Brief Communication

Lack of Association of Apolipoprotein E ε4 Genotype with Cognitive Dysfunction in Essential Tremor

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S U M M A R Y

Apolipoprotein E (APOE) ε4 genotype is associated with increased risk of Alzheimer’s disease and other types of dementia. The level of cognitive dysfunction and its progression are also different in accordance with different APOE genotypes among Alzheimer’s disease patients. Recently, essential tremor (ET) has become regarded as a multisystem disorder and many studies have shown that ET patients have cognitive deficits and an increased risk of dementia. The role of APOE ε4 in ET patients, however, remains unidentified. In this study, we investigated the impact of APOE genotype on cognitive change in ET. Among the 69 patients enrolled, 10 patients had more than one APOE ε4 allele. The neuropsychological data of the groups having APOE ε4 and non-ε4 were similar: the proportion of cognitive impairment was not different between the ε4 and non-ε4 groups. The results of our study suggest that the possibility of cognitive declines in ET is not influenced by the APOE ε4 gene burden.

1. Introduction

Essential tremor (ET) is one of the most prevalent movement disorders. Its major symptoms are postural and kinetic tremors of the distal part of the body. Recent surveys have reported that ET is not a “pure” movement disorder, and has many aspects of non-motor symptoms, such as cognitive dysfunctions, psycho-affective symptoms and cerebellar dysfunctions. A recent population-based study in central Spain has shown that ET patients with tremor onset after 65 years of age were more likely to have dementia than the healthy control group. Another prospective population-based study in New York found that ET was associated with both prevalence and risk of dementia.

The apolipoprotein E (APOE) gene is the most prevalent gene for Alzheimer’s disease (AD) and is likely to be involved in the pathogenesis of dementia. APOE ε4 also has a key role in disease progression; carriers can experience faster and more severe cognitive decline as well as having more severe Aβ deposition, gray matter atrophies, and cerebral blood flow derangement in structural and functional neuroimaging.

The effects of this gene on other types of dementia or neurodegenerative disease have been widely studied. A recent population-based, prospective study has found that APOE ε4 is associated with an increased risk for vascular dementia in an allele dose-dependent fashion. In addition, a high prevalence of APOE ε4 was found in diffuse Lewy body disease. However, no studies have been conducted regarding the impact of APOE ε4 on cognitive change in patients with ET.

Herein, we aimed to evaluate the impact of APOE ε4 haplotype on the severity of cognitive dysfunctions in elderly patients with ET.

2. Methods

2.1. Participants

Sixty-nine consecutive newly-diagnosed ET patients were enrolled in this study. The evaluation procedure involved a detailed medical history, a physical and neurological examination, and a neuropsychological assessment. The patients’ history of medical and neurological problems was obtained with consent from the patients and family members, or from other caregivers. All patients were diagnosed with having core criteria for the diagnosis of ET. These criteria include the presence of bilateral action (postural or kinetic) tremor of the hands and forearms in the absence of other neurological signs (with the exception of the cogwheel phenomena), or the presence of isolated head tremor with no signs of dystonia. The secondary criteria (duration >3 years, positive
family history, and beneficial response to alcohol) were also applied. Young-onset patients (≤50 years) were excluded from this study because they were the least affected by cognitive change. Patients were also excluded from the study if: (1) they had neurological abnormalities related to systemic or other neurological diseases, (2) they were taking medications reported to influence cognition, such as anticholinergics or beta-blocking agents, or (3) they were found to have an FMR1 gene mutation of fragile X tremor and ataxia syndrome.

Tremor severity was determined by the global tremor score. This was obtained by summing the following nine items: right and left arm tremor, as determined by history (two items); tremor at rest of either the face, lips or chin (one item); tremor at rest of all four limbs (four items); and action or postural tremor of both arms (two items), as determined by examination.

This study was approved by the local ethics committee, and each patient provided written informed consent to participate.

2.2. Neuropsychological assessment

The patients' general cognitive status and severity of dementia were evaluated by the Korean version of the Mini-Mental State Examination, Clinical Dementia Rating (CDR), and the sum of box of CDR. Several cognitive domains were assessed by conducting a detailed battery of neuropsychological tests. The tests included the digit span forward and backward test for attention and working memory, the Korean version of the Boston Naming Test for language, the Seoul verbal learning test for verbal memory (i.e. immediate recall, delayed recall, and recognition), the Rey-Osterrieth Complex Figure Test (RCFT) for nonverbal, visuospatial memory (immediate recall, delayed recall, and recognition), the RCFT copy for visuospatial function, the Color-Word Stroop Test (word reading and color reading), the Controlled Oral Word Association test (semantic: animals, grocery items; and phonemic: Korean letters) for word fluency. Frontal motor functions were assessed by motor impersistence, contrasting program, go–no go test, fist–edge–palm, alternating hand movement, alternating square and triangle, and Luria loop tests. The resulting scores of these tests were classified as abnormal if they were below the 16th percentile of age-, sex-, and education-matched normal subjects.

Dementia was diagnosed according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. In line with the concept of mild cognitive impairment suggested by Petersen and colleagues, the diagnosis of mild cognitive impairment (MCI) in patients with ET was made if at least one out of five cognitive domains were found to be abnormal.

2.3. Determination of APOE genotype

The detailed method used for APOE genotyping is described elsewhere. In brief, genomic DNA was extracted from whole-blood samples and amplified with polymerase chain reaction, as described by Wenham et al.

2.4. Data analysis

The statistical analyses were performed using SPSS software version 15.0 (SPSS, Chicago, IL, USA). Comparisons of the demographics were done using the independent-sample t-test for the continuous variables, and Pearson chi-squared test for the nominal variables. The general and specific neuropsychological functions were compared between APOE4 and non–4 groups using the analysis of covariance, including age and education status as confounding covariates. Comparisons of APOE4 allelic prevalence among normal cognition, MCI and dementia were performed using chi-squared analysis. The level of statistical significance was set at p < 0.05.

3. Results

Among the 69 patients (including seven males and 62 females; mean age ± standard deviation: 66.5 ± 8.9 years), 31, 32 and six patients were assigned to the normal cognition, MCI, and dementia groups, respectively. The participants’ mean disease duration was 7.0 ± 9.0 years and the mean duration of education was 8.1 ± 5.4 years. Ten patients had more than one APOE4 genotype (APOE: 2/4; 3; 3/4; 6 and 4/4; 1, respectively).

The data from the groups having APOE4 and non–4 were similar for the age at examination and the age at onset, gender distribution, length of education, and presence of cardiovascular risk factors. The tremor severity, as measured by the global tremor score, was not statistically different between the two groups.

There were no differences in general cognitive functions between APOE4 and non–4 groups. The data also demonstrated that there were no significant differences in all cognitive domains. In addition, the proportion of cognitive impairment was not statistically different between the +4 and non–+4 groups (Table 2).

4. Discussion

The APOE gene is recognized as the most important and powerful genetic risk factor for AD. The APOE4 genotype is likely to increase the risk of developing AD and lead to malignant clinical courses for both AD and MCI. APOE4 influences AD pathology, interacting with the metabolism of amyloid precursor protein and with the accumulation of beta amyloid peptide, thus enhancing the hyperphosphorylation of tau protein and the formation of neurofibrillary tangles.

There were no data, however, about the influence of the APOE4 gene burden on cognitive decline in patients with ET. In this study, we investigated the effect of the APOE genotype on the cognitive functions of ET, and found no significant difference in the distribution of cognitive diagnosis between APOE4 and non–4 groups. In addition, the +4 allele did not influence any of the cognitive subdomains. This result suggests that cognitive declines in ET are not influenced by APOE4 allele burden, and thus APOE4 is probably not associated with poor cognitive outcome in ET.

Although many studies have shown that ET patients have cognitive deficits and an increased risk of dementia, the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of demographics between patients with APOE4 genotype and those without.</th>
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<tbody>
<tr>
<td>General characteristics</td>
<td>Non-APOE4 (n = 59)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66.1 ± 9.2</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>Education status (yr)</td>
<td>8.0 ± 5.0</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>7.0 ± 9.4</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (18.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Global tremor score</td>
<td>4.3 ± 3.5</td>
</tr>
</tbody>
</table>

Values represent mean with standard deviation or numbers with percentages in parentheses.

Analyses were performed with the independent-sample t-test for the continuous variables, and the Pearson chi-squared test for the nominal variables.
pathophysiology of cognitive change in ET is not fully understood.
Postmortem studies in ET brain have demonstrated degenerative
changes in the cerebellum or Lewy body in the brainstem.24 In
addition, multiple lines of evidence suggest that the circuitry
involved includes the frontal–subcortical–cerebellar pathways,
which play a role in both cognitive and affective processes in
patients with ET.25

Language functions

Korean version of the Boston Naming Test
26.0 ± 19.2
26.3 ± 15.9
0.888

Calculation
9.7 ± 3.0
9.7 ± 2.5
0.808

Visualspatial functions

RCFT copy
28.9 ± 9.4
29.7 ± 6.5
0.808

Verbal memory functions (Seoul verbal learning test)
Immediate recall
19.8 ± 5.7
18.4 ± 4.0
0.478

Delayed recall
6.3 ± 3.0
6.4 ± 2.1
0.836

Stroop tests

Word
97.2 ± 32.6
105.2 ± 15.3
0.361

Color
73.9 ± 28.7
74.7 ± 18.1
0.825

Cognitive diagnosis

Normal cognition
27 (45.8)
4 (40.0)
0.942

Mild cognitive impairment
27 (45.8)
5 (50.0)

Dementia
5 (8.4)
1 (10.0)

Values represent mean with standard deviation or numbers with percentages in parentheses.
Analyses were performed by analyses of covariance, controlling for age and duration of
education.
Abnormal frontal motor function represents numbers of patients who have more
than two abnormalities of the frontal motor function tests.

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