≥18 years, 0.4%–5.6% in the population ≥40 years, and 0.8%–20.5% in the population ≥65 years.[2] However, the diagnostic accuracy of ET varies between neurologists and non-neurologists,[2] and there are currently no accepted biomarkers for ET. We have previously noted elevated plasma concentrations of aspartic acid and taurine in patients with ET.[3] If plasma concentrations of amino acids could be used as a diagnostic biomarker for ET, a simple blood test could lead to an accurate diagnosis even in medically underdeveloped areas. Therefore, we performed a retrospective case-control study to investigate plasma amino acid profiles in ET.

2 | METHODS

2.1 | Subjects

For this observational study, we recruited seven consecutive outpatients from 2016 to 2018 who had a clinical diagnosis of ET, and who had had their plasma amino acid levels measured before treatment. Retrospectively, we confirmed that all cases met the International Parkinson and Movement Disorder Society criteria for ET.[1] Namely, "(i) isolated tremor syndrome of bilateral upper limb action tremor, (ii) at least 3 years' duration, (iii) with or without a tremor in other locations, (iv) absence of other neurological signs, such as dystonia, ataxia, or parkinsonism."[1]

2.2 | Liquid chromatography-mass spectrometry

The plasma concentrations of amino acids were measured by SRL, Inc. (Japan) using liquid chromatography-mass spectrometry (LC-MS). Seven healthy volunteers were also recruited as controls for amino acid concentration measurements. Their data were released in our bulletin.[4]

2.3 | Statistics

To evaluate the differences between patients with ET and healthy controls, we performed a Wilcoxon rank-sum test (Mann-Whitney *U* test; a nonparametric statistical test) for each amino acid. Results were considered statistically significant if $p < 0.05$.

3 | RESULTS

3.1 | Patient characteristics

There were six male patients and one female. The average age at examination was 51.43 ± 24.29 (19–79) years, and age at onset was 30.71 ± 19.43 (10–62) years, with a mean disease duration of 20.71 ± 19.93 (6–58) years. Head tremor was observed in three patients (42.9%), and all seven patients had fine postural tremors in their upper fingers. Three patients (42.9%) had family histories of the same symptom (Table 1). There were no significant differences in age or the sex ratios between patients and controls (Table 2).

We performed a Wilcoxon rank-sum test to investigate differences between patients with ET and healthy controls for each amino acid; the detailed results are summarized in Table 2. Taurine, aspartic acid, threonine, glutamic acid, ornithine, total amino acids (TAA), and non-essential amino acids (NEAA) were significantly different between patients with ET and healthy controls. Aside from threonine, all of these amino acids were elevated in patients with ET.

4 | DISCUSSION

In this retrospective study, plasma concentrations of glutamic acid, aspartic acid, and taurine were significantly elevated in patients with ET compared with control subjects. This phenomenon was comparable with previous studies.[3,5] In addition, the plasma concentration of threonine was significantly lower in ET patients, while plasma ornithine, TAA, and NEAA were significantly higher compared with control subjects. However, the concentrations of plasma threonine, ornithine, and NEAA in ET patients were within normal ranges. Therefore, the pathological significance of these changes is unknown. Conversely, it is sometimes difficult for clinicians to judge whether tremors observed in patients are due to ET or Parkinson's disease (PD). Because the concentration of threonine was higher among advanced PD patients,[6] threonine could be useful for distinguishing ET from PD tremor.

Unfortunately, this study could not determine whether the increased concentrations of plasma glutamic acid, aspartic acid, and taurine were specific to patients with ET. Both glutamate and aspartate are known N-methyl-D-aspartate (NMDA) receptor agonists.[7] It is, therefore, possible that elevated plasma concentrations of glutamic acid and aspartic acid are also observed in patients with disorders associated with excessive NMDA receptors, such as Alzheimer's disease, Huntington's disease, and epilepsy.[8] Moreover, glutamate is a known agonist of both metabotropic glutamate receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and signaling dysfunction in these receptors causes spinocerebellar ataxia (SCA).[9,10] It may thus be that elevated plasma glutamic acid also occurs in patients with SCA. Regarding elevated plasma taurine concentrations, this phenomenon may reflect neuroprotective functions against glutamate-induced excitotoxicity.[11] To date, there are no reports of amino acid profiles in patients with the aforementioned neurological disorders; therefore, these profiles must be established in future studies.

Our study has two major limitations. First, the sample size is small. It is too difficult to apply correction methods for multiple comparisons, thus, we did not use any correction method. However, among amino acids, the p-value can be

TABLE 1 Characteristics of the patients

	Sex	Age at examination (years)	Age at onset (years)	Disease duration (years)	Head tremor	Postural fine tremor	Same symptom in the family
Patient 1	Male	68	10	58	+	+	−
Patient 2	Female	59	45	14	−	+	+
Patient 3	Male	22	16	6	−	+	−
Patient 4	Male	79	40	39	+	+	+
Patient 5	Male	41	30	11	+	+	−
Patient 6	Male	72	62	10	−	+	+
Patient 7	Male	19	12	7	−	+	−

TABLE 2 Comparison between patients with essential tremor and healthy controls

		Controls	Patients	*p*-value
	Age at examination (year)	44.71	51.42	0.5347
	Sex ratio (female/male)	0.16	0.75	0.5594
Amino acids	Normal value (nmol/ml)			
Taurine	39.5–93.2	71.16	151.64	0.007*
Aspartic acid	≦2.4	2.31	6.86	0.0049*
Hydroxyproline	≦21.6	7.76	6.77	1
Threonine	66.5–188.9	128.41	93.94	0.0105*
Serine	72.4–164.5	118.21	114.76	1
Asparagine	44.7–96.8	43.27	45.47	0.9015
Glutamic acid	12.6–62.5	29.97	63.84	0.0012*
Glutamine	422.1–703.8	545.36	564.89	0.7104
Sarcosine	TR	0	0	NaN
α-Aminoadipic acid	ND	0	0	NaN
Proline	77.8–272.7	144.54	152.76	1
Glycine	151.0–351.0	208.63	234.16	0.3829
Alanine	208.7–522.7	314.2	380.07	0.3829
Citrulline	17.1–42.6	23.19	33.39	0.2593
α-Aminobutyric acid	7.9–26.6	19.13	15.2	0.0973
Valine	147.8–307.0	201.66	198.31	1
Cystine	13.7–28.3	14.59	25.5	0.1282
Cystathionine	TR	0.69	0	0.3914
Methionine	18.9–40.5	21.39	21.37	0.9015
Isoleucine	43.0–112.8	53.87	57.23	0.7104
Leucine	76.6–171.3	104.81	103.11	0.8048
Tyrosine	40.4–90.3	56.89	56.39	0.7104
Phenylalanine	42.6–75.7	54.69	59.69	0.7491
γ-Amino β-hydroxybutyric acid	ND	0	0	NaN
β-Alanine	TR	2.13	3.8	0.1202
β-Amino-iso-butyric acid	TR	0.91	0.46	0.5938
γ-Aminobutyric acid	ND	0	0	NaN
Monoethanolamine	≦10.4	6.69	8.34	0.0835
Homocystine	ND	0	0	NaN
Histidine	59.0–92.0	72.93	69.86	0.9015
3-Methylhistidine	≦5.0	1.27	1.99	0.6017
1-Methylhistidine	≦18.5	2.81	0.63	0.2004
Carnosine	ND	0	0	NaN
Anserine	ND	0	0	NaN
Tryptophan	37.0–74.9	47.73	45.17	0.949
Hydroxylysine	ND	0	0	NaN
Ornithine	31.3–104.7	51.07	75.23	0.0072*
Lysine	108.7–242.2	167.93	161.84	0.9015
Arginine	53.6–133.6	84.79	68.46	0.1649
TAA	2068.2–3510.3	2565.67	2786.54	0.0262*
NEAA	1381.6–2379.4	1712.26	1976.01	0.0262*

(Continues)

TABLE 2 (Continued)

		Controls	Patients	*p*-value
EAA	660.0–1222.3	853.41	810.53	0.7104
BCAA	265.8–579.1	360.34	358.66	0.8048
EAA/NEAA	0.40–0.63	0.5	0.42	0.0825
BCAA/Total AA	0.11–0.18	0.14	0.13	0.1651
Fischer ratio	2.43–4.40	3.26	3.24	0.9015

Note: Normal values were cited from SRL. Inc. *$p < 0.05$

Abbreviations: BCAA, branched-chain amino acids; EAA, essential amino acids; NaN, not applicable; ND, not detected; NEAA, non-essential amino acids; TAA, total amino acids; TR, trace.

used as an indicator for evaluating the importance of each amino acid on differences between patients with ET and healthy controls. A large-scale study is necessary to get more decisive conclusions in the future. Second, except for the plasma amino acid data described here, there was no investigation of potentially confounding factors such as dietary habits and medications because individual clinical information was omitted to protect patient privacy.

5 | CONCLUSIONS

This is the first report to compare plasma concentrations of 39 amino acids between patients with ET and healthy controls. Concentrations of plasma glutamic acid, aspartic acid, and taurine could be useful marker for the diagnosis of ET.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

SM and RF conceived the study and collected samples. YY analyzed the results. SM and YY were involved in designing the study and drafted the manuscript. SM, TK, and YY contributed to the further writing of the manuscript. All authors reviewed and approved the final version of manuscript.

ETHICAL APPROVAL

This retrospective study was approved by the Ethics Committee of Kurume University School of Medicine (decision No. 18240 of December 27, 2018) and the Ethics Committee of Beppu University/Beppu University Junior College (decision No. 2017–13 of December 4, 2017).

INFORMED CONSENT

Written informed consent was obtained from all healthy controls.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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