

Original Article

Neuropathologic correlates of trial-related instruments for Alzheimer's disease

Jeffrey L Cummings¹, John Ringman², Harry V Vinters³

¹Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada; Departments of ²Neurology, ³Pathology & Laboratory Medicine (Neuropathology), The Mary S Easton Center for Alzheimer's Disease Research at The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Received March 13, 2014; Accepted March 28, 2014; Epub April 2, 2014; Published April 12, 2014

Abstract: To advance disease-modifying therapies, it is critical to understand the relationship between the neuropathological changes of Alzheimer's Disease (AD) and the clinical measures used in therapeutic trials. We reviewed neuropathologically proven cases of AD from the National Alzheimer's Coordinating Center (NACC) and examined correlations between neuropathological changes and clinical-trial related instruments collected as part of the Uniform Dataset (UDS). We explored the relationships between neurofibrillary tangles, neuritic plaques, and total pathology burden with immediate and delayed recall, Clinical Dementia Rating-Sum of Boxes, Functional Activity Questionnaire, Neuropsychiatric Inventory Questionnaire, and Mini-Mental State Examination scores. 169 patients in NACC database had appropriate neuropathological and clinical data. All instruments correlated highly with neuritic plaques, Braak staging, and total pathology. Correlation coefficients for the relationships were relatively modest, suggesting that the pathologic burden examined accounts for between 13 and 40% of the variance of each of the instruments assessed. We conclude that there is a strong correlation between clinical trial-related measures and neuropathology identified at autopsy in AD. The amount of variance explained by the pathology is limited and other factors, both disease- and measurement-related, contribute to the variability observed in clinical measurements.

Keywords: Clinical therapeutic trials, Alzheimer's disease (AD), neuropathological changes, clinical-trial related instruments, correlation

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized clinically by progressive decline in memory cognition and function, and pathologically by neuritic plaques (NP), neurofibrillary tangles (NFT), amyloid angiopathy (CAA), and neuronal and synapse loss [1]. Disease-modifying therapies intended to prevent, delay the onset of, or slow the progression of AD are focused on intervening in the processing of amyloid beta protein (A β), hyperphosphorylation and aggregation of tau protein into NFT's, and neurotoxic processes leading to cell death [2]. From a clinical perspective, the success of disease-modifying therapies is measured by clinical trial instruments such as the Clinical Dementia Rating - Sum of the Boxes (CDR-sb) [3], the Alzheimer's Disease Assessment Scale-cognitive portion (ADAS-cog) [4], activities of daily living (ADL) scales [5], the

Neuropsychiatric Inventory (NPI) [6], and the Mini-Mental Status Examination (MMSE) [7].

To better understand the relationship between the neuropathology of AD and clinical measures used in trials of disease-modifying agents, we investigated the correlations between neuropathological changes and scores on trial-like instruments from the National Alzheimer Coordinating Center (NACC) [8, 9] database.

Methods

The neuropathology portion of the NACC database includes the Braak and Braak stage (I-VI, based largely on the evaluation of NFT extent), a semi-quantitative rating of NP (frequent, moderate, sparse, and none), semi-quantitative rating of diffuse plaques (frequent, moderate, sparse, and none), and the presence or absence of ischemic or hemorrhagic vascular pathology. Tissue pathology scoring was based on sam-

Neuropathologic correlates of trial related instruments for AD

Table 1. Demographic features of the sample

	N	Percent
Male	95	56.2
Female	74	43.8
	N	Mean
Age at Death	169	83.6 (10.4)
Years of education	167	15.1 (3.3)
Time between first visit and death (months)	169	25.6 (7.2)
Time between last visit and death (months)	169	8.8 (5.5)
Time since onset of symptoms (years)	138	8.4 (4.1)
MMSE score at last visit	141	15.7 (9.7)
CDR sum of box score at last visit	169	10.6 (6.3)
FAQ total at last visit	140	23.8 (9.6)
NPI-Q total at last visit	169	3.6 (2.7)

ples of sections from hippocampus-entorhinal cortex, amygdala, and frontal cortex [7, 8]. The neuritic plaque count was measured in the most severely affected cortical region. The Braak and Braak NP score was classified as either no evidence of neurofibrillary degeneration; stages 1 and 2 (the neurofibrillary tangles involve the entorhinal and perirhinal cortex); stages 3 and 4 (tangles also accumulate in hippocampus and other limbic regions with limited neocortical involvement); stage 5 (neurofibrillary changes occur in association cortices); or stage 6 (neurofibrillary changes occur in primary sensory cortex) [9]. These scoring methods have been shown to have acceptable reproducibility between observers and among research centers [8, 9].

The uniform dataset (UDS) of the NACC database contains the CDR-sb [3], the MMSE [7], a neuropsychological test battery including logical memory (immediate and delayed) [10], the Functional Activity Questionnaire (FAQ) [11] as a measure of ADLs, and the NPI-Questionnaire (NPI-Q) [12]. All elements of the UDS are collected in a standardized manner using a comprehensive clinical report form that is monitored for completeness. All interviewers received training on rating scale administration prior to data collection and entry. Each of the instruments included in the UDS has established validity and reliability. The data of the UDS are double-entered into a comprehensive relational database subject to range, logic, and error checks. Data are accessed through requests to the NACC staff [8, 9].

Patients meeting National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for definite AD [13] who had clinical assessments including most of the instrument of interest were included in the analysis.

Statistical methods

Spearman's rank correlation coefficients were calculated to determine the associations between the trial-like instruments and the NACC neuropathologic measures. Multiple linear regression was used to adjust these associations for covariates of interest including edu-

cational level. All computations were done using SAS v.9.2 software.

Results

One-hundred-sixty-nine patients meeting criteria for definite AD who had complete or nearly complete neuropathologic and clinical data (as of 12/1/2009) were available in the NACC database. Ninety-five men and seventy-four women were included in the analysis. Average age at death was 83.6 years, educational level was 15.1 years (SD 3.3), and time between the last visit and death was 8.8 months (SD 5.5). Patients had been symptomatic for an average of 8.4 years (SD 4.1). MMSE score at last visit was 15.7 (SD 9.7), CDR-sb at last visit was 10.6 (SD 6.3), FAQ total score at last visit was 23.8 (SD 9.6), and NPI-Q total at the last visit was 3.6 (SD 2.7) (**Table 1**).

Correlations were examined between scores on clinical assessments on the last visit prior to death and autopsy findings for NFT (Braak and Braak stage), neuritic plaques, and total AD pathologic burden (NFT, NP, and diffuse plaques). Correlations between scale scores and NP, Braak stage, and total pathology are shown in **Table 2**. MMSE correlated at last visit with NP, Braak staging, and total pathology (all $p=0.0001$ or less). Similarly, CDR-sb correlated with NP, Braak staging, and total pathology burden (all $p<.0001$). Correlations between the sum of the immediate and delayed recall of the logical memory subscale of the Wechsler Adult Intelligence scale correlated with NP, Braak staging, and total pathology score (all $p=$

Neuropathologic correlates of trial related instruments for AD

Table 2. Correlations between clinical measures and neuropathologic findings at last visit (*p*-values in parentheses)

	Neuritic Plaques	Braak Stage	Total Pathology
MMSE	-0.29 (0.0001)	-0.35 (<.0001)	-0.39 (<.0001)
CDR-sb	0.54 (<.0001)	0.63 (<.0001)	0.64 (<.0001)
Logical Memory	-0.39 (<.0001)	-0.50 (<.0001)	-0.54 (<.0001)
FAQ Total	0.54 (<.0001)	0.56 (<.0001)	0.56 (<.0001)
NPI-Q Total	0.16 (0.04)	0.43 (<.0001)	0.36 (<.0001)

<.0001). The FAQ total score correlated with NP, Braak staging, and total pathology score ($p<.0001$). Total NPI-Q score correlated with NP ($p=0.04$), Braak staging ($p<.0001$), and total pathology burden ($p<.0001$).

The amount of variance accounted for by the pathological changes was relatively modest. Correlation coefficients for the relationship between total pathology burden and score on the last visit were MMSE (-0.39), CDR-sb (0.64), logical memory (-0.54), FAQ (0.56), and NPI-Q (0.36). This suggests that the total pathological burden accounts for between 13 and 40% of the variance of each of the instruments assessed.

We examined the influence of education on the clinicopathological correlations by co-varying for educational level. No effect of education on these relationships was identified at the 0.05 significance level.

Discussion

In this investigation using the NACC database, we identified strong correlations between all of the trial-related instruments and the basic and defining histopathologic features characteristic of AD. Correlations were strong for all elements of pathology for cognitive and functional measures (MMSE CDR-sb, logical memory, FAQ). The NPI-Q had significant correlations with both types of pathology but correlations were higher for Braak staging than for NP.

Although correlations between trial-related instrument scores and pathological changes were high, the amount of variance attributable to the pathology was limited (13-40%). Our findings suggest that other pathologic elements not captured by the NACC database may contribute importantly to the clinical-pathological correlations and underscores the complex relationship

between pathology and clinical phenomenology. There is no measure of nerve cell loss, synaptic loss, oxidative injury, Lewy neurites, or inflammation, all of which have been identified as important components contributing to AD pathology [14] and possibly influencing the clinical phenotype. The interval between final clinical assessment and autopsy may contribute to this variability. Regional severity of neuropathologic changes may further influence clinicopathological relationships. The data available in the NACC dataset are based on only a few anatomical regions.

Several previous studies have found relationships between CDR scores and NFT burden [15-18]. Though a few studies have shown a strong relationship between NP density and clinical measures [19], many have not. Roe and colleagues [20] showed that education interacted with density of NP to predict dementia, while NFT density independently predicted dementia and did not interact with education. We found no educational interaction in the current data set. Most patients in the NACC dataset had high educational levels and this may have limited our ability to identify such correlations if they exist.

Limitations of the current study include the circumscribed amount of neuropathologic data available in each case, the absence of some neuropathology information (e.g. neuron and synaptic loss), and the fact that the UDS does not include the specific instruments used in many clinical trials including the ADCS-cog, Alzheimer's Disease Cooperative study ADL scale (ADCS ADL scale) [5] and the full version of the NPI [3]. The advantages of the current data set are that it contains a relatively large number of individuals, the data are collected in multicenter trial-like circumstances, most of the instruments used are identical or similar to those used in clinical trials, and the data collection methods are of high quality.

The results of the current study suggest that disease-modifying compounds targeting the basic histopathologic features of AD can be expected to produce changes that are captured on the standard clinical rating tools. The relatively limited amount of variance attributable to

Neuropathologic correlates of trial related instruments for AD

any single pathology suggests that targeting multiple pathologies may be required for effective therapy. Variability in clinical measures underscores the utility of more direct assessments of disease activity such as cerebrospinal fluid changes, magnetic resonance imaging, or amyloid imaging in assessing the efficacy of disease-modifying interventions [21]. Collecting more comprehensive information would improve the capacity to investigate the associations between histopathologic changes of AD and clinical trial outcomes. Comprehensive understanding of the relationship between therapeutic targets and clinical measures will enhance the ability to develop urgently needed new therapies for AD.

Acknowledgements

The author would like to thank Cathy Lee, PhD, for statistical assistance. This paper was supported by an NIA Alzheimer's Disease Research Center grant (AGP5016570), a California Alzheimer's Disease Research Center grant, the Sidell-Kagan Foundation, the Jim Easton gift, a National Alzheimer's Coordinating Center (NACC), and the Daljit S. & Elaine Sarkaria Chair in Diagnostic Medicine (HVV).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jeffrey L Cummings, Cleveland Clinic Lou Ruvo Center for Brain Health, 888 West Bonneville Avenue, Las Vegas, NV 89106. Tel: 702-483-6029; Fax: 702-483-6028; E-mail: cumminj@ccf.org

References

- [1] Mendez MF, Cummings JL. *Dementia: A Clinical Approach*. 3rd ed. Philadelphia, PA: Butterworth Heinemann, 2003.
- [2] Salloway S, Mintzer J, Weiner MF, Cummings JL. Disease-modifying therapies in Alzheimer's disease. *Alzheimers Dement* 2008; 4: 65-79.
- [3] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993; 43: 2412-2414.
- [4] Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984; 141: 1356-1364.
- [5] Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997; 11 Suppl 2: S33-39.
- [6] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; 44: 2308-2314.
- [7] Folstein MF, Folstein SE, McHugh PR. "Minimal state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189-198.
- [8] Beekly DL, Ramos EM, van Belle G, Deitrich W, Clark AD, Jacka ME, Kukull WA; NIA-Alzheimer's Disease Centers. The National Alzheimer's Coordinating Center (NACC) Database: an Alzheimer disease database. *Alzheimer Dis Assoc Disord* 2004; 18: 270-277.
- [9] Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA; NIA Alzheimer's Disease Centers. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. *Alzheimer Dis Assoc Disord* 2007; 21: 249-258.
- [10] Morris JC, Weintraub S, Chui HC, Cummings J, Decarli C, Ferris S, Foster NL, Galasko D, Graff-Radford N, Peskind ER, Beekly D, Ramos EM, Kukull WA. The uniform data set (UDS): clinical and cognitive variables and descriptive data from Alzheimer disease centers. *Alzheimer Dis Assoc Disord* 2006; 20: 210-6.
- [11] Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol* 1982; 37: 323-329.
- [12] Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* 2000; 12: 233-239.
- [13] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34: 939-944.
- [14] Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J Neuropath Exp Neurol* 1997; 56: 1095-1097.
- [15] Berg L, McKeel DW Jr, Miller JP, Storandt M, Rubin EH, Morris JC, Baty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM. Clinicopathologic studies in cogni-

Neuropathologic correlates of trial related instruments for AD

- tively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch Neurol* 1998; 55: 326-335.
- [16] Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol* 2003; 60: 729-736.
- [17] Bierer LM, Hof PR, Purohit DP, Carlin L, Schmeidler J, Davis KL, Perl DP. Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. *Arch Neurol* 1995; 52: 81-88.
- [18] Giannakopoulos P, Herrmann FR, Bussière T, Bouras C, Kövari E, Perl DP, Morrison JH, Gold G, Hof PR. Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease. *Neurology* 2003; 60: 1495-1500.
- [19] Cummings BJ, Pike CJ, Shankle R, Cotman CW. Beta-amyloid deposition and other measures of neuropathology predict cognitive status in Alzheimer's disease. *Neurobiol Aging* 1996; 17: 921-933.
- [20] Roe CM, Mintun MA, D'Angelo G, Xiong C, Grant EA, Morris JC. Alzheimer disease and cognitive reserve: variation of education effect with carbon 11-labeled Pittsburgh Compound B uptake. *Arch Neurol* 2008; 65: 1467-71.
- [21] Cummings JL. Controversies in Alzheimer's disease drug development. *Int Rev Psychiatry* 2008; 20: 389-395.