Clinical-Neuropathological Correlations of Alzheimer's Disease and Related Dementias in Latino Volunteers

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Accepted 8 October 2018

Abstract. Clinical, neuropsychological, and neurological procedures used to diagnose Alzheimer's disease (AD) and related dementias were largely developed and validated in well-educated, non-Latino, English-speaking populations. Sociocultural and genetic differences in Latinos might influence the accuracy of clinical diagnosis of AD and other dementias. We aim to compare the accuracy of the clinical diagnosis of AD and related dementias in Latinos with the corresponding neuropathological diagnosis. From the UCSD Alzheimer's Disease Research Center longitudinal cohort, we selected all Latino participants who had autopsy neuropathological studies from 1991 to 2017. Participants underwent annual neurological clinical evaluations, standard neuropsychological tests, neuroimaging, and genotyping of the Apolipoprotein E. We calculated the sensitivity and specificity for the clinical diagnosis of AD against the primary pathological diagnosis. From the 34 participants with a primary neuropathological diagnosis of AD, 33 (97.1%) were correctly clinically diagnosed as having AD at the last clinical evaluation, and 1 was incorrectly diagnosed with dementia with Lewy bodies. Of the 19 participants without a primary neuropathological diagnosis of AD, 8 were incorrectly clinically diagnosed with probable AD at the last clinic evaluation. The clinical diagnosis of AD at the last clinical evaluation had 97.1% sensitivity and 57.9% specificity against autopsy-verified AD. In this Latino cohort, clinicians predicted AD pathological findings with high sensitivity but moderate specificity. Tangle-only dementia was the most common misdiagnosis. Our study suggests that current procedures and instruments to clinically determine AD in Latinos have high sensitivity compared with neuropathology, but specificity needs to be improved.

Keywords: Alzheimer's disease, dementia, Latino, Lewy bodies, neuropathology

INTRODUCTION

Widely-used clinical, neuropsychological, and neurological procedures used to diagnose

Alzheimer's disease (AD) and differentiate it from similar disorders were largely developed and validated in relatively homogeneous, well-educated, white, English-speaking populations [1–6]. When these procedures are utilized, and standardized diagnostic criteria for AD and related dementias (e.g., dementia with Lewy bodies; DLB) are applied, AD can be diagnosed at a mild stage of dementia with about 90% accuracy against autopsy verification

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of the disease [1, 2, 7–14]. It is not known, however, whether a comparable level of diagnostic accuracy would be achieved when these same procedures and clinical criteria are applied to Spanish-speaking or Spanish-English bilingual Mexican-Americans. This is a critical question given that Latinos represent nearly 20% of the U.S. population and nearly 40% of the population of the largest states, California and Texas [15]. The majority of Latinos in the U.S. (>63%), and particularly in Western states (>85%), are of Mexican-origin.

There are sociocultural differences between Mexican-Americans and well-educated white, English-speaking older adults that may affect the accuracy of our clinical diagnostic standards for AD and related dementias. These include: 1) cultural differences in the reporting of behavioral, cognitive, and functional deficits [16]; 2) on average, lower levels of education for Mexican-Americans; 3) Spanish monolingualism and Spanish-English bilingualism in that can bias neuropsychological assessment and impact diagnostic certainty [17]; and 4) a higher prevalence of vascular risk factors, such as obesity, diabetes, and heart disease [18–20]. There are also differences in genetic risk that might influence the base rate of AD and possibly age of onset [21]. For example, Apolipoprotein E (*APOE*) ϵ 4 allele frequency is lower among Mexican-Americans (ranging from 4% to 18%) compared to whites; however, these studies lacked pathological verification of AD [22, 23]. The purpose of the present study was to 1) describe the characteristics of Latino patients (predominantly Mexican-origin) who eventually came to autopsy following evaluation at an AD clinical research center, and 2) describe the accuracy of the clinical diagnosis of AD in Latino participants with pathologically-confirmed AD [24, 25].

METHODS

Participants

Between January 1991 and June 2017, 88 older adult participants with self-reported Latino ethnicity died during the course of their participation in the University of California, San Diego (UCSD) Shiley-Marcos Alzheimer's Disease Research Center (ADRC) longitudinal study. Fifty-eight (66%) of these participants underwent autopsy with neuropathological examination. Three of these 58 patients were not included in the present study because they had familial AD due to a presenilin-1

mutation (neuropathologically confirmed), and two were not included because the interval between their last clinical encounter and death was longer than 2.5 years, thus making it difficult to determine the accuracy of clinic-pathological correlations. The final sample included 53 participants. Thirty participants did not undergo autopsy and were not included in the main analysis. Of these 30 participants: 19 (63%) had clinical diagnosis of Probable AD and 1 (3%) Possible AD, 6 (20%) Normal Control, 2 (7%) at risk for AD, 1 FTD primary progressive aphasia (PPA), and 1 PDD. Overall these participants without neuropathological information were more likely to be normal (20% versus 11%) and slightly less likely to have at-risk/AD (74% versus 77%) or Non-AD (7% versus 11%) clinical diagnosis during their last clinical visit compared to the participants included in this study.

Written informed consent to participate in the ADRC longitudinal study was obtained from all participants or their caregivers consistent with California State law. Informed consent for autopsy was obtained at the time of death from the next of kin in a hierarchy or their legal representatives in accordance with California law. The research protocol was reviewed and approved by the human subjects review board at UCSD.

Clinical evaluation

Neurologic, neuropsychiatric, and neuropsychological evaluations were carried out as part of the UCSD ADRC research study protocol. The neurologic/medical evaluation included a review of history with the participant or an informant (in the case of those with cognitive impairment), a modified Hachinski ischemia score, clinical mental status testing, and a physical neurological examination. Blood pressure, glucose, cholesterol, triglyceride, and body mass index (BMI) were measured. Presence or absence of a historical diagnosis of hypertension, diabetes, atrial fibrillation, congestive heart failure, angina, and intermittent claudication, as well as history of stroke and transient ischemic attacks, were obtained from the participant or informant and a review of medical records. Participants with insulin-dependent diabetes, major stroke or neurological illness; self-reported alcohol or drug abuse were excluded from the ADRC cohort. Neuroimaging (computed tomography or magnetic resonance imaging) reports or scans were reviewed when available. Genotyping of *APOE* was performed for most participants using methods as previously described [26]. The

neuropsychiatric evaluation consisted of interviews of the participant or informant using the Diagnostic Interview Schedules (DIS [27]) for psychosis, depression, and substance dependence, and the Neuropsychiatric Inventory (NPI [28]). A battery of neuropsychological tests was administered by trained bicultural/bilingual psychometrists and reviewed by neuropsychologists (DPS, GMP).

Language of evaluation (Spanish or English) was determined based on the participant's self-reported preferred language. Translations and back-translations of questionnaires and test materials from English to Spanish were performed by bilingual psychologists, nurses, and physicians in consultation with a certified translator. Testing was conducted individually in a quiet well-lit room.

At the completion of each annual evaluation, all of the collected clinical, laboratory and radiological data was reviewed by two senior neurologists (DRG, IL, JBB, and others) who each made a diagnosis of dementia and presumed etiology. If the two neurologists disagreed on the diagnosis, a third neurologist made an additional independent diagnosis to achieve a final consensus diagnosis. Clinical diagnosis of AD was made according to NINCDS-ADRDA criteria, clinical diagnosis of DLB was made according to established consensus criteria [8, 9], and other clinical diagnoses were made according to established criteria for the various disorders.

The clinical diagnoses at the last clinical encounter were probable AD ($n = 36$), probable AD and vascular disease ($n = 3$), probable AD with Lewy bodies ($n = 2$), dementia with Lewy bodies (DLB; $n = 1$), progressive supranuclear palsy (PSP; $n = 1$), frontotemporal dementia (FTD; $n = 1$), PPA ($n = 1$), Parkinson's disease with dementia (PDD; $n = 2$), and no dementia ($n = 6$).

Neuropathology evaluation

Autopsy procedures were as follows: the brain was divided sagittally, and the left hemibrain was fixed in 10% buffered formalin, while the right hemibrain was sectioned coronally and then frozen at -70°C in sealed plastic bags. Routinely, tissue blocks from the right hemibrain of the midfrontal, inferior parietal, and superior temporal cortices, primary visual cortex in the occipital lobe, hippocampus, basal ganglia, substantia nigra, and cerebellum were removed and placed in 2% paraformaldehyde for subsequent thick sectioning by vibratome. Tissue blocks adjacent to the ones described above were

stored at -70°C for subsequent immunoblot analysis for synaptic proteins and A β species (soluble and oligomers). Vibratome sections ($40\text{ }\mu\text{m}$ thick) were stored in cryoprotective medium at -20°C for subsequent immunochemical studies. The formalin-fixed left hemibrain was serially sectioned in 1 cm slices, and tissue blocks from the regions described above were processed for histopathological examination by H&E and Thioflavin-S (Thio-S) to detect tau and amyloid- β deposits.

Brains were staged for degree of neurofibrillary tangle pathology by one pathologist (LAH) using a modification of the Braak staging scheme [29]. Estimates of neuritic plaque density were calculated using methods recommended by CERAD [30]. AD was operationalized using the NIA-Reagan consensus criteria for the postmortem diagnosis of AD, wherein Braak stage V–VI with moderately to severely dense neuritic plaques corresponds to “high likelihood” that dementia is due to AD [31]. Any degree of AD changes was recorded even if they appeared to be incidental.

DLB cases met consensus criteria for the pathologic diagnosis of DLB based on hematoxylin-eosin (H&E) staining, anti-ubiquitin immunostaining [9], and anti- α -synuclein immunostaining [8]. Cases were only construed as DLB when they had neocortical as well as brainstem Lewy bodies, and fell into either the limbic (transitional) or neocortical categories proposed in the 1996 consensus guidelines for the pathologic diagnosis of DLB [9]. Cases were not classified as DLB if Lewy bodies were only found in the amygdala [8].

All autopsied brains were examined for cerebral amyloid angiopathy (CAA) and cerebrovascular disease (CVD; i.e., hemorrhage, large artery infarction, lacunes, cortical microinfarcts, arteriosclerosis, and atherosclerosis in the Circle of Willis). The severity of CAA was semi-quantitatively measured as mild, moderate, or severe on thioflavin-S stained preparations of the midfrontal cortex, superior temporal gyrus, inferior parietal cortex, and posterior hippocampus using a method described previously [32]. Capillary CAA was not calculated. CVD, arteriosclerosis, and atherosclerosis were also semi-quantitatively measured as mild, moderate, or severe [33].

Statistical analysis

Non-parametric Wilcoxon/Kruskal-Wallis test were used to compare continuous clinical,

demographic, and pathological variables among pathologically defined groups. Chi Square test or Fisher's Exact test were used to compare ordinal and nominal variables among pathologically defined categories. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the clinical diagnosis of AD were calculated against the primary AD pathological diagnosis.

RESULTS

The 53 participants were grouped according to neuropathological diagnosis: Alzheimer's disease (AD; $n=26$), Dementia with Lewy bodies with concomitant AD (AD/DLB; $n=8$), Non-AD neurodegenerative pathology ($n=13$), or no significant brain pathology or only AD changes (No Pathology; $n=6$). The Non-AD neurodegenerative pathology group included those with tauopathy only ($n=4$), FTD ($n=3$), PSP ($n=3$), DLB ($n=2$), or PD with neocortical Lewy bodies ($n=1$). Table 1 shows the characteristics of each group. Of note, there were no significant differences among the diagnostic groups in age of onset ($p=0.22$), age at first ADRC evaluation ($p=0.54$), age at last ADRC clinical encounter ($p=0.70$), or age at death ($p=0.50$). The groups did not differ in years of education ($p=0.85$), or in sex distribution. Time intervals between onset of symptoms and death, first ADRC clinical encounter and death, or last ADRC clinical encounter and death were not significantly different among the groups ($p=0.95$, $p=0.19$, $p=0.87$, respectively). However, the No Pathology group had a significantly longer interval between the first ADRC clinical encounter and death compared to the Non-AD neurodegenerative pathology group ($p=0.0485$).

Clinical features

The No Pathology group had significantly higher Mini-Mental State Examination ($p=0.0038$) and Dementia Rating Scale ($p=0.0058$) scores than all other groups at their first ADRC evaluation (see Table 1), whereas the AD, AD/DLB, and Non-AD groups did not differ on these measures. Due to the development of severe cognitive impairment in most participants with pathology, only 13 AD, 3 AD/DLB, and 6 Non-AD participants were able to complete the Mini-Mental State Examination or Dementia Rating Scale at the last ADRC clinical encounter (i.e., within 1–2 years of death).

The prevalence of reported visual hallucinations during the course of disease was higher in the AD/DLB and Non-AD groups than in the AD and No Pathology groups. One out of 13 participants in the Non-AD group reported hallucinations, and this participant received a clinical diagnosis of Parkinson's disease (PD) without dementia at the first clinical encounter, PDD at the last clinical encounter, and a neuropathological diagnosis of PD with neocortical Lewy bodies. In contrast, two patients who received a primary neuropathological diagnosis of DLB (in the Non-AD group) never reported hallucinations. Fluctuation in awareness or cognition was not noted in any participant even though assessed by a structured questionnaire in 29 out of the 53 participants, and by review of narrative medical history in others. History of REM sleep behavior disorder (RBD) was assessed by informant interview in 20 of the 53 participants, but was reported in only two participants, both in the AD group. One of these two participants received a clinical diagnosis of DLB at the first and last clinical encounter, but had a primary neuropathological diagnosis of AD without the presence of synuclein (verified using a synuclein antibody). The other participant received a clinical diagnosis of probable AD at the first and last clinical encounter, and had a primary neuropathological diagnosis of AD without synuclein pathology (verified using an antibody to alpha-synuclein). A formal question about RBD was included in the questionnaire in 2005. Before 2005, a history of RBD was not routinely asked for.

Genetic features

APOE $\epsilon 4$ allele frequency was higher in the AD and AD/DLB groups than in the Non-AD and No Pathology groups (see Table 1). The seven participants in the AD group with Braak stage III–IV had higher APOE $\epsilon 4$ allele frequency (35.7%) than the sixteen participants in the AD group with Braak stage V–VI (12.5%) (data are not shown). None of the participants in the No Pathology group carried an APOE $\epsilon 4$ allele.

Clinical-neuropathological correlation: Last clinical encounter

Of the 34 participants with a primary neuropathological diagnosis of AD (26 AD, 8 AD/DLB), 33 (97.1%) were correctly clinically diagnosed as having AD (29 probable AD, 0 possible AD, 3 probable AD plus vascular dementia, 1 probable AD plus

Table 1
Clinical-neuropathological correlation among pathologically defined groups

Clinical	Neuropathological Groups								
	AD (26)	<i>n</i>	AD1st & DLB2nd (8)	<i>n</i>	Non-AD (13)	<i>n</i>	Normal (6)	<i>n</i>	<i>p</i>
Probable AD ^a	24 ^o	–	8 ^k	–	8 ^m	–	0	–	–
Non AD ^a	1 ^d	–	0	–	2 ⁿ	–	0	–	–
No Dementia ^a	1	–	0	–	3 ^l	–	6	–	–
Probable AD ^b	25 ^c	–	8	–	8 ^e	–	0	–	–
Non-AD ^b	1 ^d	–	0	–	5 ^f	–	0	–	–
No Dementia ^b	0	–	0	–	0	–	6	–	–
Age of Onset	73.4 ± 8.4	26	75.9 ± 5.3	8	69.6 ± 10.7	13	–	–	0.2163
Age at First Encounter	77.1 ± 7.5	26	77.6 ± 6.1	8	73.6 ± 10.6	13	74.8 ± 5.0	6	0.5355
Age at Last Encounter	83.5 ± 7.7	26	83.5 ± 7.4	8	79.5 ± 10.9	13	83.9 ± 7.1	6	0.7018
Age at Death	84.3 ± 7.7	26	86.1 ± 7.6	8	80.3 ± 10.8	13	85.1 ± 6.9	6	0.4991
1st Visit – Death Interval	7.2 ± 4.2	26	8.5 ± 4.9	8	6.7 ± 6.0	13	10.3 ± 4.7	6	0.1879
Last Visit – Death Interval	0.7 ± 0.8	26	2.5 ± 3.9	8	0.8 ± 1.0	13	1.2 ± 1.3	6	0.8727
Onset – Death Interval	10.9 ± 4.2	26	10.2 ± 3.1	8	10.7 ± 3.7	13	–	–	0.9513
Male Gender	42.3%	26	37.5%	8	61.5%	13	83.3%	6	–
Years of Education	10.0 ± 4.5	25	10.5 ± 5.0	8	11.4 ± 5.0	13	11.1 ± 3.1	6	0.8501
First Visit MMSE	20.3 ± 7.8	25	19.0 ± 4.9	7	21.3 ± 6.1	12	29.8 ± 0.4	5	0.0038 ⁱ
Last Visit MMSE	11.5 ± 6.3	13	21.7 ± 6.1	3	10.0 ± 4.6	6	29.8 ± 0.4	6	0.0007 ⁱ
First Visit DRS Total	105.4 ± 19.6	25	100.7 ± 19.3	7	105.4 ± 23.3	12	129.8 ± 5.1	6	0.0058 ⁱ
Last Visit DRS Total	84.3 ± 22.9	10	106.5 ± 13.4	2	73.0 ± 18.6	4	127.2 ± 13.6	6	0.0048 ⁱ
ApoE4 Allele Frequency	19.2%	26	29%	7	14%	11	0%	6	–
Parkinsonism	19.2%	26	43%	7	41.7%	12	0%	6	–
Hallucinations	3.8%	26	29%	7	7.7%	13	0%	5	–
Fluctuations	0%	14	0%	3	0%	7	0%	5	–
REM sleep behavior									
Disorder symptoms	20%	10	0%	3	0%	7	–	0	–

^aFirst Clinical Encounter. ^bLast Clinical Encounter. ^cThree of the 25 participants were clinically diagnosed with Alzheimer's disease (AD) plus vascular disease and showed some level of vascular disease on neuropathology not significantly different than vascular disease found in other AD participants. ^dParticipant with dementia with Lewy body (DLB) clinical diagnosis during first and last clinical encounter. ^eFour participants had tangle only neuropathology, two participants had DLB neuropathology; one participant had frontotemporal dementia (FTD) neuropathology, and one participant had progressive supranuclear palsy (PSP) neuropathology. ^fOne participant with PSP clinical diagnosis and neuropathology; one participant with FTD clinical diagnosis and neuropathology (Pick's disease); one participant with Parkinson's disease with dementia (PDD) dementia clinical diagnosis and PD with neocortical Lewy bodies and Alzheimer's Braak V neuropathology; one participant with PPD clinical diagnosis and PSP neuropathology; and one participant with PPA clinical diagnosis and frontotemporal lobar degeneration with TDP43 neuropathology. ⁱStatistically significant. ^jParticipant with depression and pseudodementia clinical diagnosis. ^kOne participant had mild cognitive impairment clinical diagnosis during first clinical encounter. ^lOne participants was considered normal, one participant had PD without dementia, and last participant had "at risk of dementia" clinical diagnosis. ^mSeven patients have clinical diagnosis of probable AD and one has clinical diagnosis of possible AD. ⁿTwo patients with clinical diagnosis of PPA and FTD during first and last clinical encounter. ^oTwenty participants had clinical diagnosis of probable AD, two participants had clinical diagnosis of AD plus vascular disease, and two participants had clinical diagnosis of possible AD. The two patients with clinical diagnosis of AD plus vascular disease showed some level of vascular disease on neuropathology not significantly different than vascular disease found in the other AD participants. DRS, Dementia Rating Scale; MMSE, Mini-Mental State Examination.

coexisting Lewy body dementia) at the last ADRC evaluation, and 1 was incorrectly diagnosed with DLB. This high sensitivity of AD clinical diagnosis did not change over time as there was only one participant with a false negative missed diagnosis of AD during the last clinical visit in 2012. This participant had received a clinical diagnosis of DLB at the first and last clinical encounters, but had a primary neuropathological diagnosis of AD without the presence of synuclein (verified using a synuclein antibody). Of the 19 participants without a primary neuropathological diagnosis of AD, 7 were incorrectly clinically diagnosed with probable AD and 1 incorrectly

diagnosed with probable AD plus coexisting Lewy body dementia at the last clinical evaluation (42.1%). The dates of these eight last clinical encounters with incorrect diagnosis of AD were not significantly different from the remaining last clinical encounters ($p = 0.90$); i.e., the specificity of AD clinical diagnosis did not change over time. Four of these 8 participants had tangle only neuropathology, two had DLB neuropathology, one had FTD neuropathology, and one had PSP neuropathology. Three of the participants with tangle only neuropathology were Braak stage IV and one of the participants with primary DLB neuropathology had coexisting AD pathology

with Braak stage IV. The other four participants had no significant associated AD pathology. Overall, the clinical diagnosis of probable AD, probable AD plus vascular dementia, or probable AD plus coexisting Lewy body dementia at the last clinical evaluation had 97.1% sensitivity and 57.9% specificity against autopsy-verified AD with a PPV of 80.5% and a NPV of 91.7%.

Eleven participants had no clinical diagnosis of probable AD during their last ADRC clinical encounter and no primary neuropathological diagnosis of AD. Six participants had no significant brain pathology and 5 participants had a primary Non-AD neuropathological diagnosis. Of the six participants with no neuropathological diagnosis, 5 were noted to have AD changes (i.e., Braak stage II with moderate neuritic and diffuse plaques) which are commonly seen in normal participants over the age of 70. One the six participants did not have AD changes. This participant had severe atherosclerosis, and only a single small lacunar infarct (location not specified). The five participants with primary Non-AD neuropathological diagnosis included one participant with PSP who received a clinical diagnosis of PSP, one with FTLT (frontotemporal lobar degeneration, Pick's disease) who received a clinical diagnosis of FTD, one with PD and neocortical Lewy bodies who received a clinical diagnosis of PDD, one with PSP neuropathology who received a clinical diagnosis of PDD, and one with FTLT with TDP43 neuropathology who received a clinical diagnosis of PPA.

Clinical-neuropathological correlation: First clinical encounter

Of the 34 participants with a primary neuropathological diagnosis of AD, 32 (94.1%) were correctly clinically diagnosed as having AD at the first ADRC evaluation. These correct initial clinical diagnosis included 27 probable AD, 2 possible AD, 2 AD plus Vascular Dementia, and 1 participant with MCI diagnosis. Of the remaining 2 patients: one was diagnosed with depression/pseudodementia and one was incorrectly diagnosed with DLB. Of the 19 participants without primary neuropathological diagnosis of AD, 7 were incorrectly clinically diagnosed with probable AD and 1 was incorrectly clinically diagnosed with possible AD. Overall, the clinical diagnosis of MCI, possible/probable AD or probable AD plus vascular dementia at the first clinical evaluation had 94.1% sensitivity and 57.9% specificity against autopsy-verified AD with PPV of 80.0% and NPV of 84.6%

Neuropathological characteristics of AD and AD/DLB groups

Braak stage was determined for 24 of 26 participants in the AD group, 12 of 13 participants in the Non-AD group, and all participants in the AD/DLB and No Pathology groups. All AD/DLB participants were Braak stage V–VI (8/8 patients) whereas only 61.5% (16/26 patients) of the AD group were Braak stage V–VI (see Table 2). One participant in the AD group was Braak stage I with moderate neuritic plaques, moderate diffuse plaques, severe amyloid angiopathy, and only a few tangles. AD was considered the best neuropathological diagnosis for this participant given that no alternative diagnosis (e.g., TDP-43 pathology) was possible at the time the diagnosis was made (in 2006). Five of 6 participants in the No Pathology group (83%), and 6 of 12 in the Non-AD group (50%), were Braak stage I–II. Five participants in the Non-AD group (42%) were Braak stage III–IV. Only one participant in the Non-AD group was Braak stage V. This participant had a clinical diagnosis of PD for 8 years prior the onset of dementia, and received a primary neuropathological diagnosis of PD with neocortical Lewy bodies and a secondary diagnosis of AD.

The AD and AD/DLB groups had similar burden of amyloid angiopathy, neurofibrillary tangles, amyloid plaques, and neuritic plaques in all four brains regions sampled, with the exception that the AD/DLB group had significantly higher amyloid plaque burden in medial frontal and inferior parietal cortex compared to the AD group ($p=0.0438$ and $p=0.0109$, respectively). The AD/DLB and Non-AD groups had similar neurofibrillary tangle burden in medial frontal cortex.

The AD group had a higher burden of amyloid angiopathy (overall) than the Non-AD and No Pathology groups ($p=0.0039$ and $p=0.0029$, respectively), and the AD/DLB group had a higher burden than the No Pathology group ($p=0.0433$). All groups had a similar level of amyloid angiopathy in the hippocampus. Amyloid angiopathy burden (overall) remained similar in the AD, AD/DLB, and Non-AD groups when analyses were restricted to those with at least one *APOE* $\epsilon 4$ allele.

Hippocampal sclerosis was more common in the AD/DLB and Non-AD groups than in the AD group, and was absent in the No Pathology group. The prevalence of ischemic infarcts was higher in the Non-AD group than in the AD and No Pathology groups. No ischemic infarcts were noted in the AD/DLB group.

Table 2
Neuropathology characteristics within pathologically defined groups

	AD (n=26)	N	AD1st & DLB2nd (8)	n	Non-AD (n=13)	n	No Dementia (n=6)	n	p
Braak 0	—	—	—	—	1	—	1	—	—
Braak 1-2	1 ^a	—	—	—	6	—	5	—	—
Braak 3-4	7	—	—	—	4	—	—	—	—
Braak 5-6	16	—	8	—	1 ^b	—	—	—	—
MF Tangles	5.3 ± 10.2	23	2.6 ± 3.0	7	0.6 ± 1.0	12	0	6	0.0082 ^d
IP Tangles	4.3 ± 5.7	19	4.2 ± 2.5	5	0.2 ± 0.4	9	0	6	0.0008 ^d
ST Tangles	7.3 ± 8.8	22	8.3 ± 4.3	7	1.4 ± 2.0	13	0.3 ± 0.5	6	<0.0001 ^d
HP Tangles	19.0 ± 18.1	23	23.0 ± 14.8	6	7.5 ± 7.9	13	1.8 ± 1.3	6	0.0003 ^d
MF Plaques	42.3 ± 12.5	23	50.0 ± 0.0	7	10.5 ± 19.3	12	8.5 ± 13.2	6	<0.0001 ^d
IP Plaques	41.2 ± 10.2	19	50.0 ± 0.0	5	5.4 ± 15.2	8	8.8 ± 13.7	6	<0.0001 ^d
ST Plaques	40.0 ± 11.4	21	40.5 ± 9.5	6	8.2 ± 19.1	12	3.2 ± 7.8	6	<0.0001 ^d
HP Plaques	16.4 ± 11.3	22	27.4 ± 15.5	5	5.7 ± 13.9	13	3.8 ± 5.0	6	0.0002 ^d
MF Amyloid	1.9 ± 1.4	22	1.7 ± 1.3	7	0.8 ± 1.4	13	0.3 ± 0.8	6	0.0182 ^d
IP Amyloid	1.8 ± 1.4	19	1.6 ± 1.5	5	0.7 ± 1.1	9	0.3 ± 0.8	6	0.0354 ^d
ST Amyloid	1.9 ± 1.4	21	0.7 ± 1.3	7	0.5 ± 1.2	13	0.2 ± 0.4	6	0.0050 ^d
HP Amyloid	1.4 ± 1.5	19	1.1 ± 1.5	7	0.6 ± 1.3	13	0.2 ± 0.4	6	0.1444
MF NRPLQS	24.7 ± 16.2	21	22.0 ± 19.3	7	2.4 ± 5.1	12	2.6 ± 4.3	6	<0.0001 ^d
IP NRPLQS	19.8 ± 12.5	17	32.8 ± 19.8	5	2.4 ± 5.0	8	3.0 ± 4.6	6	<0.0001 ^d
ST NRPLQS	18.9 ± 14.17	19	17.7 ± 13.6	7	4.2 ± 11.2	12	1.5 ± 3.7	6	<0.0001 ^d
HP NRPLQS	12.2 ± 11.0	20	19.4 ± 8.7	5	2.4 ± 6.2	13	1.2 ± 2.0	6	<0.0001 ^d
LEWY	1	1	8	8	3	3	1	1	—
HS	11.5%	26	37.5%	8	30.8%	13	0	6	—
CAA	2.1 ± 1.0	25	1.6 ± 1.1	8	0.8 ± 1.2	13	0.3 ± 0.8	6	0.0020 ^d
CAA in E4	2.2 ± 1.0	10	2.3 ± 0.6	3	3.0 ± 0.0	2	—	—	0.4155
CAA in non E4	2.0 ± 1.1	15	1.0 ± 1.2	4	0.2 ± 0.7	9	0.3 ± 0.8	6	0.0013 ^d
Ischemic Infarct	23.1%	26	0	8	38.5%	13	16.7%	6	—
Micro-Infarct	11.5%	26	12.5	8	7.7%	13	0	6	—

Wilcoxon/Kruskal-Wallis Tests. ^aParticipant was Braak I and had moderate neuritic plaques, moderate diffuse plaques, severe amyloid angiopathy, no Lewy bodies. The hippocampus had modest numbers of diffuse and neuritic plaques and only few tangles. The latter lesions are similarly sparse in layer II of the entorhinal cortex where neuron clusters contain an average of only 1 tangle each ($n=21$); Amyloid angiopathy was fairly severe in neocortex and hippocampus. The degree of Alzheimer pathology was fairly minor so as to refer to it as slight, early, or mild. No alternative neuropathological diagnosis such TDP-43 pathology in aging was available at that time in 2006.

^bParticipant with Braak V, frequent neuritic and frequent diffuse plaques, severe amyloid angiopathy, neocortical diffuse Lewy Bodies. Primary diagnosis of Lewy body disease and secondary diagnosis of Alzheimer's disease (AD). Participant had a preceding 8 year clinical history of Parkinson's disease before developing dementia. ^dStatistically Significant. MF, medial frontal; IP, inferior parietal; ST, superior temporal; HP, hippocampus; HS, hippocampal sclerosis 0=absent, 1=present; CAA, cerebral amyloid angiopathy rated on a 3 point scale 0–3; NRPLQS, Neuritic Plaques per 100X field of view; Amyloid, cerebral amyloid angiopathy rated on 3 point scale 0–3; Plaques, total plaques = diffuse plaques PLUS neuritic plaques per 100X field of view; Tangles, neurofibrillary tangles per 400X field of view.

The AD, AD/DLB, and Non-AD groups had similar prevalence of micro-infarcts. No micro-infarcts were noted in the No Pathology group.

DISCUSSION

Using standard clinical procedures and diagnostic criteria, we achieved sensitivity for the clinical diagnosis of AD in monolingual Spanish-speaking or bilingual Spanish-English-speaking, Mexican-origin Latinos that was comparable to sensitivity reported for English-speaking, non-Latino Whites. Specificity of the clinical diagnosis of AD, however, was lower than reported for English-speaking Whites [1–3, 5]. The most frequent primary neuropathology in these “false positive” clinical AD cases was, in

descending order, tangle only dementia, DLB, FTD, or PSP. Half of the participants misdiagnosed with AD (3 tangle only dementia, and 1 DLB) were Braak stage IV, and this level of neurofibrillary tangle pathology may drive the symptoms that lead to a misdiagnosis of AD. It is not surprising that specificity for the clinical diagnosis of AD was lower than sensitivity since this has been reported in studies with non-Latino Whites [34]. Furthermore, the Non-AD representation in our series was small and therefore susceptible to spurious results related to specificity, and criteria for several of the clinical diagnostic categories (e.g., DLB, FTD) were not fully evolved at the time of the diagnoses examined in the present study. Consistent with prior studies [34], clinical DLB was not accurately diagnosed. The two

patients with a primary neuropathological diagnosis of DLB both had received a clinical diagnosis of probable AD during the first and last clinical encounters. One of these participants had significant concomitant AD pathology (i.e., Braak stage IV, moderate neuritic plaques, frequent diffuse amyloid plaques) which may have reduced the ability to clinically recognize DLB. This was not the case for the second patient who had little AD pathology (i.e., Braak stage I, sparse neuritic plaques). On the other hand, the one patient who received a clinical diagnosis of DLB turned out to have a primary neuropathological diagnosis of AD without alpha-synuclein pathology. These results indicate that additional neuropsychological, biomarker, genetic, and imaging research with Mexican-origin Latinos is needed to increase the specificity of the clinical diagnosis of AD in this population, particularly for distinguishing AD from tangle only dementia or DLB from AD dementia.

A second finding from our study is that the Mexican-origin Latinos with autopsy-confirmed AD had a lower *APOE* ϵ 4 allele frequency than has been reported for non-Latino Whites (e.g., 35.7%) [24]. The *APOE* ϵ 4 allele frequency we observed was similar to that for Mexican-Americans in the Texas Alzheimer's Research and Care Consortium cohort [21] and in a prior meta-analysis [24]. It is particularly notable that Mexican-origin Latinos with AD who were Braak V–VI had an *APOE* ϵ 4 allele frequency (12.5%) similar to that previously reported for Latino and Caucasian healthy control participants [24]. Our findings are complicated, however, by an *APOE* ϵ 4 allele frequency in Mexican-origin Latinos with Braak III–IV (35.7%) that is similar to that previously reported for non-Latino Whites with AD [24]. This discrepancy may arise from the small sample size, but could reflect a difference in the relationship between the *APOE* ϵ 4 allele and AD in Mexican-origin Latino and non-Latino white populations, or unique genetic risk factors in Mexican-origin Latinos. Additional research on the relationship between *APOE* ϵ 4 allele frequency and AD pathology in Mexican-origin Latinos is clearly needed.

The study has several limitations. First, the sample size is relatively small and slightly biased with lower number of clinically normal participants compared to those who were excluded. Thus, it is difficult to draw strong inferences regarding sensitivity and specificity of the clinical diagnosis in Mexican-origin Latinos. This is offset to some degree, however, by being one of the few studies to have autopsy verification of AD and other neurodegenerative diseases in this

population. Thus, the true relationship between clinical diagnosis and ultimate neuropathological findings could be ascertained. Second, the clinical diagnoses examined in the present study were made in an academic research and tertiary referral setting where the participants had access to bicultural/bilingual staff and back-translations of test materials. These are ideal assessment situations which may not generalize well to general clinical practice where similar resources are not available. Third, our results regarding a possible lower *APOE* ϵ 4 allele frequency and reduced risk-relationship between the *APOE* ϵ 4 allele and autopsy-confirmed AD in Mexican-origin Latinos compared to non-Latino whites may not generalize to other Latino groups (e.g., Caribbean Latinos). Studies suggest that Caribbean Latinos have a higher *APOE* ϵ 4 allele frequency (similar to that of Caucasians) than Mexican-Americans. Finally, vascular co-pathology was relatively mild in our series, possibly because participants with significant stroke or with insulin-dependent diabetes were excluded from the ADRC longitudinal study. A higher degree of vascular pathology may be evident when considering the Latino community at large.

Despite these limitations, our results show that a comprehensive clinical evaluation and the use of standardized diagnostic criteria can effectively identify AD in Mexican-origin Latinos. This should instill confidence in the clinical diagnosis of AD dementia in this population for future research and in clinical practice. Recreating this diagnostic accuracy in clinical practice will require choice of language in clinical testing with access to bilingual/bicultural staff and validated back-translations of test materials.

ACKNOWLEDGMENTS

We thank Dr. P. Davies for generously providing antibody PHF-1, used in the neuropathological analyses of the tissues used in this study. The authors also thank Dr. H. Feldman for helpful comments.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/18-0789r1>).

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