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Featured Article

Mixed neuropathologies and estimated rates of clinical progression in a large autopsy sample

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Abstract

Introduction: Whether co-occurring neuropathologies interact or independently affect clinical disease progression is uncertain. We estimated rates of clinical progression and tested whether associations between clinical progression and Alzheimer's disease neuropathology (ADNP) were modified by co-occurring Lewy body disease (LBD) or vascular brain injury (VBI).

Methods: Linear mixed effects models evaluated longitudinal trends in the Clinical Dementia Rating Scale Sum of Boxes on 2046 autopsied participants seen at a U.S. Alzheimer's Disease Center.

Results: Annual clinical progression was slightly faster for ADNP + LBD compared with ADNP only ($P = .06$) and slightly slower for ADNP + VBI ($P = .003$). Differences in progression were less than expected if each neuropathology independently contributed to progression; ADNP interacted with LBD ($P = .002$) and VBI ($P = .003$). In secondary models, the effect of additional pathologies on clinical progression was greater in those with intermediate compared with high levels of ADNP.

Discussion: The impact of co-occurring pathologies on progression may depend on severity of ADNP.

Keywords: Alzheimer's disease neuropathology; Lewy body disease; Cerebrovascular disease; Mixed neuropathology; Clinical progression

1. Introduction

Up to 75% of autopsied older adults have multiple brain pathologies, known as mixed neuropathologies [1–3]. Research focusing on Alzheimer's disease, whether based on clinical criteria, biomarkers, or neuropathologic diagnosis, may ignore other relevant brain comorbidities [4]. Evidence as to whether neuropathologies interact synergistically or act independently to influence the dementia syndrome is inconsistent.

Focus has traditionally centered on concomitant vascular brain injury (VBI), such as infarcts, and Alzheimer's disease neuropathology (ADNP) [5–7]. Although one study reported a synergistic interaction between ADNP and VBI for memory scores [8], other studies suggest that ADNP and VBI do not interact [9,10]. ADNP in more severe stages may overwhelm the effects of VBI [11,12]. Lewy body disease (LBD) and ADNP also commonly coexist [13–16] and are associated with cognitive decline [17,18]. Lewy body development may be enhanced by ADNP [13,19]. Only one study reported testing whether concomitant LBD

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modified the association between ADNP and cognition, but they found no significant interactions [16].

To our knowledge, no prior studies have used statistical modeling to extensively examine whether LBD or VBI interact with ADNP in association with clinical progression over time. Such research could help clarify the role of mixed neuropathologies in clinical progression, with implications for prevention and treatment strategies. Testing interactions requires a large sample size. Thus, we used National Alzheimer's Coordinating Center (NACC) data on autopsied participants who were clinically evaluated at a U.S. National Institute on Aging-Funded Alzheimer's Disease Center (ADC). We evaluated whether autopsied older adults with ADNP with co-occurring LBD or VBI had faster overall clinical progression compared with those with single and low neuropathologies. We tested whether LBD or VBI modified the association between ADNP and progression.

2. Methods

2.1. Study sample

NACC maintains the Uniform Data Set (UDS) on participants who had been prospectively evaluated and autopsied by an ADC since September 2005. Participants were enrolled with any level of cognition and were examined annually in-person using a standard protocol, described in detail elsewhere [20,21]. Neuropathologic data were collected on participants who had died and consented to autopsy. All participants provided written informed consent, and institutional review board approval was obtained from all individual ADCs.

This analysis focused on autopsied UDS participants with at least one clinical visit between September 2005 and September 2015. Participants were excluded based on the following criteria: (1) rare cause of dementia that may conflict with neuropathologic assessment of ADNP or confound clinical conditions, such as Down's syndrome, autosomal dominant genetic diseases, or frontotemporal lobar degeneration; (2) missing information on covariates and/or neuropathologic information on ADNP, LBD, or VBI; and (3) no ADNP, LBD, or VBI but the presence of other pathologic burden such as hippocampal sclerosis, Braak stage V to VI with sparse or no neuritic plaques, frequent neuritic plaques but Braak stage 0 to II, other major pathologies, or white matter disease. In addition, in the main analyses we excluded participants without a clinical visit proximal death (e.g., last visit >2 years before death) because of concern that the rate of progression and level of impairment may change closer to death but would have been unobserved. Given these exclusions, 2046 participants with at least one clinical visit remained for analyses (see Supplementary Fig. 1 for sample flowchart). Individuals with only one visit ($n = 475$) were included in analytic models at baseline but did not contribute to longitudinal estimates.

To use additional information on VBI that was not available for all NACC participants, we conducted a subanalysis in ADC participants seen at the Oregon Health & Science University (OHSU) ($n = 211$) and the University of Washington ($n = 82$). These two ADCs have a joint agreement as part of the Pacific Northwest Dementia and Aging Neuropathology Group (PANDA) to follow the same neuropathologic assessment protocol, an additional benefit of this subanalysis. Both ADCs recruit patients seen in clinic for enrollment into the UDS; however, OHSU also recruited participants from a number of cohort studies focusing on healthy aging and described elsewhere [22–25]. Subsequently, we will use the term PANDA ADCs to refer to OHSU and University of Washington ADCs combined.

2.2. Neuropathologic features

ADCs follow consensus guidelines but conduct neuropathologic assessments according to their own protocols, which vary between sites. ADNP was defined by Consortium to Establish a Registry for Alzheimer's Disease scores of neuritic plaque density (none, sparse, moderate, and frequent) [26] and Braak stage for tau neurofibrillary pathology (none, I–II, III–IV, and V–VI) [27]. ADNP was defined regardless of a participant's cognitive status and was categorized semiquantitatively as low (no/sparse neuritic plaques and any Braak stage or any neuritic plaques and Braak stage 0–II), intermediate (moderate/frequent CERAD plaques and Braak stage III–IV), and high (moderate/frequent plaques and Braak stage V–VI). This classification overlaps with the 2012 National Institute on Aging-Alzheimer's Association criteria [28]; however, Thal et al. [29] phasing for amyloid plaques was not available for most participants. Assessment for Lewy bodies followed recognized guidelines [30]. LBD was defined as the presence of Lewy bodies in any brain region examined. LBD subtype was classified as none, brainstem predominant, limbic (transitional), neocortical (diffuse), or other or unknown region.

Cognitive impairment because of vascular disease is usually considered a result of VBI caused by vessel disorders and other vascular mechanisms [31]. We focused on VBI, as defined by gross and microscopic infarcts, because these are associated with cognitive impairment in other studies [32,33]. VBI was defined as any gross infarcts (small or large artery) or any cortical microinfarcts (infarcts in the cortex only seen microscopically) regardless of age. Some studies suggest multiple VBI, in particular microinfarcts, may be needed to affect cognition [32,34]. Information on the number of microinfarcts was not available for most NACC participants. To address this limitation, we abstracted additional data on the number of microinfarcts from neuropathology reports of autopsy PANDA ADC participants. The number (0, 1, 2, 3, or 4, or more) of cortical and subcortical microinfarcts was assessed separately following methods developed in the Honolulu Asia Aging Study [35]. Cerebral amyloid angiopathy,