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Featured Article

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

Luciano A. Sposato[a,b,*], Estefanía Ruíz Vargas[a], Patricia M. Riccio[a], Jon B. Toledo[c,d], John Q. Trojanowski[c], Walter A. Kukull[e], Lauren E. Cipriano[f], Antonia Nucera[a], Shawn N. Whitehead[a,g], Vladimir Hachinski[a]

[a]*Department of Clinical Neurological Sciences, London Health Sciences Centre, Western University, London, Ontario, Canada*
[b]*London Stroke, Dementia & Heart Disease Laboratory, Western University, London, Ontario, Canada*
[c]*Department of Pathology and Laboratory Medicine, Perelman School of Medicine, Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, USA*
[d]*Department of Internal Medicine, Houston Methodist Hospital, Houston, TX, USA*
[e]*Department of Epidemiology, National Alzheimer's Coordinating Center, Seattle, WA, USA*
[f]*Ivey Business School, Western University, London, Ontario, Canada*
[g]*Canadian Institutes of Health Research (CIHR) Group on Vascular Cognitive Impairment, Department of Anatomy and Cell Biology, Western University, London, Ontario, Canada*

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% 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

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*Corresponding author. Tel.: (519) 685-8500 ext. 32823; Fax: (519) 663-3196.

E-mail address: lucianosposato@gmail.com or lsposato@uwo.ca (L.A.S.)

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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