Parkinsonism and Related Disorders 20 (2014) 503–507

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Clinical and pathologic presentation in Parkinson's disease by apolipoprotein e4 allele status

Sarah E. Monsell [a,*], Lilah M. Besser [a], Katherine B. Heller [a], Harvey Checkoway [b], Irene Litvan [c], Walter A. Kukull [a]

[a] National Alzheimer's Coordinating Center, University of Washington, Seattle, WA 98105, USA
[b] Department of Family & Preventive Medicine, University of California, San Diego, La Jolla, CA, USA
[c] Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 23 December 2013
Received in revised form
28 January 2014
Accepted 4 February 2014

Keywords:
Parkinson's disease
APOE
Neuropathology
Clinical symptoms

ABSTRACT

Background: Apolipoprotein (APOE) e4 allele status has been linked to clinical presentation and progression in Alzheimer's disease; however, evidence for a role of APOE e4 in Parkinson's disease (PD) remains largely inconclusive. In this analysis we explored potential significant associations between APOE e4 allele status and characteristics of clinical presentation in patients with PD.
Methods: Data came from 424 subjects evaluated using the Uniform Data Set (UDS) assessment collected by the National Alzheimer's Coordinating Center. Subjects had a known year of diagnosis of PD and experienced change in motor function prior to any change in cognition. Linear and logistic regression were used to model the association between APOE e4 carrier status and clinical characteristics including measures of cognitive decline and motor and neuropsychiatric symptoms. Amyloid burden was also evaluated for a subset of patients who died and consented to autopsy.
Results: Odds of dementia were higher in APOE e4 carriers (OR = 5.15), and, on average, APOE e4 carriers scored two points worse on tests of episodic memory and the Clinical Dementia Rating Sum of Boxes assessment. There was little evidence to support an association between e4 carrier status and severity of motor features, and, of the four neuropsychiatric symptoms evaluated, only presence of hallucinations was significantly associated with APOE e4 carrier status (OR = 5.29). Neuropathology data revealed higher frequencies of neuritic and diffuse amyloid plaques in APOE e4 carriers compared to non-carriers.
Conclusions: APOE e4 allele status is associated with dementia and severity of Alzheimer's disease pathologic features in PD.

1. Introduction

Apolipoprotein (APOE) e4 allele status has been linked to clinical presentation and progression in Alzheimer's disease [1–3]; however, evidence for a role of APOE e4 in Parkinson's disease (PD) remains largely inconclusive [4–6]. In 2012, researchers at the National Institute on Aging found that the frequency of the APOE e4 allele in subjects with PD was not statistically significantly different from dementia-free controls [5].

On the other hand, smaller studies, using different measures of cognition, have found evidence of an association between e4 carrier status and cognition in PD. Tsuang et al. found higher rates of APOE e4 allele frequency among subjects with PD dementia compared to non-PD cognitively normal subjects (OR = 3.1) [7]. Similarly, Gomperts et al. found evidence of an association between APOE e4 and cognitive but not motor decline over time in PD [8]. Thus, additional research is needed to shed light on the seemingly complicated and conflicting associations observed between APOE and cognition in PD.

The National Alzheimer's Coordinating Center (NACC) houses a large, multicenter database on subjects with a wide range of cognitive and motor features, several of whom have a clinical diagnosis of PD. Data collected include subject demographics, health history, performance on neuropsychological tests, as well as presence and severity of parkinsonian and neuropsychiatric symptoms. Therefore, these data provide an excellent opportunity for studying clinical presentation of progressive neurodegenerative diseases such as PD. In this analysis, we tested the hypothesis that cognition, but not motor or neuropsychiatric symptoms in PD subjects, vary by APOE e4 allele status.

* Corresponding author.
E-mail address: smonsell@uw.edu (S.E. Monsell).

http://dx.doi.org/10.1016/j.parkreldis.2014.02.001
1353-8020/

2. Methods

2.1. Study sample

Data for this analysis were obtained from the NACC Uniform Data Set (UDS) funded by the National Institute on Aging [9,10]. All data came from the subject's initial UDS visit, recorded between September 2005 and March 2013 at one of the 34 past and present Alzheimer's Disease Centers (ADCs). Study inclusion criteria were (1) a diagnosis of PD, made by an ADC neurologist, at the initial UDS visit, (2) a known year of PD diagnosis, and (3) motor function was the first predominant change as opposed to cognition or behavior, as judged by a clinician. Research using the NACC database was approved by the University of Washington Institutional Review Board.

APOE e4 genotype, the main exposure of interest, was available for a subset of subjects and was categorized as either e4 carrier (hetero or homozygous) or non-carrier (no e4 alleles).

Characteristics of clinical presentation used in this analysis included the presence of dementia, Clinical Dementia Rating Sum of Boxes score (CDR-SB), Logical Memory delayed score, motor symptoms measured by the Unified Parkinson's Disease Rating Scale (UPDRS), and select neuropschiatric symptoms measured by the Neuropsychiatric Inventory (NPI-Q).

Cognitive function was assessed as a continuous measure using the CDR-SB [11]. The CDR grades subjects' cognitive and functional abilities in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The clinician, incorporating input from the subject's co-participant, evaluates impairment in each domain as none (0), questionable or very mild (0.5), mild (1), moderate (2), or severe (3). The scores for each domain are summed to create a Sum of Box score ranging from 0 to 18, with higher scores indicating more severe impairment.

Deficits in episodic memory were assessed using the Logical Memory IIA-Delayed Story Units Recalled test, which tests subjects' story retention ability [12]. The only tests of executive function in the UDS neuropsychological battery are the Trail Making A and B tests, which require preserved motor function [13]. As many PD subjects have substantial motor impairment, we were not able to assess executive function independent of motor impairment.

Motor features were evaluated using Levy summary scores derived from the UPDRS [14]. The Levy A score is the sum of the Levodopa-responsive symptoms, including facial expression, rigidity, and bradykinesia domains. The A score ranges from 0 to 80. The Levy B score, ranging from 0 to 20, is the sum of the Levodopa-nonresponsive symptoms of speech and axial impairment [15]. Subjects who did not receive the UPDRS or had any 'untestable' items were considered to be missing the Levy A and/or B score.

Neuropsychiatric symptoms were evaluated with the NPI-Q, in which physicians interview the co-participant about the subject's symptoms [16,17]. For this analysis, we included the items on depression or dysphoria, hallucinations, anxiety, and nighttime behavior (awake during the night, rise too early, or take excessive naps), since these symptoms are commonly associated with Alzheimer's disease and dementia with Lewy bodies [18–21].

2.2. Statistical analysis

Linear and logistic regression were used to estimate the association between APOE e4 carrier status and each individual characteristic of clinical presentation and cognitive decline. Generalized estimating equations (GEE) were used to account for clustering of subjects within an ADC [22]. An independent correlation structure with robust standard errors was employed.

Since symptoms generally worsen as PD progresses, the analytic sample was split according to years since PD diagnosis: subjects whose initial UDS visit was less than five years after their first PD diagnosis were grouped into the <5 years group, while the 5+ group comprised subjects whose initial UDS visit took place five or more years after PD diagnosis. This dichotomy allowed for a stratified analysis, where associations between e4 carrier status and clinical presentation could be evaluated separately for disease periods with potentially different patterns and severity of symptoms.

Each clinical characteristic was an outcome measurement in a model with APOE e4 status as the main predictor, resulting in nine separate regressions for each strata. Models were run both with and without adjustment for age at PD diagnosis, years since PD diagnosis, sex, and education. Frequencies of reported use of an antipsychotic medication or dopaminergic agonist (ropinirole, pramipexole, rotigotine) were compared between APOE e4 carrier groups using a Chi-squared test. A significant difference in the reported use of either class of medication would prompt inclusion of these indicators in the models for neuropsychiatric symptoms.

The GEE approach assumes that all missing data are missing completely at random, meaning that there are no patterns or trends making some subjects more likely than others to be missing data. While this is likely a reasonable assumption for the missing data on APOE genotype, we performed both a complete case analysis and an analysis using multiple imputation in order to avoid overlooking potential biases introduced by these missing data.

In the complete case analysis, only subjects with non-missing data on APOE e4 allele status and the outcome measure were included in each regression model. For the imputation model, missing values were estimated using multiple imputation with chained equations [23,24]. The cognitive scores, neuropsychiatric symptoms, Levy scores, years since PD diagnosis, age at PD diagnosis, sex, and education were used to estimate missing APOE e4 status and measures of clinical presentation. The imputation step was run 20 times, yielding 20 complete data sets. Coefficients and standard errors were combined using Rubin's rules [25], producing a single regression coefficient with corresponding confidence intervals. The complete case analysis was considered the main analysis and the imputation model a sensitivity analysis.

2.3. Neuropathology Data

APOE genotype has been linked to levels of amyloid beta in cerebrospinal fluid (CSF) and brain deposition captured via PET imaging [26,27]. Although CSF biomarker and imaging data were not available to evaluate amyloid burden, neuropathological data were available for a small number of subjects included in the analytic sample who died and had an autopsy report ($n = 29$). Using Fisher's exact test, we tested for statistically significant differences in CERAD neuritic plaque frequency (none or sparse vs. moderate or frequent) [28], as well as diffuse plaque frequency (none or sparse vs. moderate or frequent) observed at autopsy by e4 carrier status. Braak & Braak neurofibrillary stage [29] was also examined in order to evaluate the overall severity of AD neuropathologic features. Finally, Lewy body pathology was evaluated according to criteria from the Consortium on Dementia with Lewy Bodies [30,31].

3. Results

Of the nearly 600 subjects with a diagnosis of PD at the initial UDS visit and a known year of diagnosis, 424 (71%) experienced a decline in motor function prior to any decline in cognition or behavior. Approximately 55% of these subjects had APOE e4 genotype data available; there were 61 APOE e4 carriers and 171 non-carriers. There were also 192 subjects for whom APOE e4 genotype data were not available. A Chi-squared test comparing the proportion of demented subjects with APOE e4 genotype known vs. unknown was performed. The test yielded a p-value of 0.74, suggesting that subjects with dementia were not more or less likely to have a known APOE e4 genotype compared to non-demented subjects.

More than half of the subjects were diagnosed with PD five or more years prior to their first UDS visit; however, the proportion falling into each group was fairly even between e4 carriers and non-carriers (Supplemental Fig. 1).

Subject demographics and clinical characteristics are displayed in Table 1. Overall, the groups were quite similar. APOE e4 carriers were slightly older than non-carriers and more often men. Across, all groups, the main reason for participation in the ADC study was to participate in research; a much smaller portion (7–13%) enrolled in order to obtain a clinical evaluation, thus suggesting that the sample was not comprised mainly of subjects who enrolled in order to evaluate a cognitive complaint.

There was also no difference in frequency of antipsychotic medication or dopaminergic agonist use among APOE e4 carriers and non-carriers (χ^2, $p = 0.2272$ and $p = 0.8168$, respectively). Therefore, adjustment for these factors in modeling neuropsychiatric symptoms among APOE e4 carriers and non-carriers was determined to be unnecessary.

As the presence of multiple diagnoses could also influence the results, the frequencies of probable AD and dementia with Lewy bodies (DLB), in addition to PD, were calculated. Upon investigation, only two subjects had probable AD (one APOE e4 non-carrier and one with e4 status unknown). Several more subjects did have a diagnosis of DLB in addition to PD (13 APOE e4 non-carriers, nine e4 carriers, and six who did not have APOE e4 allele information). A Chi-square test was performed to determine whether or not the frequency of a DLB diagnosis varied across the e4 allele status groups. The test yielded a p-value of 0.46, thus, inclusion of these