Short Communication

A Lack of Correlation between the Incidence of Lyme Disease and Deaths due to Alzheimer's Disease

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Abstract. Reports that Lyme disease (LD) causes Alzheimer's disease (AD) have appeared in academic journals and online. If the biological agent *Borrelia burgdorferi* that causes LD also causes AD, then areas with the highest levels of LD should have significantly higher numbers of deaths due to AD compared to low LD areas. Here we show there is no statistically significant correlation between the incidence of LD and deaths due to AD in the US. Furthermore, the 13 states with the highest deaths due to AD were statistically different ($p < 0.0001$) from those with high LD incidence.

Keywords: Alzheimer's disease, *Borrelia burgdorferi*, disease incidence, lyme disease

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with no proven initiating cause. Currently over 5,000,000 individuals in the US have the disease, which is the sixth major cause of death [1]. Understanding the causes of AD is a medical priority. Lyme disease (LD), which leads to the neurodegenerative disease neuroborreliosis, is caused by the bacterium *Borrelia burgdorferi* [2]. Independent research groups have presented different lines of evidence arguing that LD can cause AD [3–6]. Thus there are valid reasons to believe that LD could cause AD. *B. burgdorferi* is a member of the spirochete family of bacteria, and spirochetes such as *Treponema pallidum* can cause dementia [7]. A diversity of postmortem techniques (e.g., ultrastructural visualization, immunolocalization, western blot,

RNA sequence analysis, ELISA, PCR, etc.) have suggested the presence of various spirochetes, including *B. burgdorferi*, in the brains of AD individuals [3–5, 8]. The relationship between LD and AD has also been supported by analysis of existing data using Koch's and Hill's Postulates [8]. What is lacking to fulfill these postulates is the isolation of functional entities (e.g., *B. burgdorferi*) followed by proof of their ability to induce AD-related events in tissue culture cells.

Two hallmarks of AD are the build-up of plaques and tangles in the brain which are linked to neurodegenerative events [9, 10]. *Borrelia burgdorferi* can induce both amyloid-β and phosphorylated tau formation in tissue culture cells [5]. Thus accumulating circumstantial evidence does suggest a link between LD and AD. A quick Internet search reveals that this link has spawned widespread concern (e.g., [11, 12]). The ongoing interest and concern makes it critical to validate or disprove any relationship between the two diseases. Here we test a simple hypothesis: If LD does cause AD, then the incidence of deaths due to AD

Table 1
Two-by-two contingency table of the states with high and low Alzheimer's disease (AD) levels that also exhibit either high or low Lyme disease (LD) levels.

	High LD	Low LD
High AD	1	7
Low AD	7	2

Fisher's exact test two-tailed p-value = 0.015. This statistically significant difference indicates a correlation between high AD and low LD and/or low AD and high LD, demonstrating that high AD is not correlated with high LD.

should higher where LD is most prevalent compared to low LD areas.

MATERIALS AND METHODS

To our knowledge, location-specific data for the reporting of cases of both LD and deaths by AD is only available for the US. The age-adjusted death rates for AD were taken from Fig. 4 in Tejada [13]. The data for the reported cases of LD by state (2002–2011) were from the Centers of Disease Control and Prevention website (June 25, 2013 [14]). Although many factors affect the accuracy of the disease including the consistency of reporting of LD and deaths AD, which will varies between states, it is assumed that this variability is negated by the comparison of 13 different states for each disease. The data sets used were the

best and most current available at the time of writing. Means and standard deviations were calculated for sets of 13 states: those with the highest incidence of LD (18.978–68.222 cases/1000) and those with low to non-existent (0.0–0.189) LD. The Mann-Whitney U test was used to determine if AD is more prevalent in states with high LD compared to those with low LD. AD incidence in the 13 states with the highest LD incidence (MN, MD, VT, NY, WI, RI, ME, PA, NJ, MA, NH, DE, and CT) was compared with AD incidence in the 13 states with the lowest LD incidence (CO, AR, OK, LA, AZ, MS, NM, UT, GA, AL, SD, MT, and WA). Hawaii, which has a zero incidence of LD, was excluded because it is a distinct entity outside of the contiguous US states. Fisher's exact test was used to determine if the 13 states with the highest AD incidence (LA, VT, CO, AL, MS, IA, KY, SC, AZ, SD, ND, TN, and WA) were also states with high LD incidence. Fisher's exact test was also used to determine if high AD was correlated with high LD in a two-by-two contingency table (Table 1).

RESULTS

The mean value for the incidence of LD was calculated for each state and plotted beside AD rates (Fig. 1). With the exception of Vermont, the 13 highest LD
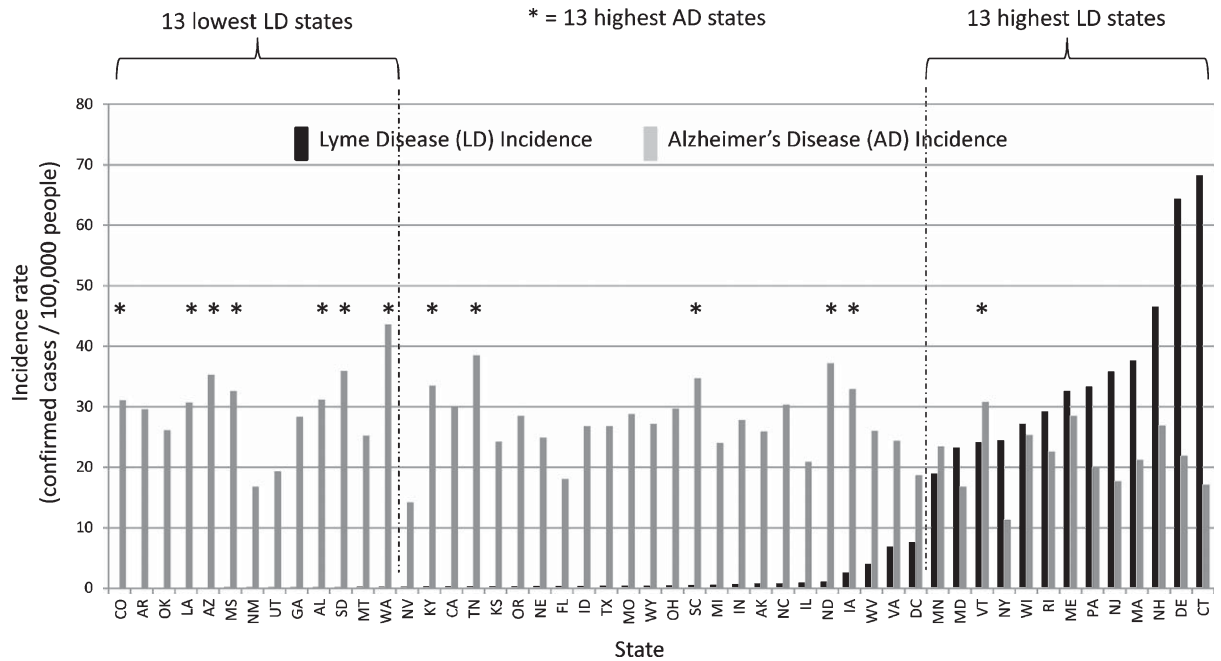

Fig. 1. Incidence of Lyme disease (LD, black) and of deaths caused by Alzheimer's disease (AD, grey) by U.S. state. States are ordered by increasing LD rate. The 13 highest and lowest LD rates (brackets) and 13 highest AD rates (*) are indicated.
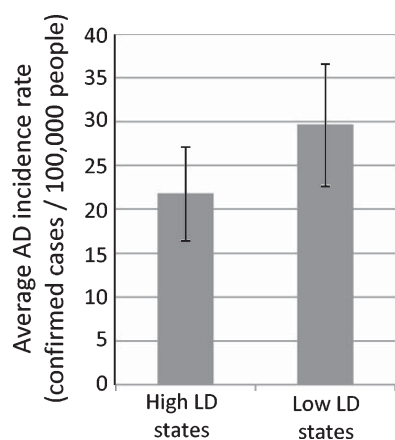
Fig. 2. Deaths by Alzheimer's disease (AD) rate in high versus low Lyme disease (LD) states.

states are different from the 13 highest AD states. In fact, 7 of the 13 highest LD states fall within the 13 states with the lowest incidence of deaths due to AD. We tested these observations against the assumption that if LD and AD were correlated, they should share most if not all of the high incidence states in common. The results of the statistical analysis reveal the 13 highest AD states are different from the 13 highest LD states ($p < 0.0001$). To determine if there is any correlation between AD and LD, the annual incidence of deaths due to AD were compared between U.S. states which had the highest and lowest incidences of LD. Although AD incidence was slightly greater in states with low LD, this difference was not significant. Therefore, AD is not more prevalent in high LD states (Fig. 2). Taken one step further, Table 1 presents a two-by-two contingency table of high and low AD states versus high and low LD states. Fisher's exact test resulted in a two-tailed p-value of 0.015 indicating a correlation between either low AD and high LD and/or high AD and low LD. This means high AD is not correlated with high LD.

DISCUSSION

If *B. burgdorferi* causes AD, then areas with the highest incidence of LD should also have significantly higher numbers of deaths due to AD. A simple graphic presentation of the incidence of LD state-by-state in the US versus the incidence of deaths due to AD clearly reveals a lack of co-incidence between these two variables. When deaths due to AD in 13 of the states with the highest incidence of LD were compared with those with the lowest, there is no statistically significant dif-

ference between them. Furthermore, if LD and AD are correlated, they would have most of the high incidence states in common. However, the 13 highest AD states are significantly different ($p < 0.0001$) from the 13 highest LD states. Moreover, Table 1 demonstrates not only a lack of correlation but rather an association between high AD and low LD suggesting one disease excludes the other. However due to the small numbers, we interpret the data as simply showing no relationship between the two diseases. The lack of correlation between the incidence of LD and AD on a state-by-state basis and the lack of any demonstrated relationship between the two diseases argue there is no link between them. In support of this, Krut et al. [15] examined the levels of AD-specific biomarkers in cerebrospinal fluid revealing that the neuroborreliosis profiles were different from the AD profiles, suggesting some of the early correlative studies between the two diseases may not be accurate.

It is important to recognize that LD and AD are two distinct diseases with different latency periods. Although LD has a predominant effect on young males aged 5–9, the disease significantly affects individuals of all ages [16]. While it might seem that a disease affecting young people might not translate to an effect in aging individuals, recent research has revealed that the cause(s) of AD occur decades before any symptoms of the disease manifest themselves [10].

The authors have used the best data available to evaluate the proposed link between LD and AD. This does not mean that these data are without issues including consistency of data collection between states and the two diseases, among other variables. What the data do reveal is that there is no evidence to argue that these two diseases are in any way related which hopefully will be communicated to those who have concerns about the relationship between LD and AD.

ACKNOWLEDGMENTS

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