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Featured Article

The limbic and neocortical contribution of α-synuclein, tau, and β-amyloid to disease duration in dementia with Lewy bodies

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Abstract

Introduction: We sought to assess the individual and combined contribution of limbic and neocortical α-synuclein, tau, and β-amyloid to duration of illness in dementia with Lewy bodies (DLB).
Methods: Quantitative digital pathology of neocortical and limbic α-synuclein, tau, and β-amyloid was assessed in 49 patients with clinically probable DLB. Regression modeling examined the unique and shared contribution of each pathology to the variance of illness duration.
Results: Patients with diffuse Lewy body disease had more severe pathology of each type and a shorter duration of illness than individuals with transitional Lewy body disease. The three pathologies accounted for 25% of the total variance of duration of illness, with 19% accounted for by α-synuclein alone or in combination with tau and β-amyloid. When the diffuse Lewy body disease group was examined separately, α-synuclein deposition significantly exceeded that of tau and β-amyloid. In this model, 20% of 24% total variance in the model for duration of illness was accounted for independently by α-synuclein.
Discussion: In DLB, α-synuclein is an important predictor of disease duration, both independently and synergistically with tau and β-amyloid.

Keywords: Lewy body; Alzheimer's disease; Pathology; Parkinsonism; REM sleep behavior disorder; Commonality analysis

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1. Introduction

The histopathology of dementia with Lewy bodies (DLB) is characterized by α-synuclein that accumulates in cell bodies as Lewy bodies and in cell processes as Lewy neurites. Lewy-related pathology has two main distributions in DLB. For some patients, it is predominantly located in brainstem, subcortical, and limbic regions, whereas for others it is diffusely distributed to neocortical regions in addition to brainstem, subcortical, and limbic regions [1]. Neuropathologic heterogeneity of DLB is further complicated by the co-occurrence of Alzheimer's disease (AD)–related pathology. Extracellular β-amyloid diffuse plaques and senile plaques with tau-positive neurites can commonly occur in DLB [2,3]. Although the density and distribution of neurofibrillary tangle (NFT) pathology is typically less in DLB than AD [4,5], some DLB patients have many NFTs [6]. In Parkinson's disease, the extent of the Lewy-related pathology on its own, and additively with tau and β-amyloid, correlates with development of dementia [7–10]. Less is known about the role of these misfolded proteins in the clinical presentation and disease course of DLB. Understanding the contribution of these protein aggregates to DLB is important, particularly, as antemortem imaging markers are being developed for each protein [11], and as the field moves forward to develop disease-modifying therapies designed to target specific proteins.

Patients with DLB tend to have a shorter survival than those with AD [5]. Rapid disease progression in DLB is often attributed to the cortical AD-related pathology [12,13], although this is not consistently found [14]. The role of α-synuclein may be underestimated when sampling is restricted to neocortical regions or in studies that do not quantify Lewy neurites. Also, there may be additive or synergistic effects of co-occurring Lewy- and AD-related pathologies that may not be evident when examining the independent contributions of each pathology [15–17]. To obtain a more representative quantitative measure of the neuronal and neuritic burden of α-synuclein and tau, and of extracellular β-amyloid, this study used digital pathology techniques. This approach allows for a more accurate estimate of pathology than semiquantitative or staging rubrics [18] and provides the opportunity to assess the separate and combined contribution of pathologies to duration of illness.

2. Methods

2.1. Participants

Participants who met criteria for clinically probable DLB (n = 49) were recruited from the Memory Disorders and Movement Disorders clinics and followed prospectively through the Mayo Clinic Alzheimer's Disease Research Center at the Mayo Clinic in Jacksonville, Florida. Annual clinical visits incorporated a clinical interview, neurologic examination, neuropsychological assessment, and a series of informant questionnaires. If the patient was untestable or unable to come to the clinic, we carried out a telephone interview and obtained the informant questionnaires. The diagnosis of DLB was made on the basis of the current criteria and required dementia plus two of four clinical features (visual hallucinations, fluctuations, parkinsonism, and rapid eye movement [REM] sleep behavior disorder) [19,20]. A non-cognitive rating of dementia severity was assessed with the Global Deterioration Scale [21]. The presence of REM sleep behavior disorder was obtained through a clinical interview and the Mayo Sleep Questionnaire [22]. The presence of fluctuations was based on a score of 3 or 4 on the 4-item Mayo Fluctuations Scale [23]. The presence of parkinsonism was based on neurologic examination and presence of two of four cardinal features of bradykinesia, such as slowness of movement, rigidity, tremor, and postural instability. The Unified Parkinson's Disease Rating Scale was used to objectively quantify parkinsonism severity [24]. Duration of illness was operationalized to represent the temporal interval from the estimated onset of cognitive impairment to time of death. This study was approved by the Mayo Clinic Institutional Review Board, and informed consent for participation was obtained from every subject and/or an appropriate surrogate.

2.2. Neuropathologic assessments

All cases underwent neuropathologic assessments that included macroscopic and microscopic evaluation. Brains were sampled using a systematic and standardized protocol, in which neocortical samples were taken before brain dissection to assure uniformity of sampling and to obtain orthogonal sections of the cortical ribbon. Tissue sections were embedded in paraffin, and 5-μm thick sections were mounted on glass slides for histological examination and immunohistochemistry. Thioflavin-S fluorescent microscopy was used to assess AD-related pathology, which included counts of NFTs and senile plaques in six cortical regions, four sectors of the hippocampus and two subregions of the amygdala and the basal nucleus of Meynert. The Braak NFT stage [25] and Thal amyloid phase [26] were assigned based on the distribution of NFTs and senile plaques, respectively, using previously published methods [27,28]. For diagnostic and staging purposes, immunohistochemistry was performed on all cases with an α-synuclein antibody (NACP, 1:3000, rabbit polyclonal; Mayo Clinic's antibody) using a protocol (formic acid pretreatment and DAKO DAB polymer signal detection) that has been shown to be comparable or better than other methods [29]. Counts of Lewy bodies (at 200× magnification) were assessed in middle frontal, superior temporal, inferior parietal, cingulate, and parahippocampal cortices, as well as the amygdala. Semiquantitative ratings of the extent of the α-synuclein pathology and neuronal loss were made in the nucleus basalis of Meynert, substantia nigra, and locus coeruleus.

When assigning subtypes of Lewy body disease, the presence, density, semiquantitative scores, and distribution of Lewy-related pathology followed recommendations of the