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Brief communication

# Brain tau deposition linked to systemic causes of death in normal elderly

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ABSTRACT

The relationship between causes of death and 4 major neurodegenerative brain proteins (beta-amyloid, tau, alpha-synuclein, and the TAR DNA-binding protein of 43 kDa (TDP-43) were assessed in 94 cognitively normal elderly participants that died without a neurodegenerative disease. There was an association between tau and causes of death ($p = 0.01$). Tau in the brain was associated with a reduced likelihood of dying from systemic cancers ($p = 0.046$), and with an increased likelihood of dying from pulmonary ($p = 0.03$) and gastrointestinal ($p = 0.049$) diseases. There were no associations between beta-amyloid, alpha-synuclein, or TDP-43 and causes of death. Tau deposition in the brain may have a relationship with systemic causes of death, including cancer, in the cognitively normal elderly.



## 1. Introduction

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, are characterized by abnormal protein deposition in the brain. The 4 most common neurodegenerative brain proteins include the fibrillary protein aggregate beta-amyloid (Scheltens et al., 2016), microtubule-associated protein tau (Scheltens et al., 2016), the synaptic protein alpha-synuclein (Spillantini et al., 1997), and the highly conserved nuclear protein TAR DNA-binding protein of 43 kDa (TDP-43; Neumann et al., 2006). These proteins can also be identified in normal elderly individuals, albeit at low levels (Knopman et al., 2003; Uchino et al., 2015). Currently, treatments targeting neurodegenerative diseases focus on these abnormal proteins as a means to reverse or halt the neurodegenerative process. Recently, there has been a movement to treat patients at the very earliest stages of neurodegeneration, even in clinically normal individuals who are deemed to be at risk for developing disease at a later stage (http://a4study.org).

Systemic diseases are also important causes of morbidity and mortality in the elderly. Little is known, however, whether treatments targeting neurodegenerative proteins in at risk normal elderly could have any consequences on systemic diseases. This is a particularly important issue given that such individuals are now being considered for treatment trials that may modify, or cleanse the brain of neurodegenerative proteins. We assessed our cohort of neurologically normal elderly individuals who had died and completed a brain autopsy, to determine whether there is any association between neurodegenerative brain proteins and systemic causes of death. We hypothesized that there would be no such associations.

## 2. Materials and methods

Ninety-four participants that had enrolled in the Mayo Clinic Study of Aging (Roberts et al., 2008) and had died between 01/01/1999 and 12/31/2012 with a final diagnosis of clinically normal. None met neuropathological diagnostic criteria for any neurodegenerative disease, including Alzheimer's disease (Montine et al., 2012), (49% female; median age at death = 88 years [IQR:82-91]; median time from final clinical diagnosis to death = 1 year [IQR:0.6–2.2]); mean Braak stage = 2 (range:0–3; Braak et al.,

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2003). This study was approved by the Mayo Clinic IRB and all participants consented to research.

For this study, cause of death was categorized as cancer related, or into 1 of the following 4 categories based on the primary organ of involvement: brain, cardiac, gastrointestinal, and pulmonary (Fig. 1A). All remaining causes of death were lumped into an "other" category. All cases had undergone standard neuropathological brain examination according to consensus recommendations (Mirra et al., 1991) by expert neuropathologists (Joseph E. Parisi, Dennis W. Dickson). The presence/absence of the 4 major neurodegenerative-associated brain proteins (beta-amyloid, tau, alpha-synuclein, and TDP-43) was determined with immunohistochemistry performed on the following regions: brainstem, basal ganglia, hippocampus, amygdala, thalamus, and neocortex (frontal, temporal, and parietal). To be considered present, there had to be >stage 0 for beta-amyloid (Thal et al., 2002)/TDP-43 (Josephs et al., 2016)/alpha-synuclein (Braak et al., 2003) and >stage I for tau (Braak and Braak, 1991). We evaluated the association between cause of death and presence of each protein using a 2-sided Fisher's exact test. Proteins significantly associated with cause of death at $p < 0.05$ were further examined using logistic regression models in which cause of death was the event and the presence of the protein was the predictor, including age at death as a covariate. We summarize the associations as age-adjusted odds ratio (OR) estimate and 95% confidence interval (CI), representing the relative odds of a given cause of death among those with the protein versus without the protein. Without "assigning directionality" or making causal assumptions, ORs <1 indicate the protein is associated with a reduced likelihood of a given cause of death, whereas ORs >1 indicate the protein is associated with an increased likelihood.

## 3. Results

There were no associations between cause of death and beta-amyloid, alpha-synuclein, or TDP-43 (Table 1). There was an association between cause of death and tau ($p = 0.01$). This association

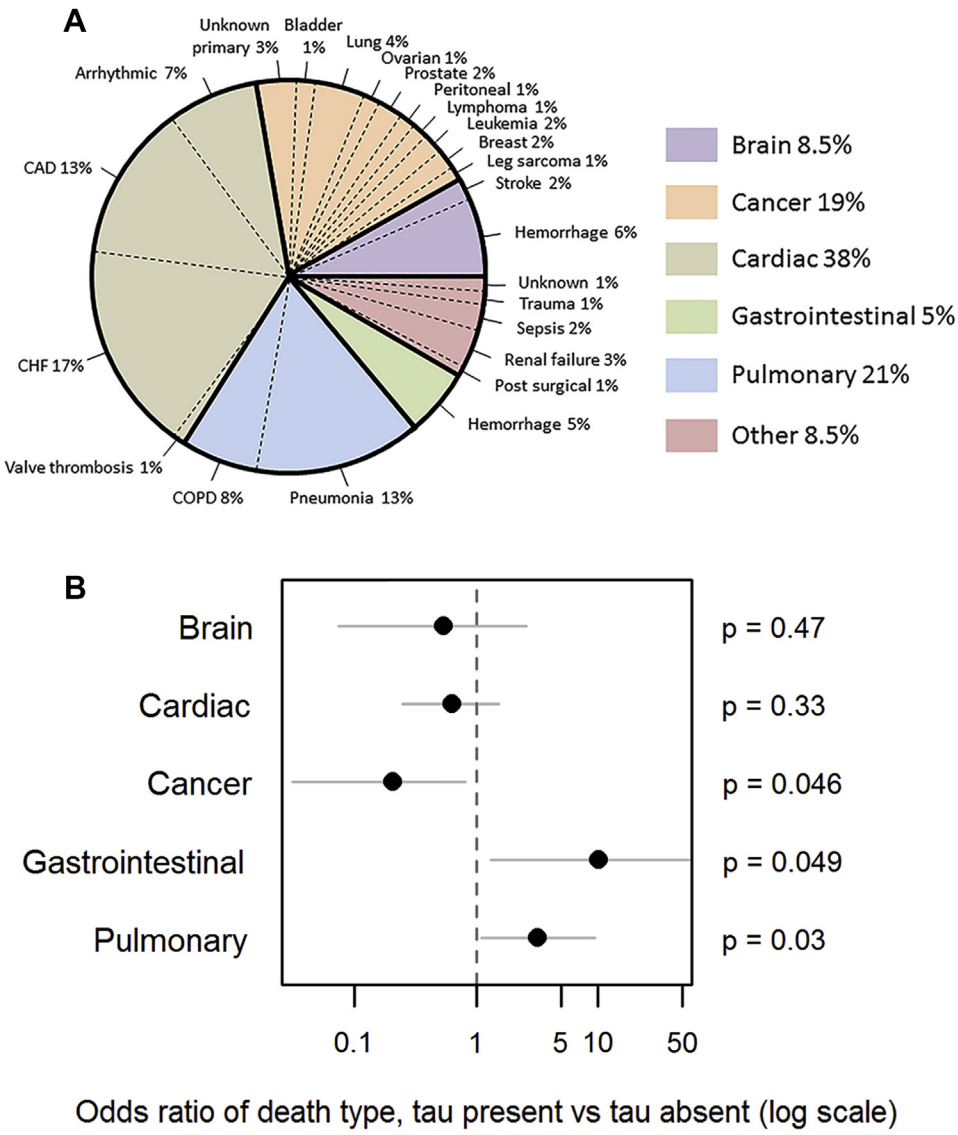


**Fig. 1.** The relationship between causes of death and neurodegenerative proteins. (A) shows the relative frequencies of causes and categories of death in the 94 neurologically normal participants. (B) shows the odds ratios and 95% CIs between causes of death and presence or absence of tau. *p*-values are from 2-sided Wald tests of the log odds from binary logistic regression models adjusted for age at death. A separate model was fit for each type of death. Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease.