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

Keith A. Josephs, MD, MST, MSc¹, Nirubol Tosakulwong, BS², Stephen D. Weigand, MS^{2,3}, Melissa E. Murray, PhD³, Jennifer L. Whitwell, PhD⁴, Joseph E. Parisi, MD⁵, Dennis W. Dickson, MD³, and Ronald C. Petersen, MD, PhD¹

¹Department of Neurology, Mayo Clinic, Rochester, MN

²Department of Health Sciences Research (Biostatistics), Mayo Clinic, Rochester, MN

³Department of Neuroscience, Mayo Clinic, Jacksonville, FL

⁴Department of Radiology, Mayo Clinic, Rochester, MN

⁵Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Abstract

The relationship between causes of death and four 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.

Keywords

mortality; tau; cancer; pulmonary disease; gastro-intestinal disease; normal aging

1. Introduction

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, are characterized by abnormal protein deposition in the brain. The four most common neurodegenerative brain proteins include the fibrillary protein aggregate beta-amyloid (Scheltens, et al., 2016), microtubule-associated protein tau (Scheltens, et al.,

Corresponding author: Keith A. Josephs, MD, MST, MSc, Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, Tel: 507-538-1038, josephs.keith@mayo.edu.

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2016), the synaptic protein alpha-synuclein (Spillantini, et al., 1997), and the highly conserved nuclear protein TAR DNA-binding protein of 43kDa (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 later developing disease (<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., 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 one of the following four categories based on the primary organ of involvement: brain, cardiac, gastrointestinal and pulmonary (Figure 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 an expert neuropathologists (DWD or JEP). The presence/absence of the four major neurodegenerative-associated brain proteins (beta-amyloid, tau, alpha-synuclein and TDP-43) were 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 two-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 estimate and 95% 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,

odds ratios <1 indicate the protein is associated with a reduced likelihood of a given cause of death while odds ratios >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 was driven by a difference in proportion between tau-positive and tau-negative participants that died from cancer versus a difference in proportion between tau-positive and tau-negative participants that died from gastrointestinal causes of death ($p=0.008$), as well as proportional differences between cancer versus pulmonary causes of death ($p=0.005$). Tau-positive participants had a reduced odds of cancer death (OR, 0.20; 95% CI 0.03–0.83; $p=0.046$) after adjusting for age at death (Figure 1B). In other words, the odds of dying from cancer in *tau-negative* participants was an estimated 4.9 (95% CI, 1.2–32.7) times higher than the odds of dying from cancer in *tau-positive* participants. Conversely, the odds of dying from gastrointestinal causes of death in tau-positive participants was 10.2 (95% CI, 1.3–213.3) times higher than the odds of dying from gastrointestinal causes of death in tau-negative participants ($p=0.049$) (Figure 1B). Similarly, the odds of dying from pulmonary causes of death in tau-positive participants was 3.2 (95% CI, 1.1–9.5) times higher than the odds of dying from pulmonary causes of death in tau-negative participants ($p=0.03$) (Figure 1B). While the majority of tau positive cases showed mixed pathology (79%), there was no evidence that the association between tau and cancer would differ between cases with isolated tau and cases with mixed pathologies. This was less clear for the associations with pulmonary and gastrointestinal disease (Supplementary Figure 1).

4. Discussion

Of our findings, the one that could have the biggest implications is the association between absence of tau and death from cancer in normal elderly which is concerning as it raises the possibility that treatments that reduce the levels of brain tau in this population could have far reaching consequences on death from cancer. We did not observe any relationship between cancer and beta-amyloid, alpha-synuclein or TDP-43, suggesting the relationship is specific to tau in normal elderly. Interestingly, an inverse association has also been identified between cancer and Alzheimer's disease (Driver, et al., 2012, Zhang, et al., 2015). Therefore, although our findings are specific to normal aging, and not disease state, these findings illuminate the fact that we need to be more cognizant of what effects targeting and treating a neurodegenerative brain disease may have outside of the brain. The results regarding gastrointestinal and pulmonary disease, while appearing less ominous, further supports an association between tau and systemic causes of death, and, hence, highlights the need for monitoring the effects of neurodegenerative treatments on systemic causes of death.

This study was based on a neuropathological cohort and hence may be biased by who undergoes autopsy. However, causes of death in our cohort were very similar to causes of death in individuals $>$ age 65 according to the 2014 US census (Supplementary Figure 2). The strengths are the very short interval between final clinical assessment and death, which increases confidence that these individuals did not exhibit clinical features of a

neurodegenerative disease prior to death, and that we were able to determine causes of death in all 94 individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- This is a mortality histological study of 94 cognitively normal elderly
- Tau was associated with a reduced likelihood of dying from systemic cancers
- Tau was associated with an increased likelihood of pulmonary and GI diseases
- Tau in the brain may be related with systemic causes of death in the elderly

Figure 1. The relationship between causes of death and neurodegenerative proteins

Panel A shows the relative frequencies of causes and categories of death in the 94 neurologically normal participants. CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease. Panel B shows the odds ratios and 95% CIs between causes of death and presence or absence of tau. P-values are from two-sided Wald tests of the log odds from a binary logistic regression models adjusted for age at death. A separate model was fit for each type of death.

Table 1

Summary of protein status by cause of death

	β-Amyloid (p = 0.82)		Tau (p = 0.01)		α-Synuclein (p = 0.96)		TDP-43 (p = 0.71)	
	Negative (n=52)	Positive (n=42)	Negative (n=61)	Positive (n=33)	Negative (n=86)	Positive (n=8)	Negative (n=68)	Positive (n=26)
Brain	3 (38%)	5 (62%)	6 (75%)	2 (25%)	7 (88%)	1 (12%)	7 (88%)	1 (12%)
Cancer	10 (56%)	8 (44%)	16 (89%)	2 (11%)	17 (94%)	1 (6%)	14 (78%)	4 (22%)
Cardiac	20 (56%)	16 (44%)	25 (69%)	11 (31%)	32 (89%)	4 (11%)	24 (67%)	12 (33%)
Pulmonary	11 (58%)	8 (42%)	8 (42%)	11 (58%)	17 (89%)	2 (11%)	12 (63%)	7 (37%)
Gastrointestinal	4 (80%)	1 (20%)	1 (20%)	4 (80%)	5 (100%)	0 (0%)	4 (80%)	1 (20%)
Other	4 (50%)	4 (50%)	5 (62%)	3 (38%)	8 (100%)	0 (0%)	7 (88%)	1 (12%)

Note: p-values are from a two-sided Fisher's exact test of the association between cause of death and protein based on a 6x2 cross-classification table.