Head injury does not alter disease progression or neuropathologic outcomes in ALS

Christina N. Fournier,
MD, MSc
Marla Gearing, PhD
Saila R. Upadhyayula,
MD
Mitch Klein, PhD
Jonathan D. Glass, MD

Correspondence to
Dr. Fournier:
christina.nicole.fournier@
emory.edu

ABSTRACT

Objectives: To study the effects of head injury on disease progression and on neuropathologic outcomes in amyotrophic lateral sclerosis (ALS).

Methods: Patients with ALS were surveyed to obtain head injury history, and medical records were reviewed. Linear regression was performed to determine if head injury was a predictor for mean monthly decline of Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R), while controlling for confounders. Head injury history was obtained from family members of ALS autopsy cases. The frequency of tau proteinopathy, brain TDP-43 inclusions, and pathologic findings of Alzheimer disease (AD) were examined in ALS cases with head injury compared to cases without. Logistic regression was performed with each neuropathologic diagnosis as an outcome measure and head injury as a predictor variable.

Results: No difference was seen in rate of decline of the ALSFRS-R between patients with head injury ($n = 24$) and without ($n = 76$), with mean monthly decline of -0.9 for both groups ($p = 0.18$). Of 47 ALS autopsy cases ($n = 9$ with head injury, $n = 38$ without), no significant differences were seen in the frequency of tau proteinopathy (11% with head injury; 24% without), TDP-43 in the brain (44% with head injury; 45% without), or AD pathology (33% with head injury; 26% without). Independent logistic regression models showed head injury was not a predictor of tau pathology ($p = 0.42$) or TDP-43 in the brain ($p = 0.99$).

Conclusions: Head injury was not associated with faster disease progression in ALS and did not result in a specific neuropathologic phenotype. The tau pathology described with chronic traumatic encephalopathy was found in ALS autopsy cases both with and without head injury.

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GLOSSARY

AD = Alzheimer disease; **ALS** = amyotrophic lateral sclerosis; **ALSFRS-R** = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CTE** = chronic traumatic encephalopathy.

Head injury has been considered as a risk factor for amyotrophic lateral sclerosis (ALS), although epidemiologic studies on this topic yield mixed results¹⁻⁷ depending on the population studied and the ability to control for confounding variables. Recurrent head injuries can be associated with chronic traumatic encephalopathy (CTE), a condition clinically associated with dementia, parkinsonism, and behavior changes. Neuropathologic findings in CTE include tau-positive neurites, glia, and neurofibrillary tangles throughout the brain, particularly concentrated in cortical sulci and in perivascular regions.⁸

A 2010 neuropathologic study⁹ described the autopsy findings of 12 professional athletes who experienced multiple head injuries and received a clinical diagnosis of CTE. Of the 12 athletes with CTE, 3 also had a clinical diagnosis of ALS. As expected, all 12 cases demonstrated the tau pathology described with CTE. Ten of the 12 cases demonstrated TDP-43 proteinopathy in the brain. The implications of this study have been debated,¹⁰⁻¹² but the authors proposed that head injury incites TDP-43 and tau-mediated neurotoxicity in certain vulnerable individuals, which can cause an ALS phenotype and accelerate neurodegeneration. If this hypothesis is true,

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From the Departments of Neurology (C.N.F., M.G., S.R.U., J.D.G.), Pathology (M.G., J.D.G.), and Environmental Health (M.K.), Emory University School of Medicine, Atlanta, GA.

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patients with ALS with a history of significant head injury would be expected to have faster disease progression compared to patients with ALS with no head injury. Additionally, head injury history should be associated with pathologic findings of tau and TDP-43 proteinopathy in an ALS population. If pathologic accumulation of both tau and TDP-43 is provoked by the same insult, then the presence of these 2 findings should be correlated in ALS cases.

METHODS **Standard protocol approvals, registrations, and patient consents.** Approval for this study was obtained from the Emory Institutional Review Board. Informed consent was obtained from all living subjects who participated in the study.

Head injury and rate of disease progression in ALS. Subjects were eligible for inclusion in this study if they received care at the Emory ALS Clinic between 2004 and 2014, had a diagnosis of ALS according to El Escorial criteria¹³ (including suspected, possible, laboratory-supported probable, probable, or definite ALS), and had at least 1 documented clinic visit and 1 or more documented measures of the Amyotrophic Lateral Sclerosis Functional Rating Scale–revised (ALSFRS-R)¹⁴ in the electronic medical record. Data were analyzed using SAS 9.3 software.

For this study, mean monthly decline of ALSFRS-R was calculated using the first documented ALSFRS-R score and assuming a score of 48, indicating normal function, at the time of symptom onset, providing the average of rate of decline from clinical onset to ALSFRS-R measurement at time of diagnosis.¹⁵ By using only the first ALSFRS-R score in this calculation, disease progression is assessed before the initiation of riluzole and non-invasive ventilation, interventions that are known to prolong survival^{16,17} but are difficult to control for given variability in usage among patients with ALS. All ALSFRS-R measurements were obtained at a single institution by clinical nurses or research coordinators with training certification by the Northeast ALS Consortium for performing this test.

Informed consent forms and surveys were distributed to eligible patients during routine clinic visits and were also mailed to patients or their family members to obtain head injury history and additional clinical information. Survey questions regarding head injury were based on the HELPS Traumatic Brain Injury screening tool, a validated questionnaire used to assess for traumatic brain injury.¹⁸ The survey included additional questions to provide detailed trauma history and clinical history. Surveys also included yes or no questions regarding participation in athletic activities (“Have you participated in sports or athletic activities?”) and history of military service (“Did you serve in the military?”). For each patient who provided consent and completed a survey, clinic notes, demographic data, diagnostic testing, and outcome measure test results were also reviewed from the electronic medical record.

Patients were classified as having a significant history of antecedent head trauma if they experienced a head injury associated with loss of consciousness or requiring hospitalization, occurring more than 1 year prior to the diagnosis of ALS. This definition is consistent with findings from previous epidemiologic studies of head injury and ALS.^{2,5} Head injury within 1 year of ALS diagnosis was excluded as these injuries are thought to occur as a result of falls from the ALS disease process.⁵ Otherwise, patients were

classified as having no significant history of head injury. To determine if the study results were dependent on the definition of head injury, secondary analyses were also performed comparing patients with ALS who reported any history of head injury to patients with ALS with no history of head injury.

Mean values and SDs were calculated for clinical and demographic variables for patients with ALS with head injury and patients with ALS without head injury. A linear regression model was created with mean monthly change of ALSFRS-R as the outcome measure and head injury as the predictor variable of interest, while controlling for variables that could potentially confound the association between head injury and ALS disease progression. Potential confounders that are known to affect rate of disease progression in ALS and could be unevenly distributed between head injury groups based on chance include age of symptom onset, familial vs sporadic disease, body mass index, bulbar vs limb onset, and presence or absence of clinical frontotemporal dementia.^{19,20} Possible confounders that could be associated with head injury and have an unknown effect on disease progression include athletic activities,²¹ military service,²² and cigarette smoking.²³ All tests were performed at the 0.05 significance level.

Head injury and neuropathologic outcomes in ALS. All Emory autopsy cases from patients with a diagnosis of ALS from 2004 to 2014 were eligible for inclusion in this study. Electronic medical records were reviewed, and head injury surveys were completed by phone or by mail from family members or next of kin.

Pathologic analysis was performed by 1 of 2 pathologists experienced at reviewing ALS autopsy cases. Cases were initially reviewed for clinical diagnosis at the time of autopsy. Subsequently, all ALS cases were re-reviewed for the presence or absence of CTE-like pathology blinded to any clinical information regarding head injury or dementia. Descriptive analyses and quantification of pathologic variables were captured in a neuropathology database and in detailed autopsy reports.

Significant head injury was again defined for this group as an event associated with loss of consciousness or requiring hospitalization, occurring greater than 1 year prior to the diagnosis of ALS. To determine if the study results were dependent on the definition of head injury, secondary analyses were also performed comparing ALS autopsy cases with any head injury history to ALS autopsy cases with no head injury history. Descriptive statistics of neuropathologic findings were performed comparing ALS autopsy cases with a history of head injury to ALS autopsy cases with no head injury history.

Pearson correlation coefficients were calculated between tau and TDP-43 proteinopathy, tau proteinopathy and Alzheimer disease (AD) pathology, and TDP-43 and AD pathology. Autopsy cases were classified as having TDP-43 proteinopathy if they had TDP-43 deposition in brain regions outside of the motor cortex. Cases were classified as having AD pathology if they met possible, probable, or definite Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) criteria.²⁴ CERAD criteria were utilized to capture pathologic evidence of AD in cases without a clinical history of dementia.

Independent logistic regression models were created with each neuropathologic finding as the outcome measure and head injury as the predictor variable of interest. For AD, the model was performed while controlling for age. All tests were performed at the 0.05 significance level.

RESULTS **Head injury and rate of disease progression in ALS.** There was no difference in the rate of decline of ALSFRS-R between patients with ALS with head injury (n = 24) and without head injury (n = 76),

Table 1 Demographic and clinical characteristics of surveyed patients with amyotrophic lateral sclerosis with and without antecedent head injury causing loss of consciousness or requiring hospitalization

Variable	Head injury (n = 24) ^a		No head injury (n = 76)	
	Mean	SD	Mean	SD
Mean monthly decline of ALSFRS-R	−0.9	0.8	−0.9	0.9
Mean age at symptom onset, y	56	13.7	55	10.6
Mean body mass index	26.9	4.7	25.7	4.4
Site of onset, n (%)				
Limb	17 (71)	0.5	53 (70)	0.5
Bulbar	7 (29)		23 (30)	
Familial disease, n (%)	0		6 (8)	0.3
Clinical diagnosis of frontotemporal dementia, n (%)	2 (8)	0.3	6 (8)	0.3
Participation in athletics, n (%)	19 (79)	0.4	39 (51)	0.5
Military service, n (%)	5 (21)	0.4	8 (11)	0.3
Smoker (lifetime history >5 pack-years), n (%)	6 (25)	0.4	28 (37)	0.5

Abbreviation: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised.

^aHead injury defined here as an event associated with loss of consciousness or requiring hospitalization, occurring >1 year prior to diagnosis of amyotrophic lateral sclerosis.

with a mean monthly decline of ALSFRS-R of −0.9 for both groups. This sample size and group distribution provided 80% power to detect a 0.4-point difference in ALSFRS-R mean monthly decline at the 0.05 significance level. Age at onset was similar for both groups, with a mean age at onset of 56 years in the head injury group and 55 in the group with no head injury. Site of onset and the presence of clinical frontotemporal dementia were similar between groups. Familial disease was seen in 6 cases (8%) without head injury and in no cases with head injury; these 6 cases

included 1 patient with an SODA4V mutation, 3 patients with C9orf72 mutations, and 2 cases with no confirmed gene mutation but ALS in a first-degree relative. Participation in athletic activities and military service were more frequent in the head injury group (table 1).

A linear regression model with mean monthly decline of ALSFRS-R as the outcome measure, head injury with loss of consciousness or requiring hospitalization occurring greater than 1 year prior to ALS diagnosis as the predictor variable of interest, and

Table 2 Linear regression with mean monthly decline of ALSFRS-R as the outcome and antecedent head injury with loss of consciousness or requiring hospitalization and potential confounders as covariates

Variable	Parameter estimate (mean monthly decline of ALSFRS-R)	95% CI	p Value
Head injury (1 = head injury with loss of consciousness or requiring hospitalization, occurring >1 year prior to diagnosis, otherwise = 0)	−0.26	−0.66 0.13	0.18
Age (1 = 60 years of age or older, otherwise = 0)	−0.10	−0.48 0.28	0.60
Site of onset (1 = limb onset, 0 = bulbar or respiratory)	−0.36	−0.74 0.02	0.07
Body mass index (1 = 27 or greater, otherwise = 0)	0.36	0.03 0.70	0.03 ^a
Familial disease (1 = familial, 0 = sporadic)	−0.84	−1.56 −0.12	0.02 ^a
Clinical diagnosis of frontotemporal dementia (1 = yes, 0 = no)	−0.01	−0.62 0.60	0.97
Athletics (1 = participated in athletics, 0 = no athletics)	0.17	−0.19 0.53	0.34
Military service (1 = yes, 0 = no)	0.35	−0.18 0.88	0.20
Smoker (1 = greater than 5 pack-year lifetime history, otherwise = 0)	−0.35	−0.71 0.01	0.06

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised; CI = confidence interval. Intercept = −0.78; $R^2 = 0.23$.

^aSignificant p value (<0.05).

potential confounders as covariates showed that head injury was not a predictor of rate of decline of ALSFRS-R (parameter estimate = -0.26 , $p = 0.18$). Participation in athletic activities (parameter estimate = 0.17 , $p = 0.34$), military service (parameter estimate = 0.35 , $p = 0.20$), and smoking (parameter estimate = -0.35 , $p = 0.06$) were not predictors of mean monthly decline in ALSFRS-R (table 2).

A linear regression model was also performed using any history of head injury as a predictor variable ($n = 58$ with head injury, $n = 42$ without head injury). Again, head injury was not a predictor

of mean monthly decline of ALSFRS-R (parameter estimate = -0.06 , $p = 0.75$).

Head injury and neuropathologic outcomes in ALS. Information regarding head injury was available for 47 autopsy cases. There were 9 cases that met the study definition for head injury and 38 cases without significant head injury. Ten of these 47 cases had the presence of tau proteinopathy, with prominent tau immunoreactivity concentrated deep in cortical sulci (figure). Clinical history and detailed pathologic findings for these 10 patients are detailed in table 3. Only one of these cases had a history of significant head injury.

No significant differences were seen in the frequency of tau proteinopathy ($n = 1$, 11% with head injury; $n = 9$, 24% without head injury), TDP-43 proteinopathy in the brain ($n = 4$, 44% with head injury; $n = 17$, 45% without head injury), or pathologic findings of AD ($n = 3$, 33% with head injury; $n = 10$, 26% without head injury) comparing ALS autopsy cases with a head injury history to ALS autopsy cases without a head injury history (table 4). A clinical diagnosis of frontotemporal dementia was noted in 2 cases (22%) with a history of significant head injury and 4 cases (11%) without significant head injury history. Pearson correlation calculations did not support relationships between tau and TDP-43 proteinopathy in the brain (correlation = -0.05 , $p = 0.75$), tau and AD pathology (correlation = -0.09 , $p = 0.55$), and TDP-43 brain pathology and AD pathology (correlation = 0.11 , $p = 0.45$).

Independent logistic regression models showed that head injury with loss of consciousness or requiring hospitalization occurring greater than 1 year prior to ALS diagnosis was not a predictor of tau pathology (OR = 0.4 , $p = 0.42$) or TDP-43 pathology in the brain (OR = 0.99 , $p = 0.99$). Head injury was not a predictor of AD pathology after controlling for age (OR = 0.86 , $p = 0.89$).

Logistic regression models were also performed using any history of head injury as a predictor variable ($n = 25$ with head injury, $n = 22$ without head injury). Any history of head injury was not a predictor of tau pathology (OR = 2.46 , $p = 0.24$) or TDP-43 pathology in the brain (OR = 1.90 , $p = 0.28$) at the 0.05 significance level. Any history of head injury was not a predictor of AD pathology after controlling for age (OR = 0.62 , $p = 0.54$).

DISCUSSION Head injury was not associated with faster mean monthly decline of ALSFRS-R or earlier age at symptom onset. Both patients with ALS with head injury history and patients with ALS without a head injury history had an average monthly decline of ALSFRS-R of -0.9 points per month, which is an expected rate of disease progression for an ALS

Figure Representative photomicrographs of neuropathologic findings in amyotrophic lateral sclerosis autopsy cases with the presence of tau pathology

The case numbers correspond with the case numbers in table 3. Case 1 (A-D): tau-positive neurites, glia, and neurofibrillary tangles in the frontal cortex of a patient with amyotrophic lateral sclerosis (ALS) without a history of head injury or athletic participation. (A) Tau immunoreactivity in the frontal cortex, most intense at the cortical region deep within the sulcus (S). (B-D) Higher power images show the frequency and density of tau immunoreactivity in the cortex, all at sulcal depths. Case 10 (E-H): tau immunoreactivity in the frontal cortex (E, G) and the parietal cortex (B, D) of a patient with ALS who had a single motor vehicle accident causing head injury with loss of consciousness 32 years prior to onset of ALS.

Table 3 Descriptive table for autopsy cases with tau proteinopathy

Case number	Age at autopsy, y	Antecedent head injury with LOC or requiring hospitalization	Any head injury	Participation in athletic activities	Clinical diagnosis of dementia	Tau pathology			Other neuropathologic diagnoses	APOE
						Neurofibrillary tangles	Tau immunoreactive neurites	Tau immunoreactive glia		
1	43	None	None	None	No	+ Entorhinal, amygdala, parietal, cingulate, insular, striatum, hypothalamus, thalamus, substantia nigra, locus ceruleus, nucleus basalis, brainstem; ++ frontal, temporal	+ Hippocampus, entorhinal, parietal, cingulate, insular, striatum, hypothalamus, thalamus, brainstem; ++ frontal, temporal	+ Entorhinal, frontal, parietal, cingulate, insular, striatum, hypothalamus, thalamus, brainstem; ++ temporal	None	E3/4
2	64	None	None	Played recreational football and baseball	No	+ Entorhinal, parietal, insular	+ Parietal cortex	+ Parietal cortex	Possible Alzheimer disease by CERAD criteria	E3/3
3	44	None	None	None	No	+ Frontal, insular, nucleus basalis	+ Frontal	+ Frontal	None	E2/3
4	55	None	Fell backwards and had a spine injury at age 45 y; never hospitalized, no LOC	None	No	+ Entorhinal, amygdala, frontal, temporal, insular, nucleus basalis, hypothalamus, thalamus, locus ceruleus	+ Temporal	+ Temporal, basal ganglia, brainstem, spinal cord	Lewy body disease; brainstem predominant type	E3/3
5	52	None	Several head injuries while playing high school football and baseball; no hospitalization or LOC	High school football and baseball	No	+ Frontal	+ Hippocampus, frontal, locus ceruleus	+ Frontal	None	E3/3
6	68	None	Fell backwards and hit head on a board 11 months before ALS diagnosis; went to hospital the next day; no LOC	None	No	+ Entorhinal, frontal, nucleus basalis, thalamus	+ Frontal	+ Frontal	Subacute microinfarct in globus pallidus	E3/3
7	52	None	Possible head injury during recreational sports as a child; no LOC or hospitalization	Childhood recreational sports	No	+ Entorhinal, amygdala, frontal, temporal, parietal, cingulate, insular, caudate, putamen, substantia nigra; ++ nucleus basalis, locus ceruleus	+ Spinal cord	+ Frontal, striatum, hypothalamus, thalamus	Frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions	Not known
8	64	None	Head injuries while playing high school football; no LOC or hospitalization	High school football; running back	No	+ Hippocampus, entorhinal cortex, amygdala, frontal	+ Frontal, parietal	+ Frontal, parietal	Frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions, possible Alzheimer disease by CERAD criteria	E3/3

Continued

Table 3 Continued

Case number	Age at autopsy, y	Antecedent head injury with LOC or requiring hospitalization	Any head injury	Participation in athletic activities	Clinical diagnosis of dementia	Tau pathology			Other neuropathologic diagnoses	APOE
						Neurofibrillary tangles	Tau immunoreactive neurites	Tau immunoreactive glia		
9	62	None	Car accident at age 17 y, hit by a horse around age 50 y; never hospitalized, no LOC	None	Yes; clinical diagnosis of frontotemporal dementia prior to onset of ALS symptoms	+ Entorhinal, cingulate, nucleus basalis	+ Frontal, parietal, temporal, locus ceruleus, spinal cord	+ Frontal, parietal, temporal	Frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions	E2/3
10	50	Motor vehicle accident with head injury and LOC at age 18 y	See previous	None	No	+ Hippocampus, entorhinal cortex, amygdala, frontal, temporal, parietal, hypothalamus, thalamus, substantia nigra, brainstem; ++ locus ceruleus	+ Hippocampus, entorhinal cortex; ++ frontal, temporal	+ Entorhinal cortex, subcortical white matter, hypothalamus, thalamus, brainstem, spinal cord; ++ frontal, temporal	None	E3/3

Abbreviations: ALS = amyotrophic lateral sclerosis; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; LOC = loss of consciousness. + = Sparse to moderate; ++ = frequent.

cohort.²⁵ The lack of association between head injury and disease progression did not change when different definitions of head injury were considered. Our data thus suggest that head injury is not associated with accelerated neurodegenerative cascades or clinical decline of patients with ALS.

A history of head injury also was not associated with a specific neuropathologic phenotype in ALS. The tau pathology described with cases of chronic traumatic encephalopathy, pathologic findings of TDP-43 proteinopathy in the brain, and Alzheimer dementia pathology all occurred equally in ALS autopsy cases with and without head injury. Additionally, tau pathology had a low correlation with TDP-43 proteinopathy, which does not support the hypothesis that a common stimulus provokes pathologic accumulation of both proteins. Pathologic heterogeneity has been described in ALS autopsy cases; however, the clinical relevance of these findings remains uncertain. The causes of tau accumulation in patients with ALS are unclear, and it is unknown whether or not aggregation of this protein provides any clues regarding disease pathogenesis. In the 2010 neuropathologic study of athletes with CTE,⁹ 2 of the 3 ALS cases demonstrated widespread tau proteinopathy throughout the brain, and 1 ALS case had tau proteinopathy only in the frontal lobe, diencephalon, and brainstem. In our series, 4 of the 10 cases had widespread tau immunoreactivity throughout the brain, and 6 cases had scattered tau immunoreactivity (table 3). Our study suggests that the tau pathology described in CTE cases is not a specific finding related to head injury in an ALS population.

Although the 2010 neuropathologic study of athletes with CTE⁹ reports the coexistence of TDP-43 and tau pathology in a cohort of CTE cases with and without ALS, these findings should be interpreted with caution. Indeed, the autopsy cases were recruited for the presence of CTE, and it is not expected that the coexistence of ALS would alter the pathologic findings of CTE. Our autopsy cases were taken from a population with ALS without regard to a history of athletic participation, head injury, or cognitive decline, and the findings from this representative ALS clinic population do not support the hypothesis that tau and TDP-43 accumulation is specific to those with these risk factors. Head injury was not associated with a distinct pathologic phenotype in ALS autopsy cases. We also hypothesized that if head injury drives the accumulation of tau and TDP-43 pathology in patients with ALS, as suggested by the 2010 publication,⁹ then patients with ALS with a history of head injury should have more aggressive disease due to the activation of these neurodegenerative cascades. However, we found no correlation between the history of head injury and the rate of

Table 4 Final neuropathologic diagnosis of amyotrophic lateral sclerosis autopsy cases in patients with and without antecedent head injury causing loss of consciousness or requiring hospitalization

Neuropathologic diagnosis	Head injury, ^a n = 9, n (%)	No head injury, n = 38, n (%)
Tau pathology: presence of tau immunoreactive neurites, glia, and neurofibrillary tangles	1 (11)	9 (24)
TDP-43 pathology: presence of TDP-43 immunoreactive inclusions in the brain outside of the motor cortex	4 (44)	17 (45)
Alzheimer disease pathology: meeting possible, probable, or definite CERAD criteria	3 (33)	10 (26)
Lewy body disease	1 (11)	2 (5)

Abbreviation: CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

^aHead injury defined here as an event associated with loss of consciousness or requiring hospitalization, occurring >1 year prior to diagnosis of amyotrophic lateral sclerosis.

progression of disease, further distancing ALS pathogenesis from head injury and echoing the criticisms voiced by other investigators.^{11,12}

A potential limitation to this study is that it could be underpowered to detect a modest effect of head injury on ALS disease progression or neuropathology. Our sample size did not allow for subgroup analysis to determine if timing of head injury or multiple head injuries has a differential effect on the ALS disease process. Additionally, ALS is a heterogeneous disease with variable rates of disease progression, but the many factors that influence differences in rate of progression have not been identified. While known confounders were controlled for, it is impossible to control for unknown factors. As head injury was obtained from family members for autopsy cases, there is potential for recall bias. However, the effects of recall bias in this study may be less of a concern given that the results did not change when different definitions of head injury were considered. Finally, our patient population was taken from a typical multidisciplinary ALS clinic setting, and professional athletes with numerous head injuries were not well-represented. Therefore, this study does not directly study the relationship between head injury and ALS in professional athletes with numerous concussions.

Unlike other epidemiologic studies that examine the prevalence of head injury in patients with ALS compared to controls, we used a different approach by examining the relationship between head injury and disease progression as well as the relationship between head injury and pathologic findings in patients with ALS. Of note, the methodology of this study did not allow us to assess the prevalence of head injury in an ALS population or compare head injury frequency to a control population. We found that head injury does not alter disease progression in ALS or affect neuropathologic outcomes in ALS autopsy cases, and these findings did not vary when

considering different definitions of head injury. Our data do not support the hypotheses that head injury accelerates neurodegenerative cascades in patients with ALS or that head injury is associated with pathologic accumulation of tau and TDP-43 in ALS cases.

AUTHOR CONTRIBUTIONS

Christina Nicole Fournier: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis, study supervision. Marla Gearing: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Saila R. Upadhyayula: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Mitch Klein: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, statistical analysis. Jonathan D. Glass: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.

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