Title

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Dementia is strongly associated with severity of hippocampal atrophy at autopsy even after accounting for degenerative neuropathologies

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Abstract

Background: Recent work from our research group has shown that dementia is strongly associated with hippocampal atrophy from in-vivo MRI even after accounting for degenerative neuropathologies. We sought to confirm this finding using ratings of hippocampal atrophy at autopsy and examining their relationship with dementia while also accounting for relevant degenerative neuropathologies.

Method: We used data from the National Alzheimer's Coordinating Center (NACC) neuropathology dataset (09/2005-05/2020). Our outcome measure was hippocampal atrophy severity assessed as part of gross findings at autopsy (NPGRHA variable, graded none/mild/moderate/severe). Inclusion criteria were availability of hippocampal atrophy rating, clinical assessment within a year before death, and death at age 65 years or older. For our independent variables we used dementia status and the following dichotomized neuropathologies: Alzheimer's disease neuropathological change (ADNC, high), hippocampal sclerosis (HS), limbic-transitional or neocortical Lewy Bodies (LB), cerebral amyloid angiopathy (CAA, moderate/severe), atherosclerosis (moderate/severe), gross infarcts, microinfarcts, and micro/macro-hemorrhages. We also examined a subset of the participants that had TAR DNA-binding protein 43 (TDP-43) assessed in the hippocampus, and due to the high correlation with HS, we excluded HS from these analyses. Ordinal logistic regressions were used for individual models of the variables of interest as well as for joint models which included dementia and all neuropathologies. All models were adjusted for age at death, sex, years of education, and months from last clinical assessment to death. We report odds ratios (OR).

Result: *Table-1* summarizes participant characteristics across hippocampal atrophy ratings (N=1148). In the ordinal logistic regressions dementia was the strongest predictor of hippocampal atrophy (OR=6.6 in individual, 3.8 in joint model), followed by HS (OR=4.3 in individual, 3.2 in joint model), then ADNC (OR=3.9 in individual, 2.4 in joint model, Figure-1A,B). Results remained consistent for the TDP-43 subset analysis (N=717, 27% TDP-43 positive in the hippocampus, TDP-43 OR=1.9 for joint model, Figure-1C).

Conclusion: In both individual and joint ordinal logistic regressions, dementia was the variable most strongly associated with hippocampal atrophy at autopsy, followed by hippocampal sclerosis, and then ADNC and TDP-43. Therefore, dementia is a significant and strong predictor of hippocampal atrophy, above and beyond common degenerative neuropathologies.

Figure-1. Odds Ratios of hippocampal atrophy severity for dementia and neuropathology variables in ordinal logistic regressions.

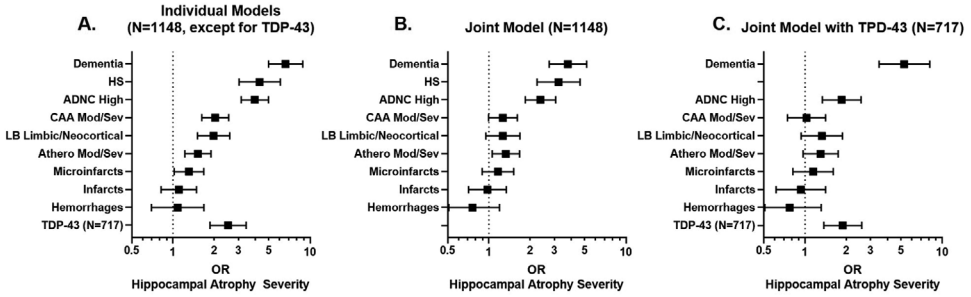

FIGURE 1

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TABLE 1

Table-1. Participant Characteristics by severity of gross hippocampal atrophy

Variables	*Hippocampal Atrophy Rating*				*P-Val*
	None (N=343)	*Mild (N=326)*	*Moderate (N=285)*	*Severe (N=194)*	
Dementia (%)	193 (56.3%)	239 (73.3%)	262 (91.9%)	190 (97.9%)	**<0.001**
Women (%)	136 (39.7%)	151 (46.3%)	134 (47.0%)	89 (45.9%)	0.2
Age at Death (SD)	83.1 (8.95)	84.6 (9.42)	82.1 (9.48)	82.9 (8.97)	0.2
Months from Last Visit to Death (SD)	6.57 (3.35)	6.36 (3.65)	5.81 (3.61)	6.08 (3.43)	**0.02**
Years of Education (SD)	16.1 (3.10)	15.7 (2.91)	15.6 (3.14)	15.4 (3.64)	**0.01**
Hippocampal Sclerosis	23 (6.7%)	12 (3.7%)	44 (15.4%)	56 (28.9%)	**<0.001**
ADNC High	96 (28.0%)	123 (37.7%)	184 (64.6%)	143 (73.7%)	**<0.001**
Limbic/Neocortical Lewy Bodies	37 (10.8%)	53 (16.3%)	65 (22.8%)	51 (26.3%)	**<0.001**
CAA Mod/Sev	80 (23.3%)	89 (27.3%)	123 (43.2%)	87 (44.8%)	**<0.001**
Atherosclerosis Mod/sev	121 (35.3%)	133 (40.8%)	127 (44.6%)	96 (49.5%)	**0.008**
Infarcts	41 (12.0%)	49 (15.0%)	45 (15.8%)	24 (12.4%)	0.4
Hemorrhages	22 (6.4%)	16 (4.9%)	19 (6.7%)	14 (7.2%)	0.7
Microinfarcts	53 (15.5%)	99 (30.4%)	73 (25.6%)	39 (20.1%)	**<0.001**

Group comparisons for continuous variables are from analysis of variance (ANOVA), and for categorical variables are from Chi-square tests. Abbreviations - ADNC: Alzheimer's disease neuropathological change. CAA: Cerebral amyloid angiopathy.