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**References**


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**LETTERS TO THE EDITOR 309**

**Polysaturated Fatty Acid Levels in the Cerebrospinal Fluid of Patients with Parkinson’s Disease and Multiple System Atrophy**

Polysaturated fatty acids (PUFAs) are the central components of neuronal and glial membrane phospholipids, and participate in brain membrane remodeling and synthesis and in signal transduction. 1 It was reported that α-synuclein, a core component of the proteinaceous aggregates found in Parkinson’s disease (PD), dementia with Lewy bodies, and multiple system atrophy (MSA) has affinity for PUFAs and interacts with PUFAs. 2 In this study, we used gas chromatography–mass spectrometry (GC–MS) to analyze the composition of PUFAs in the cerebrospinal fluid (CSF) of patients with PD and MSA.

We analyzed the CSF from 10 PD and 10 MSA patients. As a control group, we enrolled six healthy subjects and seven patients with normal pressure hydrocephalus (NPH). PD and MSA were diagnosed according to the United Kingdom Parkinson’s Disease Society Brain Bank Clinical Diagnosis Criteria and the consensus criteria for clinical diagnosis of probable MSA, respectively. The clinical stages of PD and MSA were evaluated according to the motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS-III) and the Unified Multiple System Atrophy Rating Scale (UMSARS), respectively. Informed consent was obtained from all the study subjects.

γ-Linolenic acid, linoleic acid, arachidonic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid, tricosanoic acid, and triethylenamine were purchased from Sigma (St. Louis, MO). N-methyl-N-(tert-butyldimethylsilyl) trifluoroacetamide was obtained from Pierce (Rockford, IL). The PUFAs in the CSF were determined as their tert-butyldimethylsilyl derivatives. The GC–MS analysis in SIM mode for the quantitative analysis of PUFAs was conducted with an Agilent 6890 gas chromatograph, interfaced to an Agilent 5973 mass-selective detector (70 eV, electron impact mode) and an Ultra-2 cross-linked capillary column (SE-54 bonded phase; 25 m × 0.20 mm I.D., 0.11-μm film thickness; Agilent Technologies, Atlanta, GA). Helium was used as the carrier gas, at a flow rate of 0.5 mL/min in constant flow mode. The injector, interface, and ion source were maintained at 260, 300, and 230°C, respectively. Samples were introduced in the split-injection mode (10:1). The oven temperature was set initially at 200°C for 1 min, then increased at a rate of 3°C/min to 250°C, and finally increased at 20°C/min to 300°C, where it was held for 5 min. The mass range scanned was 50–750 u at a rate of 0.99 scan/second.

The Mann–Whitney test was used to compare the means in pairs of patient groups. To determine whether a relationship among variables was present, Pearson correlation coefficients were obtained. A level of P < 0.05 was regarded as statistically significant using commercially available software (SPSS, version 12.0).

Patients with MSA had a significantly lower mean age (56.9 ± 6.7 years, mean ± SD) than control patients (70.5 ± 6.8) and those with PD (71.7 ± 4.8). The mean disease duration in patients with PD and MSA were 3.9 ± 2.8 and 3.8 ± 2.6 years, respectively. The mean UPDRS-III score of patients with PD was 34.3 ± 12.1, and the mean UMSARS score of patients with MSA was 55.3 ± 17.7.

The only PUFAs detected in the CSF from all subjects was EPA. The levels of the other PUFAs, including γ-linolenic acid, linoleic acid, arachidonic acid, DHA, and docosapentaenoic acid, were below the quantification limits. The EPA level was significantly elevated in patients with PD (16.9 ± 14 μmol/L, P = 0.021) and with MSA (17.0 ± 13 μmol/L, P = 0.006), compared with the control level (15.6 ± 0.9 μmol/L; Fig. 1A). The EPA level in healthy subjects (15.3 ± 0.6 μmol/L) was not significantly different from that in patients with NPH (15.9 ± 1.3 μmol/L).

The correlation analysis between the EPA level and disease severity revealed a significantly positive correlation between the UMSARS score and the EPA level (r = 0.8, P = 0.005; Fig. 1B). The UPDRS-III score was not correlated with the CSF EPA level (r = −0.25, P = 0.49).

The present study demonstrated that, among several PUFAs, EPA was the only one detectable in the CSF and that the CSF EPA level was significantly elevated in patients with PD or MSA, relative to controls. In addition, the EPA level showed significant positive correlation with the degree of clinical severity in patients with MSA.

Recent reports demonstrating an interaction between α-synuclein and PUFAs have suggested that PUFAs might

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promote oligomerization of toxic protein not only in α-synucleinopathy but also in amyotrophic lateral sclerosis and Alzheimer’s disease. Conversely, the oligomerization of α-synuclein seemed to have altered the level of PUFAs in pathological brain samples. Therefore, it is possible that oxygen-free radicals generated during the process of α-synucleinopathy can attack PUFAs enriched by interactions with α-synuclein, making these neuronal membranes more susceptible to further oxidative damage, which in turn could increase oxidative stress and lead to cell death. In the present study, the existence of elevated EPA levels in the CSF of patients with PD and MSA may support the idea of an interaction between α-synuclein and PUFAs. Additionally, a positive correlation between the level of EPA and disease severity in patients with MSA suggests that the increased level of EPA may result from increased oligomerization of α-synuclein, rather than increased oligomerization of α-synuclein being secondary to elevated levels of PUFAs. However, lack of significant correlation between EPA level and PD severity requires further studies encompassing correlation between the level of α-synuclein and EPA in patients with PD and MSA. Furthermore, evaluation of EPA levels in other neurodegenerative diseases of Alzheimer’s disease and progressive supranuclear palsy is needed to clarify whether EPA is a useful biomarker of α-synucleinopathy.

An in vitro study reported that EPA may exert a protective effect in neurodegenerative diseases through inhibiting apoptosis, reducing mitochondrial damage, and inhibiting inflammation. Therefore, an alternative explanation is that elevated EPA levels in patients with PD and MSA may reflect a compensatory response in neurodegenerative processes.

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FIG. 1. The level of EPA in the CSF is significantly elevated in patients with PD and MSA compared with the control level (A). Data are mean ± SD. **P < 0.05 by the Mann–Whitney test. Relationship between the level of EPA in the CSF and UMSARS, showing that disease severity in patients with MSA is positively correlated with the level of CSF EPA (r = 0.8, P = 0.005; B).