Essential Tremor with Aspartic Acidemia

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Summary: We describe two cases of typical essential tremor with aspartic acidemia and mildly increased concentrations of plasma glutamic acid. Although this is a preliminary report, we emphasize the possibility of using amino acids, including aspartic acid, as biomarkers for the detection of essential tremor.

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

INTRODUCTION

Essential tremor (ET) is one of the most prevalent movement disorders [1,2], and γ -aminobutyric acid (GABA) is thought to be the main neurotransmitter involved in the ET pathophysiology. The amino acid glutamate has also been implicated in ET [3]. Although the amino acid aspartate is less potent than glutamate in excitatory neurotransmission under normal physiological conditions, aspartate is one of the two major endogenous excitatory amino acids [4], however, its pathogenic role in ET remains unknown. We describe here two cases of typical ET with aspartic acidemia and review the literature in this field.

CASE REPORT

Case 1 was a 42-year-old man (height: 175.9 cm; weight: 75.7 kg) who first noticed a nervous tremor and writing tremor at the age of 30. A head tremor developed at the age of 38. There was no familial history of tremor. Excess sweating was observed on his palms and plantars. Neurological examination revealed no abnormalities, except for a fine head tremor at rest and a

bilateral fine postural tremor of the finger. Serum thyroid stimulating hormone (TSH) and free T4 levels were normal. Anti-thyroglobulin antibody levels were negative. Plasma aspartic acid was 9.8 nmol/ml (normal: <2.4 nmol/ml), glutamic acid was 87.6 nmol/ml (normal: 12.6–62.5 nmol/ml), taurine was 224.2 nmol/ml (normal: 39.5–93.2 nmol/ml), asparagine was 42.4 nmol/ml (normal: 44.7–96.8 nmol/ml), and β -alanine was 4.6 nmol/ml (normal: trace). Blood levels of the other 34 amino acids were within or near their normal ranges (Table). Brain magnetic resonance imaging (MRI) demonstrated no abnormalities (Figure A, B).

Case 2 was a 71-year-old woman (height: 154 cm, weight: 52 kg) who first noticed a head tremor at the age of 65. She had no family history of tremor. Upon examination, a head tremor was observed at rest, as well as a bilateral postural and kinetic hand tremor. Serum TSH, free T3, and free T4 levels were normal. Plasma aspartic acid was 4.7 nmol/ml, glutamic acid was 65.1 nmol/ml, taurine was 116.1 nmol/ml, and asparagine was 44.3 nmol/ml. Blood levels of the other 35 amino acids were near their normal ranges (Table). Brain MRI revealed no definitive evidence of abnormality (Figure C, D).

Figure. No abnormality was detected in the mid-brain or basal ganglia by fluid attenuation inversion recovery (FLAIR) images. A, B) Case 1; C, D) Case 2.

DISCUSSION

In the two cases presented, increased concentrations of plasma aspartic acid, taurine, and glutamic acid were observed. There was also a slightly reduced concentration of asparagine.

N-methyl-D-aspartate (NMDA) receptors are major ionotropic glutamate receptors composed of two obligatory GluN1 and two modulatory GluN2 (A–D) subunits located at excitatory synapses in the central nervous system [5]. ET is thought to be associated with the dysregulation of NMDA pathways [6]. Although one report suggested that aspartate does not contribute to excitatory synaptic transmission in CA1 pyramidal neurons [7], aspartate has been shown to act as an agonist to NMDA receptors [8]. The *Aspa* gene which encodes aspartoacylase, hydrolyzing N-acetyl-L-aspartic acid to aspartate and acetate, is thought to be essential for generating ET [9]. Therefore, aspartate could play an important role in the pathogenesis of ET.

It is conceivable that elevated concentrations of plasma aspartic acid are associated with raised plasma glutamic acid levels. Indeed, in a previous study, serum glutamate and aspartate levels were significantly increased in patients with ET compared with controls [10]. Unlike glutamate, opposite changes in the level of aspartate in cerebrospinal fluid were detected in patients with ET [10]. This suggests that aspartic acid

could be broken down in the central nervous system of ET patients.

Only one previous study has reported that the concentration of taurine does not differ significantly in ET patients compared with controls [10]. This contrasts with the finding in our two present cases. Taurine not only has a neuroprotective function in reducing the calcium influx from various calcium channels, including NMDA receptors, but also inhibits the apoptosis cascade [11]. We speculate that taurine levels increase reactively to protect neurons.

In conclusion, aspartic acidemia and/or glutamic acidemia could be associated with ET. Future work should compare the concentrations of amino acids among several neurological diseases such as ET, spinocerebellar ataxia, and Parkinson's disease with or without tremor to determine whether amino acids such as aspartic acid and glutamic acid could be used as biomarkers of ET.

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TABLE
The plasma concentration of amino acids of two present patients

Amino acids	Case 1	Case 2	Normal value (nmol/ml)
Aspartic acid	9.8	4.7	≤ 2.4
Glutamic acid	87.6	65.1	12.6-62.5
Taurine	224.2	116.1	39.5-93.2
Hydroxyproline	11.4	ND	≤ 21.6
Threonine	118.9	83.6	66.5-188.9
Serine	98.8	120.5	72.4-164.5
Asparagine	42.4	44.3	44.7-96.8
Glutamine	547.8	689.2	422.1-703.8
Sarcosine	ND	ND	TR
α -Aminoadipic acid	TR	ND	ND
Proline	133.6	87.7	77.8-272.7
Glycine	177.2	285.8	151.0-351.0
Alanine	355.4	268.1	208.7-522.7
Citrulline	27.9	35.1	17.1-42.6
α -Aminobutyric acid	14.7	9.1	7.9-26.6
Valine	230.3	167.5	147.8-307.0
Cystine	16.6	37.4	13.7-28.3 for Case 1, 29.4-48.7 for Case 2
Cystathionine	ND	ND	TR
Methionine	23.5	20.1	18.9-40.5
Isoleucine	58.3	44.1	43.0-112.8
Leucine	124.3	84.4	76.6-171.3
Tyrosine	56.7	58.1	40.4-90.3
Phenylalanine	53.9	46.2	42.6-75.7
γ -Amino β -hydroxybutyric acid	ND	ND	ND
β -Alanine	4.6	ND	TR
β -Amino-iso-butyric acid	ND	TR	TR
γ -Aminobutyric acid	ND	ND	ND
Monoethanolamine	7.7	ND	≤ 10.4
Homocystine	ND	ND	ND
Histidine	81.3	75.1	59.0-92.0
3-Methylhistidine	TR	ND	≤ 5.0
1-Methylhistidine	ND	ND	≤ 18.5
Carnosine	ND	ND	ND
Anserine	ND	ND	ND
Tryptophan	55.2	38.7	37.0-74.9
Hydroxylysine	ND	ND	ND
Ornithine	87.8	88.1	31.3-104.7
Lysine	206.8	179.1	108.7-242.2
Arginine	54.3	62.3	53.6-133.6

ND: not detected, TR: trace

Normal values were cited from SRL.Inc.

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