Neuroscience Letters 485 (2010) 222–227

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Neuropathology of dementia with Lewy bodies in advanced age: A comparison with Alzheimer disease

Kiren Ubhi[a,c], Kevin Peng[a], Stephanie Lessig[a], Jennilyn Estrella[b], Anthony Adame[a], Douglas Galasko[a], David P. Salmon[a], Lawrence A. Hansen[a], Claudia H. Kawas[d], Eliezer Masliah[a,b,*]

[a] Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093-0624, United States
[b] Department of Pathology, University of California, San Diego, La Jolla, CA 92093-0624, United States
[c] Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, NY 10021, United States
[d] School of Medicine, University of California, Irvine, Irvine, CA 92697-4540, United States

ARTICLE INFO

Article history:
Received 10 March 2010
Received in revised form 24 August 2010
Accepted 3 September 2010

Keywords:
Cognition
Neuropsychological assessment

ABSTRACT

Dementia with Lewy Bodies (DLB) is a common neurodegenerative disorder of the aging population characterized by α-synuclein accumulation in cortical and subcortical regions. Although neuropathology in advanced age has been investigated in dementias such as Alzheimer Disease (AD), severity of the neuropathology in the oldest old with DLB remains uncharacterized. For this purpose we compared characteristics of DLB cases divided into three age groups 70–79, 80–89 and ≥90 years (oldest old). Neuropathological indicators and levels of synaptophysin were assessed and correlated with clinical measurements of cognition and dementia severity. These studies showed that frequency and severity of DLB was lower in 80–89 and ≥90 year cases compared to 70–79 year old group but cognitive impairment did not vary with age. The extent of AD neuropathology correlated with dementia severity only in the 70–79 year group, while synaptophysin immunoreactivity more strongly associated with dementia severity in the older age group in both DLB and AD. Taken together these results suggest that the oldest old with DLB might represent a distinct group.

Lewy body disease is an heterogeneous group of neurodegenerative disorders of the aging population that includes Dementia with Lewy Bodies (DLB) and Parkinson's Disease [13] In DLB, α-synuclein containing Lewy bodies (LBs) are found in cortical and subcortical regions and accompanied in most cases by amyloid deposition and occasional tangle formation. Advanced age is an important risk factor for DLB and Alzheimer disease (AD). Previous studies have shown that advanced age modifies the severity of the neuropathology and clinical symptoms in AD [13]. Surprisingly, in the oldest old patients with AD the density of plaques and tangles and the extent of the neuronal loss is lesser than in the younger age groups [3,6,8,12,17].

Although neuropathology in advanced age has been investigated in AD, severity of neuropathology in the oldest old with DLB remains uncharacterized. To address this we compared neuropathological features and levels of a synaptic marker (synaptophysin) in DLB and AD cases in three age groups: youngest (70–79 years) years; middle (80–89 years); and oldest (≥90 years). The results demonstrate that the frequency of DLB and severity of neuropathology is less severe in the older cases compared to younger groups and that synaptophysin immunoreactivity is more closely associated with cognitive impairment in the very elderly DLB and AD cases, suggesting that the oldest old with DLB might represent a distinct group.

Cases selection for this retrospective study was based on neuropathological examination and determination of the diagnosis of AD and DLB. Cases were divided into three age groups (70–79 (Control $n = 7$, DLB $n = 53$, AD $n = 137$), 80–89 (Control $n = 7$, DLB $n = 39$, AD $n = 197$) and ≥90 years (Control $n = 2$, DLB $n = 6$, AD $n = 64$)) (Table 1).

All cases were from the Alzheimer Disease Research Center (ADRC) at the University of California, San Diego (UCSD). In most cases patients received neuropsychological testing at UCSD ADRC as part of a structured annual examination [22], Blessed Information-Memory-Concentration (BIMC), Dementia Rating Scale (DRS), and Mini-Mental State Examination (MMSE) scores are reported (Supp. Tables 1 and 2). Cases included had cognitive testing performed within 12 months of death. All subjects came to autopsy between 1985 and 2006 and postmortem interval for all cases was under 12 h. Institutional board review was obtained from the UCSD Human Research Protections Program, in accordance with the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all patients or their guardians.

* Corresponding author at: 9500 Gilman Drive, La Jolla, CA 92093-0624, United States. Tel.: +1 858 534 6209; fax: +1 858 534 6232.
E-mail address: emasliah@ucsd.edu (E. Masliah).

0304-3940/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2010.09.016

Table 1
Demographic characteristics.

Age group	Final diagnosis	*n*	Age	Gender (F/M)
70–79	Control	7	75 ± 3	3/4
	DLB	53	76 ± 3	19/34
	AD	137	75 ± 3	51/86
80–89	Control	7	85 ± 3	2/5
	DLB	39	84 ± 3	18/21
	AD	197	84 ± 3	120/77
90+	Control	2	94 ± 4	1/1
	DLB	6	96 ± 6	6/0
	AD	64	94 ± 4	45/19
Total	–	512	–	265/247

AD: Alzheimer disease; DLB: dementia with Lewy bodies.

Paraffin sections from formalin-fixed material stained with hematoxylin and eosin and thioflavin-S (TS) were used for neuropathological analysis, including assessment of plaque and tangle density in the neocortex and hippocampus as described [7,9]. In brief, TS stained sections from left midfrontal (MF), inferior parietal (IP), superior temporal (ST) neocortex and posterior level of hippocampus were examined for plaque and tangle counts. Senile plaques, both diffuse and neuritic, were counted in 100× magnification fields of maximal lesion densities from each of the 4 sections, while tangles were counted in similarly selected 400× magnification fields. Braak staging was assessed on anterior entorhinal cortex and neocortex sections [4].

Cases were subdivided into three categories via pathological analysis: non-demented age-matched controls, DLB and AD. Control cases included had very few or no plaques and no tangles. DLB diagnoses were based on pathological findings of LBs detected by immunohistochemistry with an α-synuclein antibody (Millipore, Temecula, CA) and clinical presentation of dementia, all DLB cases underwent α-synuclein immunohistochemistry for sub-classification into brainstem predominant, limbic and diffuse neocortical stages. Analysis of α-synuclein immunoreactivity was also performed in AD cases. DLB cases had sufficient total and neuritic plaques to meet 1985 National Institute of Aging (NIA) and Consortium to Establish a Registry for AD (CERAD) criteria for probable AD. However, all cases had a Braak stage less than 4, and were classified as DLB ("mixed-DLB"). Cases having a Braak stage of 5 or 6 and displaying unequivocal AD tangle pathology are classified as AD [10]. All AD cases met CERAD and NIA criteria for diagnosis [15].

Presence and severity of cerebral amyloid angiopathy (CAA) was assessed on TS preparations of MF, IP, ST and hippocampal regions. Scores from 0 to 4 were given to each sample reflecting increasing severity of CAA, this scoring is consistent with previous studies and work from this group [2,20].

Synaptophysin-immunoreactive terminals in the MF cortex were obtained by laser scanning confocal microscopy of vibratome sections immunostained with monoclonal synaptophysin antibody (1 μg/ml; Chemicon, Indianapolis, IN) [19]. All assessments were blind-coded and in duplicate. As previously described [21] additional immunocytochemical analysis was performed with a mouse monoclonal Aβ antibody (clone 82E1, Immunobiological Laboratories) to determine amyloid load in the basal ganglia of DLB cases.

Data are presented as mean ± standard deviation (SD). Means were compared using the Kruskal–Wallis test for Braak scores and one-way analysis of variance (ANOVA) for all others. The Kruskal–Wallis test was followed by Dunn's multiple comparison test and ANOVA was followed by either Student–Newman–Keuls or Bonferroni's multiple comparison tests, where appropriate. Pearson product moment correlations were used to determine the intragroup association of BIMC to total senile plaque (TP), neuritic plaque (NP), and neurofibrillary tangle (NFT) counts. Spearman rank order correlations were used to analyze relationships between BIMC and Braak stage.

A total of 512 cases were included in the study (Table 1), of these, 197 (38%) were between ages 70 and 79, 243 (48%) between ages 80 and 89, and 72 (14%) were 90 and above (Supp. Table 3). Comparing youngest (70–79) and oldest (≥90) groups, the proportion of AD cases increased significantly with increasing age (69.5% as compared to 89%). In contrast, proportion of DLB cases as a percentage of all cases (DLB and AD) decreased significantly with increasing age (27% as compared to 8%) (Table 1), while 64/398 (16%) of AD cases were above 90 years, only 6/98 (6%) DLB cases were above 90 years ($\chi^2 = 5.64$; $p = 0.018$).

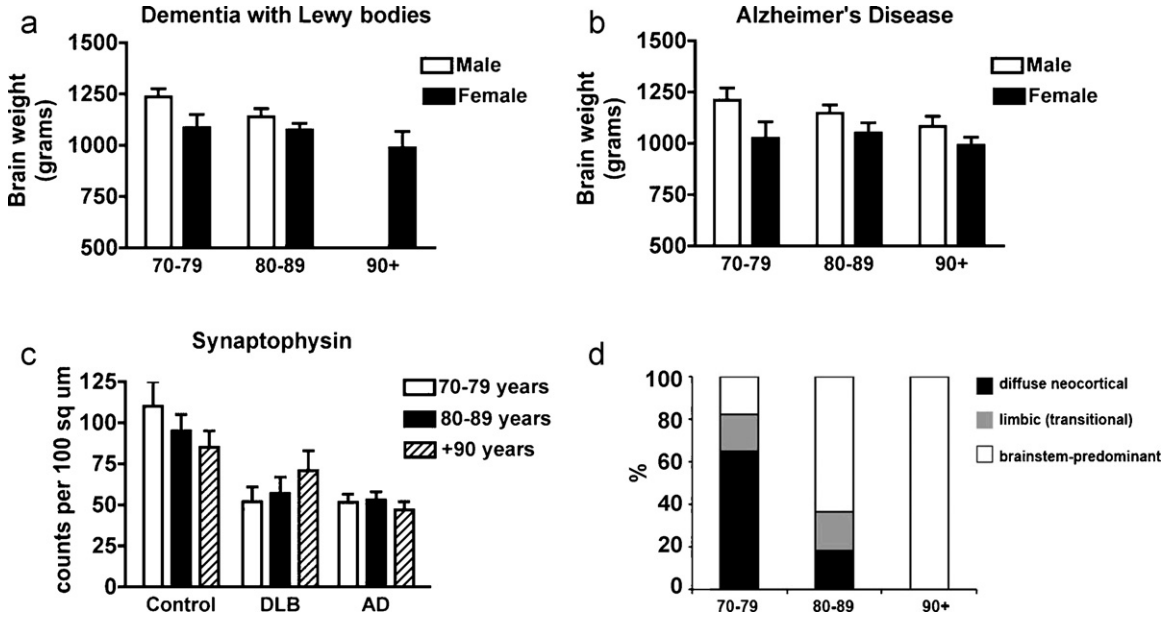

Fig. 1. Neuropathological indices in DLB and AD.
(a) Brain weight in Dementia with Lewy Bodies (DLB) and (b) Alzheimer disease (AD) patients. (c) Synaptophysin immunoreactivity in the frontal cortex of control, DLB and AD cases. (d) Breakdown of LB type (brainstem-predominant, limbic [transitional], or diffuse neocortical).