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Pathologic correlates of aging-related tau astrogliopathy: ARTAG is associated with LATE-NC and cerebrovascular pathologies, but not with ADNC

Yuriko Katsumata[1,2], **Xian Wu**[1,2], **Khine Zin Aung**[1,2], **Kathryn Gauthreaux**[3], **Charles Mock**[3], **Shelley L. Forrest**[4,5], **Gabor G. Kovacs**[4,5], **Peter T. Nelson**[1,6]

[1]Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, 40506

[2]Department of Biostatistics, University of Kentucky, Lexington, KY, 40506

[3]National Alzheimer's Coordinating Center, Department of Epidemiology, University of Washington, Seattle, WA, 98105

[4]Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Canada

[5]Laboratory Medicine Program and Krembil Brain Institute, University Health Network, Toronto, Canada.

[6]Department of Pathology, Division of Neuropathology, University of Kentucky, Lexington, KY

Abstract

Age-related tau astrogliopathy (ARTAG) is detectable in the brains of over one-third of autopsied persons beyond age 80, but the pathoetiology of ARTAG is poorly understood. Insights can be gained by analyzing risk factors and comorbid pathologies. Here we addressed the question of which prevalent co-pathologies are observed with increased frequency in brains with ARTAG. The study sample was the National Alzheimer's Coordinating Center (NACC) data set, derived from multiple Alzheimer's disease research centers (ADRCs) in the United States. Data from persons with unusual conditions (e.g. frontotemporal dementia) were excluded leaving 504 individual autopsied research participants, clustering from 20 different ADRCs, autopsied since 2020; ARTAG was reported in 222 (44.0%) of included participants. As has been shown previously, ARTAG was increasingly frequent with older age and in males. The presence and severity of other common subtypes of pathology that were previously linked to dementia were analyzed, stratifying for the presence of ARTAG. In logistical regression-based statistical models that included age and sex as covariates, ARTAG was relatively more likely to be found in brains with limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), and in brains with comorbid cerebrovascular pathology (arteriolosclerosis and/or brain infarcts). However, ARTAG was not associated with severe Alzheimer's disease neuropathologic change (ADNC), or primary age-related tauopathy (PART). In a subset analysis of 167 participants with neurocognitive testing data, there was a marginal trend for ARTAG pathology to be associated with cognitive impairment as assessed with MMSE scores (P=0.07, adjusting for age, sex, interval

Correspondence: Peter T. Nelson MD PhD, Rm 575 Lee Todd Bldg, University of Kentucky, 789 S. Limestone Ave., Lexington, KY 40536, Telephone # (859) 218-3862, pnels2@email.uky.edu.

between final clinic visit and death, and ADNC severity). A limitation of the study was that there were missing data about ARTAG pathologies, with incomplete operationalization of ARTAG according to anatomic region and pathologic subtypes (e.g., thorn-shaped or granular-fuzzy astrocytes). In summary, ARTAG was not associated with ADNC, whereas prior observations about ARTAG occurring with increased frequency in aging, males, and brains with LATE-NC were replicated. It remains to be determined whether the increased frequency of ARTAG in brains with comorbid cerebrovascular pathology is related to local infarctions or neuroinflammatory signaling, or with some other set of correlated factors including blood-brain barrier dysfunction.

Keywords

Astrocytes; MAPT; Aging; Tauopathy; Amygdala; Small vessel disease; Stroke; Infarction; VCID; Thorn-shaped astrocytes

1. Introduction

Age-related tau astrogliopathy (ARTAG) is a common pathologic feature of brain aging (Di et al., 2023; Iida et al., 2021; Kovacs et al., 2016; Kovacs et al., 2017c; Resende et al., 2020; Yagita et al., 2022). The diagnostic hallmark of ARTAG is phosphorylated tau protein (pTau)-immunoreactive inclusions within astrocytes (Kovacs et al., 2016; Kovacs et al., 2017c). Tau-immunoreactive astrocytes in ARTAG may display a range of histomorphologic appearances, including so-called thorn-shaped astrocytes in subpial, subependymal, and white matter regions (Ikeda et al., 1998; Ikeda et al., 1995; Schultz et al., 2004). Other subtypes of ARTAG include “granular-fuzzy astrocytes” and astrocytic pTau aggregates that can be seen in gray matter (Kovacs et al., 2016).

Much remains to be learned about ARTAG, including the clinical-pathological correlations (Iida et al., 2021; Robinson et al., 2018). No clinical biomarker is currently known to reliably identify individuals with ARTAG during life and the pathogenetic mechanism(s) that underlie ARTAG are largely unknown. In the present study, we focused on the pathological correlates of ARTAG.

Pathologic lesions in aging brains often occur in combinations—pathologically “pure” (only a single lesion-type represented) patterns of brain pathology are relatively unusual in persons beyond age 80(Jellinger, 2022; Kapasi et al., 2017; Kovacs et al., 2013; McAleese et al., 2016). Different pathologic comorbidities may either synergize with each other (one pathology exacerbating the other) or else may be caused by common “upstream” factors wherein both pathologies may result from shared original cause(s), such as genetic or environmental factors (Chornenkyy et al., 2019). On the other hand, some common mixed pathologies can be observed in the same brain coincidentally after having developed independently. Teasing out the various complex pathoetiological mechanisms requires a broad repertoire of experimental systems, but primarily, relevant insights must be gathered from autopsy cohort studies to analyze clues about how the different lesion subtypes correlate with each other in the aging human brain.

A specific context where astrocytic pTau pathology can be seen is in brains affected by traumatic brain injury (TBI) and/or chronic traumatic encephalopathy (CTE) (Bachstetter et al., 2021; Bieniek et al., 2021; Forrest et al., 2019; McKee et al., 2009). This establishes that environmental influences (specifically mechanical trauma) can cause ARTAG-like pathological phenomena. However, the main pathological hallmark of TBI/CTE appears to be intraneuronal, rather than intra-glial pTau lesions(Butler et al., 2022).

Open questions remain about other pathological correlates between ARTAG and common neurodegenerative pathologies, e.g., tauopathies such as Alzheimer's disease neuropathologic change (ADNC) (Montine et al., 2012) and primary age-related tauopathy (PART) (Crary et al., 2014). Other common proteinopathies include Lewy body diseases (LBD) (Attems et al., 2021) and limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) (Nelson et al., 2019). Indeed, a recent study on 101 individuals from a European ageing community-dwelling cohort demonstrated an association of LATE-NC with the presence of subpial, subependymal, and perivascular ARTAG (Forrest et al., 2022). Importantly, cognitive decline is not only linked to neurodegenerative proteinopathies. There are also multiple subtypes of cerebral vascular pathologies (Skrobot et al., 2016), which reflect ischemia, metabolic insufficiency, hemorrhage, and/or neuroinflammation, and can have a strong influence on neurological function. Whereas many of these pathologies have been shown to have synergistic influence on each other, and/or common upstream risk factors, their dispositions with regard to the presence or absence of ARTAG are incompletely characterized to date.

Here we analyzed data relating to pathologic correlates of ARTAG in the National Alzheimer's Coordinating Center (NACC) data set. This publicly available data storage and dissemination resource includes anonymized information that has been aggregated from the US National Institute on Aging–funded Alzheimer's Disease Research Centers (ADRCs). Contributory ADRCs vary in their recruitment practices and assessment protocols while providing standardized assessment instruments. In the participants with any ARTAG workup data available, the presence or absence of ARTAG was tested for associations with the presence and severity of other subtypes of pathology that were previously linked to dementia. Factoring in relevant covariates such as sex and age at death, we found that ARTAG was positively associated with LATE-NC and cerebrovascular pathologies, but not with the other common age-related tauopathies, ADNC or PART.

2. Methods

2.1. Study participants

Participants were assessed using the standardized NACC Uniform Data Set (UDS) (Beekly et al., 2007; Besser et al., 2018a) at their local ADRC approximately annually, including participant demographics, health history, physical and neurological exams, and AD and related dementias symptomology. Standardized data collected on neuropathological features present at the time of death are available for participants who were assessed with the UDS and who consented to autopsy (Besser et al., 2018b; Mock et al., 2020). Participants who met the study's eligibility criteria were selected from the June 2023 (NACC62) data freeze. These were restricted to participants who died and underwent autopsy since 2020

(when ARTAG data collection was started in the NACC dataset). In the analyzed sample, we excluded participants who had at least one rare disease (e.g., frontotemporal lobar degeneration [FTLD], multiple system atrophy [MSA], and others) shown in Supplementary Table 1 and included those with autopsy data available. We further limited to ADRCs with ≥2 eligible participants with autopsy confirmed (and reported to NACC) ARTAG (Supplementary Table 2). Because the focal point of the current study was on common aging-related conditions, we limited the sample to individuals beyond age 60 at death.

2.2. Neuropathology data

ARTAG data were provided from a subset of the ADRCs after that parameter was included starting in 2020 (NACC Neuropathology (NP) Data Set v11). The ARTAG related variables includes the presence ARTAG with 0 = no and 1 = yes (the variable name in NACC NP v10 dictionary is NPARTAG), severity of ARTAG with 1 = mild, 2 = moderate, and 3 = severe (NPATGSEV), and anatomical localizations of ARTAG in amygdala and/or frontal neocortex (NPATGAMY with 0 = no and 1 = yes and NPATGFRN with 0 = no and 1 = yes). Specifically subtyped (i.e., subpial, subependymal, perivascular, white and gray matter) ARTAG neuropathology data are only from the amygdala and frontal cortex in this data set. Tau NFTs was operationalized according to Braak NFT stages (Braak and Braak, 1991) and categorized into four (Stage 0, Stage I or II, Stage III or IV, and Stage V or VI). Regional progression of amyloid plaques was represented by four categorized Thal Phase ratings (Phase 0, Phase 1-2, Phase 3, and Phase 4-5) (Thal et al., 2002). Density of neocortical neuritic plaques were based on Consortium to Establish a Registry for Alzheimer's Disease (CERAD) ratings (none, sparse, moderate, and frequent) (Mirra, 1997; Mirra et al., 1991). TDP-43 neuropathologies were specified in three brain regions: amygdala, entorhinal/inferior temporal cortex and/or hippocampus, and neocortex. Lewy body pathology (LBP) data were dichotomous with 0 = none and 1 = present. For cerebrovascular pathologies, data were available on cerebral amyloid angiopathy (NACCAMY) (none, mild, moderate, and severe), arteriolosclerosis (NACCARTE) (none, mild, moderate, and severe), infarcts and lacunes (NPINF) (no and yes), microinfarcts (NACCMICR) (no and yes).

2.3. Associations between ARTAG and cerebrovascular/cardiovascular risk factors

Diabetes was defined as 0 = no and 1 = yes using any history of diabetes from the participants' health history and the clinician-assessed medical conditions forms (DIABETES and DIABET) and a history of antidiabetic medication (NACCDBMD) at the last NACC UDS visit. Hypertension and hypercholesterolemia conditions were determined in the similar way with diabetes using five variables for hypertension (HYPERTEN, HXHYPER, HYPERT, NACCAHTN, and NACCHTNC) and three variables for hypercholesterolemia (HYPCHOL, HYPCHOL, and NACCLIPL), respectively. Any history of heart attack/cardiac arrest (CVHATT, 0 = no and 1 = yes) was measured in the subject health history and congestive heart failure (CONGHRT, 0 = no and 1 = yes) present was measured in the clinician-assessed medical conditions form.

2.4. Cognitive tests

Cognitive test scores at the last visit were drawn from the NACC Uniform Data Set (UDS) (Weintraub et al., 2009), including Mini Mental State Examination (MMSE) (Folstein et

al., 1975), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Animal and Vegetable Naming (Morris et al., 1989), Wechsler Memory Scale-Revised (WMS-R) Logical Memory – immediate and delayed (Wechsler, 1987), Craft Story 21 Recall – immediate and delayed (Craft et al., 1996), and Digit span forward and backward trials(Richardson, 2007). Since the MoCA, Craft Story 21 Recall – immediate and delayed, and Number Span Test: Forward and Backward were introduced in the NACC UDS version 3 from March 2015, replacing MMSE, WMS-R Logical Memory – immediate and delayed, and Digit span forward and backward trials, we transformed the new battery scores into equivalent old battery scores based on Monsell and colleagues' crosswalk study (Monsell et al., 2016). We included participants who had these cognitive test scores at the last visit measured within 6 years before death.

2.5. Statistical analysis

All statistical analyses were conducted in R version 4.2.1(R Core Team, 2021). We estimated odds ratio (OR) and its 95% confidence interval (CI) to examine the associations of NP and CVD risk factors with the ARTAG binary outcomes (i.e., NPARTAG with 0 = no and 1 = yes) using a logistic regression with covariates. We ran two logistic regression models with different set of the covariates: (1) adjusted for age at death and sex (Model 1); (2) additionally adjusted for the number of *APOE* ε4 alleles and Braak NFT stage with four response categories (Model 2). The second model was built to remove ADNC effects. For examining the association between cognitive test scores and ARTAG, we also included time-interval between the last visit and death as a covariate in both the models.

3. Results

After exclusions were applied, the final analytic sample included 504 participants sourced from 20 ADRC autopsy cohorts. The mean age at death was 82.7 years (standard deviation (SD) = 9.9), the mean of years in education was 16.7 (SD = 7.9), and 53.4% were females. 36.2% had one ε4 allele and 9.2% had two ε4 alleles (Table 1). More than half of the participants had severe ADNC (Braak NFT stages V or VI) and ~90% had any Aβ plaques, ~80% Thal Aβ phase 3 or higher (Table 2). Approximately one-third of included participants (~35%) had TDP-43 pathology in amygdala, hippocampus, and/or entorhinal cortex (Table 2).

The focus of the study was on ARTAG – astroglial pTau pathology – of which photomicrographs are depicted in Figure 1; any detected positive ARTAG in the brain was considered to be a positive case (the subtypes are described in Supplemental Table 3). Among included participants, 222 (44.0%) had autopsy-confirmed ARTAG (NPARTAG=1). These cases were derived from 20 different ADRCs (Supplementary Table 2). The median number of ARTAG cases per ADRC was 9.5; range 2-28 ARTAG cases per ADRC. The median number of controls per ADRC was 10.5; range 1-28 non-ARTAG controls per ADRC. There were trends for ARTAG to become more common in advanced age, and it was relatively frequently observed in males (Figure 2). For all subsequent analyses, we ran separate logistic regression models, factoring in at least age and sex as covariates, for each of the pathologies as an independent variable.

Table 3 shows that the associations of the presence or absence of ARTAG with other neuropathologies, adjusted for age at death and sex (these covariates were necessary as shown in the data in Figure 2). TDP-43 pathology observed in amygdala and neocortex were significantly associated with ARTAG when adjusting for age at death and sex (OR >2 for each). Relative to LATE-NC Stage 0 (no detected TDP-43 pathology), LATE-NC stages 1, 2, and 3 each showed association with the presence of ARTAG. By contrast, the same model did not detect associations between ARTAG and ADNC or LBD pathologies.

We also observed the significant associations between cerebrovascular pathologies and ARTAG (Table 4). Here we included a model that factored in ADNC because there have been shown to be synergies between ADNC and cerebrovascular pathologies—thus Model 1 adjusted for age at death and sex whereas Model 2 additionally adjusted for the number of the *APOE* ε4 alleles and three categorized ("B") Braak NFT stages. The significant association with infarcts and lacunes were robust (OR = 1.83 and 95% CI = 1.10 – 3.06 in Model 1 and OR = 2.19 and 95% CI = 1.28 – 3.82 in Model 2).

Since ARTAG and ADNC stand as separate from PART, and the three together constitute the major three subtypes of aging-related tauopathy, we performed a separate analysis of the association between PART severity (Braak stages I/II vs III/IV in cases lacking amyloid plaques) and ARTAG. In the participants who had probable PART, Braak NFT scores as operationalized above were not significantly associated with ARTAG (Table 5).

Although the main focus of the present study was on pathological (ARTAG)-pathological comorbidity associations, we also performed additional association tests between clinical parameters with eventual ARTAG diagnosis at autopsy. We first evaluated the associations between cardiovascular risk factors with ARTAG, pursuant to the findings of positive associations between cerebrovascular pathology and ARTAG (Table 4). We did not find any significant associations of CVD risk factors with ARTAG (Table 6). Next, we tested the results of neurocognitive testing and eventual ARTAG diagnoses among the 441 participants who had a final clinic visit within 6 years between the last follow-up visit and death. Again, because ADNC has a strong impact on cognition, we included a model that adjusted only for age at death, sex, and the interval between the last clinical visit and death (Model 1) and a separate model that also adjusted for the number of the *APOE* ε4 alleles and Braak NFT stages (Model 2). These results are shown in Table 7, with the caveat that approximately 2/3rd of the participants in the total sample lacked neurocognitive testing (sample sizes for each test are shown in Table 7). Factoring in the sample size consideration, there was a possible nominal trend for MMSE scores to be lower in those with ARTAG ($P<0.1$).

4. Discussion

The main goal of the current study was to assess associations between ARTAG and other brain pathologies in the NACC Neuropathology data set. Data from over 500 autopsied research participants, derived from 20 different ADRCs, were analyzed. In these individuals, the presence of ARTAG was increasingly frequent with more advanced age, with male sex, and was more likely to be found in brains with LATE-NC. ARTAG was also more likely

to occur in those with comorbid CVD pathology. However, participants with more severe ADNC, or PART, were not relatively likely to have comorbid ARTAG.

Astrocyte pathobiology and its relationship to dementia is a rapidly expanding field of research (Escartin et al., 2021; Patani et al., 2023; Price et al., 2021), complementing the more widespread emphasis on neuronal degenerative changes. Pathological mechanisms that originate and/or evolve through non-neuronal microenvironments (subpial or white matter regions) may spread, and coexisting pathologies may reflect complex mechanisms: shared upstream risk factors, or direct synergistic influence where one pathology promotes the other. Thus, the present study of comorbid pathologies can provide insights into pathogenesis for both ARTAG and for the other pathologic features seen in aging brains. As suggested by Kovacs et al, "[protein astrogliopathies] might indicate astrocytic contribution to spreading or clearance of disease-associated proteins, however, this might lead to astrocytic dysfunction and eventually contribute to the degeneration of neurons." (Kovacs et al., 2017a)

Previously published studies found that ARTAG was relatively likely to be observed in brains with comorbid TDP-43 pathology and/or LATE-NC (Prater et al., 2022). For example, Forrest et al (Forrest et al., 2022) showed that ARTAG, and a novel tau pathology termed age-related tau oligodendrogliopathy (ARTOG), were associated with LATE-NC. In a separate Japanese autopsy series of cases lacking severe ADNC, Yokota et al reported that the presence of amygdala granular fuzzy astrocytes was associated with LATE-NC as well as with tau-immunoreactive argyrophilic grains (Yokota et al., 2023). There are other clues that the pathoetiology of astrocytic tau pathology can be linked to TDP-43 proteinopathy. For example, a *TARDBP* mutation was linked to a pathological phenotype that included ARTAG-like glial tau pathology (Gelpi et al., 2014). Further, a case was identified with *GBE1* mutations leading to both ARTAG-like and TDP-43 pathologies (Uemura et al., 2023). Another well-characterized FTLD-linked *GRN* mutation also showed both ARTAG-like and TDP-43 pathologies (Gomez-Tortosa et al., 2019). In a larger autopsy series, ARTAG was indeed relatively common in brains affected by FTLD-TDP (Koga et al., 2022). Moreover, hippocampal sclerosis of aging has been linked to both LATE-NC and ARTAG (Sordo et al., 2023). The mechanism(s) underlying the synergy or common roots between TDP-43 pathology and ARTAG are currently unknown.

It is notable that ARTAG, has been described to be common in brains affected by main forms of tauopathies, especially progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (Kovacs et al., 2017b; Kovacs et al., 2017c; Kovacs et al., 2018a). However, both PSP and CBD are relatively uncommon, with less than 1:100 lifetime risk (Coyle-Gilchrist et al., 2016). The connection between ARTAG and the most prevalent tauopathy – ADNC – is less clear. Kovacs et al reported that ADNC was associated with white matter lobar ARTAG (Kovacs et al., 2017b; Kovacs et al., 2017c). In separate studies by Grinberg and colleagues, ARTAG was found relatively commonly in atypical AD cases (Nolan et al., 2019; Resende et al., 2020), which may represent a set of distinct phenotypes in themselves. The present study did not find any positive association between ARTAG and ADNC severity. With the caveat that the NACC data set has sparse data on lobar ARTAG,

this set of observations seems to argue against a general tendency for misfolding proteins to correlate with ARTAG.

The current study's finding of an association between ARTAG and CVD pathology is novel. It is remarkable that both ARTAG and CVD pathologies become increasingly common with advanced age (unlike ADNC, which levels off and apparently decreases in frequency among persons beyond age 90 years) (Farfel et al., 2019; Nelson et al., 2011; Nelson et al., 2013). However, the positive association that was observed between ARTAG and CVD pathology in the present study was not due to this potential confounder, as age was factored into a regression model as a covariate. We note that in a prior study a positive association was found between Circle of Willis atherosclerosis and ARTAG, but that association did not survive correction in a multivariable statistical model (Kovacs et al., 2018a). The mechanism underlying the association between CVD pathology and ARTAG is presently unknown. Notably, we queried the associations between ARTAG and various cerebrovascular/ cardiovascular risk factors (clinical history of diabetes, hypertension, hypercholesterolemia, myocardial infarction, and heart failure as indicated by self-report at the time of the last clinic visit), and none of these risk factors emerged as having been associated with ARTAG at autopsy. A credible hypothesis is that CVD-linked perturbations (ischemia, hemorrhage, and/or neuroinflammation), due to vascular pathology in aging, promotes astrocyte tau pathology. This may correspond to the known linkages between brain trauma and astrocytic tau pathology (Forrest et al., 2019). Intriguingly, as with the prior study by Kovacs and colleagues (Kovacs et al., 2017b), there was a consistent trend for men's brains to be affected by ARTAG more frequently than females. This observation could conceivably be linked to sex-linked differential risk for traumatic brain injury (Eom et al., 2021; Gupte et al., 2019). There also may be connections between ARTAG, LATE-NC, and cerebrovascular pathologies (see (Blevins et al., 2020; Harrison et al., 2021; Neltner et al., 2014)). The convergence of medial temporal lobe age-related pathologies suggest overlapping pathogenesis that might include barrier dysfunction (Forrest et al., 2022), an alteration that, together with water-ion imbalances has been suggested to be important factors in the development of ARTAG (Kovacs et al., 2018b). However, these hypotheses need to be tested in future studies.

There were limitations to the current study. There was incomplete data to indicate the location (e.g., subpial, subependymal, white matter, gray matter, anatomical region) and cellular subtypes (e.g. granular-fuzzy or thorn-shaped astrocytes) of the ARTAG. Data on the severity of ARTAG also had a high level of incompleteness. It is hoped that future iterations of the NACC Neuropathology Data Set will have more replete data on ARTAG locations and subtypes. We note that the overall frequency of ARTAG (44% of the study sample) in the present study comports relatively well with prior studies, which suggests that there was not an extremely large number of false-negatives. Beyond the shortcomings to the ARTAG-specific data, there are relatively well-known challenges in population representativeness of autopsy cohorts, and specifically as applies to the NACC Neuropathology Data Set: All 20 ADRCs from which cases were obtained have some overlapping biases including relative paucity of Blacks and Hispanics, as well as exclusion criteria (lack of substance abuses, lack of some neuropsychiatric changes) that make the research participants studied not representative of a broader population(Arce Renteria et al., 2023; Gauthreaux et al.,

2023). Furthermore, the academic clinics from which these cases derived were indeed “AD research centers”, and both the clinics and the participants themselves may be selected based on interest in AD/amnestic dementia. Biases of “Alzheimer’s-type” dementia may overlook some other common dementia types such as Lewy body diseases and subtypes of CVD (Gauthreaux et al., 2023). We also note that the data are not very quantitative and some parameters for which numeric data (e.g., number of microinfarcts rather than a dichotomous Yes/No parameter for their presence/absence) would have been more optimal. The sample size was not large enough to discover small sample-size phenomena and this may relate to both pathological and clinical phenomena studied. For example, it is important to note that the cerebrovascular pathologies but not the clinical cardiovascular risk factors were linked to ARTAG pathology, applying the $P<0.05$ statistical cutoff. However, there was an odds ratio of ~2 for the association between myocardial infarction and ARTAG. In the future, a study with larger sample sizes may enable a more confident test of the null hypothesis.

In conclusion, an analysis of aggregated data sourced from several dozen academic research centers provided fresh insights into associations between ARTAG and co-pathologies in the aging brain. ARTAG was more likely to occur in brains with comorbid brain infarcts, and in males. It remains to be seen whether the association between ARTAG and CVD pathology is related to local infarction-related biochemical signaling, or with some other set of correlated factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AD	Alzheimer’s disease

ADNC	Alzheimer’s disease neuropathologic change
ADRCs	Alzheimer’s Disease Research Centers
APOE	Apolipoprotein E
ARTAG	age related tau astrogliopathy
CDR®	Clinical Dementia Rating Dementia Staging Instrument
CVD	Cerebrovascular disease
CTE	chronic traumatic encephalopathy
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
FTLD-TDP	Frontotemporal lobar degeneration with TDP-43 inclusions
LATE-NC	Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change
MCI	Mild cognitive impairment
NACC	National Alzheimer’s Coordinating Center
PART	primary age-related tauopathy
pTau	Phosphorylated tau protein
TBI	Traumatic brain injury
TDP-43	TAR DNA-binding protein 43
UDS	Uniform Data Set

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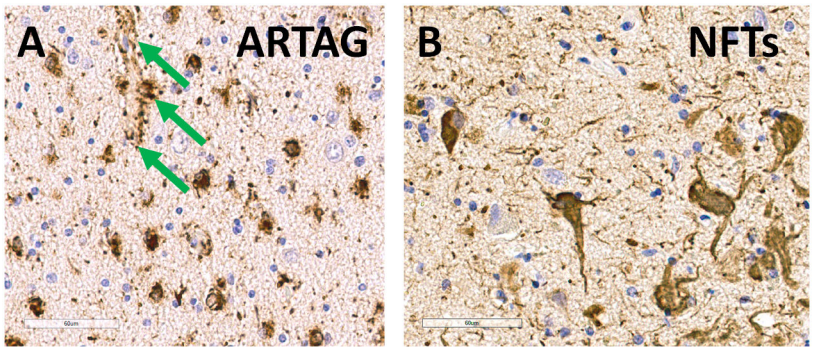

Figure 1. Photomicrographs depict age-related astrogliopathy (ARTAG; A) in comparison with Alzheimer's/PART-type neurofibrillary tangles (NFTs; B) in the same brain, stained immunohistochemically for phosphorylated tau (pTau) labeled brown.

The tissue was counterstained with hematoxylin (blue, highlighting cell nuclei). Panel A shows pTau within compact white matter thorn-shaped astrocytes in the amygdala region. In the present study, the location most noted to harbor ARTAG was the amygdala. Highlighted with green arrows is ARTAG pathology surrounding a small blood vessel. By contrast, Panel B shows larger, intraneuronal NFTs in the entorhinal cortex. Scale bars = 60microns in both panels. The pTau antibody used here was the monoclonal PHF-1 (1:500 dilution), a gift from Dr. Peter Davies.

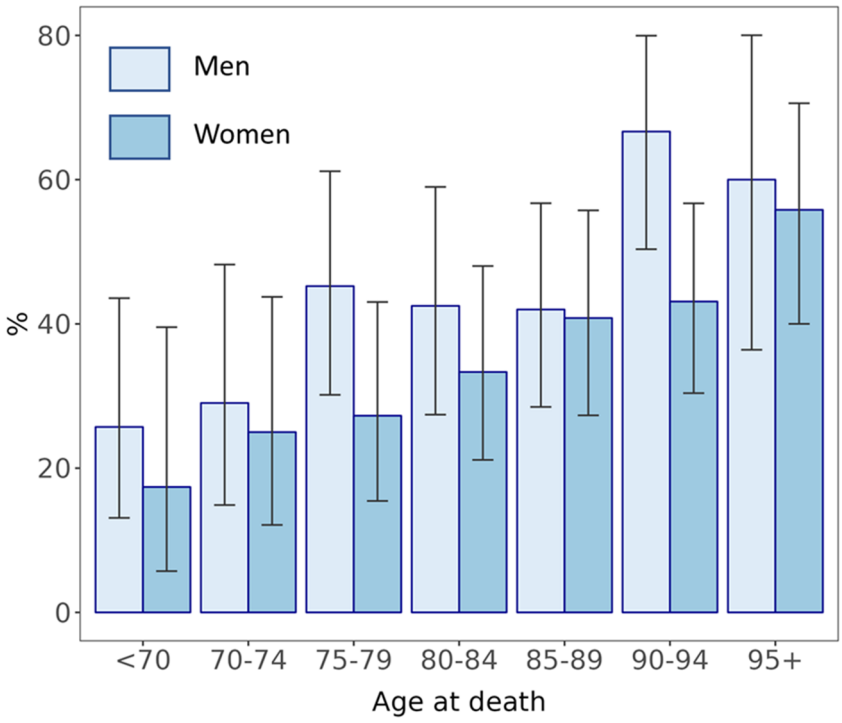

Figure 2. Percent of brains with ARTAG, stratifying by age and sex, in the NACC Data set.
Pale bars represent men and darker blue bars represent women. Shown are results from the NACC Data set among autopsied subjects with ARTAG status known (n=504), sourced from 20 different independent United States Alzheimer's Disease Research Centers. In this sample there were two general trends: ARTAG was more frequent with aging, and in males. These findings are compatible with prior results from a separate sample of research volunteers (Kovacs et al., 2018a). Error bars = stdev.

Table 1.

Demographic and *APOE* alleles of included subjects

Characteristics	**n = 504**
Age at death, mean ± SD	82.7 ± 9.9
Years in education, mean ± SD	16.7 ± 7.9
Sex, n (%)	
Male	235 (46.6)
Female	269 (53.4)
APOE genotype, n (%)	
−/−	251 (54.7)
−/ε4	166 (36.2)
ε4/ε4	42 (9.2)

Table 2.

Neuropathologic features of included subjects

Characteristics		Overall (n = 504)	ARTAG		P-value*
			No (n = 282)	Yes (n = 222)	
Braak NFT stage, n (%)					
	0	12 (2.4)	9 (3.2)	3 (1.4)	0.045
	I-II	84 (16.8)	48 (17.1)	36 (16.3)	
	III-IV	109 (21.8)	49 (17.5)	60 (27.1)	
	V-VI	296 (59.1)	174 (62.1)	122 (55.2)	
Thal phase, n (%)					
	0	48 (9.5)	26 (9.2)	22 (9.9)	0.54
	1-2	51 (10.1)	25 (8.9)	26 (11.7)	
	3	51 (10.1)	26 (9.2)	25 (11.3)	
	4-5	354 (70.2)	205 (72.7)	149 (67.1)	
Neuritic plaques, n (%)					
	No	111 (22.0)	61 (21.6)	50 (22.5)	0.72
	Sparse	56 (11.1)	29 (10.3)	27 (12.2)	
	Moderate	101 (20.1)	54 (19.1)	47 (21.2)	
	Frequent	236 (46.8)	138 (48.9	98 (44.1)	
TDP-43 in amygdala, n (%)					
	No	304 (64.0)	192 (73)	112 (52.8)	6.0×10^{-6}
	Yes	171 (36.0)	71 (27)	100 (47.2)	
TDP-43 in hippocampus/EC, n (%)					
	No	237 (62.4)	134 (68.7)	103 (55.7)	0.011
	Yes	143 (37.6)	61 (31.3)	82 (44.3)	
TDP-43 in neocortex, n (%)					
	No	390 (94.0)	211 (97.2)	179 (90.4)	0.0037
	Yes	25 (6.0)	6 (2.8)	19 (9.6)	
Lewy bodies, n (%)					
	No	295 (58.6)	163 (57.8)	132 (59.7)	0.72
	Yes	208 (41.4)	119 (42.2)	89 (40.3)	
Cerebral amyloid angiopathy, n (%)					
	None	148 (29.4)	78 (27.7)	70 (31.5)	0.28
	Mild	171 (33.9)	106 (37.6)	65 (29.3)	
	Moderate	124 (24.6)	66 (23.4)	58 (26.1)	
	Severe	61 (12.1)	32 (11.3)	29 (13.1)	
Arteriolosclerosis, n (%)					
	None	68 (13.5)	47 (16.7)	21 (9.5)	0.0027
	Mild	201 (40.0)	123 (43.8)	78 (35.1)	

Characteristics		Overall (n = 504)	ARTAG		P-value*
			No (n = 282)	Yes (n = 222)	
	Moderate	163 (32.4)	79 (28.1)	84 (37.8)	
	Severe	71 (14.1)	32 (11.4)	39 (17.6)	
Infarcts and lacunes, n (%)					
	No	422 (84.1)	250 (89)	172 (77.8)	8.7×10^{-4}
	Yes	80 (15.9)	31 (11)	49 (22.2)	
Microinfarcts, n (%)					
	No	398 (79.0)	32 (82.3)	166 (74.8)	0.047
	Yes	106 (21.0)	50 (17.7)	56 (25.2)	

* P-value is calculated by Fisher's exact test

SD = standard deviation; NFT = neurofibrillary tangles

Table 3.

Associations between ARTAG (NPARTAG = 0 or 1) and other neurodegenerative protein pathologies

Neuropathology	OR*	95% CI*
Braak NFT stage *		
0	Reference	
I-II	1.88	0.50 – 9.16
III-IV	2.58	0.69 – 12.45
V-VI	2.15	0.61 – 10.05
Thal phase		
0	Reference	
1-2	1.17	0.52 – 2.65
3	1.16	0.51 – 2.64
4-5	0.99	0.53 – 1.87
Neuritic plaques		
No	Reference	
Sparse	0.92	0.47 – 1.80
Moderate	1.04	0.60 – 1.83
Frequent	1.20	0.74 – 1.96
TDP-43 in amygdala		
No	Reference	
Yes	**2.05**	**1.37 – 3.07**
TDP-43 in hippocampus/EC		
No	Reference	
Yes	1.54	0.99 – 2.41
TDP-43 in neocortex		
No	Reference	
Yes	**3.22**	**1.29 – 9.23**
LATE-NC stage		
0	Reference	
1	**3.12**	**1.50 – 6.81**
2	**1.81**	**1.13 – 2.91**
3	**4.60**	**1.82 – 13.26**
Lewy bodies		
No	Reference	
Yes	1.04	0.72 – 1.51

LATE-NC = limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; OR=Odds ratio; CI=Confidence interval; *The OR and CI are adjusted for age at death and sex

Table 4.

Associations between ARTAG (NPARTAG = 0 or 1) and cerebrovascular pathologies

Neuropathology	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Cerebral amyloid angiopathy				
None	Reference			
Mild	0.81	0.51 – 1.30	0.83	0.49 – 1.42
Moderate	1.18	0.72 – 1.95	1.13	0.63 – 2.04
Severe	1.09	0.59 – 2.03	0.86	0.42 – 1.76
Arteriolosclerosis				
None	Reference			
Mild	1.34	0.74 – 2.48	1.28	0.69 – 2.43
Moderate	**2.01**	**1.09 – 3.78**	**2.16**	**1.13 – 4.20**
Severe	**2.34**	**1.15 – 4.85**	2.12	0.99 – 4.61
Infarcts and lacunes				
No	Reference			
Yes	**1.83**	**1.10 – 3.06**	**2.19**	**1.28 – 3.82**
Microinfarcts				
No	Reference			
Yes	1.26	0.81 – 1.98	1.39	0.86 – 2.25

Model 1 is with the adjustment of age at death and sex, and Model 2 is with the additional adjustment of the number of the ε4 alleles in *APOE* and four categorized Braak NFT stage.

Table 5.

Participants who had Probable PART (CERAD neuritic plaque score = None) and Braak = 0 to IV (n = 107)

Braak NFT stage*	OR	95% CI
0-II	Reference	
III-IV	1.72	0.66 – 4.52

*CI = Confidence interval; Regression model factors in covariates age of death and sex.

Table 6.

Associations between ARTAG (NPARTAG = 0 or 1) and cerebrovascular/ cardiovascular risk factors

Cerebrovascular/ cardiovascular risk factors	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Diabetes				
No	Reference		Reference	
Yes	1.01	0.59 – 1.72	1.10	0.62 – 1.95
Hypertension				
No	Reference		Reference	
Yes	0.84	0.55 – 1.29	0.89	0.57 – 1.40
Hypercholesterolemia				
No	Reference		Reference	
Yes	0.94	0.65 – 1.37	1.09	0.74 – 1.62
Heart attack/cardiac arrest				
No	Reference		Reference	
Yes	1.68	0.34 – 9.13	2.36	0.40 – 15.76
Congestive heart failure present				
No	Reference		Reference	
Yes	1.24	0.56 – 2.81	1.14	0.51 – 2.63

Model 1 is with the adjustment of age at death and sex, and Model 2 is with the additional adjustment of the number of the ε4 alleles in *APOE* and four categorized Braak NFT stage.

Table 7.

Associations between ARTAG (NPARTAG = 0 or 1) and cognitive assessment scores.

Cognitive test	N available out of total N=504 in sample*		Model 1**		Model 2**	
	ARTAG	Non-ARTAG	$\hat{\beta}$ (SE)	P-value**	$\hat{\beta}$ (SE)	P-value**
MMSE	79	88	−2.06 (1.07)	0.055	−1.76 (0.96)	0.070
Logical Memory – immediate	78	110	−1.42 (0.96)	0.14	−0.89 (0.86)	0.30
Logical Memory – delayed	76	105	−1.47 (1.03)	0.16	−0.91 (0.93)	0.33
Animal Naming	80	114	−1.84 (1.02)	0.073	−1.43 (0.96)	0.14
Vegetable Naming	79	110	−0.52 (0.83)	0.53	−0.17 (0.78)	0.83
Digit span forward trials	81	112	0.25 (0.36)	0.49	0.40 (0.35)	0.25
Digit span backward trials	80	112	0.39 (0.39)	0.32	0.54 (0.37)	0.14

*N=441 participants had final clinic visit within 6 years between the last follow-up visit and death

**Model 1 is with the adjustment of age at death, sex, and years between the last visit and death, and Model 2 is with the additional adjustment of the number of the ε4 alleles in *APOE* and four categorized Braak NFT stage.

MMSE = Mini Mental State Examination; $\hat{\beta}$ = Estimate of regression coefficient; SE = Standard error; **−P-value applied two-tailed test