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Association Between Psychosis Phenotype and APOE Genotype on the Clinical Profiles of Alzheimer's Disease

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Abstract

Background: Psychosis is a common phenomenon in Alzheimer's disease (AD). The *APOE* $\epsilon 4$ allele is the strongest genetic risk factor for the development of AD, but its association with psychosis remains unclear.

Objective: We investigated the associations between psychosis, subdivided into delusions and hallucinations, as well as *APOE* $\epsilon 4$ allele on cognitive and functional outcomes. Secondly, we investigated the associations between *APOE* $\epsilon 4$, Lewy bodies, and psychosis.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Methods: Data from the National Alzheimer's Coordinating Center (NACC) were used. Nine hundred patients with a confirmed diagnosis of AD based on the NIA-AA Reagan were included in the analysis. Global cognition was assessed using the Mini-Mental State Exam (MMSE) and functional status was assessed using the Functional Activities Questionnaire (FAQ). Psychosis status was determined using the Neuropsychiatric Inventory Questionnaire (NPI-Q). Factorial design was used to assess the effects of psychosis and *APOE* ϵ 4, as well as their interaction.

Results: Psychosis and the presence of *APOE* ϵ 4 were both associated with lower MMSE scores, while only psychosis was associated with higher FAQ scores. Furthermore, patients with hallucinations had lower MMSE and higher FAQ scores than patients with only delusions. There was a significant interaction effect between psychosis and *APOE* ϵ 4 on MMSE scores, with *APOE* ϵ 4 negatively affecting patients with hallucinations-only psychosis. *APOE* ϵ 4 was positively associated with the presence of Lewy body pathology, and both were found to be more prevalent in psychotic patients, with a stronger association with hallucinations.

Conclusion: Psychosis in AD was associated with greater cognitive and functional impairments. Patients with hallucinations—with or without delusions—conferred even greater deficits compared to patients with only delusions. The *APOE* ϵ 4 allele was associated with worse cognition, especially for patients with hallucination-only psychosis. *APOE* ϵ 4 may mediate cognitive impairment in the hallucinations phenotype through the development of Lewy bodies. Our findings support that subtypes of psychosis should be evaluated separately.

Keywords

Delusions; hallucinations; psychosis; lewy bodies; Alzheimer's disease; *APOE*; cognition; neuropathology

1. INTRODUCTION

In addition to cognitive decline, nearly half of Alzheimer's disease (AD) patients develop psychotic symptoms over the course of the illness [1], with one in three patients developing delusions and one in six patients developing hallucinations [2]. Patients with Alzheimer's disease and psychosis may represent a distinct clinical phenotype with more adverse outcomes, including increased cognitive and functional decline, a faster disease progression, premature institutionalization, increased caregiver burden and a higher rate of mortality [3–7].

The strongest genetic risk factor for Alzheimer's disease is the Apolipoprotein E (*APOE*) gene, which has three common allelic forms: ϵ 2, ϵ 3, and ϵ 4. The ϵ 2 allele, which is rare in the population, appears to be protective [8], while inheritance of the ϵ 4 allele significantly increases the risk of Alzheimer's in a dose-dependent manner [9, 10]. One copy of the ϵ 4 allele is estimated to triple the likelihood of AD while two copies increases the likelihood by 15 times [10]. The ϵ 4 allele is believed to increase the neuropathological hallmarks of AD, including increased neurofibrillary tangles and senile plaques [11].

The impact of the *APOE* ϵ 4 allele on the risk of AD has prompted several studies to consider the relationship between *APOE* ϵ 4 and the risk of psychosis [12]. However, the results have been conflicting, with some studies reporting a positive association [13–19]

while the majority did not find any association [20–32]. Recently, the *APOE* ϵ 4 allele has been linked to the development of Lewy bodies [19, 33]. Given that Lewy body pathology is a core feature of Lewy body dementia (DLB), a dementia type where psychosis is highly prevalent, and that Lewy bodies co-occur with Alzheimer pathology 50% of the time [34], it has been speculated that *APOE* ϵ 4 promotes psychosis through the formation of Lewy bodies [19]. Overall, a consensus has yet to be reached regarding the effect of *APOE* ϵ 4 on the risk of psychosis. The variability of previous findings may stem from differences in psychosis classification, sample characteristics, and criteria used for AD diagnosis. Most studies typically group hallucinations and delusions into a broad psychosis cluster [35]. While there are benefits of combining the symptoms, including greater sample size and easier classification, there is evidence to suggest delusions and hallucinations have distinct mechanisms and neural circuitry [7]. It is conceivable that combining both forms of psychosis may confound the effects of *APOE* ϵ 4 [7]. Furthermore, *APOE* genotype may affect the sexes differently. Kim *et al.* recently found that the *APOE* ϵ 4 allele increases the risk of psychosis through the development of Lewy bodies, but the effect was female specific [19]. As such, the association may be dependent on the demographic of the sample. Moreover, most studies relied on a clinical diagnosis of AD, which is more prone to error, rather than the gold standard neuropathological diagnosis of AD. In our previous study, we found that using a clinical diagnosis can result in false associations due to the high rates of misdiagnosis [36, 37].

Previous studies typically focused on the association between *APOE* ϵ 4 and the risk of developing psychosis, but neglected to investigate how *APOE* ϵ 4 influences the clinical profiles of AD patients who develop psychosis, subdivided into those with delusions versus hallucinations. The current study investigated the relationship between the *APOE* ϵ 4 allele and psychotic symptoms, stratified into those with delusions and, or, hallucinations, on cognitive and functional outcomes in a large sample of neuropathologically confirmed AD patients. Secondly, we also investigated how *APOE* ϵ 4 and Lewy bodies may be associated with the development of psychosis.

2. METHODS

2.1. Data Source

Data from the National Alzheimer's Coordinating Center (NACC) database collected between September 2005 and December 2015 were used. The NACC database is a secondary database that pools data from past and present Alzheimer's disease Centers (ADC) in the United States that longitudinally follows subjects with AD and other dementias. This analysis used data from 34 ADCs. Each subject received standardized clinical assessment including neuropsychological screening and neurological exams. Subjects were followed approximately annually for as long as they are able and willing to participate.

2.2. Subject Criteria

We included subjects from the database with a neuropathological diagnosis of AD based on the NIA-AA Reagan criteria [38], which combines the density of neocortical neuritic

plaques (CERAD) [39] and Braak Stage for neurofibrillary tangles [40]. Subjects with an NIA-AA Reagan of “high probability of AD” were included, which corresponded to a “frequent neuritic plaque” on CERAD and Braak Stage of V or VI. Cases with discordant Braak and CERAD were excluded from analysis. Patients with a primary diagnosis of brain injury, central nervous system neoplasm, Down’s syndrome, or Huntington’s disease were excluded. *APOE* genotype was determined by the individual centers and confirmed by the Alzheimer’s Disease Genetic Consortium (ADCG). Lewy body pathology was assessed using alpha-synuclein immunohistochemistry, and Lewy body severity was classified based on the Dementia with Lewy Bodies consortium [41]. During analysis Lewy bodies was dichotomized into “yes” if Lewy bodies was present in any regions of the brain, or “no”, if there were no Lewy bodies present.

2.3. Psychosis Status Designation

The Neuropsychiatric Inventory Questionnaire (NPI-Q) completed by a caregiver was used to identify subjects who developed psychosis as well as the subtype of psychosis. Subjects with no history of psychosis were classified as the control non-psychotic group (AD–P), while subjects with any form of psychosis at any point in the illness were classified as the psychotic group (AD+P). The psychotic group was further divided into three non-overlapping subgroups: those with delusions only (AD+D), hallucinations only (AD+H), or both delusions and hallucinations (AD+DH).

2.4 Cognitive and Functional Assessment

Global cognition was evaluated using the Mini-Mental State Exam (MMSE) while functional status was measured using the Functional Activity Questionnaire (FAQ). FAQ was completed by an informant, and is negatively correlated with functional status (i.e. lower FAQ scores correspond to increased functional impairment). The clinical assessment at the last visit prior to death was used. The age of cognitive decline was based on a clinician’s assessment.

2.5. Statistical Analysis

To evaluate the influences of *APOE* $\epsilon 4$ and psychosis on MMSE and FAQ outcomes, a 2 (*APOE* $\epsilon 4$ status: yes or no) by 4 (psychosis status: never-psychotic, delusion-only, hallucination-only, or both delusions and hallucinations) independent factorial design was performed using Statistical Package for the Social Sciences (SPSS), version 21. MMSE and FAQ were entered separately as the dependent variable, while age and education were entered as covariates. Post-hoc tests were performed with the significance level set at $p = 0.05$, and multiple comparisons between all the psychosis groups were corrected with the Bonferroni method. Differences in demographic data, including age at clinical visit, age of cognitive decline, age of death, age of psychosis development, and years of education were evaluated using oneway ANOVAs (for normally distributed data) or the Kruskal-Wallis test (for non-parametric data). Independent t-tests or Mann-Whitney post hoc tests were subsequently used to further identify pairwise differences between psychosis groups. Differences in sex, Lewy bodies, and *APOE* $\epsilon 4$ allele status between psychosis groups were assessed using the chi-square test of independence for categorical variables. Statistical significance was set at $p = 0.05$. The demographic and Lewy body statistical analyses were

not corrected for multiple corrections as they were not the primary study objective. The study was approved by the St. Michael's Hospital Research Ethics Board (REB).

3. RESULTS

We identified 900 subjects from the NACC database who had confirmed AD at autopsy with *APOE* ϵ 4 status, NPI-Q, MMSE, and FAQ data (Fig. 1). The sample included 455 AD-P and 445 AD+P subjects. The AD+P group was further divided into 223 AD+D, 83 AD+H, and 139 AD+DH. The demographics of the subjects, separated based on psychosis status, are summarized in Table 1.

There were significant main effects of both psychotic status ($p < 0.001$, Fig. 2) and *APOE* ϵ 4 status ($p = 0.013$, Fig. 3) on MMSE scores, while only psychotic status had a significant effect on FAQ scores ($p < 0.001$, Fig. 4), after controlling for age and education. Both covariates were significantly related to MMSE scores ($p < 0.001$, $p = 0.022$ for age and education, respectively) but were not significant for FAQ scores. Subjects with one or more copies of the *APOE* ϵ 4 allele had lower MMSE scores than subjects without any *APOE* ϵ 4 allele (Fig. 3). Post-hoc tests for the effect of psychosis showed that AD+H and AD+DH groups had lower MMSE scores than AD-P, and AD+DH had lower MMSE than AD+D (Fig. 2). All psychotic subgroups had significantly higher FAQ scores than AD-P ($p = 0.047$ for AD+D, $p < 0.001$ for AD+H and AD+DH), with AD+H and AD+DH groups having significantly higher FAQ scores than AD+D ($p = 0.048$, $p = 0.007$, respectively; Fig. 4).

Importantly, there was a significant interaction effect between the psychosis subtype and *APOE* ϵ 4 status on MMSE scores ($p = 0.039$). Specifically, AD+H subjects' cognition was significantly more negatively affected by the presence of an *APOE* ϵ 4 allele (Fig. 5).

There was a significant difference in age of cognitive decline and the age of death between psychosis groups ($p = 0.006$ for both). Post-hoc tests showed that the AD+H group had a younger age of cognitive decline and a younger age of death compared to both the AD-P ($p = 0.003$, $p = 0.004$, respectively) and AD+D groups ($p = 0.003$, $p = 0.002$, respectively). Subjects in the AD+DH group also had a younger age of cognitive decline ($p = 0.050$) and younger age of death compared to AD+D ($p = 0.037$). There was no significant difference in the age of developing psychosis between the psychotic groups.

There was a significant positive association between the presence of *APOE* ϵ 4 allele and Lewy body pathology ($p = 0.046$). AD+P subjects had significantly more Lewy body pathology and more frequent *APOE* ϵ 4 alleles than non-psychotic subjects ($p < 0.001$, $p = 0.024$, respectively). Specifically, AD+H and AD+DH subjects had significantly more Lewy body pathology than non-psychotic subjects ($p < 0.001$, $p = 0.009$, respectively), and AD+H had significantly more Lewy body pathology than AD+D ($p = 0.036$). AD+DH subjects had significantly more frequent *APOE* ϵ 4 allele than AD-P ($p = 0.043$).

The analyses were repeated separately for each sex (male $n = 506$; female $n = 394$), and the same significant associations remained with the exception of the loss of significance of association between *APOE* ϵ 4 and Lewy body pathology due to reduction of sample size.

4. DISCUSSION

In the current study, we investigated the associations between psychosis and *APOE* $\epsilon 4$ status with cognitive and functional outcomes in a large sample of neuropathologically confirmed AD patients. We also investigated the association between *APOE* $\epsilon 4$ and Lewy body pathology. Psychosis during the course of AD was associated with greater cognitive and functional impairments. Further delineation of psychotic symptoms showed clinical differences between AD patients with delusions versus hallucinations. Specifically, patients with hallucinations, with or without the co-occurrence of delusions, showed greater cognitive and functional impairments at the last visit prior to death compared to AD patients with only delusions. Our study was novel in additionally considering the influence of *APOE* $\epsilon 4$ on clinical outcomes. We found that one or more copies of the *APOE* $\epsilon 4$ allele was associated with greater cognitive impairment across all subjects, but was not significantly associated with functional status. Interestingly, the association between *APOE* genotype and cognition was also dependent on the psychotic phenotype. Having at least one *APOE* $\epsilon 4$ allele was associated with marked detriment to the cognitive status of AD patients with hallucination-only psychosis, whereas it had little effect on other forms of psychosis and those with no psychosis (Fig. 5).

Our findings are consistent with previous studies that have reported increased cognitive and functional decline in psychotic AD patients as a whole [1–3, 42–44], and greater cognitive and functional deficits associated with hallucinations compared to delusions [6, 45, 46]. Delusions have been found to manifest earlier in the disease course than hallucinations, so it has been speculated that differences in cognitive ability dictates the form of psychosis: patients with milder cognitive decline tend to exhibit delusions while patients with more advanced cognitive impairment tend to exhibit hallucinations [46, 47]. In the current sample, patients with hallucinations were younger and had a younger age of death than non-psychotic and delusional patients, but there were no differences in the age of psychosis development. Our findings show that hallucinations do not manifest later in the disease, but do support that hallucinations appear to reflect a more advanced disease progression characterized by increased cognitive and functional impairment. Furthermore, age and education were entered as covariates into the model, which meant that cognitive and functional outcomes were not attributed to these sociodemographic variables.

Our results suggest that having one or more copies of the *APOE* $\epsilon 4$ allele was associated with exacerbated cognitive impairment, with a significantly stronger association for individuals who developed hallucinations-only psychosis. The *APOE* $\epsilon 4$ allele is one of the best-established genetic risk factors for the development of AD, but its association with psychosis within AD is conflicting. A recent review by Shah and colleagues (2017) reported that there were inconsistent findings of increased, decreased, or no association between *APOE* $\epsilon 4$ and the risk of developing psychosis [48]. In one of the largest studies to date, DeMichele-Sweet and colleagues used the NACC database to investigate the association between *APOE* $\epsilon 4$ and AD+P in 2,317 subjects, but did not find an association [49]. These conflicting results could be due to differences in the definition and subtyping of psychosis; the use of clinical versus neuropathologically confirmed AD cohorts; as well as the statistical analysis methods employed. More than half of previous studies combined

delusions and hallucinations under a broad category of psychosis [50]. Although there are benefits to this approach, including a larger sample size and the clear overlap between the two symptoms, there is evidence mounting from neuroimaging and neuropathological studies showing that they are distinct entities [7]. We found in the current study that there may be a stronger association between *APOE* ϵ 4 and hallucinations. Therefore combining delusions and hallucinations can obscure important differences between them. Moreover, the studies that did separate delusions and hallucinations had smaller sample sizes in each group. Previous studies were also mostly based on a clinical diagnosis of AD, in contrast to the current study, which used patients with a neuropathological diagnosis of AD. To our knowledge there have only been two studies that utilized neuropathologically confirmed AD cohorts. Weiner and colleagues used AD patients with a neuropathological confirmation, and found that the *APOE* ϵ 4 allele was marginally associated with delusions and hallucinations [17]. Similarly, Kim and colleagues from our lab used neuropathologically confirmed AD patients from the NACC database and found that the *APOE* ϵ 4 allele was associated with an increased risk of developing psychosis in a dose-dependent manner, but only in females [19]. In a recent study using NACC data, we showed that using a clinical diagnosis of AD can produce false associations that are driven by misdiagnosis, and that using a neuropathologically confirmed cohort would generate more accurate results [36]. Therefore, conflicting findings may reflect different approaches.

Given that psychosis, in particular hallucinations, is a prominent feature in Lewy body pathologies [51–53], it is possible that AD subjects with psychosis, especially those with hallucinations, share a common mechanism with patients with Lewy body pathologies. Fischer and colleagues previously found that psychosis in AD was not related to AD pathology load, but was related to Lewy body pathology [36]. Similarly, Sweet and colleagues also did not find an association between psychosis and AD pathology after controlling for Lewy bodies [54]. It has been previously demonstrated that the *APOE* ϵ 4 allele may mediate psychosis through the development of Lewy bodies [19, 33, 55, 56]. Chung *et al.* [33] found that having at least one *APOE* ϵ 4 allele increased the likelihood of having Lewy body pathology in addition to AD pathology, and that the presence of Lewy bodies increased the risk of, as well as the severity of, delusions and hallucinations. The authors concluded that AD patients with and without accompanying Lewy body pathology have separate phenotypes. Kim *et al.* suggested that Lewy body formation is a mediating factor between the *APOE* ϵ 4 allele and psychosis, but only in females with two copies of the ϵ 4 allele [19]. Consistent with these studies, we found that the *APOE* ϵ 4 allele was positively correlated with increased Lewy body pathology, and that both *APOE* ϵ 4 and Lewy bodies were more prevalent in patients with psychosis. Although the association between *APOE* ϵ 4 and Lewy bodies was not significant after subdividing the analysis by sex, it could be due to dichotomizing the presence of *APOE* ϵ 4 alleles rather than considering the number of copies. On the other hand, some studies have not found an association between Lewy bodies and psychiatric symptoms in AD patients [58–60]. Again, factors such as gender, combining delusions and hallucinations, and using clinical AD cohorts rather than neuropathological cohorts may contribute to the discrepancies.

Overall, our study had several strengths. We only used patients with a confirmed diagnosis of AD through neuropathological examination, and delusions and hallucinations were

analyzed separately to gain a more specific understanding of each phenotype. Also, patients were followed up approximately annually, which permitted multiple assessments of psychosis, thus allowing a more accurate categorization of their psychosis status. There were some limitations of the current study. The NACC data was pooled from multiple sites, so there can be slight deviations in the data collection between sites. Also, we did not look at symptom trajectory, but only the cognitive and functional outcomes at the last visit prior to death. Our study was also correlational in nature and does not allow for causal inferences. It would be of interest to know what the causes of death were, but unfortunately that data was not available. The NPI-Q was also limited in that it mainly probed for persecutory delusions, so other types of delusions could have been overlooked. Delusional subtype, such as persecutory delusions or misidentification delusions, may additionally have separate neurobiology. For instance, patients with misidentification delusions may have more advanced decline compared to patients with persecutory delusions [61, 62]. Lastly, the subgroups were very modest in size, especially in the AD+H group with only 83 subjects. As such, the conclusions should be taken with caution. Future studies should further explore how other genes of interest, including genes contributing to Lewy bodies, may play a role in psychosis [12]. Future studies should also explore how genetics may influence neuroimaging findings to gain a deeper understanding of the pathophysiological basis of psychosis.

CONCLUSION

In conclusion, our study confirmed that psychosis in AD is associated with greater cognitive and functional impairments at the last visit prior to death. Patients with hallucinations—with or without delusions—confer even greater deficits compared to patients with only delusions. The association between *APOE* genotype and cognition was dependent on the psychotic phenotype. The presence of one or more *APOE* ϵ 4 alleles was associated with greater cognitive impairment in individuals with hallucination-only psychosis, but had limited effect on cognition in other psychosis phenotypes. We found that *APOE* ϵ 4 was correlated with the presence of Lewy body pathology, which may be a mediating factor in psychosis. Our findings support that delusions and hallucinations in AD may represent sub-syndromes that have distinct clinical trajectories and underlying mechanisms [7, 57]. Therefore, there is a need to distinguish psychotic symptoms in evaluating and assessing patients with AD. However, disentangling them may be challenging, given that they may co-exist, or manifest during different times over the disease course

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Fig. (1).

Flow chart showing the number of cases with available data, and the breakdown into psychosis groups.

Fig. (2). MMSE scores between psychosis groups. * indicates significant difference compared to AD -P; † indicates significant difference compared to AD+D. $p < 0.05$, Bonferroni corrected. Error bars represent standard deviation.

Fig. (3). MMSE scores between subjects with and without the *APOE* ε4 allele. * indicates significant difference compared to AD-P, $p < 0.05$, Bonferroni corrected. Error bars represent standard deviation.

Fig. (4).

FAQ scores between psychosis groups. * indicates significant difference compared to AD-P; † indicates significant difference compared to AD+D. $p < 0.05$, Bonferroni corrected. Error bars represent standard deviation.

Fig. (5). Interaction between *APOE* ε4 allele and psychosis on MMSE scores. The AD+H group showed significantly poorer MMSE scores in the presence of *APOE* ε4 compared to all other subgroups. Error bars represent standard deviation.

Table 1.

Subject demographic separated by psychosis status.

Group	AD-P (n=455)		AD+P (n=445)		AD+D (n=223)		AD+H (n=83)		AD+DH (n=139)	
	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%	Mean/n	SD/%
Age	77.7	10.6	76.5	10.7	77.8	10.3	74.7 [*] †	11.0	76.0 [*]	10.9
Age of cognitive decline	69.3	10.6	68.2	10.8	69.6	10.4	66.2 [*] †	10.7	67.6 [†]	11.0
Age of death	79.1	10.4	78.2	10.8	79.5	10.3	76.2 [*] †	11.1	77.5 [†]	10.9
Age convert to psychosis			76.9 (51.2% of valid cases)	10.8	77.3 (54.8% of valid cases)	10.9	74.7 (53.3% of valid cases)	11.1	78.0 (44.4% of valid cases)	10.4
Education	15.4	3.1	15.0	3.2	15.1	3.1	15.2	2.7	14.5	3.7
Male	264	58.0%	242	54.4%	121	54.3%	51	61.4%	70	50.4%
MMSE	14.6	8.2	11.7 [*]	7.9	13.1	7.7	10.1 [*]	8.7	10.3 [*] †	7.3
FAQ	23.7	8.0	26.1 [*]	5.8	25.2 [*]	6.5	27.3 [*] †	5.6	27.5 [*] †	4.9

* significant compared to AD-P (p<0.05)

† significant compared to AD+D (p<0.05)