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Authors

Savica, Rodolfo
Beach, Thomas G
Hentz, Joseph G
et al.

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Lewy body pathology in Alzheimer's disease: A Clinical-pathologic prospective study

Rodolfo Savica[1,2] **[Conception, organization, execution of research, Statistical analysis - design, execution and review, Writing of the first draft, Critical review and revision of final version]**, **Thomas G. Beach**[3] **[Statistical analysis - design, execution and review, Critical review and revision of final version]**, **Joseph G. Hentz**[4] **[Critical review and revision of final version]**, **Marwan N. Sabbagh**[6,8,11] **[Critical review and revision of final version]**, **Geidy Serrano**[3] **[Critical review and revision of final version]**, **Lucia I. Sue**[3] **[Critical review and revision of final version]**, **Brittany N. Dugger**[7] **[Critical review and revision of final version]**, **Holly A. Shill**[8] **[Critical review and revision of final version]**, **Erika Driver-Dunckley**[9] **[Critical review and revision of final version]**, **John N. Caviness**[9] **[Critical review and revision of final version]**, **Shyamal H. Mehta**[9] **[Critical review and revision of final version]**, **Sandra A. Jacobson**[10] **[Critical review and revision of final version]**, **Christine M. Belden**[5] **[Critical review and revision of final version]**, **Kathryn J. Davis**[3] **[Critical review and revision of final version]**, **Edward Zamrini**[5] **[Critical review and revision of final version]**, **David R. Shprecher**[5,6] **[Critical review and revision of final version]**, and **Charles H Adler**[9] **[Critical review and revision of final version]**

[1]Department of Neurology, Mayo Clinic, Rochester, MN

[2]Department of Health Science Research, Mayo Clinic, Rochester, MN

[3]Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ

[4]Section of Biostatistics, Mayo Clinic Arizona

[5]Cleo Roberts Center, Banner Sun Health Research Institute, Sun City, AZ

[6]Department of Neurology, University of Arizona College of Medicine, Phoenix, AZ

[7]Department of Neurology, University of California Davis, Davis, CA

[8]Barrow Neurological Institute, Phoenix, AZ

[9]Department of Neurology, Mayo Clinic College of Medicine, Scottsdale, Arizona

[10]Department of Psychiatry, University of Arizona College of Medicine, Phoenix, AZ

[11]Cleveland Clinic Foundation, Cleveland, OH

Abstract

Objective: Identify clinical features predictive of Lewy body pathology in AD patients in an ongoing longitudinal clinicopathologic study.

Corresponding author: Rodolfo Savica, MD, PhD, Department of Neurology, Mayo Clinic, Rochester, MN 55905, Savica.rodolfo@mayo.edu.

Material & Methods: We queried the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) database for dementia cases with AD pathology (1997–2015). Subjects received longitudinal comprehensive clinical evaluations including motor/neuropsychological assessment and Apo-E4 genotype. All cases were autopsied and had standard neuropathological assessments for AD and Lewy-type synucleinopathy (LTS). Subjects were categorized based on standardized pathological criteria with AD cases that had LTS but did not meet DLB pathologic criteria being categorized as ADLB. We performed pairwise comparison between the different diagnoses and a multivariable modeling to identify clinical symptoms that predict the pathological diagnosis.

Results: We identified 32 DLB/AD, 54 ADLB, 70 AD only, and 41 PDD/AD cases. AD subjects with LTS pathology had higher UPDRS II and III total scores as well as higher individual scores compared to AD alone. While depression scales and Trail-making Test A correlated significantly with LTS, other neuropsychological variables were not significantly different. Apo E4 occurrence was similar in all groups (40–49%).

Conclusions: Our study suggests that the presence (or absence) of LTS influences motor and non-motor clinical findings in AD patients. These findings may lead to biomarkers that allow for more targeted treatment of AD.

Keywords

Alzheimer’s disease; Lewy bodies; neuropsychology; pathology

Introduction

Neurodegenerative disorders are complex diseases characterized by gradual clinical progression. Alzheimer’s disease (AD) is the most common dementia and accounts for about 60% of cases (1); the second most common is dementia with Lewy bodies (DLB). Cognitive decline is the most common symptom of all forms of dementia; however, AD and DLB share additional clinical and pathological features. Indeed, neurofibrillary tangles and amyloid plaques are the typical pathologic findings of AD; whereas α-synuclein deposits forming Lewy bodies (LB) and related neuritic pathology are the characteristic features of DLB. Given the clinical overlap, the definitive diagnosis of these disorders is still based on the pathology findings at autopsy, although certain clinical symptoms and features may improve the diagnostic accuracy during a patient’s lifetime. While clinical diagnosis of DLB has relatively high specificity (>80%), the sensitivity is low (20–40%) (2). In addition, autopsy studies have shown coexisting AD pathology in most DLB cases, and ≥60% of AD cases have Lewy-type synucleinopathy (LTS) pathology (AD with LBs that do not meet DLB pathological criteria, or AD with DLB) (3). Neuroimaging and electrophysiological tests may differentiate between the different disorders but are not validated by autopsy studies, nor are they specific for these disorders. Also, these tests may not be accessible to all the medical professionals involved in the care of these patients.

We report the findings of an autopsy series of dementia cases with neuropathologically confirmed AD. We identified a number of clinical features that may predict the presence of co-occurring LTS in the post-mortem pathological exam. Our study will further elucidate the

role of specific motor and non-motor findings in the diagnosis of the LTS deposition and the clinical features of AD cases with mixed pathology that do not meet the criteria for DLB.

Material & Methods

Case Ascertainment

We queried the database of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) to identify all cases of dementia with a pathologic diagnosis of AD from 1997 to 2015 with autopsies performed by Banner Sun Health Research Institute Brain and Body Donation Program (BBDP). Details regarding the clinical and pathologic methods of AZSAND and the BBDP have previously been published (4, 5). Briefly, all subjects enrolled in the study live in Maricopa County, AZ, and sign an IRB-approved written informed consent (or have written informed consent signed by a legal representative). From enrollment until death, patients have annual clinical assessments and then donate their brains and other organs after death. We included only individuals with a pathological diagnosis of AD; we excluded all other neurodegenerative disorders.

Clinical Assessment

Each participant received annual physical, neurological, and cognitive examinations by movement disorder and behavioral neurology specialists. Further details have been described previously (5–7). All subjects underwent a standardized neuropsychological test battery including tests to explore global cognitive function and specific cognitive domains such as Hamilton depression scale (HAM-D), Geriatric Depression Scale (GDS), Functional Assessment Questionnaire (FAQ), Mini Mental State Examination (MMSE), Judgement of Line Orientation, Clock Drawing, Stroop Interference, Controlled Oral Word Association Test (COWAT), Animal Fluency (AVLT), Boston Naming Test (BNT), Trail Making Test A and B. The movement examination included the complete Unified Parkinson Disease Rating Scale (UPDRS) for all subjects. In addition, Apo E4 genetic analyses were performed in each subject enrolled.

Neuropathology assessment

All subjects underwent autopsy and a standardized neuropathological assessment; details regarding neuropathological collection are reported elsewhere (4) (5). All cases had neuritic plaque density ratings done according to the Consortium to Establish a Registry for Alzheimer Disease (CERAD) criteria for the diagnosis of AD (8), and all cases were assigned a Braak neurofibrillary stage and were rated according to National Institute on Aging (NIA)-Reagan criteria (9, 10).

Subjects received a clinicopathological diagnosis of AD if they had a clinical history of dementia and were classified as “intermediate” or “high” according to the NIA-Reagan criteria (10). PDD was differentiated from DLB according to the third DLB consortium criteria; PDD was diagnosed if diagnostic criteria for PD were met (11), and parkinsonism began at least one year before diagnosis of dementia. Otherwise, if distribution of LTS met “intermediate” or “high” criteria then diagnosis of DLB was assigned (12). Subjects with LTS histopathology were classified according to the Unified Staging System for Lewy Body

Disorders (13) after immunohistochemical detection of phosphorylated α -synuclein on 5 μm paraffin sections pretreated with proteinase K (6).

The cases were divided into four diagnostic groups according to their clinical features plus AD and LTS histopathology (13): DLB/AD, PDD/AD, ADLB, and AD only. ADLB cases were cases that met the pathologic criteria for AD and had LTS pathology present that was insufficient to meet clinical or pathological criteria for either PD or DLB (5).

Tissue-processing methods have been previously described (4, 5). Briefly, the cerebrum was cut in the coronal plane at the time of brain removal into 1 cm thick slices and then divided into left and right halves. The slices from the right half were frozen between slabs of dry ice while the slices from the left half were fixed by immersion in neutral-buffered 4% formaldehyde for 48 hours at 4 degrees C. Formaldehyde-fixed paraffin-embedded sections were stained with hematoxylin and eosin, while large-format, 40–80 μm-thick formaldehyde-fixed sections were stained for plaques, tangles and other features using Gallyas, Thioflavin-S and Campbell-Switzer methods (14). Thioflavin-S is one of two methods recommended and validated for neuritic plaque density grading by CERAD (8, 15). The Braak neurofibrillary tangle (NFT) staging followed the original protocol and was originally described using the Gallyas stain (16) on similarly thick sections.

Statistical Analysis

Mean levels were compared among groups by using one-way analysis of variance, and proportions were compared among groups by using the Pearson chi-square test. Pairwise comparisons of adjusted means were made by using a general linear model with terms for group, age, sex, and e4 carrier status.

Results

We identified 584 cases with a final clinicopathological diagnosis; among these there were 32 cases of DLB/AD, 54 ADLB, 41 PDD/AD and 70 AD only.

Table 1 summarizes the demographic characteristics and motor/neuropsycholgical test scores of the four groups. The mean (SD) age at death differed between groups: 84.2 (7.2) in the DLB/AD, 86.9 (7.1) years in the ADLB group, 81.6 (6.0) in the PDD/AD, and 87.7 (6.7) in the AD-only group.

The mean activity of daily living as well as mean motor scores (UPDRS parts II and III) were higher in subjects with LTS (table 1). Multiple neuropsychological tests (COWAT, HAM-D, BNT, AVLT Total Learning, and Trail-making test A) as well as HAM-D correlated significantly with LTS pathology.

Hoehn and Yahr staging was also higher in the ADLB group. On the cognitive tests, AVLT Total Learning (p=0.02) and BNT (p=0.05) were worse in ADLB compared to AD alone.

However, when we performed an additional analysis comparing DLB/AD cases with ADLB, the adjusted mean total scores of Hoehn and Yahr Scale (Δ 1.39, 95%CI: 0.64 to 2.14; p = <0.001) and UPDRS III were significantly different (Δ17, 95%CI 8 to 26, p = <0.001).

Interestingly, rigidity (p = <0.001) and bradykinesia (p = 0.003) were still significantly different whereas tremor (p=0.32). HAM-D (p = 0.15), geriatric depression scale (p = 0.58), AVLT Total Learning (p= 0.35), and Trail-making tests A-B (p = 0.23 and 0.70) were not statistically different. Notably, there was no difference in the presence of Apo E4 between groups with 40–50% occurrence (table 1).

Discussion

This study found that a number of clinical symptoms and neuropsychological features are correlated with the presence of postmortem LTS pathology among patients with pathologically confirmed AD. In particular, the overall score of UPDRS II and III and a number of individual items within the examination that represent the frontal functions were associated with the presence of LTS pathology at autopsy.

Our results suggest that the presence of LTS has clinical relevance even when the density and/or distribution of LTS does not meet DLB criteria. The phenotypical characteristics of the frontal-dysexecutive dysfunction and motor parkinsonian impairment may be defined by the presence of LTS in specific preferential locations of the brain such as the basal ganglia and the frontotemporal cortex. Thus, LTS in the presence of AD has significant impact on clinical symptoms and signs that may be considered markers in the future. Even in ADLB patients (i.e., AD patients without the diagnosis of DLB), UPDRS II and III were higher than in AD alone.

A number of previous studies have shown that DLB and AD differ in their neuropsychological profiles. In particular, differences in the Trail Making Test A, Boston Naming Testing, AVLT, and the Rey-Osterreich complex figure distinguished DLB from AD (17). In fact, AD cases seemed to have a more specific impairment of the memory domain, but DLB cases had greater impairment in the visuospatial and executive functions (17). Our study further highlights the importance of neuropsychological testing, not only in the diagnosis of DLB but also to identify LTS pathology in AD patients that don’t meet DLB pathological criteria. Interestingly, our results in ADLB and DLB are consistent with the previous study: Trail Making, BNT, GDS, and HAM-D were tests that detected more severe impairment and predicted LTS. Furthermore, the GDS and the Hamilton depression score support a possible role for the frontotemporal emotional circuit in these diseases.

The treatment of neurodegenerative diseases is still based on symptomatic agents. Disease-modifying treatments are being studied, but these data suggest that the presence of LTS may influence clinical findings and could affect trial outcomes. If LTS is present in a higher number of cases in one treatment group than the other, or if a high number of individuals in both groups have LTS, this may affect the original power analysis or bias the results unintentionally. Indeed, mixed pathology is associated with faster cognitive decline in subjects with mild cognitive impairment or dementia, and shorter survival times (18–20) Thus, subjects with concurrent LB pathology in the treatment arm of a trial may reduce the chance of showing a clinically meaningful benefit. Furthermore, the relationship between LBs and amyloid is still unclear, and it is unknown whether LBs might confer resistance to anti-amyloid therapies.

Our study has a number of strengths. We performed comprehensive clinical and neuropathological assessments in a standardized manner. Our study is based on a large neuropathological series; in addition, most of our subjects have volunteered from the community rather than being collected at a tertiary care center. On the other hand, our case distribution was limited by being predominantly very elderly, well-educated, middle- and upper-income individuals originally from the Midwest or the northeastern United States residing in Maricopa County, Arizona. Case composition may also be affected by volunteer bias, and subjects may be more aware of neurodegeneration because of incipient disease or because of personal and familial awareness.

This study identified clinical differences in AD with and without concomitant LTS, even in subjects whose LB pathology did not meet criteria for DLB. In particular, higher UPDRS parts II and III scores and impairment of the executive and visual functions on cognitive testing was significantly correlated to the presence of LTS in the brains of individuals with dementia but who did not meet criteria for DLB. Future studies are needed to confirm and expand these findings in order to predict the presence of LTS in subjects with AD.

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Conflict of Interests and Sources of Funding:

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Conflicts of Interest

RS receives research support from NIH.

TGB receives grant support from the Arizona Alzheimer's Consortium, National Institutes of Health and MJFF, performs contracted research for Navidea Biopharamaceuticals and Avid Radiopharmaceuticals, and serves as a paid consultant with Genentech, GSK, Roche and Ventana.

JGH received research grant funding for this project from the NIH.

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LIS reports no disclosures.

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EZ reports no disclosures.

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Table 1.

Comparison between the demographic and clinical characteristics of the four pathology groups.

	DLB/AD	ADLB	AD	PDD/AD	P
Age at Death (y); mean (SD), N	84.2 (7.2), 32	86.9 (7.1), 54	87.7 (6.7), 70	81.6 (6.0), 41	<.001
Female	15/32 (47%)	22/54 (41%)	42/70 (60%)	12/41 (29%)	.01
ApoE e4	15/32 (47%)	27/54 (50%)	29/65 (45%)	16/40 (40%)	.81
UPDRS II Total; mean (SD), N	15.2 (13.3), 30	9.9 (11.9), 52	6.9 (8.9), 67	23.0 (10.4), 37	<.001
UPDRS III Total; mean (SD), N	34 (26), 31	24 (25), 49	17 (20), 66	46 (18), 39	<.001
Hoehn & Yahr; mean (SD), N	2.30 (1.90), 28	1.39 (1.81), 49	0.84 (1.52), 61	3.66 (0.90), 37	<.001
COWATTotal (0–120); mean (SD), N	20.5 (12.7), 11	24.2 (10.3), 25	25.3 (10.9), 38	15.4 (5.7), 18	.007
HAM-D; mean (SD), N	6.7 (3.8), 18	5.7 (3.2), 26	4.8 (3.4), 43	7.6 (3.8), 20	.02
Boston Naming Test (0–30); mean (SD), N	12.8 (12.4), 4	11.6 (8.3), 9	18.7 (6.3), 17	22.4 (3.6), 9	.01
Trail Making Test A (0–150 seconds); mean (SD), N	101 (45), 13	92 (45), 22	85 (39), 42	132 (29), 17	.001
Trail Making Test B (0–300 seconds); mean (SD), N	226 (90), 9	254 (71), 19	237 (88), 32	283 (59), 13	.28
AVLT Total Learning (0–75); mean (SD), N	19.1 (9.5), 12	16.0 (9.7), 24	24.3 (9.5), 35	22.8 (8.2), 16	.009
AVLT LTM A7 (0–15); mean (SD), N	1.3 (1.6), 11	1.5 (2.3), 24	2.1 (2.6), 35	2.1 (1.8), 16	.55

Hamilton depression scale (HAM-D), Geriatric Depression Scale (GDS), Functional Assessment Questionnaire (FAQ), Mini Mental State Examination (MMSE), Judgement of Line Orientation, Clock Drawing, Stroop Interference, Controlled Oral Word Association Test (COWAT), Animal Fluency, AVLT, Boston Naming Test (BNT), Trail Making Test A and B. The complete Unified Parkinson Disease Rating Scale (UPDRS)