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Influence of APOE genotype in primary age-related tauopathy

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Abstract

The term “Primary age-related tauopathy” (PART) was coined in 2014 to describe the common neuropathological observation of neurofibrillary tangles without associated beta-amyloid (Aβ) pathology. It is possible for PART pathology to be present in both cognitively normal and cognitively impaired individuals. Genetically, Apolipoprotein E (APOE) ε4 has been shown to occur less commonly in PART than in Alzheimer’s disease (AD). Here, we investigate the relationships between PART, AD and those pathologically normal for age, with an emphasis on APOE and cognition, using 152 selected participants from The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age and the Manchester arm of the Brains for Dementia Research cohort. APOE genotype differed between PART and AD with APOE ε2 more common in the former and APOE ε4 more common in the latter. Individuals with definite PART were less likely to be cognitively impaired than those with AD and those with pathology considered pathologically normal for age. We postulate that the lack of Aβ in definite PART cases may be due either to an increased frequency of APOE ε2 or decreased frequency of APOE ε4 as their resulting protein isoforms have differing binding properties in relation to Aβ. Similarly, an increased frequency of APOE ε2 or decreased frequency of APOE ε4 may lead to decreased levels of cognitive impairment, which raises questions regarding the impact of Aβ pathology on overall cognition in elderly subjects. We suggest that it may be possible to use the increased frequency of APOE ε2 in definite PART to assist neuropathological diagnosis.

Keywords: Primary age-related tauopathy, Alzheimer’s disease, APOE, Cognition

Introduction

For many years, neuropathologists have observed neurofibrillary tangles (NFTs) without associated beta-amyloid (Aβ) pathology in the brains of aged individuals both with and without cognitive impairment. NFTs are almost ubiquitous in the brains of older people [22]. Significant tau burden (Braak tau stage III-IV) but few Aβ plaques have been observed in 2–10% of individuals in community-based settings [15, 21, 29]. The inability to assign a diagnosis of Alzheimer’s disease (AD) to cognitively impaired individuals with these findings led to terms such as “senile dementia with tangles” or “tangle-only dementia” [11]. In those cognitively intact, “age-related changes” were often cited. To address this phenomenon, the term “primary age-related tauopathy” (PART) was suggested and consensus guidelines on diagnosis were proposed [6].

PART has been shown to be equally as common in males and females [8]. Although cognitive impairment can be present or absent in PART, the age group primarily affected (over 75 years) commonly report subjective memory issues. However, these memory complaints generally do not progress to dementia in those with a post-mortem diagnosis of PART [16].
PART is primarily diagnosed post-mortem. Macroscopically, no significant brain abnormalities are usually present although widespread cerebral atrophy has been documented in some cognitively impaired cases [1]. Microscopically, NFTs are found in similar regions to those affected by AD but with the notable exception of the neocortex. Thus, those with PART are generally considered Braak tau stage III or lower. For PART diagnosis, Aβ load should be minimal (or absent). A maximum Thal phase of 2 is required. Stratification into ‘possible PART’ and ‘definite PART’ is based on the level of Aβ burden (Table 1). Secondary pathologies have been noted in PART including cerebrovascular pathology [12], argyrophilic grains, hippocampal sclerosis, and TAR DNA-binding protein 43 (TDP-43) [13, 37]. Other secondary findings in PART, such as cerebral amyloid angiopathy (CAA) [12] and Lewy bodies [13] are less common. The presence of co-existing pathologies are unsurprising as mixed brain pathologies are often found in aged individuals [14].

It is well known that apolipoprotein E (APOE) ε4 carriers are at a greater risk of AD [32] whereas APOE ε2 carriers are thought to be at lower risk of AD [27] but at a greater risk of CAA–related haemorrhage [18]. Previous studies have shown that APOE ε4 is less frequently found in PART when compared to AD [2, 3, 6, 36]. Conversely, APOE ε2 has been shown to be more common in PART when compared to AD [3, 6]. Other studies have shown that microtubule associated protein tau (MAPT) H1/H1 haplotype is more commonly found in PART than in AD [28].

Here, using selected participants from The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age (UMLCHA) and the Manchester arm of the Brains for Dementia Research (BDR) cohort, we investigate the relationships between PART, AD and those pathologically normal for age, with an emphasis on APOE and cognition. We demonstrate that APOE genotype differs between PART and AD with APOE ε2 more common in the former and APOE ε4 more common in the latter. Furthermore, we show that individuals with definite PART were less likely to be cognitively impaired than those with AD and those with pathology considered pathologically normal for age implying that Aβ load may impact on cognitive outcome.

**Materials and methods**

**Participants and study design**

The present study uses selected participants from UMLCHA and the Manchester arm of the BDR cohort. Clinical and neuropathological characteristics of these cohorts have been previously described [24–26].

As the present study aims to assess relationships between AD, PART and those considered pathologically normal for age, there was a need to exclude a number of participants from each cohort (BDR 84 excluded; UMLCHA 54 excluded). The following exclusion criteria were applied to ensure suitability:

- Participants with primary neuropathological diagnosis other than AD, PART or pathologically normal for age
- Participants with significant confounding pathology (such as Lewy bodies). Note that cases with CAA were included in the analyses.
- Participants with no available APOE genotype
- Participants with a high probability of cognitive impairment due to vascular pathology (as measured by vascular cognitive impairment neuropathology guidelines [31]).

After applying the exclusion criteria, 152 participants (72 BDR and 80 UMLCHA) were considered eligible for the present study (Additional file 1: Table 1).

**Clinical assessment**

The two cohorts conducted different assessment schedules to assign cognitive status. UMLCHA used the modified Telephone Instrument for Cognitive Status (TICSm) score with a cut-off point of 21 and BDR used the Clinical Dementia Rating (CDR) with a cut-off point of 0.5. Scores for TICSm and CDR have been shown to be highly correlated [30]. For the present study, we also used patient notes obtained via the participants’ general practitioner, cause of death (on death certification) and information gained from Brain Bank Coordinator (PT) to ensure the

### Table 1  Inclusion criteria for the four groups used in the present study

| Study group                  | Characteristics for inclusion                          |
|------------------------------|--------------------------------------------------------|
| Normal pathology for age     | Braak stage 0                                          |
|                              | Thal phase 0–1                                         |
|                              | No other significant pathological changes               |
| AD pathological changes      | Braak stage III or higher                              |
|                              | Thal phase 3 or higher                                  |
|                              | No other significant pathological changes               |
| Possible PART                | Braak stage III or lower                                |
|                              | Thal phase 1–2                                         |
|                              | No other disease associated with NFTs present           |
| Definite PART                | Braak stage III or lower                                |
|                              | Thal phase 0                                           |
|                              | No other disease associated with NFTs present           |

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assignment of cognitive status at death was as accurate as possible.

**Pathological methods**
The pathological methods associated with these cohorts have been previously described in detail [25, 26].

In short, donated brains were cut down the mid-line to result in two hemispheres. One hemisphere (usually the left) was fixed in 10% neutral buffered formalin for at least three weeks. The other hemisphere was frozen at −80 °C.

Standard blocks were dissected from fixed tissue (as according to BDR protocols) and processed into paraffin wax blocks. One paraffin section (6 µm) was cut from each block and stained with haematoxylin and eosin. Furthermore, paraffin sections (6 µm) were cut and used in immunohistochemistry for Aβ (Cambridge Bioscience, clone 4G8, 1:3000), tau proteins phosphorylated at Ser202 and Thr205 (Innogenetics, monoclonal AT8, 1:750), phosphorylated α-synuclein (polyclonal antibody (#1175), 1:1000 [23]), phosphorylated and non-phosphorylated TDP-43 (Proteintech, polyclonal antibody, 1:1000) and p62 (BD Transduction Labs, monoclonal, 1:100). For antigen retrieval, sections were either immersed in 70% formic acid for 20 min (for Aβ only) or microwaved in 0.1 M citrate buffer, pH 6.0 (all other antibodies) prior to incubation with primary antibody.

Consensus criteria were used to ascertain presence and stage of neurodegenerative disease. Final neuropathological diagnoses were assigned by experienced neuropathologists (DM & FR).

**Study group assignment**
Criteria for inclusion into the four study groups included in this study can be found in Table 1.

**Genetic analysis**
DNA was extracted from frozen brain tissue using REDExtract-N-Amp™ Tissue PCR Kit (Sigma) or from blood (3 cases). The APOE genotype was determined using routine polymerase chain reaction methods [34].

**Statistical analyses**
Chi squared test was used to analyse whether there were differences in sex, severity of CAA, frequency of APOE ε4 allele(s) and frequency of APOE ε2 allele(s) between allocated pathology groups. Fisher’s Exact test was used when the expected count was less than five. T test assessed differences in age at death.

Logistic regression was used to investigate whether adjustment for sex and age at death made any difference to significant outcomes when analysing presence of APOE ε4 allele(s) and presence of APOE ε2 allele(s) between allocated pathology groups.

A p value of <0.05 was considered significant.

**Results**

**Demographics**
Demographic information, stratified by pathology group, can be found in Table 2. Overall, 61.2% of participants were female. 50% of all participants were cognitively impaired. Mean age at death was 84.4 (±9.2) years.

There was a significantly greater proportion of females in the possible PART group compared with the AD pathological changes group (χ²=3.848; p=0.050) and the definite PART group (χ²=5.771; p=0.016). As expected, there was a significantly greater proportion of cognitively impaired individuals in the AD pathological changes group when compared with the pathologically normal for age group (χ²=17.388; p<0.001), the possible PART group (χ²=32.395; p<0.001) and the definite PART group (χ²=51.119; p<0.001). Likewise, there were significantly more cognitively impaired individuals in the possible PART group when compared with the definite PART group (χ²=5.819; p=0.016). There were also significantly more cognitively impaired participants in the pathologically normal for age group when compared with the definite PART group (χ²=7.407; p=0.006).

Mean age at death was significantly higher in the possible PART group compared with the pathologically normal for age group (p=0.037) and the AD pathological changes group (p=0.001). Similarly, mean age at death was significantly higher in the definite PART group compared with the AD pathological changes group (p=0.015).

**Table 2** Demography of eligible cases stratified by pathology group

|                        | Normal for age | AD pathological changes | Possible PART | Definite PART |
|------------------------|----------------|-------------------------|---------------|---------------|
|                        | n   | %       | n     | %     | n  | %     | n   | %    |
| Sex (female)           | 9   | 60.0    | 49    | 59.0  | 23 | 79.3  | 12  | 48.0 |
| Cognitive impairment at death | 4   | 26.7    | 66    | 79.5  | 6  | 20.7  | 0   | 0    |
| Age at death (Mean ± s.d) | 79.7 (± 14.1) | 83.0 (± 9.2) | 88.3 (± 6.1) | 87.1 (± 6.4) |
CAA
In the AD pathological changes group, 45.8% of individuals had moderate to severe CAA pathology. In the PART pathology groups, moderate to severe CAA was much less prevalent (possible PART 20.7%; Definite PART 4%) and was completely absent from those considered pathologically normal for age. Proportionally, moderate to severe CAA was significantly more likely in with AD pathological changes than those with possible PART ($\chi^2 = 5.674; p = 0.017$) or definite PART ($\chi^2 = 14.539; p < 0.001$). There were no differences in severity of CAA between possible and definite PART groups ($\chi^2 = 3.315; p = 0.069$).

APOE genotype
Breakdown of APOE genotype can be found in Fig. 1.

As expected, APOE 3,3 was the most common genotype (55.3%). When stratifying by group, APOE 3,3 was the most common genotype in the pathologically normal for age (60.0%), possible PART (82.8%) and definite PART (68.0%) groups. All cases of APOE 4,4 were found in the AD pathological changes group. In addition, 39.8% of cases in the AD pathological changes group were APOE 3,4. The genotype APOE 2,4 was only present in the AD pathological changes group.

Allele frequency of APOE ε4/APOE ε2, stratified by pathology group, can be found in Fig. 2.

The APOE ε4 allele appeared more frequently in the AD pathology group when compared with those pathologically normal for age ($\chi^2 = 6.803; p = 0.009$), those with possible PART ($\chi^2 = 20.547; p < 0.001$) and those with definite PART ($\chi^2 = 17.297; p < 0.001$).

APOE ε2 allele was found more frequently in the pathologically normal for age group when compared with the AD pathology group ($\chi^2 = 4.957; p = 0.026$). Likewise, APOE ε2 allele was more frequent in the definite PART group when compared with the AD pathology group ($\chi^2 = 7.327; p = 0.007$).

Regression analysis showed that sex and age at death had no effect on the outcome of significant results found for presence of APOE ε4 when comparing AD pathology group with pathologically normal for age group (OR = 5.928, p = 0.011), possible PART group (OR = 0.071; p = 0.001) and definite PART group (OR = 0.081; p = 0.001). Likewise, controlling for sex and age at death had no effect on the significant outcome found for presence of APOE ε2 when comparing definite PART group and AD pathology group (OR = 4.196; p = 0.032). However, sex and age at death affected the significant outcome found for presence of APOE ε2 when comparing pathologically normal for age group and AD pathology group (OR = 0.304; p = 0.113).

When considering CAA, the APOE ε4 allele was found more frequently in those individuals with moderate to severe CAA ($\chi^2 = 17.778; p < 0.001$) than none to mild CAA. There was no such difference when applying the same analysis to those with the APOE ε2 allele.

Discussion
Our results show that the APOE ε2 allele appeared significantly more frequently in those found to be definite PART when compared with those who had AD pathological changes at death. Conversely, the APOE ε4 allele was more frequently found in those with AD pathological changes when compared with possible PART, definite PART or those pathologically normal for age. Present data are consistent with an earlier, less extensive study which pre-dates the inception of PART consensus criteria [9] and also a more recent study on individuals older than 85 years of age at death [3].
Previous studies have shown average age at death of those with PART to be higher than those with AD pathology [12]. Here, we show that, although those with AD pathological changes died at a younger age than those with PART changes, the difference was not statistically significant. This is probably due to different recruitment strategies of the two cohorts with BDR being case/control and UMCHA more community or population based. These differences have been discussed in an earlier publication [26].

Cognitive impairment due to PART pathology is not yet fully understood. The majority of those with PART diagnosed post-mortem are considered to be non-demented [16] and it is thought that cognitive impairment is mainly associated with very severe PART pathology [6]. We show that cognitive impairment was only found in 20% of individuals with possible PART and was completely absent in those considered definite PART. Interestingly, there were significantly more individuals with cognitive impairment in the pathologically normal for age group when compared with those in the definite PART group. One interpretation could be statistical ‘noise’, though at p = 0.006, this would be unlikely. Another could be the inclusion of individuals at Thal phase 1, which reflects cortical Aβ pathology at its earliest stage, in the pathologically normal for age group as cognitive impairment can be apparent in individuals with a low burden of Aβ pathology [35]. This finding could also be due to the increased frequency of APOE ε2 in the definite PART group when compared with the pathologically normal for age group. It is worthy of note that our group has recently shown that carrying APOE ε2 may increase the chances of remaining cognitively normal [27].

The role of APOE ε4 as a risk factor for AD has been known for many years [4, 32] as has the role of APOE ε2 as a protective agent against AD [5]. APOE ε4 carriers are more likely to have significant Aβ load [20] whereas APOE ε2 carriers have a reduced Aβ burden [7]. Hence, in the present study, those with classic AD pathological changes (tau and Aβ) were more likely to carry APOE ε4 whereas those with definite PART were more likely to carry APOE ε2 and, thus, show no Aβ pathology.

This raises the question of what influence (if any) APOE ε2 has on the disease process. By definition, there is a lack of Aβ in PART and it is possible that APOE ε2 has an effect on amyloidogenesis or clearance of Aβ [17]. Likewise, it is also possible that the lack of Aβ in PART may be due to an absence of APOE ε4, which is known to strongly facilitate the deposition of Aβ [19], rather than the presence of APOE ε2, which may simply have a ‘neutral’ effect. However, a recent study [10] has shown that Aβ levels in those with APOE 2,4 genotype increased at half the rate with respect to increasing age when compared with those with APOE 3,4 which suggests that APOE ε2 has an effect on Aβ deposition even in those with a coexisting APOE ε4 allele. If APOE ε2 does in fact play a part, it may prevent deposition of Aβ by binding and stabilising it in brain parenchyma or vessels. If Aβ is excreted from the brain via perivascular channels and the role of APOE ε4 protein is to stabilise Aβ within the brain tissue and vessels, then the lack of Aβ in brain tissue in those with APOE ε2 ought to result in low levels of CAA. Here, we show that this is the case as those with APOE ε4 were more likely to have moderate to severe CAA whereas there was no such difference when applying the same analysis to those with the APOE ε2.

Another potential role for APOE could be the facilitation of NFTs in PART. Work using induced pluripotent stem cells which were differentiated into cultures of forebrain excitatory neurons has already shown that the presence of APOE ε4 can speed up the spread of tau pathology [33]. Another study has shown that the APOE ε2 allele is associated with a greater tau burden in brains with progressive supranuclear palsy (PSP) and that those with APOE ε2/ε2 genotype were found to have increased risk of PSP and corticobasal degeneration [38]. However, we have shown a lack of NFTs in those considered pathologically normal for age with APOE ε2 which would argue against such a role. Hence, the role of APOE ε2 seems to be restricted to any influence it may have over Aβ deposition. Although NFTs and Aβ coexist in AD, it is clear that Aβ is not (always) a prerequisite for NFT formation as, in PART, NFTs can occur independently of Aβ deposition. It is possible that, even in AD, the two pathological events are coincidental rather than causal.

Conclusions

The differences in APOE allele frequency between the groups in the present study supports the conclusion that PART and AD are distinct entities. We show that those with definite PART are significantly more likely to carry APOE ε2 allele(s) and be considered cognitively normal at death compared to those with AD pathological changes. In addition, those with possible/definite PART are less likely to carry APOE ε4 allele(s) than those with AD pathological changes. We postulate that the lack of Aβ in definite PART cases may be due either to an increased frequency of APOE ε2 (or decreased frequency of APOE ε4) in these cases. Similarly, an increased frequency of APOE ε2 (or decreased frequency of APOE ε4) leads to decreased levels of cognitive impairment, which raises questions regarding the impact of Aβ pathology on overall cognition in elderly subjects. It may be possible to use the increased frequency of APOE ε2 in definite PART to assist neuro-pathological diagnosis.
Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s40478-020-01095-1.

Additional file 1. Table 1. Neuropathological overview of the 152 eligible participants. Description of data: Breakdown of neuropathological findings which was used to determine pathology groups for the present study. (XLSX 23 kb)

Abbreviations
AJ: Juxtamyloid; AD: Alzheimer’s disease; APOE: Apolipoprotein E; BDR: Brains for Dementia Research; CAA: Cerebral Amyloid Angiopathy; CDR: Clinical dementia rating; MAPT: Microtubule associated protein tau; NFTs: Neurofibrillary tangles; PART: primary age-related tauopathy; PSP: Progressive Supranuclear Palsy; TDP-43: TAR DNA-binding protein 43; TICSm: Modified Telephone Instrument for Cognitive Status; UMLCHA: The University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age.

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Authors’ contributions
AR devised and designed the study, performed all statistical analysis and wrote the paper. YD performed immunohistochemistry and assisted with preparation of the manuscript. FR finalised neuropathological diagnosis and assisted with preparation of the manuscript. JM performed immunohistochemistry and assisted with preparation of the manuscript. PT provided clinical data for BDR cohort. MH helped to finalise clinical cognitive impairment diagnosis and provided clinical data for UMLCHA cohort. AP assisted with preparation of the manuscript. NP finalised clinical cognitive impairment diagnosis and provided clinical data for UMLCHA cohort. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by Manchester Brain Bank Management Committee (REC reference 19/NE/0242). Under conditions agreed with the Research Ethics Committee, The Manchester Brain Bank can supply tissue or data to researchers, without requirement for researchers to apply individually to the REC for approval.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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