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TDP-43 Deposition in Prospectively Followed, Cognitively Normal Elderly Individuals: Correlation with Argyrophilic Grains but not Other Concomitant Pathologies

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Abstract

TAR DNA-binding protein 43 (TDP-43) has been heavily researched in recent years due to its involvement in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Several studies have also sought to investigate the frequency of TDP-43 deposition in other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, but there has been relatively little work focused on the prevalence, distribution and histopathological associations of abnormal TDP-43 deposits in the brains of cognitively normal elderly subjects. We screened thick, free-floating coronal sections of mesial temporal lobe from 110 prospectively-followed and autopsied cognitively normal subjects (age range 71–100 years) using an immunohistochemical method for phosphorylated TDP-43. We found a 36.4% prevalence of pathologic TDP-43, mostly in the form of neurites while perikaryal cytoplasmic neuronal inclusions were uncommon and intranuclear inclusions were rare. With respect to other concomitant pathologies commonly found in elderly individuals, cases with TDP-43 had a greater prevalence of argyrophilic grains (ARG) (40% vs. 18.6%) and overall ARG density (moderate vs. sparse). There were no additional associations with other concomitant pathologies, including cerebral white matter rarefaction, incidental Lewy bodies, neurofibrillary tangles or amyloid plaques. These results indicate deposition of TDP-43 occurs in a substantial subset of cognitively normal elderly subjects and is more common in those with ARG, supporting some previous studies linking pathological TDP-43 deposition with ARG and other pathological tau protein deposits.

Keywords

amygdala; hippocampus; TAR DNA binding protein; aging; neuropathology; argyrophilic grains

Introduction

TAR DNA binding protein 43 (TDP-43) is a nuclear protein implicated in exon skipping and transcriptional regulation [28]. Abnormal aggregates of TDP-43, readily identified by their abnormal phosphorylation, have been identified within ubiquitin-positive, tau- and α-synuclein-negative inclusions in subjects with frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). Furthermore, several other neurodegenerative diseases such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease (PD) and hippocampal sclerosis dementia frequently have concurrent TDP-43

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deposition, ranging from 25–50% in AD to 7% in PD [17,28,37,40]. However, few studies have been specifically focused on determining the prevalence, setting and significance of TDP-43 deposition in cases lacking a defined clinicopathological neurodegenerative disease, i.e. normal elderly individuals.

The prevalence of abnormal TDP-43 deposition amongst normal elderly controls has been reported as ranging between 0–29% [14,28,40]. One of these studies demonstrated an increased frequency of TDP-43 deposition with age, noting an absence of positivity in those less than 65 years of age [14]. Numerous other pathologies have been known to deposit within the brains of elderly individuals, often without clear clinical effects. Previous studies of TDP-43 deposition have not examined its relationship with such "incidental" autopsy findings. The principle abnormal protein aggregates found in AD; senile, amyloid or neuritic plaques composed of β-amyloid, as well as neurofibrillary tangles (NFTs) and neurites composed of phosphorylated tau protein, are present in most cognitively normal individuals, and the distribution and densities of these overlap those seen in subjects with clinicopathological AD [41,34,31,7,11,10,9,8,4,38]. Furthermore, the main aggregate protein in PD, α-synuclein, is detected in approximately 10–25% of clinically healthy people over the age of 60, and this prevalence increases with age [22,1,16,15]. White matter rarefaction, known in the radiological literature as white matter hyperintensities, leukoaraiosis or "small vessel ischemic injury", is commonly found in older individuals and has been correlated with gait abnormalities [25,27]. Additionally, argyrophilic grains (ARG) are present at a frequency of 16–22% in normal elderly persons [33,21].

Understanding whether TDP-43 deposition coincides with any other common aging neuropathologies might provide further insight into its significance and the molecular mechanisms of this protein deposition.

Methods

Case Selection

All samples were obtained through autopsies of subjects enrolled in the Brain and Body Donation Program (BBDP) at Banner Sun Health Research Institute between 1998 and 2011. The BBDP recruits normal elderly subjects predominantly from the surrounding Sun Cities retirement communities. These independently living volunteer research subjects are followed prospectively with annual standardized clinical assessments for the rest of their lives. Cases (Table 1) were clinically characterized as previously described [3] through standardized periodic neurological and neuropsychological assessments and review of private medical records, self-report and telephone interviews with spouses and/or caregivers. All cases underwent autopsy and a standardized neuropathological assessment; resulting in the assignment of clinicopathological diagnoses according to published recommendations. The median postmortem interval (PMI) of all autopsied BBDP subjects is 3.2 hours [3]. This ensures the highest quality brain tissue for research purposes.

Cases were selected using strict inclusion and exclusion criteria to ensure the series consisted of non-demented elderly individual cases lacking sufficient criteria to warrant a clinicopathological diagnosis of a neurodegenerative disease. We defined elderly as subjects who were greater than 70 years of age at the time of death. A diagnosis of non-demented was based on a Mini Mental State Examination (MMSE) [12] score of 25 or greater within 2 years prior to death (Table 1) and absence of a clinical diagnosis of dementia or other defined major neuro-clinicopathologic diagnosis. Additionally, cases were excluded if the PMI was greater than 12 hours or if acute infarcts were present in the hippocampus or amygdala.

Tissue processing and histological methods

Detailed methods and neuropathological diagnostic criteria are listed in a previous publication that details our standard protocol [3]. In brief, the cerebrum was sliced in the coronal plane at the time of brain removal into 1 cm thick slices and then divided into left and right halves. Slices from the right half were frozen between sheets of dry ice while slices from the left half were fixed by immersion in buffered 4% formaldehyde for 48 hours at 4 degrees C. Paraffin-embedded sections were stained with hematoxylin and eosin while large-format, 80 μm-thick frozen sections were stained for plaques, tangles and other inclusions using Gallyas, Thioflavine-S and Campbell-Switzer methods [5]; these sections were used to assess, using a four point quantitative scale, the densities of senile plaques (all types considered together) and neurofibrillary tangles (NFT). Additionally, Braak stage for neurofibrillary degeneration was determined [6] and neuritic plaque densities were graded based on the templates provided by the Consortium to Establish a Registry for Alzheimer's disease (CERAD) [26]. Data from the following areas are recorded in our database: frontal, temporal, parietal, and entorhinal cortices as well as the hippocampus. Formalin-fixed, paraffin-embedded sections were used for immunohistochemistry with an antibody against phosphorylated α-synuclein peptide (1:10,000; rabbit polyclonal anti-human phosphoserine 129) with densities of pathology graded on a five point scale in 10 brain regions [30,39]. Neuropathologic assessment was performed blinded to clinical categorization and diagnosis was assigned according to published criteria [24,3,32,19,26,33]. Significant cerebral white matter rarefaction was defined as exceeding 25% of the total centrum semiovale area within one or more cerebral lobes [3]. ARG were assessed through visualization of spindle-shaped lesions on Gallyas and graded on a scale of none, mild, moderate and severe [33,21]. Lewy bodies were staged based on the Unified Staging System [2]. All cases were examined by the same neuropathologist (TGB), who was blinded to clinical and demographic status at the time of initial review.

For this study, additional hippocampal and/or amygdalar temporal lobe sections were selected from each of the 110 subjects. Immunohistochemistry was performed on 40μm free-floating sections of the mesial temporal lobe using an antibody against phosphorylated TDP-43 peptide (1:10,000 rabbit polyclonal antihuman phosphoserine 409/410, a generous gift from Dr. Haruhiko Akiyama, Department of Psychogeriatrics, Tokyo, Japan) [18,29] with nickel-enhanced 3, 3′-diaminobenzidine (DAB) as the chromogen.

Blinded primary interpretation of all cases was performed by a single observer (SJA). TDP-43 positivity, location of positivity, and morphology were recorded. Each positive case was subsequently reviewed and confirmed by the consensus of two additional investigators (BND, TGB) who were also blinded to case demographics.

Statistical analysis

Statistical analyses were performed with Sigma Plot 12.1 (Systat Software, Inc. San Jose, CA) and Microsoft Excel (Microsoft Corporation, Redmond, WA). Student's t-tests or Mann-Whitney rank sum analysis were used to determine if group quantitative differences were significant. Chi squared analyses were used to determine whether there were proportional differences between groups. For all tests, the criterion for significance was set at $p < 0.05$.

Results

Of 110 cognitively normal elderly brains, 40 showed pathological TDP-43 positivity in the hippocampus and/or amygdala (36.4%), with the amygdala being the most common location for TDP-43 deposition. Of these, the deposits most often took the exclusive form of

dystrophic neurites (DN); in 33/40 (82.5%) cases (figure 1). Neuronal perikaryal cytoplasmic inclusions (NCI) were present along with dystrophic neurites in 5/40 (12.5%) cases. In one case alone (2.5%), case #3, neuronal intranuclear inclusions (NII), were seen in the entorhinal cortex. Deposits were often found amongst corpora amylacea located subpially and in the subependymal region of the temporal horn of the lateral ventricle. The most frequent location was in the subpial region of the semilunar and ambient gyri of the amygdala. Deposits were also found in the subpial subiculum, fimbria and alveus. Additional descriptions of individual TDP-43 positive cases are listed in Table 2. Although the overall positivity in this series was 36.4%, a subset of these positive cases, 14/40 (35%), revealed miniscule amounts of positive staining. Many of these cases had just one or two positive neurites, associated with corpora amylacea, in the entire 40μm section. The close association of pathological TDP-43 with corpora amylacea has also been mentioned in a previous study [14].

There were no statistically significant differences between cases with and without TDP-43 inclusions with respect to age at death, CERAD neuritic plaque density, Braak NFT stage, and plaque and tangle densities in the entorhinal, hippocampus and temporal lobes (Table 3, Ps > 0.08). Of 40 positive subjects, 18 were female and 22 male, with no significant difference in gender ratios as compared to TDP-43-negative subjects. With respect to other concomitant pathologies commonly found in elderly individuals, cases with TDP-43 had were more likely to have ARG (40% vs. 18.6%; $p = 0.03$). Of these, subjects with higher ARG scores were more likely to have positive pathological TDP-43 staining than those with lower ARG scores. There were no differences between TDP-43-positive and negative cases in terms of the proportion with incidental Lewy bodies or cerebral white matter rarefaction.

When the cohort is broken down by decade of death, TDP-43 positivity was documented in 4/13 (30.8%) of the 70–79 year old cohort, 17/60 (28.3%) of the 80–89 year old cohort and 17/39 (43.6%) of the 90–99 year old cohort. There was one subject over the age of 100 years at the time of death that did not have pathological TDP-43 protein deposition.

Discussion

No study to date has examined a large series of documented, prospectively followed non-demented elderly subjects to determine both the prevalence of pathological TDP-43 staining as well as its concurrence with other neuropathological features commonly found in the elderly. We found phosphorylated TDP-43 deposits in the hippocampus and/or amygdala in 36.4% of 110 non-demented aged individuals. Additionally, there was a significant association of pathological TDP-43 with argyrophilic grains (ARG). Other common normal aging neuropathological findings, including senile plaques, neurofibrillary tangles, cerebral white matter rarefaction and incidental Lewy bodies, showed no association, although further and more detailed studies would be necessary to confirm these negative findings.

In one of the first reports of TDP-43 pathology in normal aging, Nakashima-Yasuda and colleagues reported a 3% frequency (n = 1) in a series of 33 individuals aged 63–87 [28], while in a small study of two control cases, ages 48 and 63, Hasegawa did not observe TDP-43 positivity [17]. Another study including 63 neurologically normal individuals found 2/63 or 3% of cases showed abnormal TDP-43 deposition [40]. There has been only one prior study that incorporated standardized clinical assessment with immunohistochemical demonstration of TDP-43 in a large series; in this study, 10/60 (17%) were positive for TDP-43 [14], and when only looking at subjects over the age of 65, the percentage increased to 29%, with no positive cases under the age of 65. [14].

Characterized by spindle-shaped lesions in neuronal processes predominantly within mesial temporal lobe limbic regions, often accompanied by abnormal, phosphorylated tau-positive glia, ARG are of uncertain clinical significance [21,36,33,20]. They are found in subjects with dementia but are also common in cognitively unimpaired older people as well as together with other neuropathological conditions [21,23,35]. ARG are commonly found in association with temporal lobe neurofibrillary tangles, particularly Braak stage IV, leading to the suggestion that they may represent distal dendrites and/or axons of neurons undergoing active neurofibrillary degeneration [33]. Interestingly, a recent study on patients with ALS revealed concomitant ARG pathology in 38% of their subjects [35]. This is not the first report of ARG in ALS. Yokota reported a case study of coexisting ALS and ARG disease in a non-demented patient in 2007 [42]. At present, it is unclear whether ARG and TDP-43 are benign incidental findings in the elderly or may eventually lead to clinically manifest disease had the subjects lived long enough.

Although the relationship between the deposition of tau positive ARG and pathologic TDP-43 deposition remains unclear, it is tempting to speculate there is a synergistic or common pathological mechanism resulting in the accumulation of these abnormal protein forms. Fujishiro and colleagues found in a small series of 15 subjects with ARG as well as dementia or schizophrenia, 60% (or 9 of 15) of cases exhibited concomitant TDP-43 pathology [13]; furthermore, those cases with concomitant TDP-43 pathology were statistically more likely to be in a higher severity stage of ARG; we confirmed this likelihood to association with a more severe stage of ARG. Fujishiro and colleagues also reported that, in some of the cases with ARG and TDP-43 pathology, co-localization of phospho-tau and phospho-TDP-43 within individual grains as well as within individual neuronal perikarya was observed in the entorhinal cortex and amygdala, although in most such structures, co-localization was more often not present [13]. As most ‘primary’ TDP-43 proteinopathies are of younger onset, the pathological mechanisms might also be different from that seen in our “normal aging” group here. The relationship between tau and TDP-43 pathology therefore seems to be inconsistent and at present it is still unclear why subjects with ARG are more likely to possess TDP-43 pathology [37].

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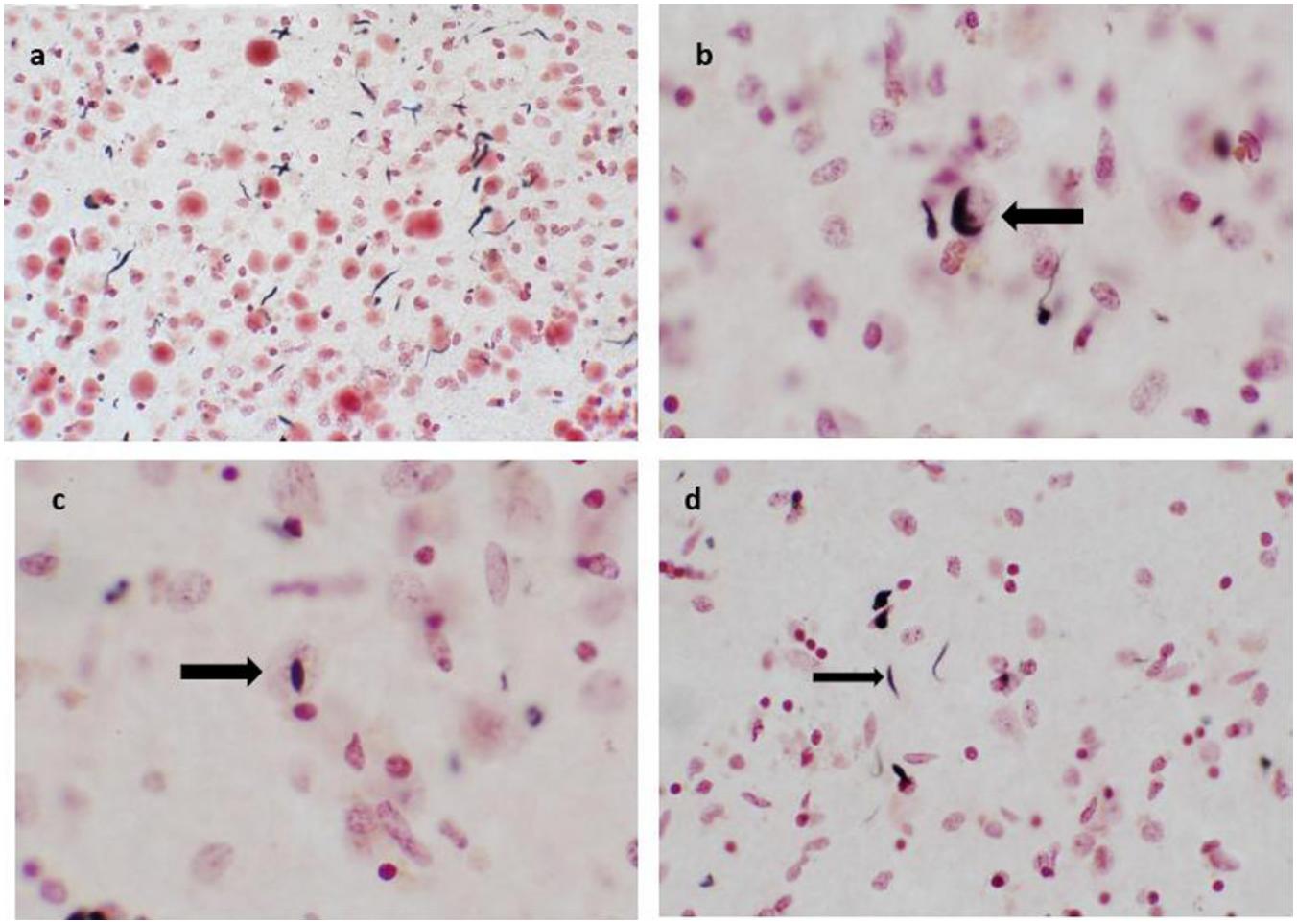

Fig. 1.

Examples of TDP-43 deposits in normal elderly subjects **a** Dystrophic neurites associated with corpora amylacea, subpial zone of amygdala, magnification 20X **b** Neuronal cytoplasmic inclusion, parahippocampal gyrus, magnification 40X **c** Intranuclear inclusion, hippocampus, magnification 40X **d** Dystrophic neurites, amygdala, magnification 40X.

Table 1

Subject Characteristics. All data is listed as mean ± standard deviation unless otherwise noted.

	Total series
N (M:F)	54:56
Age at death	86 ± 6.0
Braak NFT stage- median (range)	III (I–IV)
CERAD plaque score- median (range)	sparse (none-frequent)
MMSE	28 ± 2
PMI	3.3 ± 0.35

Abbreviations: M = Male, F = Female, CERAD = Consortium to Establish a Registry for Alzheimer's disease, NFT = neurofibrillary tangles, MMSE = Mini-Mental State Exam, PMI = post mortem interval, Stdev = standard deviation

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Table 2

Neuropathology of TDP-43 positive cases.

Case #	Location of Positivity	Inclusion Type	Age at death	ARG	WMR	iLB
1	Amygdale	DN	75	N	N	N
2	Amygdale	DN	77	Y	Y	N
3	parahippocampal gyrus	DN, NII	78	Y	Y	Y
4	amygdala	DN	83	N	N	Y
5	amygdala	DN	84	N	N	Y
6	parahippocampal gyrus	DN	84	N	N	N
7	hippocampus	DN	85	N	Y	N
8	amygdala	DN	86	Y	N	Y
9	amygdala	DN	86	Y	N	N
10	amygdala	DN	87	N	N	N
11	amygdala	DN	87	N	Y	N
12	subiculum	DN	88	N	Y	N
13	amygdala	DN	88	N	N	Y
14	parahippocampal gyrus /amygdala	DN, NCI	90	Y	Y	Y
15	parahippocampal gyrus	NCI	90	Y	N	N
16	amygdala	DN, NCI	90	Y	Y	N
17	amygdala	DN	91	N	N	N
18	parahippocampal gyrus and amygdala	DN, NCI	91	Y	Y	N
19	amygdala	DN, NCI	91	Y	Y	N
20	amygdala	DN, NCI	91	Y	Y	N
21	amygdala	DN	91	N	N	N
22	amygdala	DN	91	Y	N	N
23	subiculum / parahippocampal gyrus	DN	92	Y	N	Y
24	amygdala	DN	92	N	Y	Y
25	amygdala	DN	94	N	Y	Y
26	amygdala	DN	97	N	Y	N
27*	amygdala	DN	96	N	N	N

Case #	Location of Positivity	Inclusion Type	Age at death	ARG	WMR	iLB
28*	subiculum / parahippocampal gyrus	DN	98	Y	N	N
29*	subiculum / parahippocampal gyrus	DN	73	N	N	N
30*	subiculum / parahippocampal gyrus	DN	88	N	N	N
31*	amygdala	DN	89	N	Y	N
32*	parahippocampal gyrus and amygdala	DN	91	N	N	N
33*	amygdala	DN	82	Y	N	N
34*	hippocampus	DN	84	N	N	N
35*	subiculum / parahippocampal gyrus	DN	96	N	Y	N
36*	parahippocampal gyrus and amygdala	DN	88	N	N	N
37*	subiculum / parahippocampal gyrus	DN	85	N	N	N
38*	subiculum / parahippocampal gyrus	DN	90	N	Y	N
39*	amygdala	DN	91	Y	N	Y
40*	amygdala	DN	85	Y	N	N

DN = dystrophic neurites, NCI = neuronal cytoplasmic inclusions, NII = intranuclear inclusions, ARG = argyrophilic grains, WMR = white matter rarefaction, iLB = incidental Lewy bodies, Y = yes, N = no.

* in cases 27–40 TDP-43 deposits were very rare, having less than 5 deposits in the entire 40μm section.

Table 3

Subject characteristics of TDP-43 positive and negative cases.

Variable	TDP-43 Negative	TDP-43 Positive	P values
N (M:F)	32:38	22:18	0.46
Age at death yrs- mean ± SD (range)	86 ± 6.2 (71–100)	88 ± 5.6 (73–98)	0.09
Braak NFT stage- median (range)	III (I–IV)	III (I–IV)	0.12
Entorhinal NFT score- median (range)	frequent (none-frequent)	frequent (mild-frequent)	0.37
Temporal Lobe NFT score- median (range)	sparse (none-frequent)	sparse (none-frequent)	0.69
Hippocampus NFT score- median (range)	moderate (none-frequent)	moderate (sparse-frequent)	0.13
CERAD plaque score- median (range)	sparse (none- frequent)	sparse (none-frequent)	0.80
Entorhinal plaque score- median (range)	none (none-frequent)	sparse (none-frequent)	0.63
Temporal Lobe plaque score- median (range)	sparse (none-frequent)	sparse (none-frequent)	0.71
Hippocampus NFT score- median (range)	none (none-frequent)	none (none-frequent)	0.96
ARG positive cases, n (%)	13 (19%)	16 (40%)	**0.03**
Average ARG Density	sparse	moderate	**0.02**
WMR positive cases, n (%)	34 (49%)	16 (40%)	0.50
Incidental LB cases, n (%)	13 (19%)	10 (25%)	0.58
PMI	3.0 ± 1.3	3.0 ± 1.3	0.92

Abbreviations: M = Male, F = Female, NFT = Neurofibrillary tangles, CERAD = Consortium to Establish a Registry for Alzheimer's disease, ARG = Argyrophilic grains, WMR = White matter rarefaction, LB = Lewy bodies, MMSE = Mini-mental state exam, PMI = Post mortem interval; Stdev = standard deviation.