Archives of Gerontology and Geriatrics 65 (2016) 231–238

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

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

Neuropsychiatric symptoms and Apolipoprotein E: Associations with eventual Alzheimer's disease development

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ARTICLE INFO

Article history:
Received 8 February 2016
Received in revised form 10 April 2016
Accepted 11 April 2016
Available online 14 April 2016

Keywords:
Alzheimer's disease
Apolipropotein e
Apoe ε4
Neuropsychiatric symptoms
Delusions
Apathy
Disinhibition
Agitation
Hallucinations
Anxiety
Elation
Irritability
Motor disturbance
Sleep disturbance
Appetite disturbance

ABSTRACT

Objective: Alzheimer's disease (AD) is the result of neurodegeneration, which manifests clinically as deficits in memory, thinking, and behavior. It was hypothesized that neuropsychiatric symptoms and the apolipoprotein E genotype increase the likelihood of Alzheimer's disease development.
Methods: Utilizing data from the National Alzheimer's Coordinating Center, information from evaluations of 11,453 cognitively intact participants was analyzed. Survival analysis was used to explore relationships between individual neuropsychiatric symptoms as determined by the Neuropsychiatric Inventory Questionnaire, apolipoprotein E, and eventual AD diagnosis. Cox proportional hazard models were utilized to explore the main effects and synergistic (additive and multiplicative) interactions.
Results: This study provided evidence for an increased hazard of developing AD among participants with any of the symptoms assessed by the NPI-Q. The hazard of developing AD was almost thirteen times higher for $_{\varepsilon}4$ carriers with delusions and eleven times greater for those with apathy and disinhibition. Statistically significant hazards ($p > 0.001$) were also realized by $_{\varepsilon}4$ carriers with hallucinations; agitation; depression; anxiety; elation; apathy; irritability; and motor, sleep, and appetite disturbances.
Conclusions: Findings suggest that neuropsychiatric symptoms are associated with eventual AD diagnosis among a group of cognitively asymptomatic participants at baseline. Many studies begin with a group of participants already impacted by AD diagnosis. The longitudinal analysis of a group of participants who, at baseline, demonstrated no observable signs of AD was a strength of this study. This investigation contributes to the literature exploring an increased hazard of AD due to potential modifiable risk factors and genetic biomarkers such as apolipoprotein E.

Alzheimer's disease due to dementia (AD) is a fatal condition caused by cerebral matter neurodegeneration. Diagnosis of AD is often clinical in nature, as observable symptoms pertaining to memory, cognition, and attention most often inform the diagnosis (Meng & D'Arcy, 2013). Cognitive degeneration and accumulation of plaques and tangles may begin more than 25 years earlier than any observable clinical signs of AD (Bateman et al., 2012). It is well accepted that AD dementia arises from a complex pathophysiological process, and many diagnosed with AD dementia passed through a stage of mild cognitive impairment first (McKhann, Knopman, Chertkow, Hyman, & Kawas, 2011).

The current study examined the occurrence of behavioral symptoms contained within the Neuropsychiatric Inventory Questionnaire) (Cummings, 1997) among cognitively asymptomatic subjects and the effect on the hazard of AD dementia diagnosis among apolipoprotein (APOE) $_{\varepsilon}4$ carriers. These symptoms include delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, sleep disturbance, motor disturbance, appetite fluctuations, and irritability.

Inherited genes create a predisposition for AD dementia increasing susceptibility, though do not ensure development. APOE has been associated with increased susceptibility in sporadic late-onset AD cases (Bennett et al., 1995). Compared to non-APOE $_{\varepsilon}4$ carriers, the risk is two to four times greater in those with one

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http://dx.doi.org/10.1016/j.archger.2016.04.006
0167-4943/

ε4 allele. The risk is 12 times greater in those with two ε4 alleles (Hollingworth, Harold, Jones, Owen, & Williams, 2011). AD onset may occur seven to nine years earlier for each additional ε4 allele compared to non- ε4 carriers (Ashford, 2004). The presence of ε2 is considered to be neuroprotective (Talbot et al., 1994). The presence of ε3 and ε4 confer greater risks (Schipper, 2011). However, the presence of ε3, may confer protective benefits relative to ε4 (Aboud, Mrak, Boop, & Griffin, 2012). The mechanism behind APOE risk is not fully understood; nevertheless, APOE ε3 may decrease the rate at which β-amyloid protein, the precursor to plaques, is cleared from the brain. The APOE ε4 allele appears to slow this process more than other alleles. One study found that decreasing APOE ε3 and ε4 by half in mice led to an increase in β-amyloid clearance in the brain (Jiang et al., 2008).

Gene-environment interaction (Belsky, Moffitt, & Caspi, 2013) offers a framework to consider the differential effects of susceptibility genes in concert with variable environmental influences. This hypothesis suggests that different genotype combinations respond to the environment and psychosocial factors in a varied manner, but that select interactions may serve to increase or decrease risk of particular conditions.

Several studies have examined neuropsychiatric symptoms relative to AD development. Okura et al. (2010) utilized data from the Aging, Demographics, and Memory Study to examine neuropsychiatric symptoms (NPS) such as "agitation, depression, apathy, delusions and hallucinations" relative to AD development. Depression was the most commonly occurring neuropsychiatric symptom for those with cognitive impairment without dementia, as well as mild, moderate, and severe dementias in respondents 71 years of age and older. Many studies previously examining neuropsychiatric symptoms used regional data and focused on groups with mild cognitive impairment or dementia. Okura et al. were among the first to include a clinically asymptomatic (n = 303) nationally representative sample with regard to the prevalence of these symptoms while taking into account the degree of cognitive impairment.

Applying a similar approach, Peters et al. (2013) examined subjects with cognitive impairment without dementia (CIND) (n = 230). The researchers observed the conversion rate from CIND to AD. Their findings indicated that APOE ε4 was a risk factor, as were nighttime behaviors and the presence of even one neuropsychiatric symptom. The findings indicate that even mild neuropsychiatric symptoms create a risk for dementia.

As D'Onofrio, Panza, Seripa, Sancarlo, and Paris (2011) found in their study of the presence and absence of neuropsychiatric symptoms in those with AD (n = 322), there was not a significant association between APOE and NPS. For carriers of APOE ε4 and those diagnosed with AD, there was an increased risk of certain affective syndromes. Results of the aforementioned study contribute to the unresolved debate around the role of APOE ε4 and depression, and identify the need for larger samples and longitudinal designs to enhance the literature. This recommendation was supported by van der Linde, Stephan, Sawa, Dening, and Brayne (2012), who, following their systematic review of the literature, expressed the need for longitudinal studies, larger sample sizes, and the inclusion of commonly cited behavioral and psychological instruments to better understand risk and the course of illness for those with behavioral and psychological risk factors.

This study had three hypotheses. First, it was hypothesized that the main effects of individual neuropsychiatric symptoms and positive ε4 carrier status will increase the hazard of eventual AD diagnosis. Second, it was hypothesized that the additive effects of individual NPS in combination with positive ε4 carrier status will results in statistically significant hazards of eventual AD diagnosis. Last, it was hypothesized that the multiplicative interaction effects of individual NPS in combination with positive ε4 carrier status will result in statistical significant hazards of eventual AD diagnosis.

1. Methods

Data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) were examined. The information in the UDS is collected during yearly meetings with subjects (or provided by a chosen close friend, family member, neighbor, or caregiver) and trained clinicians. These interviews acquire demographic information; family history; health history; medications used; and a physical is conducted including imaging and labs. Participants are assessed using rating scales concerning cognitive, physical, psychological, and neuropsychological domains. These rating instruments include: the Clinical Dementia rating (CDR) (sum of boxes and global) (Morris, 1993), the Geriatric Depression Scale (Yesavage et al., 1983), the Functional Activities Questionnaire (Pfeffer, Kurosaki, Chance, & Filos, 1982), and a clinician judgement of symptoms. Neuropsychological testing includes the Montreal Cognitive Assessment (Nasreddine et al., 2005), the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975), Logical Memory Immediate, Logical Memory Delayed, Digit Span Forward, Digit Span Backward, Category Fluency (Animals and Vegetables), Trail Making Test, WAIS-R Digit Symbol, and the Boston Naming Test (National Alzheimer's Coordinating Center, 2005). A diagnosis regarding dementia status is often determined by a group of two or more clinicians, neuropsychologists, or the examining physician (National Alzheimer's Coordinating Center, 2010).

The variables utilized for this study included normal cognition, probable AD, the symptoms listed in the neuropsychiatric inventory questionnaire (NPI-Q) (Cummings, 1997), and APOE genotype. Normal cognition is defined as a CDR global score of zero and/or neuropsychological testing within the normal range. Sporadic late-onset AD was the outcome of interest and is referred to as probable AD throughout this study. This variable was formed through a combination of cognitive status and etiologic diagnosis (dementia and probable AD) in order to rule-out dementia due to other causes. Probable AD is diagnosed within the UDS using criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Those meeting the original 1984 NINCDS-ADRDA criteria also met the 2011 criteria (McKhann et al., 2011). The criteria is a composite and requires that a patient or subject meet the criteria for all-cause dementia. This requires an interference with usual work and activities, a decline in functioning, a rule-out of delirium and other psychiatric explanations for the cognitive presentation, and cognitive and/or behavioral impairment in at least two additional domains. Probable AD is diagnosed as the criteria for dementia is met, and the participant meets additional criterion. This criterion includes a gradual onset, demonstrable decline in cognitive presentation, and determination of amnestic, non-amnestic, or executive functioning impairment (McKhann et al., 1984).

The current study focused on behavioral symptoms on the NPI-Q (Cummings, 1997), an assessment tool, which is completed by trained health professionals. These professionals are certified as interviewers through a training mechanism administered by the University of California, Los Angeles and the NACC. Variables included in this study are the presence and absence of delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, motor disturbance, nighttime behaviors, and appetite disturbance.

APOE is measured by the presence or absence of ε4, denoted by the terms *ε4 carrier* and *non-carrier*. An ε4 carrier has the potential to possess one or two ε4 alleles, while a non-carrier possess other combinations of APOE, none of which contain ε4.