Published in final edited form as:

Neurology. 2008 May 6; 70(19 Pt 2): 1850–1857. doi:10.1212/01.wnl.0000304041.09418.b1.

Abnormal TDP-43 immunoreactivity in AD modifies clinicopathological and radiological phenotype

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Abstract

Background—TAR DNA-binding protein 43 (TDP-43) is one of the major disease proteins in frontotemporal lobar degeneration with ubiquitin immunoreactivity. Approximately 1/4 of subjects with pathologically confirmed Alzheimer's disease (AD) have abnormal TDP-43 (abTDP-43) immunoreactivity. The aim of this study was to determine if subjects with pathologically confirmed AD and abTDP-43 immunoreactivity have distinct clinical, neuropsychological, imaging or pathological features compared to subjects with AD without abTDP-43 immunoreactivity.

Methods—Eighty-four subjects were identified that had a pathological diagnosis of AD, neuropsychometric testing, and volumetric MRI. Immunohistochemistry for TDP-43 was performed on sections of hippocampus and medial temporal lobe, and positive cases were classified into one of three types. Neuropsychometric data was collated and compared in subjects with and without abTDP-43 immunoreactivity. Voxel-based morphometry was used to assess patterns of gray matter atrophy in subjects with and without abTDP-43 immunoreactivity compared to age and gender matched controls.

Results—Twenty-nine (34%) of the 84 AD subjects had abTDP-43 immunoreactivity. Those with abTDP-43 immunoreactivity were older at onset and death, and performed worse on the Clinical Dementia Rating scale, Mini-Mental State Examination and Boston Naming Test than subjects without abTDP-43 immunoreactivity. Subjects with and without abTDP-43 immunoreactivity had medial temporal and temporoparietal gray matter loss compared to controls; however, those with abTDP-43 immunoreactivity showed greater hippocampal atrophy. Multivariate logistic regression adjusting for age at death demonstrated that hippocampal sclerosis was the only pathological predictor of abTDP-43 immunoreactivity.

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Search Terms: Alzheimer's disease [26], volumetric MRI [130], and Neuropsychological Assessment [205]

Disclosure: DSK has been a consultant to GE HealthCare, GlaxoSmithKline and Myriad Pharmaceuticals, has served on a Data Safety Monitoring Board for Neurochem Pharmaceuticals, and is an investigator in a clinical trial sponsored by Elan Pharmaceuticals. BFB is an investigator in a clinical trial sponsored by Myriad Pharmaceuticals. RCP has been a consultant to GE Healthcare and has served on a data safety monitoring board in a clinical trial sponsored by Elan Pharmaceuticals.

Conclusions—The presence of abTDP-43 immunoreactivity is associated with a modified AD clinicopathological and radiological phenotype.

Introduction

Frontotemporal lobar degeneration with ubiquitin-immunoreactive inclusions (FTLD-U) is the most common pathology underlying the frontotemporal lobar degenerations (FTLD).¹ The TAR DNA-binding protein 43 (TDP-43) has been identified as one of the major disease proteins in neuronal and glial inclusions in FTLD-U.² The clinical syndrome most commonly associated with FTLD-U is behavioral variant frontotemporal dementia, characterized by behavioral and personality changes and executive dysfunction.³ The average age of onset of subjects with FTLD-U is less than 65 years old; however, age at onset can be as old as 89 years,⁴ and MRI typically reveals a frontotemporal pattern of gray matter loss.⁵

Recently it has been shown that approximately 25% of subjects with pathologically confirmed Alzheimer's disease (AD) also have abnormal TDP-43 (abTDP-43) immunoreactivity;⁶ however, the significance of abTDP-43 immunoreactivity in AD is unknown. The abTDP-43 immunoreactivity in AD was confirmed as pathologic by immunohistochemistry and biochemistry.⁶ Furthermore, whenever abTDP-43 immunoreactivity occurred in AD, there was a loss of the normal nuclear staining of TDP-43.⁶ Our primary aim therefore was to determine if subjects with pathologically confirmed AD and abTDP-43 immunoreactivity had distinct clinical, neuropsychological, imaging or pathological features compared to subjects with AD without abTDP-43 immunoreactivity. The technique of voxel-based morphometry (VBM) was chosen to assess MRI patterns of volume loss across groups of AD subjects with and without abTDP-43 immunoreactivity because it is automated and can assess regional patterns of atrophy throughout the entire brain without requiring any *a priori* assumptions concerning which structures to assess.

Given a recently proposed classification scheme for FTLD-U that has been reported to correlate with clinical phenotype,⁷ as a secondary aim, we also set out to classify cases with abTDP-43 immunoreactivity and to assess whether there were any clinical, neuropsychological, imaging or pathological differences among the different types.

Materials and Methods

Subject selection

The neuropathology database of the Alzheimer's Disease Research Center (ADRC) and Patient Registry (ADPR) were queried to identify all subjects with 1) AD type pathological changes that meet criteria for at least intermediate probability AD⁸ with Braak neurofibrillary tangle (NFT) stage IV or greater;⁹ 2) neuropsychometric testing; and 3) a usable volumetric MRI scan. All subjects had been studied prospectively with yearly clinical evaluations, cognitive and neuropsychometric testing and MRI's. The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,¹⁰ and the clinical diagnosis of AD was made based on National Institute on Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders criteria.¹¹ Written informed consent was obtained for participation in the studies, which were approved by the Mayo Institutional Review Board.

A total of 84 subjects met all criteria. The clinical records were queried by an experienced behavioral neurologist (KAJ), blinded to neuropathologic data, to extract age at onset and death, and measures of cognitive and functional impairment (Mini-Mental State Examination (MMSE)¹² and Clinical Dementia Rating Sum of Boxes (CDR-SB¹³)) at the time of first

clinical assessment when dementia was diagnosed, at the time of MRI scan, and at the time of the last clinical assessment closest to death.

Neuropsychometric testing

The neuropsychometric test scores closest to the time of death were compared between AD subjects with and without abTDP-43 immunoreactivity. The assessment closest to death was chosen to better correlate with pathological data. Tests chosen for analysis included an executive function test (Trail Making Test B¹⁴); language function tests (Boston Naming Test¹⁵ and Controlled Oral Word Association Test¹⁶), and learning and memory tests (Auditory Verbal Learning Test¹⁷ and Wechsler Memory Scale-Revised¹⁸). Percentile scores were derived from the Mayo Older American Normative Studies (MOANS) norms,¹⁹⁻²¹ which are age adjusted.

Apolipoprotein E genotyping

Apolipoprotein E testing was performed on 82 of the 84 subjects using the single-day ApoE method used by Crook et al,²² with modifications as previously described.²³

Pathological methods

All subjects underwent standardized neuropathological examination using the recommended diagnostic protocol for AD.²⁴ In each case Braak NFT stage⁹ and plaque score was determined.²⁴ Diagnosis of AD was made according to the National Institute on Aging and Reagan Institute Working Group (NIA-Reagan) criteria.⁸ Additional pathology, including Lewy bodies (LBs) was recorded. The presence of hippocampal sclerosis (HpScl) was diagnosed if there was neuronal loss and gliosis in subiculum and CA1 regions of the hippocampus that was disproportionate to the degree of neurofibrillary degeneration.⁶

For each subject a standardized section of medial temporal lobe that included hippocampus, parahippocampal gyrus, occipitotemporal gyrus and inferior temporal gyrus was analyzed with TDP-43 immunohistochemistry (1:8000; ProteinTech group, Chicago, IL). Abnormal TDP-43 immunoreactivity was assessed and classified (DWD and DAS) based on the scheme proposed by Mackenzie and co-workers.⁷ Type 1 was characterized by moderate-numerous abTDP-43 immunoreactive neurites and neuronal cytoplasmic inclusions (NCI) predominantly within layer II of the cortex and a variable density of granular cytoplasmic inclusions within granule cells of the dentate gyrus of the hippocampus. Some Type 1 cases also had neuronal intranuclear inclusions (NII). Type 2 was characterized by long neurites in middle and upper cortical layers with sparse or no NCI and usually no NII. Dentate fascia inclusions were usually round Pick body-like inclusions. Type 3 was characterized by NCI with sparse neurites again most numerous in upper cortical layers. The dentate gyrus in Type 3 had variable NCI. Cases with abTDP-43 immunoreactivity that was sparse and sometime associated with NFT and that did not fit into any of the above three types were classified as histological Type 0.

Genetic Analysis

All subjects with stored DNA that and NII underwent genetic screening for mutations in all 13 exons in the progranulin gene, as previously described.²⁵ Subjects with NII were chosen for genetic screening since NII have been identified in all pathologically confirmed subjects with progranulin mutations.²⁶

Image analysis

All subjects had a T1-weighted volumetric MRI scan acquired at 1.5T (22×16.5cm or 24×18.5cm FOV, 25° flip angle, 124 contiguous 1.6mm thick coronal slices). If a subject had more than one MRI, then the MRI closest to death was chosen to better correlate the

neuroimaging findings with postmortem pathology. An optimized method of VBM, implemented using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>),²⁷ was used to assess the patterns of gray matter atrophy in each group compared to a group of 84 living healthy controls that were age and gender-matched to the study cohort. All controls were recruited through the ADRC/ADPR and have been previously defined.²⁸ The processing steps were performed as previously described.^{28, 29} Briefly, all MR scans were normalized to a customized template created from all subjects in the study. The spatial normalization was optimized by first segmenting the images and then normalizing the grey matter images to the customized grey matter template. The normalization parameters were then applied to the original whole head. The images were then segmented using customized prior probability maps, modulated, and smoothed with an 8mm full-width at half-maximum smoothing kernel.

A single subject condition and covariate model was used to compare the smoothed modulated gray matter images between the groups of AD subjects with and without abTDP-43 immunoreactivity and controls at a statistical threshold of $p < 0.05$ corrected for multiple comparisons using the family wise error (FWE). Age and gender were included as nuisance variables. Direct comparisons between the AD subjects with and without immunoreactivity were performed correcting for multiple comparisons using the false discovery rate (FDR)³⁰ at $p < 0.05$ due to the hypothesis driven nature of these statistical tests. In addition, direct comparisons were performed between the TDP-43 immunoreactive subjects with and without HpScl, as well as between the different histological types (0, 1 and 3).

Statistical methods

Statistical analyses were performed utilizing the JMP computer software (JMP Software, version 6.0.0; SAS Institute Inc, Cary, NC) with α set at 0.05. All binary data were compared across groups with Chi-square test. A pooled t-test was used to compare continuous data across both groups. CERAD and NIA Reagan data was converted into an ordinal scale for the purposes of statistical analysis (CERAD: 0=O, 1=A, 2=B and 3=C; NIA-Reagan, 0= low probability of AD, 1= intermediate probability and 2 = high probability). Logistic regression was used to assess the relationship of disease severity measures (CDR-SB and MMSE scores) adjusted for age at testing, with the presence of abTDP-43 immunoreactivity. Similar analysis was conducted for pathological variables adjusted for age at death. A multivariate logistic regression model was built by including age at death and adding any pathological variable that was significant ($p \leq 0.1$) with univariate analysis to determine which model best predicted abTDP-43 immunoreactivity. Since each of the primary associations evaluated in this study was of interest in its own right and not data-driven, we did not adjust for multiple comparisons.^{31, 32}

In a secondary analysis assessing associations across histological types 0, 1 and 3, Chi-square test was used to analyze nominal data, while analysis of variance test was used for continuous data or ordinal data treated as continuous.

Results

Of the 84 subjects with intermediate to high probability AD pathology, 29 subjects (34%) had evidence of abTDP-43 immunoreactivity (Table 1). All 29 subjects received a clinical diagnosis of Alzheimer's type dementia prior to death and in none was the clinical diagnosis of any of the frontotemporal dementia variants or MND made. Those with abTDP-43 immunoreactivity were older at onset and at death. After adjusting for age at death, those with abTDP-43 immunoreactivity had clinically more severe dementia with worse CDR-SB ($P=0.03$) and MMSE scores ($P=0.01$), than those without abTDP-43 immunoreactivity. The MMSE scores at dementia onset were also worse in those with abTDP-43 immunoreactivity compared with those without ($p=0.03$).

Neuropsychometrics

Neuropsychometric results are shown in table 2. By using MOANS scores,¹⁹⁻²¹ which adjust for age, as well as adjusting for education, those with abTDP-43 immunoreactivity performed worse on the Boston Naming Test¹⁵ ($P=0.04$) than those without abTDP-43 immunoreactivity. There was no difference between the groups on any other neuropsychometric score, or from time of disease onset to time at testing.

Apolipoprotein E genotyping

There was no difference in apolipoprotein E4 allele frequency between those with and without abTDP-43 immunoreactivity (Table 1).

Pathology—After adjusting for age at death, HpScl ($P=0.008$) and the presence of LBs ($p=0.04$) were more frequent in the group of subjects with abTDP-43 immunoreactivity compared to those without any immunoreactivity ($P=0.008$), and those with abTDP-43 immunoreactivity had lower brain weights at death ($P=0.04$) (Table 1). In the multivariate analysis only HpScl ($P=0.02$), but not the presence of LBs ($P=0.19$) predicted TDP-43 immunoreactivity. There was no difference in age at death, CDR-SB or MMSE scores between subjects with abTDP-43 immunoreactivity with and without HpScl.

Using the classification scheme of Mackenzie et al. for FTL-D-U,⁷ seven of the 29 cases with abTDP-43 immunoreactivity were classified as Type 1, one case as Type 2, and 16 cases were classified as Type 3 (Figure 1). Five cases had sparse abTDP-43 immunoreactivity and could not be classified and were considered to have Type 0. Demographic, clinical and pathological variables were similar across all types (Table 3). For neuropsychological variables, only the Boston Naming Test scores was different across the three types ($P=0.03$). The Boston Naming Test score was highest in Type 0 (mean: 6.8 (SD: 1.3)), followed by Type 1 (mean: 4 (SD: 2.9)) then Type 3 (mean: 3.2 (SD: 2.0)). Most of the abTDP-43 immunoreactivity in Type 0 was associated with NFT in subiculum or entorhinal cortex. They did not have abTDP-43 immunoreactive neurites or NII. Only one of the five cases had sparse inclusions in the dentate granule cell layer of the hippocampus. Ten (34%) of the 29 cases with abTDP-43 immunoreactivity had NII. Neuronal intranuclear inclusions were most frequent in Type 1 ($P=0.03$) compared with other types.

Genetics

Of those subjects with NII, seven were screened and all seven were negative for any mutation in the progranulin gene.

Imaging

There was a trend for those with abTDP-43 immunoreactivity to be slightly older at time of scan than those without abTDP-43 immunoreactivity, although there was no difference between the groups in time from disease onset to scan, or time from scan to death (Table 1). Voxel-based morphometry adjusting for age at scan showed a similar pattern of gray matter loss in those with and without abTDP-43 immunoreactivity compared to controls (Figure 2A and B). Both groups showed a pattern of gray matter loss predominantly involving medial temporal lobes and temporoparietal neocortex when compared to controls ($P < 0.05$, corrected for multiple comparisons using the FWE). When directly compared (Figure 2C), however, those with abTDP-43 immunoreactivity showed evidence of greater volume loss in medial temporal lobe, particularly the hippocampus, than those without abTDP-43 immunoreactivity ($P < 0.05$ corrected for multiple comparisons using the FDR). Although the subjects without abTDP-43 immunoreactivity seemed to show a more widespread pattern of cortical loss than

those with abTDP-43 immunoreactivity, on direct comparison no regions showed greater gray matter loss in the group without abTDP-43 immunoreactivity.

Since HpScl was identified as being a predictor of abTDP-43 immunoreactivity on multivariate analysis, we also performed a secondary analysis comparing the subjects with abTDP-43 immunoreactivity with and without HpScl. No differences were identified between these groups (uncorrected, $P < 0.001$). In addition, no differences were identified between histological types 0, 1 and 3 (uncorrected, $P < 0.001$).

Discussion

In this study we found that 34% of AD subjects had abTDP-43 immunoreactivity in medial temporal lobe structures. There were a number of clinical, neuropsychological, imaging and pathological differences between those with and without abTDP-43 immunoreactivity, suggesting that the presence of abTDP-43 immunoreactivity in AD may be associated with a modified phenotype.

Abnormal TDP-43 has been identified as one of the major disease proteins in FTL-DU and has been suggested to be specific to neuronal inclusions and neurites in FTL-DU and sporadic ALS.² Recent studies, however, have shown abTDP-43 immunoreactivity in AD⁶, Parkinson dementia complex of Guam,³³ and Lewy body disease.³⁴ The current study, and another,⁶ showed that 23-34% of AD subjects have some abTDP-43 immunoreactivity. Those with abTDP-43 immunoreactivity scored worse on the CDR-SB closest to death and MMSE at dementia onset and closest to death, as well as on a neuropsychological test of confrontation naming. In addition, they had more hippocampal atrophy on MRI and more frequent HpScl at autopsy. These results were not driven by longer disease durations or older age. It seems biologically plausible that in those with abTDP-43 immunoreactivity the presence of HpScl might be driving the worse hippocampal atrophy,³⁵ however, within the group of subjects with abTDP-43 immunoreactivity there was no difference in hippocampal volume loss in those with and without HpScl. This suggests that abTDP-43 immunoreactivity, independent of HpScl, is associated with hippocampal atrophy.

The overall pattern of volume loss observed in affected groups compared to controls was typical of volume loss observed in AD suggesting that AD pathology is the main driving force of the overall patterns of atrophy. On direct comparison of affected groups however we observed more hippocampal atrophy in those with abTDP-43 immunoreactivity. Severe hippocampal atrophy has been observed in certain variants of frontotemporal dementia, such as semantic dementia and behavioral variant frontotemporal dementia.³⁶ Therefore, the question arises as to whether the presence of abTDP-43 immunoreactivity signifies the presence of an underlying frontotemporal dementia. Unfortunately, we are unable to determine exactly how much atrophy is being driven purely by the presence of abTDP-43 immunoreactivity, and how much is being driven purely by HpScl.

Subjects with abTDP-43 immunoreactivity were cognitively more impaired at the time of first and last clinical evaluation. Whereas the MMSE was different at dementia onset and closest to death, the CDR-SB was not different at dementia onset, only closest to death. This suggests that the difference in cognitive measures between subjects with and without abTDP-43 is amplified with disease progression, although findings just before death are more difficult to interpret. These differences were also unlikely to be driven by the higher frequency of HpScl in those with abTDP-43 immunoreactivity, since there were no differences in CDR-SB or MMSE between those with and without HpScl. Subjects with abTDP-43 immunoreactivity showed greater deficits in confrontation naming as measured by the Boston Naming Test. This is not surprising, since studies have implicated the hippocampus to play a role in poor

performance on the Boston Naming Test.³⁷ We did not find any difference, however, on Trail Making B and Controlled Word Association Tests, in keeping with absence of any difference in volume loss in the frontal lobes assessed on VBM, since these two neuropsychological tests are associated mainly with frontal lobe impairment.^{38, 39} There was also no difference on tests of memory, which is not surprising, since both groups with and without abTDP-43 immunoreactivity had high probability AD.⁸ A limitation to the neuropsychological battery completed in these subjects was the number of executive test performed.

It could be hypothesized that the presence of abTDP-43 immunoreactivity in subjects with AD represents concomitant AD and FTLN-U.⁶ The high frequency of HpScl in the abTDP-43 immunoreactive group supports this hypothesis since HpScl is highly associated with FTLN-U.^{35, 40} The fact that those with abTDP-43 immunoreactivity were cognitively and functionally worse than those without immunoreactivity could be due to the combined effects of AD and FTLN-U. The average age of onset of subjects with FTLN-U pathology has been reported to be less than 65, and although the average age of onset of our subjects with abTDP-43 immunoreactivity was greater than 65-years, the average age is within the range reported for FTLN-U.⁴ Subjects with FTLN-U pathology have a striking pattern of frontotemporal volume loss on MRI. It is therefore possible that the AD pathology may have masked that pattern, especially if the AD pathology occurred before the FTLN-U pathology. The fact that those with abTDP-43 immunoreactivity also had lower brain weights at autopsy further supports this hypothesis of dual pathologies, as well as a hypothesis of more aggressive disease in those with abTDP-43 immunoreactivity.

Several classification schemes have been proposed for FTLN-U and one has been reported to show correlation with clinical phenotypes.⁷ When the latter classification was applied to AD, the majority of the cases had abTDP-43 immunoreactivity consistent with Type 3. It has been suggested that this type is associated with behavioral variant frontotemporal dementia and sometimes motor neuron disease.⁷ None of our subjects with abTDP-43 immunoreactivity had motor neuron disease or a clinical diagnosis of frontotemporal dementia. Moreover, we did not find any significant differences between the three types. The lack of differences across the types in AD, unlike in FTLN-U, may not have meaningful significance, possibly because the AD pathology may be masking the features of FTLN-U. In addition, NII have been reported to be characteristic of FTLN linked to progranulin mutations.²⁶ However, all of our AD cases with abTDP-43 immunoreactivity and NII screened for progranulin mutations were negative.

The significance of increased LBs in AD with abTDP-43 immunoreactivity is unclear. However, abTDP-43 immunoreactivity has been observed in subjects with LBs.^{26, 34} It is unlikely that the presence of LBs played a role in worse hippocampal atrophy in the abTDP-43 immunoreactive group, since VBM analysis of subjects with Lewy body disease show, on average, less hippocampal volume loss than in AD.²⁸

Acknowledgments

KAJ is supported by the NIH Roadmap Multidisciplinary Clinical Research Career Development Award Grant (K12/NICHD)-HD49078. Co-authors on this study are also supported by NIH grants P50-AG16574, U01-AG06786, R01-AG11378, P50-NS40256 and the generous support of the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation.

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Figure 1.

abTDP-43 immunoreactivity in AD was classified into one of three histologic types according to the scheme proposed by Mackenzie et al.⁷ with medial temporal cortex (A, B and C) and dentate fascia of the hippocampus (D, E and F). Type 1 had neuronal cytoplasmic inclusions and short neurites in the cortex (A) and granular cytoplasmic inclusions in the dentate fascia (D). Some cases had intranuclear inclusions (inset). Type 2 had neurites but few or no cytoplasmic inclusions in the cortex (B) and characteristic long, tapering neurites (inset); round, Pick body-like inclusions were noted in the dentate fascia (E). Type 3 had cytoplasmic inclusions with few neurites in the cortex (C) and variable dentate fascia inclusions (F).

Figure 2.

Results of VBM showing similarity in the patterns of gray matter atrophy in both groups of subjects with and without abTDP-43 immunoreactivity on a 3D render. Panel A shows the patterns of gray matter atrophy in AD subjects without abTDP-43 immunoreactivity compared to controls (corrected for multiple comparisons using the FWE, $p < 0.05$). Panel B shows the patterns of gray matter atrophy in the AD subjects with abTDP-43 immunoreactivity compared to controls (corrected, $p < 0.05$). Panel C shows greater hippocampal loss observed in the abTDP-43 immunoreactive subjects compared to the AD subjects without abTDP-43 immunoreactivity overlaid on a representative slice through the customized template (corrected for multiple comparisons using the FDR, $p < 0.05$).

Table 1
Demographic, clinical and pathologic findings in AD with and without TDP-43 immunoreactivity

Numbers shown are mean and standard deviation. α = P values shown are adjusted for age at death; β = P values shown are adjusted for age at test. MMSE = Mini Mental State Examination; CDR = Clinical dementia rating; HpScl = Hippocampal sclerosis; LBs = Lewy bodies (For the abTDP-43 immunoreactive group: 9/11 had diffuse cortical LBs and 2/11 had limbic LBs. For the abTDP-43-negative group: 9/10 had diffuse cortical LBs and 1/10 had limbic LBs). MMSE and CDR-SB completed at onset of dementia and at the time of last clinical evaluation

	With abTDP-43 immunoreactivity (N=29)	Without abTDP-43 immunoreactivity (N=55)	P value
Sex F:M	21:8	39:16	0.90
Education	13.4 (3.1)	14.0 (2.8)	0.39
Age at onset, yrs	78.7 (9.5)	72.5 (11.5)	0.02
Age at death, yrs	87.6 (8.7)	81.8 (11.3)	0.02
Total Disease duration, yrs	9.0 (3.8)	8.6 (3.6)	0.61
Age at first clinical evaluation, yrs	82.2 (9.4)	75.3 (10.6)	0.007
Time from disease onset to first clinical evaluation, yrs	3.5 (2.2)	3.0 (2.1)	0.30
Time from first clinical evaluation-death, yrs	5.3 (2.4)	6.1 (3.2)	0.24
MMSE score at first clinical evaluation	20.3 (3.8)	22.3 (4.4)	0.03 ^{β}
CDR Sum of Boxes score at first clinical evaluation	6.2 (3.2)	5.2 (2.7)	0.22 ^{β}
Age at last clinical evaluation, yrs	86.1 (8.7)	80.4 (11.2)	0.02
Time from disease onset to last clinical evaluation, yrs	7.4 (3.5)	7.2 (3.8)	0.82
Time from last clinical evaluation-death, yrs	1.5 (1.9)	1.4 (1.4)	0.62
MMSE score at last clinical evaluation	14.5 (6.4)	19.8 (7.1)	0.01 ^{β}
CDR Sum of Boxes score at last clinical evaluation	14.2 (4.5)	11.5 (6.3)	0.03 ^{β}
Number of subjects with HpScl	9 (31%)	2 (4%)	0.008 ^{α}
Number of subjects with LBs	11 (38%)	10 (18%)	0.04 ^{α}
Frequency of APOE4 allele	62%	57%	0.63
Braak stage	5.4 (0.7)	5.3 (0.8)	0.09 ^{α}
CERAD Score	2.5 (1.0)	2.5 (0.8)	0.43 ^{α}
NIA -Reagan	2.9 (0.3)	2.8 (0.4)	0.06 ^{α}
Brain weights, gms	1101(135)	1163(162)	0.04 ^{α}
Demographics at the time of MRI			
Age at MRI scan	83.8 (9.2)	78.4 (11.1)	0.03
Time from onset-MRI scan, yrs	5.1 (2.7)	5.2 (3.1)	0.95
Time from MRI scan-death, yrs	3.8 (2.6)	3.5 (2.3)	0.51
MMSE score at the time of MRI scan	17.4 (6.5)	18.3 (7.4)	0.60
CDR Sum of Boxes score at the time of MRI scan	9.4 (5.1)	7.7 (4.7)	0.13

Table 2
Neuropsychometric test scores

Data represent Mayo Older American Normative Studies (MOANS) age- and education-adjusted mean percentile scores ($\pm$ standard deviation) for each subtest. Mean MOANS in a control population =10, SD =3.

	With abTDP-43 immunoreactivity (N=29)	Without abTDP-43 immunoreactivity (N=55)	P value
Age at test	83.7 (9.1)	78.5 (11.2)	0.02
Time from disease onset to time of testing, yrs	5.1 (2.9)	5.1 (2.8)	0.96
Time from completion of test to death, yrs	3.9 (2.4)	3.4 (2.4)	0.36
Executive Function			
Trail Making Test B	4.0 (2.4)	5.0 (3.2)	0.60
Language Function			
Boston Naming Test	4.0 (2.4)	5.1 (3.8)	0.04
Controlled Oral Word Association Test	3.3 (1.4)	3.9 (2.7)	0.35
Memory Function			
WMS-R Logical Memory II Delayed Recall	3.9 (2.8)	5.1 (3.8)	0.18
WMS-R Visual Reproduction II Delayed Memory	4.8 (2.7)	4.3 (2.6)	0.50
Auditory Verbal Learning Test 30-minute Delay	5.9 (2.2)	5.6 (2.7)	0.75

Table 3
Demographic, clinical and pathological findings by FTLD-U types

Numbers shown are mean and (standard deviation) except for the column for type 2 (N=1). ANOVA test was used to compare variables across types 0, 1 and 3. MMSE = Mini Mental State Examination; CDR = Clinical dementia rating; HpScl = Hippocampal sclerosis; LBs = Lewy bodies. MMSE and CDR-SB completed at dementia onset and the time of last clinical evaluation

	Type 0 (N=5)	Type 1 (N=7)	Type 2 (N=1)	Type 3 (N=16)	P value
Sex F:M	5:0	4:3	1:0	11:5	0.36
Education	13.2 (3.3)	13.4 (3.8)	12	13.6 (3.0)	0.98
Age at onset, yrs	81.4 (7.8)	77.3 (10.6)	74.9	78.6 (10.2)	0.77
Age at death, yrs	90.1 (7.8)	86.0 (7.4)	85.4	87.7 (9.9)	0.74
Total Disease duration, yrs	8.8 (1.6)	8.7 (4.8)	10.5	9.0 (4.1)	0.98
Age at first clinical evaluation, yrs	75.8 (11.0)	81.1 (8.8)	75.9	81.9 (9.7)	0.20
Time from disease onset to first clinical evaluation, yrs	3.5 (2.2)	3.8 (2.8)	1.0	2.6 (1.6)	0.30
Time from first clinical evaluation-death, yrs	5.3 (2.5)	4.9 (2.4)	9.5	6.4 (3.4)	0.24
MMSE score at first clinical evaluation	22.2 (4.3)	19.6 (3.8)	23	20.5 (4.1)	0.30
CDR Sum of Boxes score at first clinical evaluation	5.3 (2.6)	5.7 (3.5)	4	6.4 (3.4)	0.55
Age at last clinical evaluation, yrs	89.2 (7.7)	85.4 (7.4)	83.4	85.6 (10)	0.72
Time from disease onset to last clinical evaluation, yrs	7.8 (1.1)	8.2 (4.8)	8.5	6.9 (3.6)	0.23
Time from last clinical evaluation-death, yrs	1.0 (0.6)	0.6 (0.3)	2.0	2.1 (2.3)	0.15
MMSE score at last clinical evaluation	16.5 (2.6)	14.5 (9.2)	6	13.7 (7.4)	0.79
CDR Sum of Boxes score at last clinical evaluation	12.2 (3.3)	14.9 (4.7)	18	12.3 (4.8)	0.59
Number of subjects with HpScl	2 (40%)	1 (14%)	0	6 (38%)	0.50
Number of subjects with LBs	1 (20%)	3 (43%)	0	7 (44%)	0.62
Frequency of APOE4 allele	60%	57%	100%	69%	0.85
Braak stage	5.2 (0.4)	5.7 (0.5)	4	5.7 (0.6)	0.31
CERAD Score	2.2 (1.3)	2.6 (1.1)	3	2.6 (0.8)	0.74
NIA -Reagan	3 (0)	3 (0)	3	2.9 (0.4)	0.45
Brain weights, gms	1059(101)	1135 (138)	850	1115 (135)	0.61
Demographics at the time of scan					
Age at MRI scan	88.1 (8.0)	82.5 (9.1)	77.3	83.5 (9.9)	0.56
Time from onset-MRI scan, yrs	6.7 (1.6)	5.2 (2.9)	2.4	4.8 (2.8)	0.41
Time from MRI scan-death, yrs	2.1 (1.2)	3.5 (3.6)	8.1	4.2 (2.2)	0.24
MMSE score at the time of MRI scan	18.0 (3.2)	16.7 (8.4)	19	17.5 (7.1)	0.95
CDR Sum of Boxes score at the time of MRI scan	8.3 (4.4)	8.6 (6.1)	7	10.3 (5.2)	0.65