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TDP-43 and Alzheimer's Disease Pathologic Subtype in Non-Amnestic Alzheimer's Disease Dementia

Aradhana Sahoo[a], **Alexandre Bejanin**[b,i], **Melissa E. Murray**[h], **Nirubol Tosakulwong**[d], **Stephen D. Weigand**[d], **Amanda M. Serie**[h], **Matthew L. Senjem**[e], **Mary M. Machulda**[f], **Joseph E. Parisi**[g], **Bradley F. Boeve**[b], **David S. Knopman**[b], **Ronald C. Petersen**[b], **Dennis W. Dickson**[h], **Jennifer L. Whitwell**[c], and **Keith A. Josephs, MD, MST, MSc**[b]

[a]Mayo Clinic School of Medicine, Rochester, MN, USA

[b]Departments of Neurology (Behavioral Neurology), Mayo Clinic, Rochester, MN, USA

[c]Departments of Radiology (Radiology Research), Mayo Clinic, Rochester, MN, USA.

[d]Departments of Health Science Research (Biostatistics), Mayo Clinic, Rochester, MN, USA

[e]Departments of Information Technology, Mayo Clinic, Rochester, MN, USA

[f]Departments of Neuropsychiatry (Neuropsychology), Mayo Clinic, Rochester, MN, USA

[g]Departments of Laboratory Medicine and Pathology (Neuropathology), Mayo Clinic, Rochester, MN, USA

[h]Department of Neuroscience (Neuropathology), Mayo Clinic, Jacksonville, FL, USA

[i]Inserm, Inserm UMR-S U1237, Université de Caen-Normandie, GIP Cyceron, Caen, France

Abstract

Background: TDP-43 has been shown to be strongly associated with memory loss, smaller hippocampal volumes, and faster rates of hippocampal atrophy in Alzheimer's disease (AD) patients with an amnestic presentation. Whether TDP-43 has any clinical or anatomical associations in AD patients with a non-amnestic phenotype is unknown.

Objective: To determine whether TDP-43 plays a significant role in the clinic-anatomic features of non-amnestic AD.

Methods: All cases with pathologically confirmed intermediate-high probability AD from 1996–2012 were identified and retrospectively sub-classified into amnestic versus non-amnestic dementia at the time of presentation. Neurofibrillary tangle counts were performed in those with a non-amnestic presentation using thioflavin-S microscopy in the hippocampus and three neocortical regions, and all cases were subtyped into hippocampal-sparing, limbic-predominant, and typical AD pathology. TDP-43 immunoreactivity was used to assess for the presence of TDP-43. Statistical analyses helped determine whether pathologic subtype or TDP-43 was more strongly associated with clinico-imaging features.

Correspondence to: Keith A. Josephs, MD, MST, MSc, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel.: 507-538-1038; Fax: 507-538-6012; josephs.keith@mayo.edu.

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Results: Out of 172 pathologically confirmed AD cases, 36 (19%) were classified as non-amnestic. Twenty-five of these 36 (69%) had typical pathology, 0 limbic-predominant pathology, and 11 (31%) hippocampal-sparing pathology. Eleven (44%) of the 25 cases with typical pathology were TDP-43+. Of the 11 cases with hippocampal-sparing pathology, 4 (36%) were TDP-43+. There were no differences in demographic, clinical, or neuroimaging features in those with TDP-43 versus those without except for older age at onset (p=0.02) and age at death (p=0.02) in those with TDP-43. AD pathological subtype accounted for slightly more of the variances in the neocortex than TDP-43.

Conclusion: In non-amnestic AD, we find little evidence that clinical or anatomical features of the disease are related to TDP-43.

Keywords

Alzheimer's disease; atypical AD; non-amnestic; TDP-43

INTRODUCTION

Alzheimer's disease (AD) is the most prevalent progressive neurodegenerative condition leading to dementia in the elderly. Clinical presentations for AD dementia can largely be broken down into two categories for simplicity: amnestic and non-amnestic [1]. Amnestic AD dementia describes a presentation that is predominantly characterized by episodic memory loss that can be confirmed objectively with neuropsychological testing. Non-amnestic AD dementia describes a presentation in which memory loss is not the chief complaint or most prominent problem, and there is objective evidence on neuropsychological testing confirming these findings. Patients presenting with a non-amnestic AD dementia can complain of difficulties with language or visuospatial/perception deficits; behavioral impairment and executive dysfunction are less common [2]. A non-amnestic presentation of AD can therefore sometimes overlap with other conditions, for example frontotemporal dementia [3–5], but postmortem pathological examination of brain specimens can confirm the diagnosis of AD [4, 6].

Tau immunoreactive neurofibrillary tangles (NFT) and neuritic plaques typically characterize the neuropathology of AD. Deposition of hyperphosphorylated tau proteins starting in the transentorhinal cortex and progressing to the hippocampus and primary cortices of the brain is the most common pattern seen in AD, and is thus described as the typical AD pathology [7]. However, descriptions of other patterns of NFT deposition have recently emerged, including limbic predominant AD and hippocampal-sparing AD (HpSp) [7]. In the former, NFT deposits in limbic regions while leaving the neocortex relatively spared; in HpSp pathology, the limbic and transentorhinal regions are relatively spared, with the NFT favoring deposition in the neocortices. Studies have revealed that patients with typical, limbic, and HpSp subtypes present differently from one another clinically and anatomically [6, 7].

Recently, transactive response DNA binding protein of 43 kDa (TDP-43) has emerged as a topic of interest in the realm of AD dementia. This protein was initially described in its role in HIV-1 gene expression and has been shown to act as a transcriptional repressor, binding

both RNA and DNA, and modulating gene splicing [8, 9]. TDP-43 deposition in the brain of patients with AD is strongly associated with memory loss, smaller hippocampal volumes, and faster rates of hippocampal atrophy [10–12]. It is unknown, however, whether TDP-43 has any clinical or anatomical associations in patients with a non-amnestic presentation.

Thus, our main aim of this study was to take a closer look at patients with a non-amnestic AD dementia and examine whether or not clinical and anatomic features varied by the presence of TDP-43. As a secondary aim, we also investigated whether AD pathologic subtype or TDP-43 was more strongly associated with the clinico-imaging features in non-amnestic AD dementia. Given that the effect of TDP-43 is on memory, our main hypothesis is that TDP-43 would show little-to-no association with memory loss or hippocampal atrophy in patients with a non-amnestic presentation.

METHODS

Subject selection

We identified subjects who were demented prior to death and who had met pathological criteria for intermediate-high probability AD from the Mayo Clinic Rochester neuropathological database based on inclusion criteria that are described in a previous study [2]. Briefly, subjects had to be amyloid positive and meet the NIA-Reagan criteria, with a Braak neurofibrillary tangle stage of IV to VI, completed antemortem volumetric MRI imaging of the head by standardized protocol [13], and have been prospectively recruited and followed longitudinally in the Mayo Clinic Alzheimer's Disease Research Center (ADRC).

One hundred seventy-five cases were identified, with all of them having consented to and undergone detailed clinical evaluations including neuropsychological testing, apolipoprotein E (APOE) genotyping, and brain autopsy. These 175 cases were evaluated for amnestic versus non-amnestic presentation at the initial visit by an experienced behavioral neurologist (K.A.J.), who was blinded to pathological subtype and the presence or absence of TDP-43. The initial visit was selected because over time, as a result of progressive neurodegeneration, it is more difficult to differentiate amnestic AD dementia from non-amnestic AD dementia. Detailed methods used to make this clinical distinction based on the chief complaint and neuropsychological testing have been previously described [2]. Of these 175 cases, three cases were excluded due to insufficient information in the medical records, while the other 172 were classified as being either non-amnestic or amnestic. For this study, only those classified as having a non-amnestic dementia were further analyzed for TDP-43 status and stage and pathological AD subtype [12]. Demographic information, results of neuropsychiatric testing, pathological variables, and imaging variables were compared across the different pathological subtypes, with special attention being given to TDP-43 status. Neuropsychiatric scores are reported as MOANS (Mayo's Older Americans Normative Studies), which accounts for age. Neuroimaging variables were calculated at the time closest to death in order to have the smallest illness duration between MRI and death. Therefore, we assessed two time points in this study: time from earliest evaluation to death (clinically) and time closest to death (MRI).

Pathological procedures

Pathological procedures were previously described in detail [12]. Briefly, NFT densities were measured via thioflavin-S fluorescence in the hippocampal CA1 region, subiculum, middle frontal, inferior parietal, and superior temporal cortical regions and were examined for intracellular and extracellular NFT counts, which were averaged for each of the five regions. We then followed an algorithm utilizing hippocampal and cortical NFT counts and the ratio of hippocampal-to-cortical counts as described in our previous study [7] in order to classify subjects into limbic AD pathology, hippocampal sparing (HpSp) AD pathology, and typical AD pathology.

In addition, the presence of TDP-43 immunoreactive neuronal cytoplasmic inclusions, dystrophic neurites, or neuronal intranuclear inclusions in the amygdala was used to classify cases as TDP-43 positive. We also categorized the TDP-43 positive cases into six stages based on published criteria: stage I, TDP-43 deposition is limited to the amygdala; stage II, TDP-43 deposition extends into entorhinal cortex and/or subiculum; stage III, TDP-43 deposition extends into hippocampus dentate granule cell layer and/or occipitotemporal cortex; stage IV, TDP-43 extends into the inferior temporal cortex; stage V, TDP-43 extends into brain stem regions and stage VI TDP-43 deposition extends into frontal cortex and/or basal ganglia [14, 15].

All neuropathological examinations were conducted in accordance with the recommendations of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [16, 17].

Imaging analyses

All subjects had undergone a volumetric MRI using a standardized protocol, as previously described [13]. If subjects had more than one MRI, the MRI closest to death was selected for analysis. Atlas-based parcellation using the automated anatomical labelling atlas was used to calculate grey matter volumes of the hippocampus as well as three cortical regions-of-interest: lateral frontal, lateral parietal, and lateral temporal cortex, as previously described [18]. Left and right volumes were averaged. Total intracranial volume (TIV) was calculated to allow a correction for head size.

Statistical analysis

All analyses were performed in the whole group of non-amnestic AD cases as well as separately within the typical and hippocampal sparing subtypes (no cases were limbic predominant). Demographic variables were compared between those with and without TDP-43 using Fisher's exact or t-tests. Linear regression was performed with TDP status being the predictor and the outcome being either one of six clinical test scores (Mini–Mental Status Examination [MMSE], Clinical Dementia Rating Scale Sum of Boxes [CDR-SB], the Logical memory delayed recall subtest of the Wechsler Memory Scale [WMS memory] MOANS, the Boston Naming Test [BNT] MOANS, the Control Oral Word Association Test [COWAT] MOANS, and the block design subtest of the Wechsler Adult Intelligence Scale [WAIS-block design]) MOANS and for one of four brain volumes (hippocampus, lateral frontal, lateral parietal, and lateral temporal) modeled as a percentage of TIV. All non-

MOANS regression analyses were adjusted for age at death. We did not adjust neuropsychiatric variables because age is already accounted for with the MOANS scores. These regression models are equivalent to a two-group ANCOVA and allow us to evaluate mean neuropsychological or volumetric values by TDP-43 status after accounting for potential confounding due to age. $p<0.05$ was considered statistically significant. We used bootstrap resampling with 10,000 replicates to compare the coefficient of determination (R^2) for a model with age at death and pathological AD subtype versus a model with age at death and TDP-43 status. The summary statistic for this comparison was the proportion of bootstrap samples for which the R^2 was higher for the pathological AD subtype. Proportions far from 50% are interpreted as evidence that one factor tended to account for more of the observed variability in the response than another. We calculated 95% confidence intervals for Cohen's d using bootstrap methods with 10,000 replicates. The 95% confidence intervals in the table provide an indication of the precision of our estimates. Ninety-five percent confidence intervals that do not include the null value of zero are equivalent to a statistical test with $p<0.05$.

RESULTS

Of the 172 cases that were reviewed for this study, 36 (21%) were identified as having a non-amnestic AD dementia. Of these 36 cases, 15 (42%) were TDP-43 positive (Table 1). Overall, patients with TDP-43 were significantly older at onset and at death ($p = 0.02$). After adjusting for the age of death, and with MOANS models, there were no significant clinical or neuroimaging differences between those with and without TDP-43. Those with TDP-43 were more likely to have hippocampal sclerosis ($p=0.02$) and less likely to be CERAD frequent for beta-amyloid deposition ($p=0.02$). No between-group differences were observed for vascular disease ($p=0.06$), Lewy bodies ($p>0.99$), hypertension ($p=0.24$), diabetes ($p>0.99$), or dyslipidemia (0.70). Finally, only 1 out of 36 patients presented argyrophilic grain pathology.

Of the 36 non-amnestic AD dementia subjects, 25 (69%) had typical pathology, 0 had limbic-predominant pathology, and 11 (31%) had HpSp pathology. Of the 25 subjects who had typical pathology, 11 (44%) were TDP-43 positive and 14 (56%) were TDP-43 negative. There were no clinical (MMSE, CDR-SB, WMS memory, BNT, COWAT, and WAIS-block), imaging, or pathological differences for those with typical pathology with and without TDP-43. Of the 11 non-amnestic AD dementia subjects with HpSp pathology, 4 (36%) were TDP-43 positive and 7 (64%) were TDP-43 negative. There were no clinical, imaging, or pathological differences for those with HpSp pathology with and without TDP-43.

The results of the bootstrap evaluation of whether pathologic subgroup or TDP-43 status accounted for a greater fraction of observed variation in the response after adjusting for age can be seen in Table 2. While neither age, AD pathological subtype, nor TDP-43 accounted for an appreciable proportion of the variances in the outcome measures, there was some suggestion that AD pathological subtype may play a slightly stronger role in accounting for lateral frontal and possibly temporal and parietal volumes than TDP-43.

DISCUSSION

It has previously been demonstrated that TDP-43 status is associated with memory loss and hippocampal atrophy in AD, but these studies examined populations with both amnestic and non-amnestic presentations [2, 12, 18]. We hypothesized in this study that by excluding subjects with an amnestic presentation, we would less likely observe any association between memory loss and hippocampal atrophy and TDP-43. In keeping with our hypothesis, we found that the presence of TDP-43 did not correlate with memory loss or hippocampal atrophy once the cohort was limited to those with a non-amnestic AD phenotypic presentation.

The fact that we did not see any association between TDP-43 and hippocampal volume may be due to the fact that the hippocampus is relatively preserved in AD cases with a non-amnestic presentation [6, 7]. It has also been hypothesized that in those with amnestic and late-onset AD, a stronger association between rates of hippocampal atrophy and TDP-43 exists, whereas tau may play a bigger role in hippocampal atrophy rates in those with non-amnestic and early-onset AD [11]. In this non-amnestic and relatively young cohort, it is possible that tau is driving the hippocampal atrophy rather than TDP-43, which would explain the lack of difference between TDP-43 positive and negative groups.

Another explanation for the apparent lack of association between TDP-43 and memory loss and hippocampal atrophy may lie in the severity of the patients studied in terms of Braak staging. The greatest differences between TDP-43 positive and TDP-43 negative groups seem to be seen at Braak stage IV, with less robust differences observed at higher Braak stages [18]. In this cohort, the majority (87%) of our patients, regardless of TDP-43 status, were Braak stage VI. At Braak stage VI, there is extensive neocortical involvement, indicating advanced disease. At this point, the widespread tau deposition may dwarf any association of TDP-43 with memory loss and hippocampal atrophy [18]. Additionally, we cannot rule out the possibility that another unexplored pathologic process at play in non-amnestic AD has masked these associations. Finally, we cannot entirely exclude the fact that our small sample size prevented us from observing subtle associations, the effects sizes were indeed small.

In accordance with previous studies showing a tight relationship between limbic-predominant pathology and amnestic AD phenotype [7], none of the patients with a non-amnestic presentation had pathology predominating in the limbic area. Instead, patients presented with cortical involvement and had either typical AD pathology or, in a lower proportion, HpSp pathology. While neither AD pathology subtype nor TDP-43 seems to be important players in accounting for the clinical and imaging variables analyzed in this study, there was some suggestion that AD pathological subtype is playing a slightly stronger role in volumetric measurements than is TDP-43. Interestingly, the regions that showed this trend are those that are relatively more affected in non-amnestic AD, i.e., lateral frontal, temporal, and parietal cortices. We did not find any evidence for an association between TDP-43 and hippocampal atrophy, however.

Importantly, 41.5% of this cohort of non-amnestic AD patients had TDP-43 pathology. This further emphasizes that TDP-43 is not an epiphenomenon across the AD spectrum. In line with the idea that co-pathologies increase with age [19], these patients were older than those without TDP-43, more likely to have hippocampal sclerosis, and tended to have more cardiovascular disease. Future studies could further assess the differential effect of these pathologies in middle-aged and older adults.

In summary, in cases in which memory is relatively spared, TDP-43 does not appear to play a strong role in the presence of the other clinical features or anatomy that dominate the presentation. The findings from this study therefore suggest that there may be important differences between amnestic and non-amnestic AD in regards to the role of TDP-43. Further studies that directly compare those with non-amnestic AD presentations to those with the amnestic presentation may reveal more differences in pathophysiology in the varying phenotypes of AD dementia. Additionally, an analysis examining the TDP-43 status and pathological subtype associated with the various presentations within the umbrella of non-amnestic AD, including posterior cortical atrophy [20] and logopenic variant primary progressive aphasia [21–23], would be helpful in further defining the pathophysiology of this heterogeneous group.

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Table 1.

Subject characteristics in the Atypical AD Dementia cohort

	All subjects (n = 36)	TDP + (n = 15)	TDP – (n = 21)	p	TDP Effect Size, Cohen's d
Demographics					
No. Female, n (%)	14 (39%)	6 (40%)	8 (38%)	>0.99	
Education, y	14 [12, 16] (8, 20)	14 [12, 16] (8, 18)	15 [12, 16] (8, 20)	0.45	
APOE ε4 carrier, n (%)	19 (53%)	8 (53%)	11 (52%)	>0.99	
Age at onset, y	64 [56, 73] (46, 91)	70 [62, 76] (50, 91)	61 [55, 68] (46, 85)	0.02	
[1]Disease duration, y	5 [4, 7] (1, 9)	5 [4, 7] (3, 9)	5 [4, 7] (1, 9)	0.86	
Age at death, y	73 [64, 82] (52, 98)	78 [70, 87] (56, 98)	69 [61, 76] (52, 89)	0.02	
[2]Time from presentation to death, y Hypertension, n (%) Diabetes, n (%) Dyslipidemia, n (%)	6 [4, 7] (2, 10) 19 (70%) 4 (15%) 11 (41%)	6 [4, 7] (3, 9) 10 (83%) 2 (17%) 4 (33%)	5 [3, 7] (2, 10) 9 (60%) 2 (13%) 7 (47%)	0.44 0.24 >0.99 0.70	
Neuropsychological tests					
Mini-Mental State Exam score *	21 [18, 25] (8, 29)	23 [20, 26] (13, 29)	20 [17, 24] (8, 29)	0.29	0.40 (−0.34, 1.12)
CDR Sum of Boxes *	4.1 [1.9, 6.0] (0.5, 12.0)	3.4 [1.0, 5.5] (0.5, 12.0)	4.7 [3.0, 6.0] (1.0, 9.5)	0.44	−0.28 (−1.30, 0.53)
WMS logical memory delayed recall MOANS	4 [2, 5] (2, 11)	5 [2, 6] (2, 11)	3 [2, 4] (2, 9)	0.17	0.50 (−0.20, 1.14)
Boston Naming MOANS	6 [2, 8] (2, 13)	6 [2, 8] (2, 12)	6 3 [3, 8] (2, 13)	0.59	−0.19 (−0.85, 0.52)
Controlled Oral Word Association Test MOANS	7 [4, 8] (2, 13)	7 [4, 10] (2, 13)	6 [4, 8] (2, 12)	0.59	0.19 (−0.52, 0.87)
WAIS - block design MOANS	6 [2, 9] (2, 14)	5 [2, 9] (2, 10)	6 [2, 8] (2, 14)	0.73	−0.18 (−1.16, 0.95)
Pathological variables					
Braak stage, n (%)				0.44	
4	1 (3%)	1 (7%)	0 (0%)		
5	4 (11%)	1 (7%)	3 (14%)		
6	31 (86%)	13 (87%)	18 (86%)		
TDP stage, n (%)					
I		1 (7%)			
II		4 (27%)			
III		2 (13%)			
IV		3 (20%)			
V		4 (27%)			
VI		1 (7%)			
CERAD Frequent, n (%)	32 (89%)	11 (73%)	21 (100%)	0.02	
Infarction, n (%)	3 (8%)	3 (20%)	0 (0%)	0.06	
Vascular disease positive, n (%)	3 (8%)	3 (20%)	0 (0%)	0.06	

	All subjects (n = 36)	TDP + (n = 15)	TDP – (n = 21)	p	TDP Effect Size, Cohen's d
Hippocampal sclerosis positive, n (%)	4 (11%)	4 (27%)	0 (0%)	0.02	
Lewy bodies positive, n (%) Argyrophilic positive, n (%)	11 (31%) 1 (3%)	5 (33%) 1 (7%)	6 (29%) 0 (0%)	>0.99	
Imaging variables (% of TIV) *					
Hippocampus	0.43 [0.40, 0.45] (0.28, 0.59)	0.42 [0.40, 0.45] (0.28, 0.48)	0.43 [0.41, 0.46] (0.34, 0.59)	0.79	−0.10 (−0.67, 0.57)
Lateral frontal	3.38 [2.96, 3.78] (2.34, 4.54)	3.35 [2.78, 3.79] (2.34, 4.31)	3.39 [2.98, 3.78] (2.65, 4.54)	0.88	−0.06 (−0.79, 0.68)
Lateral parietal	1.84 [1.63, 2.03] (1.16, 2.45)	1.96 [1.75, 2.10] (1.57, 2.45)	1.76 [1.56, 2.03] (1.16, 2.34)	0.18	0.49 (−0.30, 1.16)
Lateral temporal	3.65 [3.27, 3.96] (2.77, 4.65)	3.68 [3.18, 4.03] (2.77, 4.65)	3.62 [3.51, 3.70] (2.97, 4.38)	0.67	0.16 (−0.68, 1.04)

* p-values are adjusted for age at death.

AD, Alzheimer's disease; APOE, apolipoprotein E; CDR, Clinical Dementia Rating; MOANS, Mayo's Older Americans Normative Scale; WMS, Wechsler Memory Scale; WAIS, Wechsler Adult Intelligent Scale; TDP, TAR DNA-binding protein; HpSp, hippocampal sparing; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; TIV, total intracranial volume

1 Disease duration is the time from recorded onset date to the last MRI scan.

2 Time from presentation to death is the time from clinical testing to death.

Cognitive data were from first available testing. Data shown are mean [IQR] (range)

Table 2.

Results of bootstrap analysis (B = 10,000) to compare R-squared for model with age at death and AD pathology versus model with age at death and TDP status.

Clinical / Imaging variable	R-squared from age-only model	R-squared from age and AD pathology model	R-squared from age and TDP model	Estimated chance R-squared higher with age and AD pathology model
MMSE	0.0085	0.0086	0.04	34%
CDR-SB	0.068	0.081	0.085	46%
Boston Naming	0.19	0.20	0.21	46%
WMS logical memory	0.00	0.05	0.027	57%
Control Oral Word	0.045	0.047	0.08	35%
Hippocampus	0.058	0.058	0.06	57%
Lateral frontal	0.001	0.097	0.002	83%
Lateral parietal	0.08	0.186	0.129	68%
Lateral temporal	0.00	0.087	0.006	74%