TDP-43 DEPOSITION IN PROSPECTIVELY FOLLOWED, COGNITIVELY NORMAL ELDERLY INDIVIDUALS: A CORRELATIVE STUDY

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INTRODUCTION

- TDP-43 is a nuclear protein implicated in exon skipping and transcriptional regulation
- Abnormally phosphorylated TDP-43 is the main disease protein in amyotrophic lateral sclerosis and frontotemporal lobar degeneration
- Few studies have been conducted to determine the prevalence, setting and significance of TDP-43 deposition in normal elderly individuals.
- Prior studies reported the prevalence of TDP-43 deposition in their control groups to be somewhere between 0 and 29%
- There are pathologies which are frequently found within brains of elderly individuals such as amyloid plaques, neurofibrillary tangles, incidental Lewy bodies, white matter rarefaction and argyrophilic grains.

Questions:

1) What is the frequency of TDP-43 positivity in a series of cognitively normal elderly individuals?
2) Does TDP-43 positivity correlate with other common pathologies incidentally found within brains of elderly individuals?

METHODS

- 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 population sampled is not representative of the entire US elderly population in that it is primarily comprised of Caucasian elderly with higher socioeconomic status, and educational level, who live longer than the average American
- Cases lacking a defined clinicopathologic diagnosis, and without dementia were chosen(Table 1 lists series demographics)
- 40-80um formalin fixed microtomed sections of the amygdala and/or hippocampus were then screened with an antibody raised against TDP-43 (1:10,000 rabbit polyclonal antihuman phosphoserine 409/410)
- Student's t-tests or Mann-Whitney rank sum analysis were used to determine if group quantitative differences were significant, while Chi squared analyses were used to determine whether proportional differences existed between groups

Table 1. Series demographics

	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

Table 2. Neuropathology of TDP-43 positive cases

Case #	Location of Positivity	Inclusion Type	Age at death	ARG	WMR	iLB
1	amygdala	DN	75	N	N	N
2	amygdala	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
27*	amygdala	DN	96	N	N	N
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.

TDP-43 Deposits in Cognitively Normal Elderly

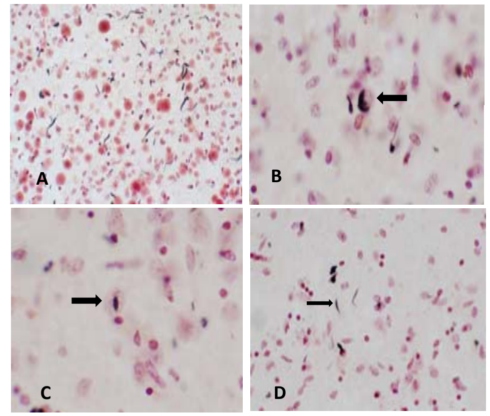

Figure 1. A. Dystrophic neurites associated with corpora amylacea, perimeter of amygdala, 20X, B. Neuronal cytoplasmic inclusion, parahippocampal gyrus, 40X , C.. Intranuclear inclusion, hippocampus 40X ,D. Dystrophic Neurites , amygdala, 40X

Table 3. Demographic data 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
CERAD plaque score - median (range)	sparse (none-frequent)	sparse (none-frequent)	0.80
ARG positive cases, n (%)	13 (19%)	16 (40%)	**0.03**
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

CONCLUSIONS

- We found phosphorylated TDP-43 deposits in the hippocampus and/or amygdala in 36.4% of 110 non-demented aged individuals a rate which is higher than that found in the literature.
- Our inclusion of only those cognitively normal individuals older than 70 years coupled with the increased thickness and alternate preservation method of the brain sections (40-80 µm free-floating as compared to 6 µm paraffin embedded) utilized is most likely responsible for the higher number of TDP-43 positive cases in this study.
- Additionally, there was a significant association of pathological TDP-43 with argyrophilic grains.

Significance:

- Although the relationship between the deposition of tau positive ARG and pathologic TDP-43 deposition remains unclear, it is possible aggregation of one protein may help seed the aggregation of another.
- What this may allude to is that the significant number of positive TDP-43 cases in prospectively followed, non-demented elderly individuals is consistent with either a benign aging process or early or mild neurodegenerative disease.

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