7-2017

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HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2017 September 11.

Published in final edited form as:

Alzheimers Dement. 2017 July ; 13(7): 770–777. doi:10.1016/j.jalz.2016.12.002.

Milder Alzheimer's disease pathology in heart failure and atrial fibrillation

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Abstract

Introduction—Heart failure (HF) and atrial fibrillation (AF) have been associated with a higher risk of Alzheimer's disease (AD). Whether HF and AF are related to AD by enhancing AD neuropathological changes is unknown.

Methods—We applied network analyses and multiple logistic regression models to assess the association between HF and AF with severity of AD neuropathology in patients from the National Alzheimer's Coordinating Center database with primary neuropathological diagnosis of AD.

Results—We included 1593 patients, of whom 129 had HF and 250 had AF. HF and AF patients were older and had milder AD pathology. In the network analyses, HF and AF were associated with milder AD neuropathology. In the regression analyses, age (odds ratio [OR] 0.94, 95%

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Author contributions: Luciano A. Sposato: study concept and design, statistical analysis and interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision; Estefanía Ruíz Vargas: statistical analysis (network analysis) and drafting of the manuscript; Patricia M. Riccio: drafting of the manuscript and critical revision of the manuscript for important intellectual content; Jon B. Toledo: critical revision of the manuscript for important intellectual content; John Q. Trojanowski: critical revision of the manuscript for important intellectual content; Walter A. Kukull: critical revision of the manuscript for important intellectual content; Lauren E. Cipriano: statistical analysis supervision and critical revision of the manuscript for important intellectual content; Antonia Nucera: critical revision of the manuscript for important intellectual content; Shawn N. Whitehead: drafting of the manuscript and critical revision of the manuscript for important intellectual content; and Vladimir Hachinski: critical revision of the manuscript for important intellectual content and supervision of the study.

confidence interval [CI] 0.93–0.95 per 1-year increase in age, P <.001) and the interaction term HF × AF (OR 0.61, 95% CI 0.40–0.91, P = .014) were inversely related to severe AD pathology, whereas *APOE* ε4 genotype showed a direct association (OR 1.68, 95% CI 1.31–2.16). Vascular neuropathology was more frequent in patient with HF and AF patients than in those without.

Discussion—HF and AF had milder AD neuropathology. Patients with milder AD lived longer and had more exposure to vascular risk factors. HF and AF patients showed a higher frequency of vascular neuropathology, which could have contributed to lower the threshold for clinically evident dementia.

Keywords

Atrial fibrillation; Heart failure; Dementia; Alzheimer's disease; Vascular dementia; Neuropathology

1. Introduction

Heart failure (HF), atrial fibrillation (AF), and dementia are major health care challenges that become more prevalent with age [1–3]. The number of people over 65 years will increase from 420 million in 2000 to 1 billion by 2030 [4]. Therefore, this segment will grow from 7% to 12% of the population [4]. In consequence, the number of individuals living with dementia is predicted to escalate from 35.6 million in 2010, to 65.7 million in 2030, and 115.4 million in 2050 [1]. Similarly, the prevalence of AF in the US population is expected to increase from 5.2 million in 2010 to 12.2 million in 2030 [2].

HF and AF constitute promising targets for dementia prevention. Evidence suggests that HF and AF are associated to a higher risk of cognitive impairment and dementia, irrespective of stroke history [5,6]. Whereas data from population-based studies show that HF is associated with a higher risk of Alzheimer's disease (AD) [7,8], AF is not associated equally with all types of dementias [6]. Although there is evidence supporting the association between AF and dementia secondary to cerebrovascular disease, the relationship between AF and AD is still controversial [6]. One study that examined neuropathological changes associated with AF found that patients with permanent AF were 40%–50% more likely to have AD changes than those without AF, but these associations were not statistically significant [9].

Whether the higher AD risk of HF and AF is mediated through a greater burden of AD pathological changes is unknown. Several possible mechanisms may enhance AD-related pathological processes in HF and AF patients. Amyloid β clearance may be compromised in HF patients, whereas stroke-free AF patients have reduced hippocampal volume compared with matched subjects without AF, meaning that AF could be implicated in direct or indirect neurodegenerative processes [10,11]. Also, AF-related brain infarcts may potentiate AD pathological changes through secondary mechanisms [12].

In the present study, we aimed to investigate whether there is an association between HF and AF with severe AD neuropathology among cases with primary diagnosis of AD from the National Alzheimer's Coordinating Center (NACC) database.

2. Methods

The NACC was established by the National Institute on Aging in 1999 with the aim of enabling collaborative research (U01 AG016976). The NACC collects data from 34 past and present National Institute of Aging–funded Alzheimer's disease Centers across the USA. For this study, neuropathological data were collected from the NACC Neuropathology Data Set, and clinical data from the same cases were obtained from the NACC Uniform Data Sets [13–15]. The Uniform Data Set has gathered information about demographic data, clinical manifestations, clinical diagnoses, neurological examination, functional status, neuropsychological assessment, genetic data, and neuropathological diagnoses since 2005.

For most of the neuropathological diagnoses, two categories were available: primary or contributing. For the purpose of this study, we selected cases with primary AD diagnosis. Cases received an AD neuropathological diagnosis based on Braak staging [16] and Consortium to Establish a Registry for Alzheimer's Disease scores for likelihood of AD [17] if cases reached an intermediate probability. As such, the study cohort comprised patients with primary neuropathological diagnosis of AD without contributing cerebrovascular disease or with a degree of vascular neuropathology that did not reach the threshold for mixed dementia. This was possible because NACC includes two categories for vascular neuropathology (1) CVD (cerebrovascular disease), in which vascular neuropathology was classified as a primary or contributing neuropathology (Items 20E1-20E2 in Neuropathology Data Set) and (2) VP (vascular pathology) (Item 12), in which vascular neuropathology was recorded but did not reach a threshold deemed sufficient to contribute to clinical status. Cases in which AD was only contributing and not the primary neuropathological diagnosis were excluded. We decided to restrict the study population to patients with primary AD diagnosis because we wanted to test the hypothesis of whether HF and AF are implicated in pathophysiological mechanisms of AD degeneration. This would have been impracticable if we used a cohort comprising patients with mixed dementia in which secondary AD only represented a contributing secondary pathological mechanism.

We recorded data regarding sex, age at the onset of cognitive decline, age at the last visit, age at death, years of education, history of hypertension, AF, diabetes mellitus, hyperlipidemia, smoking (more than 100 cigarettes smoked in a lifetime), stroke, transient ischemic attack (TIA), and HF. These variables were coded as absent, recent/active, or remote/inactive. We merged active and inactive categories and compared them with the "absent" category. For the purpose of this study, patients were considered to have AF and HF based on their medical history (in any of all the available Uniform Data Set visits, form A5). We defined four clinical phenotypes (CPs) according to the presence or absence of HF and AF—(1) CP1: no HF and no AF, (2) CP2: AF without HF, (3) CP3: HF without AF, and (4) CP4: HF and AF present. History of stroke was defined by the presence of an affirmative response in any of the following three variables comprised in the original data set: stroke, history of stroke, and temporal relationship between stroke and onset of cognitive impairment.

We used Braak stages (extent of neurofibrillary tangles) to classify the severity of AD-related neuropathological findings into severe (stages V/VI) and milder (stages III/IV) [16].

Neuropathological vascular features comprised microinfarcts, lacunar macroscopic infarcts (lacunes), and larger macroscopic infarcts. The criteria used by the neuropathologists to assess the vascular features are described in the Neuropathology Diagnosis Coding Guidebook (https://www.alz.washington.edu/NONMEMBER/NP/npguide9.pdf). We defined four neuropathological profiles (NPs) on the basis of AD and vascular neuropathology—(1) NP1: Braak III/IV + vascular neuropathology, (2) NP2: Braak III/IV without vascular neuropathology, (3) NP3: Braak V/VI + vascular neuropathology, and (4) NP4: Braak V/VI without vascular neuropathology.

We used the NACC neuropsychological battery to assess cognitive status in the last visit before death [15]. The battery comprised the following domains and tests—(1) general cognitive impairment: Mini-Mental State Examination [18]; (2) executive functions: Digit Span Backward (Wechsler Memory Scale—Revised) [19], Digit Symbol Coding (Wechsler Adult Intelligence Scale—Revised) [20], and Trail Making Test, Part B [21]; (3) memory: immediate and delayed recall (Story A, Wechsler Memory Scale—Revised) [19]; (4) language: animal and vegetable list generation (verbal fluency) [22] and Boston Naming Test (naming) [23]; (5) attention: Digit Span Forward (Wechsler Memory Scale—Revised) [18] and Trail Making Test, Part A [20–24]. The dementia-related functional status was assessed according to the Clinical Dementia Rating (CDR) sum of boxes [25].

2.1. Statistical analysis

We performed univariate analyses to compare demographic characteristics, vascular risk factors, vascular comorbidities, and neuropathological findings between patients with and without AF and HF. The c^2 to compare proportions and one-way analysis of variance to compare means across the four CPs. All tests were two tailed, and a *P* value <.05 was deemed statistically significant. We developed a forward step-by-step multiple logistic regression model to test whether AF and HF were associated with severe AD pathology (Braak stages V/VI). This model was adjusted for demographic data (e.g., age and sex), risk factors (e.g., hypertension, hyperlipidemia, smoking, and diabetes mellitus), and history of stroke/TIA. Measures of association were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We estimated the proportion of severe AD pathological findings (e.g., Braak stages V/VI), vascular neuropathology (e.g., microinfarcts, lacunes, or larger infarcts), and the frequency or each of the four prespecified NPs based on AD findings and vascular neuropathology across the four prespecified clinical HF/AF phenotypes. We used IBM SPSS Statistics 20.0 for Macintosh (IBM Corp.) for all statistical analyses.

As a post hoc analysis based on preliminary results of this study, we developed logistic regression analyses to identify predictors of early death. For this purpose, we used the lowest quintile of age at death (<72 years) as the dependent variable.

2.2. Network analysis

We built a network by relating demographic variables, risk factors, comorbidities, and pathological findings. We divided the data set into training and validation sets. The links between these variables, or nodes, were calculated by using relative risk as the correlation measure. We retained only relative risks that where above a certain threshold, which was

defined on the basis of the limit at which the giant component was first detected [26]. We identified connections that were stronger among patients with HF and AF than among patients without. We performed a modularity analysis based on the concept of topological overlap (analysis of the structure of the density and pattern of connections of the nodes within the network) to determine how variables were connected between each other [27]. For the network analyses, we were unable to use continuous variables; thus, we dichotomized age into <82 and 82 years on the basis of the median age of the cohort at death.

3. Results

The study cohort comprised 1593 patients with primary diagnosis of AD (Fig. 1). A total of 129 patients had HF (8.1%) and 250 had AF (15.7%). Comparisons of demographic data, vascular risk factors, comorbidities, clinical diagnoses, and neuropathological findings across the four CPs are shown in Table 1. AD patients with HF and AF were older at the time of onset of cognitive decline and at death, had less frequent severe AD changes on neuropathological examination, and had more frequent noncontributory vascular neuropathology than those without HF or AF. Clinically, patients with HF and AF were more frequently considered as having normal cognition and were more often diagnosed as having dementia because of cerebrovascular disease than those without. Hypertension and all vascular comorbidities were more common in HF and AF patients than in those without. In general, cognitive performance and overall functional status (CDR) were better in patients with HF + AF than in those without (Table 2).

In the logistic regression model for severe AD changes, age (OR 0.94, 95% CI 0.93–0.95 per 1-year increase in age, $P < .001$) and the interaction term HF × AF (OR 0.61, 95% CI 0.40–0.91, $P = .014$) were inversely related to severe AD pathology, whereas *APOE* ε4 genotype showed a direct association (OR 1.68, 95% CI 1.31–2.16). Adding the interaction term *APOE* ε4 × HF × AF did not significantly affect these results.

We used a threshold of 1.20 for the network analyses (Fig. 1). The giant component comprised all vascular findings on neuropathological examination. The modularity analysis showed that the network had a high density of connections between HF, AF, vascular risk factors, and stroke, which belonged to the same module. HF and AF were only connected with milder AD neuropathological findings, and there was lack of connection with Braak stages V/VI. Conversely, HF and AF were highly connected to vascular neuropathology.

The frequency of severe AD pathology significantly decreased across clinical AF/HF phenotypes CP1 to CP4 (Fig. 2, panel A). Likewise, there were increasing proportions of vascular neuropathology across the same groups (Fig. 2, panel B). As shown in Fig. 3, the NPs AF and HF showed less severe AD pathology and more vascular neuropathology; and the combination of HF and AF had an additive effect resulting in even less frequent severe AD changes and more frequent vascular neuropathology.

HF (OR 0.29, 95% CI 0.09–0.94), AF (OR 0.22, 95% CI 0.11–0.45), and Braak stages V/VI (OR 3.07, 95% CI 1.87–5.04) were significantly associated with early death in the post hoc logistic regression model (Fig. 2).

4. Discussion

Evidence suggests that stroke risk factors such as midlife hypertension and obesity, diabetes, smoking, and physical inactivity and comorbidities such as HF and AF are independently associated with an increased risk of AD and vascular cognitive impairment [6–8,28]. Contrary to our hypothesis, in the present study of cases from the NACC database with primary diagnosis of AD, we found that patients with HF and AF had less frequent severe AD changes on neuropathological examination than those without.

In the logistic regression models for severe AD pathology, the odds of showing severe AD pathology decreased by 5% per 1-year increase in age at death and 39% for patients who had both HF and AF. The network analyses showed an association between HF and AF with milder AD neuropathology. Together, these findings suggest that HF and AF occur more frequently in patients with milder AD pathology, who because of a more benign AD course may present with cognitive decline at older ages, live longer, and are more exposed to vascular risk factors leading to a higher prevalence of cardiovascular comorbidities [29]. This is further reinforced by the fact that severe AD pathology increased 3-fold the risk of early death in the study cohort and also by the finding of younger age of onset of cognitive decline among AD patients without HF or AF [2,30].

Another potential explanation for our findings is that HF and AF precede dementia symptoms and lead to overt dementia not by enhancing AD pathology, but rather by a higher prevalence of vascular neuropathology. Subjects with milder AD pathology would be clinically diagnosed with AD only in the presence of enough vascular neuropathology to lower the threshold for cognitive impairment [31], As such, the higher frequency of AD diagnosis among HF and AF patients found in prior studies may be explained by symptomatic and asymptomatic brain infarcts uncovering mild forms of AD [5,6]. Interestingly, the severity of vascular neuropathology in this cohort was a priori regarded as nonsignificant enough to clinically influence on cognitive performance by expert NACC neuropathologists. Indeed, HF and AF showed an additive effect in the proportion of patients with milder AD changes and greater vascular neuropathology. Also, AD patients with HF and AF had slightly better age- and sex-adjusted cognitive performances and overall functional status as those without, further supporting the idea that apparently nonclinically relevant vascular neuropathology may have lowered the threshold for cognitive impairment in older HF and AF patients who had milder AD neuropathology [31].

Our findings suggest that the apparent association between HF and AF with higher risk of AD is unlikely mediated through the enhancement of primary AD-related mechanisms. The higher proportion of primary AD with apparently, but not so, noncontributing vascular neuropathology among HF and AF patients and the additive effect of HF and AF on the frequency of vascular neuropathology suggest that brain infarcts otherwise regarded as nonclinically contributory to the diagnosis of dementia by expert pathologists could still play a role in secondary pathophysiological AD processes. Indeed, brain infarcts can lead to remote localized cortical thinning through degeneration of connecting fiber tracts, on top of the primary structural brain damage produced by ischemia itself [32]. Experimental and preliminary clinical data suggest that pre-existing amyloid may stimulate secondary cortical

neurodegenerative processes after acute stroke [7]. Chronic stroke-related inflammation is also involved in secondary neurodegenerative processes and seems to be independent of prior amyloid deposition [12]. However, all these findings need to be further validated.

This study has limitations. First, information about the presence of HF and AF was not systematically investigated and came from the subjects' medical history as recorded retrospectively during their follow-up visits. This might have resulted in the underdiagnosis of the both conditions. However, it also reflects how history of HF and AF is usually investigated in routine clinical practice. Also, based on the large sample size, the finding of less severe AD pathology in patients who had HF or AF seems unlikely to be because of chance. This is further reinforced by the adjustment for significant confounders in the logistic regression models. Second, the retrospective ascertainment of HF and AF hinders the identification of the time sequence in the association between HF/AF and dementia. Third, we did not have information regarding the localization of brain infarcts, which would have likely enriched the analysis. Fourth, information about prescribed oral anticoagulants, antiplatelet agents, and other drugs were not available in the NACC data set. This precluded us from adjusting the regression models for drugs that have the potential to reduce the incidence of dementia or to delay its diagnosis. Despite this, the role of antithrombotic agents in dementia prevention is unknown. Fifth, our results are not generalizable to all types of dementia. The study cohort was designed to test the study hypothesis among patients with primary diagnosis of AD and not other dementias. Although this is a highly selected population, it still constitutes the most frequent type of dementia, and the results of this study are relevant to explain how HF and AF help to lower the threshold of cognitive impairment in patients with mild AD neurodegenerative changes.

Our study suggests that subjects with milder AD pathology live longer. Hence, they are exposed to a greater burden of vascular risk factors and have higher odds of developing HF and AF. As a result, rather than being considered as possible causes of AD, HF and AF may be possibly regarded as markers of milder AD pathology, lowering the threshold for the detection of cognitive impairment in subjects with milder AD pathology because of a higher presence of vascular neuropathology. In other words, HF and AF seem to contribute to the clinical expression of dementia in individuals with milder forms of AD, who would otherwise be able to function within cognitively acceptable limits. Strategies implemented during early adulthood to prevent HF and AF, and to effectively manage both conditions early after their diagnoses, may help delay the clinical expression of dementia among patients with milder forms of AD.

Acknowledgments

The NACC database is supported by UO1 AG016976 and the Penn ADCC by AG10124. John Q. Trojanowski is the William Maul Measey-Truman G. Schnabel, Jr, Professor of Geriatric Medicine and Gerontology. The authors appreciate the ongoing support of Creighton Phelps, PhD, and Marcelle Morrison-Bogorad, PhD, from the National Institute on Aging (NIA) in developing the Uniform Data Set and the cooperation of all NIA-supported ADC directors and their staff in its implementation. Thanks to all the Clinical, Neuropathology, and Data Management Core and Leaders and their associates for their input and responses to many surveys and questionnaires. The authors had no conflicts of interest. The NACC database is funded by NIA/NIH grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (principal investigator [PI] Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI

Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Steven Ferris, PhD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016570 (PI David Teplow, PhD), P50 AG005131 (PI Douglas Galasko, MD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P50 AG005136 (PI Thomas Montine, MD, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), and P50 AG005681 (PI John Morris, MD). Luciano A. Sposato is supported by the Edward and Alma Saraydar Neurosciences Fund and by the Opportunities Fund of the Academic Health Sciences Centre Alternative Funding Plan of the Academic Medical Organization of Southwestern Ontario (AMOSO). Walter A. Kukull is funded primarily by a NIH grant U01 AG016976 (NACC). Lauren E. Cipriano is supported by the Natural Science and Engineering Research Council of Canada. Jon B. Toledo is supported by P01 AG032953, PO1 AG017586, P30 AG010124, and P50 NS053488 grants.

Disclosures: Luciano A. Sposato has received speaker honoraria and travel support from Boehringer Ingelheim. Patricia M. Riccio reports no disclosures. Estefanía Ruíz Vargas reports no disclosures. Jon B Toledo has received research support from Eli-Lilly. John Q. Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is co-inventor and he received revenue from the sale of Avid to Eli Lily as co-inventor on imaging-related patents submitted by the University of Pennsylvania. He receives research support from the NIH, GSK, Janssen, and several nonprofits. Walter A. Kukull, Lauren E. Cipriano, Antonia Nucera, Shawn Whitehead, and Vladimir Hachinski report no disclosures.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed and Scopus) sources. Relevant citations are cited throughout the text. Evidence suggests that heart failure (HF) and atrial fibrillation (AF) are associated with a higher risk of cognitive impairment and dementia, including Alzheimer's disease (AD), irrespective of stroke history. The mechanisms behind these associations are still unknown.
2. Interpretation: Our findings suggest that HF and HD may be markers of milder AD pathology. Both HF and AF may contribute to a higher apparent dementia incidence by making milder forms of otherwise sub-clinical AD become clinically evident because of more frequent coexisting vascular neuropathology.
3. Future directions: Further studies should investigate the temporal association between HF, AF, and AD and whether clinically overt AD can be delayed or prevented by avoiding HF and AF and/or by optimizing their treatment.

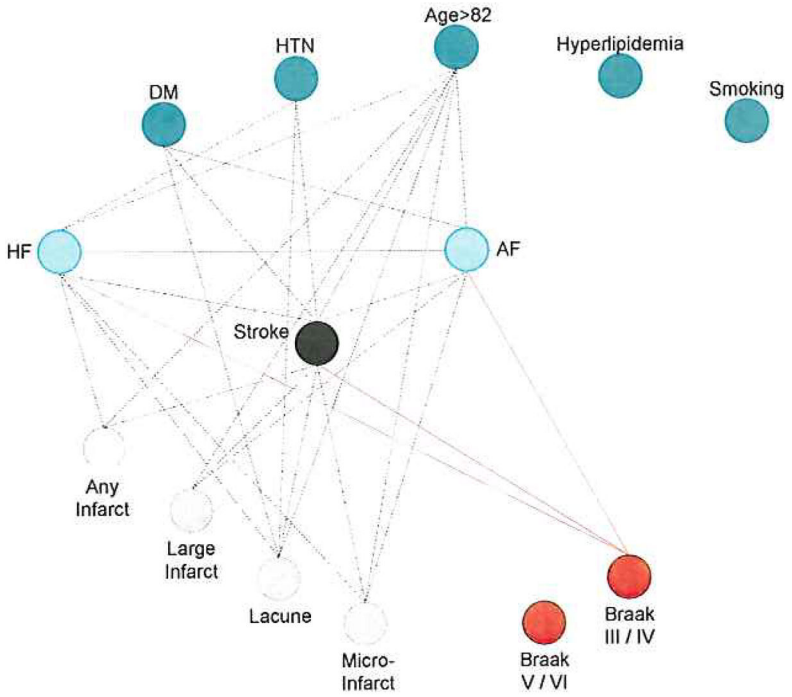

Fig. 1.

Network analyses for neuropathological Alzheimer's disease (AD) findings. Each variable is shown in a circle (node). Risk factors are shown in dark green, heart failure (HF) and atrial fibrillation (AF) in light green, stroke in black, vascular neuropathological findings in gray (borders in dotted lines), and Braak stages in red. The lines between circles are present only when the degree of association between the connected variables is higher than the prespecified threshold of 1.2. HF and AF are connected with milder AD pathology (Braak stages III/IV). They are also highly connected with age, diabetes, hypertension, stroke, and vascular neuropathology.

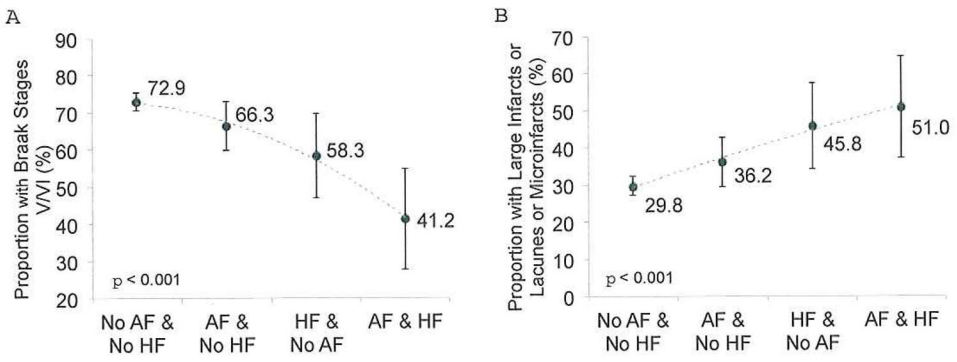

Fig. 2.

Frequency of severe Alzheimer's disease (AD) pathological findings and vascular neuropathology in patients with and without atrial fibrillation (AF) and heart failure (HF). Panel A shows the proportion of severe AD pathological findings (e.g., Braak V/VI) on neuropathological examination for patients (i) without AF or HF, (ii) with AF, (iii) with HF, and (iv) with AF + HF. Panel B shows the proportion of vascular neuropathology for the same groups. Circles represent the proportion with neuropathological findings, and vertical lines account for the 95% confidence intervals.

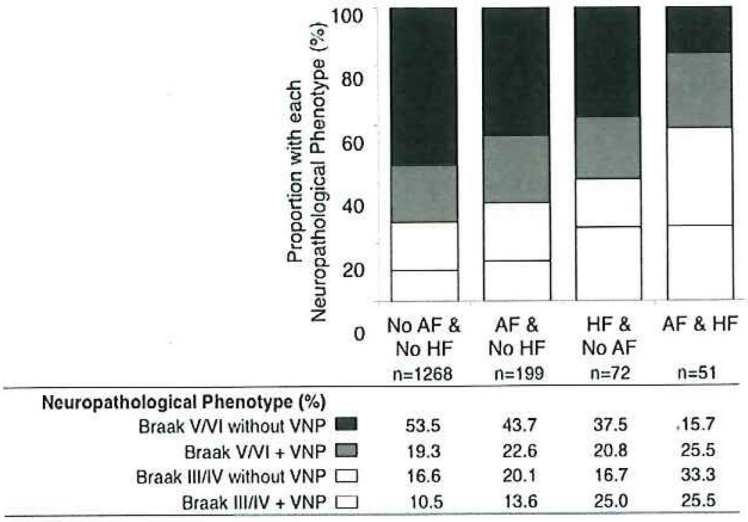

Fig. 3.

Frequency of neuropathological profiles (NPs) of Alzheimer's disease (AD) and vascular neuropathology in patients with and without atrial fibrillation (AF) and heart failure (HF). The figure shows the proportion of four prespecified NPs of AD findings and vascular neuropathology (e.g., Braak III/IV + vascular neuropathology, Braak III/IV without vascular neuropathology, Braak V/VI + vascular neuropathology, and Braak V/VI without vascular neuropathology) for patients (i) without AF or HF, (ii) with AF, (iii) with HF, and (iv) with AF + HF. VNP: vascular neuropathology (e.g., larger infarcts, lacunes, or microinfarcts).

Table 1

Comparison of demographic data, vascular risk factors, and comorbidities between AD patients with and without AF and AD

	No AF and no HF	AF and no HF	HF and no AF	AF and HF	*P* value
Demographics					
Age of onset of cognitive decline, mean ± SD (years)	70.6 ± 11.1	75.5 ± 8.7	77.8 ± 9.8	83.4 ± 8.8	<.001
Age at death, mean ± SD (years)	79.2 ± 10.4	84.4 ± 7.8	86.5 ± 7.6	88.9 ± 7.2	<.001
Years between last assessment and death, mean ± SD	0.8 ± 1.1	0.7 ± 1.1	0.5 ± 0.8	0.6 ± 1.0	.029
Years of education, % (n)	15.1 ± 3.2	15.2 ± 3.2	14.1 ± 3.4	14.6 ± 4.0	.19
Male sex, % (n)	54.4 (692/1271)	59.3 (118/199)	54.2 (39/72)	47.1 (24/51)	.79
Vascular risk factors					
Hypertension, % (n)	54.2 (689/1271)	61.1 (121/198)	76.4 (55/72)	82.4 (42/51)	<.001
Diabetes mellitus, % (n)	9.7 (123/1269)	14.6 (29/199)	8.3 (6/72)	9.8 (5/51)	.55
Hyperlipidemia, % (n)	47.5 (596/1256)	50.8 (100/197)	50.7 (36/71)	54.0 (27/50)	.22
Smoking, % (n)	45.1 (559/1240)	46.4 (91/196)	59.4 (24/49)	49.0 (24/49)	.09
Comorbidities					
Atrial fibrillation, % (n)	0.0 (0/1271)	100.0 (199/199)	0.0 (0/72)	100.0 (51/51)	<.001
HF, % (n)	0.0 (0/1271)	0.0 (0/199)	100.0 (72/72)	100.0 (51/51)	<.001
Coronary artery disease, % (n)	15.0 (190/1268)	25.1 (50/199)	41.7 (30/72)	32.0 (16/50)	<.001
Prior TIA, %(n)	10.2 (130/1271)	14.1 (28/199)	13.9 (10/72)	19.6 (10/51)	.011
Prior stroke, % (n)	11.0 (140/1271)	18.6 (37/199)	22.2 (16/72)	25.5 (13/51)	<.001
Clinical diagnoses					
Normal cognition, % (n)	3.5 (45/1271)	7.0 (14/199)	2.8 (2/72)	9.8 (5/51)	.026
Probable or possible AD, % (n)	80.8 (991/1226)	82.2 (152/199)	80.0 (56/70)	73.9 (34/46)	.46
Mixed AD + cerebrovascular disease, % (n)	6.0 (73/1226)	12.4 (23/185)	15.7 (11/70)	19.6 (9/46)	<.001
Neuropathology					
Pure AD	38.9 (491/1271)	32.7 (65/199)	34.7 (25/72)	31.4 (16/51)	.08
Primary AD and noncontributory vascular neuropathology	19.4 (246/1271)	25.6 (51/199)	31.9 (23/72)	39.2 (20/51)	<.001
Braak stages V and VI, % (n)	72.9 (926/1271)	66.3 (132/199)	58.3 (42/72)	41.2 (21/51)	<.001
Vascular findings					
Larger infarcts, % (n)	8.4 (106/1265)	13.1 (26/199)	11.1 (8/72)	19.6 (10/51)	.002
Lacunar infarcts, % (n)	14.7 (187/1268)	16.6 (33/199)	26.4 (19/72)	27.7 (14/51)	.001

	No AF and no HF	AF and no HF	HF and no AF	AF and HF	*P* value
Microinfarcts, % (n)	17.4 (221/1268)	20.6 (41/199)	20.8 (15/72)	29.4 (15/51)	.022
Either larger infarcts, lacunes or microinfarcts, % (n)	29.8 (378/1268)	36.2 (72/199)	45.8 (33/72)	51.0 (26/51)	<.001

Abbreviations: AD, Alzheimer's disease; AF, atrial fibrillation; HF, heart failure; SD, standard deviation; TIA, transient ischemic attack.

NOTE. Clinical diagnoses may overlap (addition of the frequency of different diagnoses does not equal 100%), thus the sum of proportions is higher than 100%. Other diagnoses include Lewy body dementia, corticobasal degeneration, frontotemporal dementia, and progressive supranuclear palsy.

Table 2

Comparison of neuropsychological performance and functional status of AD patients with and without AF

	No AF and no HF	AF and no HF	HF and no AF	AF and HF	*P* value
Neuropsychological performance					
General cognitive function					
Mini-Mental State Examination, mean ± SD, Z score	−11.3 ± 7.6	−10.7 ± 7.4	−9.8 ± 6.6	−7.2 ± 6.6	.012
Executive functions					
Digit Symbol Coding, mean ± SD, Z score	−1.8 ± 1.6	−1.7 ± 1.5	−1.9 ± 1.2	−1.4 ± 1.4	.68
Digit Span Backward (Trials), mean ± SD, Z score	−1.3 ± 1.2	−1.2 ± 1.2	−1.0 ± 1.2	−0.8 ± 1.1	.06
Trail Making Test B, mean ± SD, Z score	−2.6 ± 2.0	−2.8 ± 1.9	−3.2 ± 1.6	−2.3 ± 1.6	.52
Memory					
Immediate memory, mean ± SD, Z score	−2.1 ± 1.3	−2.2 ± 1.4	−1.9 ± 1.4	−1.4 ± 1.2	.022
Delayed memory, mean ± SD, Z score	−1.9 ± 1.2	−1.9 ± 1.3	−1.8 ± 1.1	−1.2 ± 1.2	.015
Language (verbal fluency and naming)					
Boston, mean ± SD, Z score	−3.5 ± 3.0	−3.3 ± 2.7	−2.4 ± 2.7	−2.6 ± 2.4	.13
Animal list, mean ± SD, Z score	−2.1 ± 1.2	−1.8 ± 1.2	−1.8 ± 1.2	−1.5 ± 1.1	.002
Vegetable list, mean ± SD, Z score	−1.4 ± 1.2	−1.3 ± 1.2	−1.2 ± 1.1	−0.7 ± 1.3	.008
Attention					
Digit Span Forward (Trials), mean ± SD, Z score	−1.3 ± 1.5	−1.0 ± 1.4	−0.9 ± 1.3	−0.6 ± 1.4	.012
Trail Making Test A, mean ± SD, Z score	−4.0 ± 3.0	−3.9 ± 3.1	−4.0 ± 3.0	−3.4 ± 2.8	.85
CDR sum of boxes, mean ± SD	11.8 ± 6.0	11.5 ± 6.2	10.8 ± 6.1	7.7 ± 6.3	<.001

Abbreviations: AD, Alzheimer's disease; AF, atrial fibrillation; CDR, clinical dementia rating; HF, heart failure; SD, standard deviation.