ApoE alleles, depression and positive affect in multiple sclerosis

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Abstract

Background—The role of apolipoprotein E (ApoE) alleles has received recent attention in depressive disorders, the ApoE ε4 conferring greater risk for poorer outcomes, and the ApoE ε2 allele providing some protective effects. Depression is common in multiple sclerosis (MS) and the role of ApoE alleles is unknown.

Aims—To evaluate ApoE alleles in relation to symptoms of depression in a cohort of patients with MS participating in the Sonya Slifka Longitudinal Multiple Sclerosis Study (Slifka Study). To examine risk and protection, depressed mood and positive affect were each investigated with respect to the ApoE ε4 and ApoE ε2 alleles, respectively.

Results—Of the total 101 participants, 22.8% were ApoE ε2 carriers and 21.8% were ApoE ε4 carriers. Hierarchical linear regression analyses suggested that after controlling for demographics, disease duration, and disability, ApoE ε2 significantly predicted increased positive affect (R²Δ = 0.05, F(1,94) = 5.44, P = 0.02) and was associated with decreased severity of depressive symptoms, although this did not reach statistical significance (R²Δ = 0.03, F(1,94) = 3.44, P = 0.06). ApoE ε4 did not significantly predict depression status.

Conclusion—The presence of the ApoE ε2 allele in this study is suggested to be protective against depressive symptoms in our subsample of patients recruited from the Slifka Study. These findings are consistent with reports in psychiatric populations linking ApoE ε2 with decreased incidence of depressive disorders. Further investigation would be warranted to understand the role of ApoE genotypes and risk for depressive symptoms.

Keywords
genetics; multiple sclerosis; quality of life
Introduction

Apolipoprotein E (ApoE) functions as a major lipid carrier protein in the brain and nervous system and has gained significant attention as a potential risk factor for the susceptibility and prognosis of neuro-degenerative conditions because its putative role in myelin repair and immunomodulation. In multiple sclerosis (MS), research to date has focused primarily upon the role of the ApoE alleles as a genetic risk factor for increased disease susceptibility and disease severity [1–3]. A role for ApoE polymorphism (ApoE ε4 alleles) has been proposed as a risk factor for cognitive impairment in MS [41–8]. However, a recently published meta-analysis including over 4000 MS cases showed that variation at ApoE does not distinguish a relapsing-remitting from primary-progressive disease course or influence disease severity measured using the Expanded Disability Status Score (EDSS) and disease duration information [9].

The role of ApoE alleles has received recent attention in depressive disorders, with the ApoE ε4 conferring greater risk for poorer outcomes and the ApoE ε2 allele perhaps providing some protective effects. ApoE ε4 carriers may have an earlier onset of depressive disorders, increased severity of depressive symptoms, and a more chronic course of depression compared with noncarriers [10–12]. Other studies, however, observe no relationship among depression and ApoE ε4 [13,14]. Conversely, there may be a protective affect of the ApoE ε2 allele in major depression: the ApoE ε2 allelic frequency in major depressive disorder (MDD) has been observed to be significantly lower than that among healthy controls [15]; among patients with severe depression, the presence of an ApoE ε2 allele appeared to predict a positive response to electro-convulsive therapy [16,17].

Depression is common among patients with MS, with lifetime risk for MDD over 50% [18] and 12-month prevalence rates at 71–15% [19]. Given these high rates, risk factors for depression specific to the MS disease processes have been suggested and include such factors as neuropathological disease burden and inflammation [20,21]. In addition, increasing functional disability has also been associated with an increased risk of developing depressive symptoms [22,23]. To the best of our knowledge, genetic risk factors for depression in MS have not been investigated.

The purpose of the present investigation was to evaluate the relationship between ApoE alleles and symptoms of depression in a cohort of patients with MS participating in the Sonya Slifka Longitudinal Multiple Sclerosis Study (Slifka Study). Because we were looking at both risk and protective factors, we also examined positive affect as a countervailing phenotype to depression. We hypothesized that the presence of the ApoE ε4 allele would be associated with increased depressive symptom severity and decreased positive affect, and that the ApoE ε2 allele would be associated with decreased depressive symptoms severity and increased positive affect.

Methods

The Sonya Slifka Longitudinal MS Study

The Slifka Study is a longitudinal study of over 2000 people with MS initiated and funded by the National Multiple Sclerosis Society (NMSS) and designed and conducted by Abt Associates, Inc. The study cohort is broadly representative of the MS population in the United States and includes people with the spectrum of disease course and severity, disability, sociodemographic, and healthcare provider characteristics. Epidemiological, clinical, and health services data are collected semiannually by computer-assisted telephone interviews. Specific methodological procedures are described previously [24,25].
Patient selection

From the larger Sonya Slifka Study, all participants who were diagnosed within 12 months of the baseline interview (n = 482) were asked upon the initial interview to provide blood samples for genetic and immunologic studies and complete a questionnaire on health and ancestry. Of these, 295 provided informed consent and completed questionnaires. Participants who were nonwhite, did not have a MS care provider-confirmed diagnosis of definite MS, had another auto-immune disease, chronic illness, or significant history of alcohol or substance abuse, or were pregnant at the time of the baseline interview were excluded. Phlebotomy kits, instructions, and mailing materials were mailed to 191 eligible participants; 158 participants obtained blood specimens at local laboratories that were then shipped with a cold gel pack for arrival within 24 h as a central laboratory (ACM Medical Laboratory, Rochester, New York) for preparation and storage. Four specimens were not usable as they had not shipped within 24 h. Upon receipt, buffy coat and plasma were separated, apportioned into aliquots, and stored at −70 degrees. Genotyping was completed by conventional means, which included the extraction of high molecular weight DNA from buffy coats using a standard desalting procedure. High molecular weight DNA was extracted from buffy coats using a standard desalting procedure. APOE genotypes were determined using a combination of two exon 4 Single Nucleotide Polymorphism (SNP), rs7412 (C/T) at position 158 (ABI predesigned) and rs429358 (C/T) (custom TaqMan assay designed on File Builder 2.0 software) at position 112. Genotyping assay PCRs were carried out in 384-well plates using Applied Bio-systems TaqMan Universal PCR Master Mix on an ABI GeneAmp PCR System 9700. The plates are then read on an ABI 7900HT Sequence Detection System using SDS 2.0 software (Applied Biosystems, Foster City, CA, USA). Generation of genotypes is performed blind to clinical status. Hardy Weinberg equilibrium was tested using the random permutation procedure [23].

For the present study, participants who previously provided serum were invited to participate in a short neuropsychiatric telephone interview and asked for permission to use demographic and clinical data from the Slifka Study database and samples for genetic analyses. Of these participants, 9 reported that they were not interested, 2 reported that they no longer carried a diagnosis of MS, 2 were deceased, and 32 could not be reached by telephone or mail. A total of 101 participants agreed and provided complete data for the present study.

Behavioral assessment

Two measures evaluating mood and affect were administered by clinical evaluators trained by a licensed PhD level clinical psychologist. The Patient Health Questionnaire-9 (PHQ-9) is commonly used to rate depression symptom severity and make a diagnosis of possible MDD [26]. Severity of symptoms (range 01–27) and presence versus absence of possible MDD were used as dependent variables in this investigation. The positive affect scale of the Positive and Negative Affect Schedule (PANAS-P) [27] was used to assess positive affect that is largely independent of depression [28]. Scores can range from 101–50 for the PANAS-P.

Disability assessment

The Patient-determined Disease Step (PDDS) was used to measure neurological disability in this investigation. The PDDS consists of an eight-level measure of disability status (0 = normal to 8 = bedridden) analogous to the provider-administered Expanded Disability Status Scale (EDSS) [29]. The PDDS correlates highly with the EDSS (spearman r = 0.93) [30].
Data analytic strategy

We conducted descriptive analyses of patient demographic and disease characteristics, PHQ-9, PANAS-P, and ApoE allele frequency. Subsequently, we conducted regression analyses evaluating patient demographic (age, education, and gender) and disease characteristics [disease duration (i.e., years since onset of symptoms) and PDDS] and the presence of ApoE ε2 allele as predictors of PHQ-9 depression severity scores and PANAS-P score. Predictors were entered in three separate steps to determine the proportion of variance explained above and beyond the previous step. These hierarchical regression analyses were repeated with the presence of the ApoE ε4 allele.

Results

Patient and disease characteristics are presented in Table 1. In all, 23% of participants were ApoE ε2 carriers and 22% of participants were ApoE ε4 carriers. Distribution of ApoE genotypes and haplotypes was consistent with previous reviews of ApoE distribution in MS [31]. PHQ-9 severity mean was 7.3 ± 5.0, indicating minimal depressive symptoms overall. Patients meeting criteria for a probable diagnosis of MDD based on PHQ-9 ≥ 16 were 9.0%. Mean PANAS-P score was 32.1 ± 8.5.

Stepwise regression analyses predicting PHQ-9 symptom severity are presented in Table 2. Results suggest that overall, demographics and disease duration (years since symptom onset) did not significantly predict PHQ-9 symptom severity. Greater disability as measured by the PDDS was significantly associated with increased depression severity (P < 0.0001). Finally, the presence of the ApoE ε2 allele was nearing significance as a predictor of depression symptom severity, accounting for an additional 3% of the variance above and beyond all other predictors.

Hierarchical stepwise regression analyses predicting PANAS-P positive affect are presented in Table 3, with predictors entered in the same order as above. Results indicate that PDDS was significantly associated with decreased positive affect (P < 0.05) and the presence of the ApoE ε2 allele was associated with greater levels of positive affect (P < 0.05). The ApoE ε2 allele accounted for an additional 5% of the variance above and beyond all other predictors.

Presence of the ApoE ε4 allele did not significantly predict PHQ-9 depression symptom severity (P = 0.27) or PANAS-P positive affect (P = 0.35).

Although the sample sizes were small, univariate group comparisons among ApoE genotypes were conducted in attempts to clarify the role of specific ApoE genotypes. Due to reduced sample sizes, genotype comparisons were not made using ε2/ε2 and ε4/ε4 groups. Participants with ε2/ε3 genotype reported significantly reduced depressive symptoms on the PHQ-9 and increased positive affect on the PANAS compared with participants without ε2/ε3 (PHQ-9: 5.55 ± 3.5 vs. 7.94 ± 5.4, t = 2.48, P = 0.02; PANAS: 5.55 ± 3.5 vs. 7.94 ± 5.4, t = 2.48, P = 0.03, respectively). Similarly, ε2/ε4 also had reduced PHQ-9 scores than participants without ε2/ε4 (4.5 ± 1.4 vs. 7.62 ± 5.2, t = 3.78, P < 0.01), but there was no significant difference among these two groups on the PANAS.

Discussion

The purpose of this investigation was to evaluate the presence of the ApoE ε2 and ε4 alleles in relation to symptoms of depression and positive affect in a cohort of well-characterized patients with MS. Our primary hypotheses that the ApoE ε4 allele would be associated with increased depression and decreased positive affect were not supported in this investigation. However, the presence of the ApoE ε2 allele appeared to be protective against depressive...
symptoms in our subsample of patients recruited from the Sonya Slifka Longitudinal Study. In addition, the ApoE ε2 allele was associated with increasing levels of positive affect. Disability as measured by the PDDS also remained a significant predictor of both depressive symptoms and positive affect, consistent with previous observations [22,23]. To the best of our knowledge, this is the first evaluation of ApoE allele frequency and depression in MS.

Decreased ApoE concentrations in cerebrospinal fluid in patients with MS have been documented with a corresponding decrease in intrathecal ApoE synthesis leading to the hypothesis that ApoE synthesis influences MS exacerbation over time [32,33]. The ApoE protein has been associated with regeneration of axons and myelin after lesions of central and peripheral nervous tissue [34], and its isoforms have been shown to have differential effects on neuronal growth [35]. Though studies evaluating depression in association with axonal damage and regeneration have not been conducted in MS, signs of axonal damage have been observed among depressed patients in other populations [36].

The distributions of ApoE haplotypes in our study were consistent with studies of ApoE in other MS cohorts [31]. In addition, the findings reported here are consistent with reports in psychiatric populations linking ApoE ε2 with decreased incidence of depressive disorders [15]. The lack of association between ApoE ε4 and depression is also consistent with the literature [13,14]. The small sample size in this investigation along with potential recruitment biases from the larger sample of persons enrolled in the Sonya Slifka study are limitations, and a prospective study evaluating these alleles in relation to neuropsychiatric symptoms in a larger cohort of persons with MS is warranted to increase confidence in these gene-behavior associations.

Importantly, these findings are novel and must be interpreted with caution. It is critical that this work be carefully replicated. Identifying patients at risk for depression based on genetic factors would have important implications for both patient care and could prompt differential consideration of patients identified with specific biomarkers [37].

Acknowledgments

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References


### Table 1

**Patient and disease characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (x ± SD)</td>
<td>46.9 ± 9.88</td>
</tr>
<tr>
<td>Educational level: % college degree or above</td>
<td>60.4%</td>
</tr>
<tr>
<td>Gender: % female</td>
<td>83.2%</td>
</tr>
<tr>
<td>MS Course: % relapsing-remitting</td>
<td>80.0%</td>
</tr>
<tr>
<td>Disease duration (years since symptom onset), (x ± SD)</td>
<td>8.4 ± 6.3</td>
</tr>
<tr>
<td>PDDS (x ± SD)</td>
<td>2.1 ± 1.2</td>
</tr>
<tr>
<td>PHQ-9 severity score, (x ± SD)</td>
<td>7.3 ± 5.0</td>
</tr>
<tr>
<td>PHQ-9 diagnosis of major depressive disorder</td>
<td>9.0%</td>
</tr>
<tr>
<td>PANAS – positive affect scale score, (x ± SD)</td>
<td>32.1 ± 8.5</td>
</tr>
<tr>
<td>ApoE ε2/2 allele</td>
<td>1.0%</td>
</tr>
<tr>
<td>ApoE ε2/3 allele</td>
<td>18.8%</td>
</tr>
<tr>
<td>ApoE ε2/4 allele</td>
<td>3.0%</td>
</tr>
<tr>
<td>ApoE ε3/3 allele</td>
<td>62.8%</td>
</tr>
<tr>
<td>ApoE ε3/4 allele</td>
<td>15.8%</td>
</tr>
<tr>
<td>ApoE ε4/4 allele</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

MS, multiple sclerosis; PDDS, Patient-determined Disease Steps; PHQ-9, Patient Health Questionnaire-9; PANAS, Positive and Negative Affect Scale; ApoE, Apolipoprotein E.
Table 2

Regression: predictors of PHQ-9 depression symptom severity

<table>
<thead>
<tr>
<th>Step</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>Std. $\beta$</th>
<th>$\Delta F$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: demographics (age, education, and gender)</td>
<td>0.05</td>
<td>0.02</td>
<td>0.11</td>
<td>1.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Step 2: Disease duration</td>
<td>0.06</td>
<td>0.02</td>
<td>0.07</td>
<td>0.41</td>
<td>0.52</td>
</tr>
<tr>
<td>Step 3: PDDS</td>
<td>0.18</td>
<td>0.14</td>
<td>0.36</td>
<td>14.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Step 4: Presence of ApoE ε2</td>
<td>0.21</td>
<td>0.03</td>
<td>-0.18</td>
<td>3.4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

PHQ-9, Patient Health Questionnaire-9; PDDS, Patient-determined Disease Steps; ApoE, Apolipoprotein E.
Table 3

Regression: predictors of PANAS-P positive affect

<table>
<thead>
<tr>
<th>Step</th>
<th>R²</th>
<th>Δ R²</th>
<th>Std. β</th>
<th>Δ F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: demographics (age, education, and gender)</td>
<td>0.03</td>
<td>0.03</td>
<td>0.15</td>
<td>1.1</td>
<td>0.36</td>
</tr>
<tr>
<td>Step 2: disease duration</td>
<td>0.05</td>
<td>0.01</td>
<td>-0.12</td>
<td>1.28</td>
<td>0.26</td>
</tr>
<tr>
<td>Step 3: PDDS</td>
<td>0.10</td>
<td>0.06</td>
<td>-0.24</td>
<td>14.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Step 4: Presence of ApoE ε2</td>
<td>0.15</td>
<td>0.05</td>
<td>0.23</td>
<td>5.44</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

PANAS, Positive and Negative Affect Schedule; PDDS, Patient-determined Disease Steps; ApoE, Apolipoprotein E.