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EDITORIAL COMMENT

The Head and the Heart

The Alzheimer's Connection*

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One in 9 people ≥65 years of age in the United States has Alzheimer's disease (AD), which is estimated to double by 2050 (1). This equates to about 4.4 million of the estimated 44 million people with AD worldwide in 2015 (1). In contrast, cardiovascular disease remains the most common cause of morbidity and mortality worldwide, with heart failure affecting an estimated 5.7 million U.S. adults (2,3). With the enormous toll of heart failure, the impact of AD may not seem nearly as daunting (2,3). Or is it?

AD is characterized by disruption of the blood-brain barrier, mitochondrial impairment, oxidative stress, and neuroinflammation related to amyloid-beta (Aβ) peptide accumulation, tau hyperphosphorylation, and decreases in acetylcholine levels (1). The most prevalent hypothesis for AD pathogenesis is the amyloid hypothesis, which proposes that accumulation of the Aβ peptide triggers an immune response that drives neuroinflammation and cell death (4). On top of dozens of preclinical studies implicating proteotoxicity, striking direct evidence for its role in human AD has been reported (5).

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In this issue of the *Journal*, Troncone et al. (6) ask whether the misfolded protein aggregation that causes the progressive cognitive dysfunction in AD also affects the heart. The investigators examined carefully processed brain and heart specimens from patients with clinically confirmed AD for Aβ protein aggregates so they could link proteotoxic protein concentration to cardiac performance data. They identified Aβ aggregates within cardiomyocytes and the cardiac interstitium in 4 patients with histopathologically confirmed AD, whereas no Aβ aggregates were found in the unaffected control patients. They sought to add functional significance to these findings by demonstrating slower relaxation velocity and prolonged calcium transients in cardiomyocytes isolated from 1 of the AD hearts. Echocardiographic evaluation of left ventricular diastolic function in a separate cohort of patients with AD identified impaired relaxation at an earlier age compared with age-matched control subjects. They also found a striking incremental age-dependent increase in left ventricular wall thickness in AD patients. Although these findings will require confirmation in larger populations, they represent an intriguing, and potentially paradigm-shifting, advance in our understanding of a highly morbid and largely untreatable disorder.

The investigators indicate the fact that heart failure is a risk factor for cognitive decline. Although the present study does not allow the mechanistic link between these 2 seemingly unrelated phenomena, innovative studies over the past 15 years may help bring some context to this supposition. First, the presence of proteotoxic soluble misfolded proteins (pre-amyloid oligomers) is common in most patients with heart failure investigated in multiple studies, but not in control subjects (7,8). With this recognition, the investigators went on to determine that the presence of misfolded proteins alone in cardiomyocytes could induce heart failure and rapid demise in vivo. Briefly, these studies involved mice with cardiomyocyte expression of an aggregate-prone protein (a

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Huntington's disease [HD] polyglutamine 83 repeat) and a control mouse expressing a shorter version of the same protein (an HD polyglutamine 19 repeat). They found that the cardiomyocyte expression of aggregate-prone polyglutamine 83 rapidly induces heart failure and death, whereas the shorter polyglutamine 19 version did not aggregate and had no deleterious effects on the heart (9). Patients with HD are at increased risk for developing heart failure (10), and mouse (11) and *Drosophila* (12) models of HD develop cardiomyopathy and arrhythmias. Interestingly, deposition of mutant huntingtin aggregates in the skeletal muscle of patients with HD and mouse models is associated with progressive muscular weakness (13). However, it is not clear that patients with AD are at increased risk for developing heart failure (14). None of the 4 patients with evidence of cardiac Aβ deposition in the present study had a history of heart failure (6). The grade 1 or 2 abnormalities in ventricular relaxation identified in the echocardiography cohort are very mild compared with the advanced diastolic dysfunction associated with cardiac amyloidosis and not necessarily expected to lead to clinical manifestations (6). Given the unfortunate prevalence of AD, expanded, focused, and longitudinal clinical research approaches should address this question readily.

Although the investigators present the first correlation of cardiac performance and Aβ protein deposition in the hearts of patients with AD, deposition of Aβ has been found in the vasculature in previous studies. Not only is Aβ deposited in the wall of cerebral microvessels in patients with AD, but it also is pathognomonic of cerebral amyloid angiopathy (15,16). Although much of what is known about Aβ is derived from studying cerebral vasculature, Aβ is present in human atherosclerotic lesions and platelets (17). Moreover, circulating levels of Aβ40 have been used to independently (from age, sex, glomerular filtration rate, left ventricular ejection fraction, high-sensitivity C-reactive protein, and high-sensitivity troponin T) predict cardiovascular death and major adverse cardiac events in patients with coronary heart disease and are associated with arterial stiffness progression, incident subclinical atherosclerosis, and incident coronary heart disease (18,19). Although the role of Aβ proteotoxicity in the pathogenesis of atherosclerosis has not been tested directly, these findings suggest that it is another mechanism to consider in patients with neurodegenerative proteotoxic diseases (AD, HD, Parkinson's disease), as well as proteotoxic diseases in other organs, such as the heart (e.g., mutation-associated desminopathies/myofibrillar myopathies, muscular dystrophies, and amyloidosis [mutation and senile forms], among others).

Like most preliminary reports, this paper raises as many questions as it answers. What is the source of the Aβ protein aggregates in the hearts of patients with AD? Similar deposits have been found in other organs of patients with AD (20), suggesting that circulating Aβ deposits variably in end organs. Multiple recent studies indicate that exosomes containing Aβ are released into the circulation from cells in the central nervous system (21). Intracellular processing of amyloid precursor protein generates Aβ peptides. Aβ typically is degraded in lysosomes but also can be packaged into intraluminal vesicles within the late endosomal compartment. These vesicles can fuse with the plasma membrane and are released as exosomes. Exosomes containing tau protein are also secreted into the bloodstream in Parkinson's disease (22), although deposition in the heart has not been described. These discoveries have led to the provocative notion that circulating exosomes may serve as a biomarker for disease severity in neurodegenerative disorders.

The therapeutic options for treating proteotoxicity in neurodegenerative and cardiac disease are emerging. In animal models of cardiomyocyte-specific pre-amyloid oligomer disease, up-regulation of autophagy and exercise extend the lives of mice considerably, indicating that the clearance of these aggregated proteins through these mechanisms was therapeutic (23,24).

Although the role of diet and exercise has been primarily guided toward prevention, its role in therapy may not be fully appreciated for many practical reasons (25). The current pharmacological therapies for AD primarily target symptoms (e.g., acetylcholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists) and, more recently, etiology-based therapies that target amyloid and tau are in development (1). In a recent landmark publication, Sevigny et al. (5) presented striking support of the amyloid hypothesis of AD in a double-blind, placebo-controlled, phase 1b randomized trial (Multiple Dose Study of Aducanumab [BIIB037] (Recombinant, Fully Human Anti-Aβ IgG1 mAb) in Participants With Prodromal or Mild Alzheimer's Disease); NCT01677572) using a human monoclonal antibody selectively targeting aggregated Aβ (aducanumab) (5,26). When patients with prodromal or mild AD were treated monthly with aducanumab for 1 year, a reduction in Aβ was identified using florbetapir positron emission tomographic imaging in a dose- and time-dependent manner (5). This paralleled a slowing of clinical decline (5). Like many preclinical studies preceding these findings, the aggregate-associated proteotoxicity appears to be mechanistically linked to the

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