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.

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.

| TABLE 1 | Characteristics of the patients |
|---|---|---|---|---|---|---|---|
| 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 | − | + | − |

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 \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and signaling dysfunction in these receptors causes spinocerebellar ataxia (SCA).9,10 It may 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 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                  |          |          |          |
| Taurine                      | 39.5–93.2| 71.16    | 0.007*   |
| Aspartic acid                | ≤2.4     | 2.31     | 0.0049*  |
| Hydroxyproline               | ≤21.6    | 7.76     | 1        |
| Threonine                    | 66.5–188.9| 128.41  | 0.0105*  |
| Serine                       | 72.4–164.5| 118.21  | 1        |
| Asparagine                   | 44.7–96.8| 43.27    | 0.9015   |
| Glutamic acid                | 12.6–62.5| 29.97    | 0.0012*  |
| Glutamine                    | 422.1–703.8| 545.36  | 0.7104   |
| Sarcosine                    | TR       | 0        | NaN      |
| α-Aminoadipic acid           | ND       | 0        | NaN      |
| Proline                      | 77.8–272.7| 144.54  | 1        |
| Glycine                      | 151.0–351.0| 208.63  | 0.3829   |
| Alanine                      | 208.7–522.7| 314.2   | 0.3829   |
| Citrulline                   | 17.1–42.6| 23.19    | 0.2593   |
| α-Aminobutyric acid          | 7.9–26.6 | 19.13    | 0.0973   |
| Valine                       | 147.8–307.0| 201.66  | 1        |
| Cystine                      | 13.7–28.3| 14.59    | 0.1282   |
| Cystathionine                | TR       | 0.69     | 0.3914   |
| Methionine                   | 18.9–40.5| 21.39    | 0.9015   |
| Isoleucine                   | 43.0–112.8| 53.87   | 0.7104   |
| Leucine                      | 76.6–171.3| 104.81  | 0.8048   |
| Tyrosine                     | 40.4–90.3| 56.89    | 0.7104   |
| Phenylalanine                | 42.6–75.7| 54.69    | 0.7491   |
| γ-Amino β-hydroxybutyric acid| ND       | 0        | NaN      |
| β-Alanine                    | TR       | 2.13     | 0.1202   |
| β-Amino-iso-butyric acid     | TR       | 0.91     | 0.5938   |
| γ-Aminobutyric acid          | ND       | 0        | NaN      |
| Monoethanolamine             | ≤10.4    | 6.69     | 0.0835   |
| Homocystine                  | ND       | 0        | NaN      |
| Histidine                    | 59.0–92.0| 72.93    | 0.9015   |
| 3-Methylhistidine            | ≤5.0     | 1.27     | 0.6017   |
| 1-Methylhistidine            | ≤18.5    | 2.81     | 0.2004   |
| Carnosine                    | ND       | 0        | NaN      |
| Anserine                     | ND       | 0        | NaN      |
| Tryptophan                   | 37.0–74.9| 47.73    | 0.949    |
| Hydroxylysine                | ND       | 0        | NaN      |
| Ornithine                    | 31.3–104.7| 51.07   | 0.0072*  |
| Lysine                       | 108.7–242.2| 167.93  | 0.9015   |
| Arginine                     | 53.6–133.6| 84.79   | 0.1649   |
| TAA                          | 2068.2–3510.3| 2565.67| 0.0262*  |
| NEAA                         | 1381.6–2379.4| 1712.26| 0.0262*  |

(Continues)
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.

ACKNOWLEDGMENTS

We thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. Published with written consent of the patient.

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.

REFERENCES

1. Bhatia KP, Bain P, Bajaj N, et al. Consensus Statement on the classification of tremors: from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov Disord. 2018;33:75-87.
2. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010;25:534-541.
3. Miura S, Fujikawa R, Taniwaki T. Essential tremor with aspartic acidemia. Kurume Med J. 2016;63:81-84.
4. Fujioka R, Nagai J, Yamanishi Y, Shibata H. Correlation analysis between thyroid-related hormones and the plasma concentration of amino acids. Bulletin Beppu Univ JC. 2019;38:17-23.
5. Málly J, Barányi M, Vizi ES. Change in the concentrations of amino acids in CSF and serum of patients with essential tremor. J Neural Transm. 1996;103:555-560.
6. Figura M, Kúsmierska K, Bucior E, et al. Serum amino acid profile in patients with Parkinson’s disease. PLoS One. 2018;13:e0191670.
7. Chen PE, Geballe MT, Stansfeld PJ, et al. Structural features of the glutamate binding site in recombinant NR1/NR2A N-methyl-D-aspartate receptors determined by site-directed mutagenesis and molecular modeling. Mol Pharmacol. 2005;67:1470-1484.
8. Parsons MP, Raymond LA. Extrasynaptic NMDA receptor involvement in central nervous system disorders. Neuron. 2014;82:279-293.
9. Meera P, Pust SM, Otis TS. Cellular and circuit mechanisms underlying spinocerebellar ataxias. J Physiol. 2016;594:4653-4660.
10. Hoxha E, Tempia F, Lippolito P, Miniaci MC. Modulation, plasticity and pathophysiology of the parallel fiber-Purkinje cell synapse. Front Synaptic Neurosci. 2016;8:35.
11. Wu JY, Prentice H. Role of taurine in the central nervous system. J Biomed Sci. 2010;17:S1.

How to cite this article: Miura S, Kamada T, Fujikawa R, Yamanishi Y. Plasma amino acids in patients with essential tremor. Clin Case Rep. 2021;9:e04580. https://doi.org/10.1002/ccr3.4580

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.

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

TABLE 2 (Continued)