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Head Injury Does Not Alter Disease Progression or Neuropathologic Outcomes in Amyotrophic Lateral Sclerosis (ALS)

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Head Injury Does Not Alter Disease Progression or Neuropathologic Outcomes in Amyotrophic Lateral Sclerosis (ALS)

By

Christina Fournier, MD

An abstract of a thesis submitted to the Faculty of
James T. Laney Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
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Abstract

Head Injury Does Not Alter Disease Progression or Neuropathologic Outcomes in Amyotrophic Lateral Sclerosis (ALS)
By Christina Fournier, MD

Background: Head injury has been examined as a risk factor for ALS that potentially accelerates neurodegeneration. A causal relationship between head injury and ALS has been proposed after observing pathologic findings of tau proteinopathy (the pathologic finding described with chronic traumatic encephalopathy (CTE)) and TDP-43 accumulation in the brains of professional athletes with ALS.

Methods: ALS patients were surveyed to obtain head injury history, and clinical information was obtained from medical records. Head injury was defined as an event associated with loss of consciousness or requiring hospitalization, occurring greater than 1 year prior to ALS diagnosis. Demographic and clinical information from ALS patients with head injury was compared to ALS patients without. Linear regression was performed to determine if head injury is a predictor for rate of disease progression, as measured by the revised ALS functional rating scale (ALSFRS-R), while controlling for confounders.

Additionally, head injury history was obtained from family members of ALS autopsy cases. The frequency of tau proteinopathy, TDP-43 proteinopathy in the brain, and pathologic findings of Alzheimer dementia (AD) were examined in ALS cases with head injury compared to ALS 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 ALSFRS-R between ALS patients with head injury (n=24) and without (n=76), with mean monthly ALSFRS-R 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 proteinopathy 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 significant predictor of tau pathology (OR=0.4, p=0.42) or TDP-43 brain pathology (OR=0.99, p=0.99).

Conclusion: Head injury was not associated with faster disease progression in ALS. Additionally, head injury did not result in a specific neuropathologic phenotype in ALS. The tau pathology described with CTE occurred in ALS autopsy cases both with and without head injury.

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INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a fatal and incurable neurodegenerative disease that causes progressive deterioration of the voluntary motor system. The etiology of ALS is unknown, but head injury has been explored as an environmental risk factor that may incite neurodegenerative cascades and contribute to ALS pathogenesis. Head injury not only causes mechanical damage to the brain, but also triggers inflammatory and excitotoxic cascades [1]. Neuroinflammatory and excitotoxic pathways are thought to provoke and accelerate motor neuron death in ALS [2, 3]. These deleterious effects of head injury have also been studied in other neurodegnerative diseases, including Alzheimer Dementia (AD) [4, 5].

A study by McKee and colleagues in 2010 [6] argued for a causal link between head injury and ALS. This paper described the autopsy findings of 12 professional athletes who experienced multiple head injuries and received a clinical diagnosis of chronic traumatic encephalopathy (CTE). CTE is associated with clinical findings of dementia, parkinsonism and behavior changes and neuropathologic findings of tau-positive neurites, glia, and neurofibrillary tangles throughout the brain [7]. Of the 12 athletes with CTE, 3 also had a clinical diagnosis of ALS. One of these 3 had familial ALS. As expected, all 12 of these cases demonstrated the tau pathology described with CTE. Additionally, 10 of the 12 cases, including the 3 ALS cases, demonstrated TAR DNA-binding protein of 43 kDa (TDP-43) proteinopathy in the brain, the pathologic finding associated with frontotemporal dementia and some ALS cases. The implications of this study have been debated, but the authors argued that "the shared presence of 2 aggregated phosphorylated proteins *[TDP-43 and tau]* associated with neurodegeneration in the great majority of cases argues against the coincidental occurrence of CTE and sporadic ALS, suggesting instead that a common stimulus provokes the pathological accumulation of both proteins [6]." Mckee et al proposed that "traumatic axonal injury may also accelerate TDP-43 accumulation, aggregation, and dislocation to the cytoplasm and thereby enhance its neurotoxicity [6]."

In summary, McKee et al argued that head injury triggers tau and TDP-43 accumulation in certain vulnerable individuals, which causes ALS and accelerates neurodegeneration. If this hypothesis is true, ALS patients with a history of significant head injury would be expected to have faster disease progression compared to ALS patients with no head injury history. 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 we would expect the presence of these two findings to be correlated in ALS autopsy cases.

Therefore, the objectives of this study are to determine if head injury is associated with faster disease progression in ALS and to determine if ALS autopsy cases with head injury history have a different neuropathologic phenotype compared to ALS autopsy cases without head injury history.

BACKGROUND

The incidence of ALS throughout the world is estimated at 1.5 – 2.5 per 100,000 per year [8]. Average survival after diagnosis is 3 years, with death occurring from respiratory failure [9]. Approximately 90% of ALS cases are sporadic, and the other 10% of cases are familial, typically with an autosomal dominant pattern of inheritance [10]. Ten to fifteen percent of ALS cases demonstrate coexisting frontotemporal dementia (FTD) [1, 2], and up to half of ALS patients demonstrate abnormalities on cognitive testing, particularly with executive function [11]. Pathologically, patients with ALS and frontotemporal dementia demonstrate abnormal deposition of TDP-43 throughout the brain [12]. This pathology is also seen in some ALS cases without clinical evidence of dementia.

The etiology of ALS is unknown, but many mechanisms have been implicated in the disease process including glutamate excitotoxicity [13], [14], mitochondrial dysfunction [15], oxidative stress [16], [17], and immune-mediated factors [18]. Environmental factors have also been studied as possible risk factors for ALS including participation in athletics [3], military service [19], smoking [20], and head injury [21].

Head injury has been explored as a potential risk factor for ALS, but this relationship remains controversial and is poorly understood. This issue garnered international media attention after several reports of elite athletes developing ALS at higher rates than expected. Among a group of 24,000 professional soccer players from the top 3 Italian divisions between 1960 – 1996, 33 players were diagnosed with ALS [22]. More recently, this concern regained media notoriety when several National Football League (NFL) players in the United States were diagnosed with ALS. A recent study by Lehman and colleagues found that while former NFL football players have a lower overall mortality compared to age-matched controls, they do have a higher risk of mortality from ALS [23].

Even in non-athlete populations, some epidemiologic studies suggest as association between head injury and ALS. One study of mostly male veterans showed that head injury associated with loss of consciousness or requiring hospitalization was associated with an increased odds ratio for ALS [24]. Another study in the New England area found that repeated head injury requiring medical attention, but not a single head injury or limb injury, was associated with an increased risk for ALS [21].

In contrast, other epidemiologic studies do not uphold this association. One retrospective cohort study of high school students in Rochester, Minnesota from 1946 - 1956 found that high school football players were not at increased risk for developing ALS or other neurodegenerative diseases compared to non-athlete men [25]. A large case-control study in Sweden found no convincing association between previous hospitalization for severe head injury and the subsequent development of ALS. They did note an increased prevalence of severe head injury only in the year prior to ALS diagnosis, which was interpreted as falls associated with the ALS disease process [26]. A United Kingdom study utilizing trauma history from a medical records database found no association between antecedent head or limb trauma and ALS [27].

Experimental data on trauma and ALS are limited and also yield mixed results. One study of a pre-symptomatic SOD1 ALS rat model showed that spinal cord injury did not accelerate motor neuron death or disease progression compared to SOD1 ALS rats without injury [28]. However, another animal study of the pre-symptomatic SOD1 ALS mouse model showed an impaired ability to recover from facial motor nerve axotomy compared to controls, suggesting an increased susceptibility to trauma [29]. If the findings of this study translate to humans, then it is possible that head injury can accelerate neurodegeneration in ALS.

METHODS

Approval for this study was obtained from the Emory Institutional Review Board. Informed consent was obtained from all living subjects that 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 – 2014, had a diagnosis of ALS according to El Escorial criteria [30] (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 revised ALS Functional Rating Scale score (ALSFRS-R) in the electronic medical record.

The ALSFRS-R is an ordinal rating scale (0 through 4) used to determine the ALS patient's self-assessment of their ability and need for assistance in 12 activities or functions. This is a validated scale that provides a total score (best of 48) from four sub-scores that assess speech and swallowing (bulbar function), use of upper extremities (cervical function), gait and turning in bed (lumbar function), and breathing (respiratory function) [31]. This scale is frequently used as a method for determining the rate of functional decline in ALS clinical research studies and is routinely performed at each Emory ALS clinic visit. The mean monthly decline of ALSFRS-R is typically between -0.7 and – 1 point per month with a linear rate of decline throughout disease progression [32].

For this study, mean monthly decline of ALSFRS-R was calculated using the first documented ALSFRS-R score and assuming a score of 48 at the time of symptom onset. 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 [33, 34] but are difficult to control for given variability in usage among patients with ALS.

Informed consent forms and surveys were distributed to eligible patients during routine clinic visits to the Emory ALS Center 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 for assessing for traumatic brain injury [35]. The survey included additional questions to provide detailed trauma history and clinical history. For each patient that 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 greater than 1 year prior to the diagnosis of ALS. This definition is consistent with findings from previous epidemiologic studies of head injury and ALS [24], [26]. 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 ALS patients with any head injury history to patients with no head injury history. A sample size of 101 patients was needed to detect a 0.1 point difference between groups in mean monthly decline of ALSFRS-R with 80% power assuming a type 1 error rate of 5%.

Mean values and standard deviations were calculated for clinical and demographic variables for ALS patients with head injury and ALS patients 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 (BMI), bulbar vs. limb onset, and presence or absence of clinical frontotemporal dementia [36, 37]. Possible confounders that could be associated with head injury and have an unknown effect on disease progression include athletic activities [38], military service [19], and cigarette smoking [20]. 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 -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 one of two board certified pathologists experienced at reviewing ALS autopsy cases. Slides were reviewed in a blinded manner, such that the reviewer did not know the patient's identity, clinical history, or head injury history when performing the assessment. 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 cases to ALS autopsy cases with no head injury history.

Pearson correlation coefficients were calculated between tau and TDP-43 proteinopathy, tau proteinopathy and 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 CERAD criteria [39].

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 ALS patients with head injury (n = 24) and without head injury (n = 76), with a mean monthly decline of ALSFRS-R of -0.9 for both groups. Age of onset was similar for both groups, with a mean age of onset of 56 in the head injury group and 55 in the group with no head injury. Site of onset and the presence of clinical FTD were similar between groups. Familial disease was seen in 8% cases without head injury and in no cases with head injury. 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 potential confounders as covariates showed that head injury was not a statistically significant predictor of rate of decline of ALSFRS-R at the 0.05 significance level (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 statistically significant predictors of mean monthly decline of ALSFRS-R at the 0.05 significance level (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 in ALSFRS-R (parameter estimate = -0.06, p = 0.75) (Table 3).

Head Injury and Neuropathologic Outcomes in ALS

Information regarding head injury was available for 47 autopsy cases. There were 9 cases with head injury and 38 cases without 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 and without head injury (Table 4).

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) (Table 6).

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 statistically significant predictor of tau pathology (odds ratio = 0.4, p = 0.42) (Table 6) or TDP-43 pathology in the brain at the 0.05 significance level (odds ratio = 0.99, p = 0.99) (Table 7). Head injury was not a predictor of AD pathology after controlling for age (odds ratio = 0.86, p = 0.89) (Table 8).

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 statistically significant 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. Head injury was not a predictor of AD pathology after controlling for age (OR = 0.62, p = 0.54).

DISCUSSION AND CONCLUSION

Head injury was not associated with faster mean monthly decline in ALSFRS-R or earlier age of symptom onset. Both ALS patients with head injury history and ALS patients without a head injury history had an average monthly decline in ALSFRS-R of -0.9 points per month, which is an expected rate of disease progression for a typical ALS cohort [32]. The lack of association between head injury and disease progression did not change when different definitions of head injury were considered. The findings in this study do not suggest that head injury accelerates neurodegenerative cascades or clinical decline in patients with ALS.

A history of head injury was not associated with a specific neuropathologic phenotype in ALS. The tau pathology described with cases of CTE, pathologic findings of TDP-43 proteinopathy, and AD pathology all occurred in ALS autopsy cases both with and without head injury without significant differences. Additionally, tau pathology had a low correlation with TDP-43 proteinopathy, which refutes the hypothesis that a common stimulus provokes pathologic accumulation of both proteins. Pathologic heterogeneity has been previously 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 towards uncovering disease pathogenesis.

Although the study by McKee and colleagues [6] reports the coexistence of TDP-43 and tau pathology in their cohort of CTE cases with and without ALS, these findings should be interpreted with caution. The pathologic observations by McKee et al [6] did not provide sufficient evidence for a common pathway of protein aggregation or disease pathogenesis in ALS patients with a history of head injury. In fact, the neuropathologic findings in our study from a representative ALS clinic population did not support the hypothesis that head injury is associated

with tau and TDP-43 accumulation. Head injury was not associated with a distinct pathologic phenotype in our series of ALS cases.

There are several limitations to this study. This study 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 in this study, it is impossible to control for unknown factors. It is also possible that some ALS cases were misclassified by head injury status when family members or next of kin were surveyed on past events. However, given that results did not change with different definitions of head injury, misclassification is unlikely to play a significant role in the study results. Finally, the patient population in this study 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 have looked for a higher odds ratio of ALS in people with head injury compared to people with no head injury, this study utilizes 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. We found that head injury does not alter disease progression in ALS or affect neuropathologic outcomes in ALS autopsy cases. These findings 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.

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Table 1. Demographic and Clinical Characteristics of surveyed ALS patients with and without antecedent head injury causing loss of consciousness or requiring hospitalization

	Head Injury* n = 24		No head injury n = 76	
Variable	**mean**	**standard deviation**	**mean**	**standard deviation**
Mean monthly decline in ALSFRS-R	**-0.9**	0.8	**-0.9**	0.9
Mean age at symptom onset (years)	56	13.7	55	10.6
Mean Body Mass Index (BMI)	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

***Head Injury defined here as an event associated with loss of consciousness or requiring hospitalization, occurring > 1 year prior to diagnosis of ALS**

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 in ALSFRS-R)	95% Confidence Interval		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 (BMI) (1 = BMI of 27 or greater, otherwise = 0)	0.36	0.03	0.70	0.03*
Familial disease (1 = familial, 0 = sporadic)	-0.84	-1.56	-0.12	0.02*
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

intercept = -0.78

R-squared = 0.23

significant p-values (<0.05) marked with an asterix (*)

Table 3. Linear regression with mean monthly decline of ALSFRS-R as the outcome and any head injury and potential confounders as covariates

Variable	Parameter Estimate (mean monthly decline in ALSFRS-R)	95% Confidence Interval		p-value
Head injury (1 = any history of head injury, otherwise = 0)	**-0.06**	**-0.42**	**0.31**	**0.75**
Age (1 = 60 years of age or older, otherwise = 0)	-0.14	-0.52	0.25	0.48
Site of onset (1 = limb onset, 0 = bulbar or respiratory)	-0.36	-0.75	0.02	0.06
Body Mass Index (BMI) (1 = BMI of 27 or greater, otherwise = 0)	0.36	0.02	0.70	0.04*
Familial disease (1 = familial, 0 = sporadic)	-0.77	-1.50	-0.05	0.04*
Clinical Diagnosis of Frontotemporal dementia (1= yes, 0 = no)	-0.02	-0.64	0.60	0.95
Athletics (1 = participated in athletics, 0 = no athletics)	0.14	-0.24	0.53	0.46
Military service (1 = yes, 0 = no)	0.32	-0.22	0.85	0.25
Smoker (1 = greater than 5 pack-year lifetime history, otherwise = 0)	-0.31	-0.68	0.05	0.09

intercept = -0.79

R-squared = 0.22

significant p-values (<0.05) marked with an asterix (*)

Table 4. Final Neuropathologic Diagnosis of ALS autopsy cases in patients with and without antecedent head injury causing loss of consciousness or requiring hospitalization

Neuropathologic Diagnosis	Head Injury* n = 9	No head injury n = 38
Tau pathology: presence of tau immunoreactive neurites, glia, and neurofibrillary tangles	1 (11%)	9 (24%)
TDP-43 pathology: presence of frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions	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%)

***Head Injury defined here as an event associated with loss of consciousness or requiring hospitalization, occurring > 1 year prior to diagnosis of ALS**

Table 5. Pearson correlation calculations between tau and TDP-43 proteinopathy, tau and AD pathology, and TDP-43 and AD pathology.

Neuropathologic Diagnoses evaluated for Pearson Correlation		Sample Correlation	95% Confidence Interval		p-value
Tau pathology: tau immunoreactive neurites, glia, and neurofibrillary tangles	**TDP-43 pathology:** frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions	-0.05	-0.33	0.24	0.75
Tau pathology: tau immunoreactive neurites, glia, and neurofibrillary tangles	**Alzheimer Disease pathology:** meeting possible, probable, or definite CERAD criteria	-0.09	-0.37	0.20	0.55
TDP-43 pathology: frontotemporal lobar degeneration with TDP-43 immunoreactive inclusions	**Alzheimer Disease pathology:** meeting possible, probable, or definite CERAD criteria	0.11	-0.18	0.39	0.45

Table 6. Logistic regression with dichotomous outcome of Tau pathology as outcome measure and antecedent head injury associated with loss of consciousness or requiring hospitalization as predictor variable

Variable	Odds Ratio	95% Confidence Interval		p-value
Head injury*	0.40	0.04	3.67	0.42

*Head Injury defined here as an event associated with loss of consciousness or requiring hospitalization, occurring > 1 year prior to diagnosis of ALS

intercept parameter estimate = -1.1701

-2 Log L = 47.9

Table 7. Logistic regression with dichotomous outcome of TDP-43 pathology in the brain as outcome measure and antecedent head injury associated with loss of consciousness or requiring hospitalization as predictor variable

Variable	Odds Ratio	95% Confidence Interval		p-value
Head injury*	0.99	0.23	4.26	0.99

*Head Injury defined here as an event associated with loss of consciousness or requiring hospitalization, occurring > 1 year prior to diagnosis of ALS

intercept parameter estimate = -0.21

-2 Log L = 64.6

Table 8. Logistic regression with dichotomous outcome of Alzheimer Disease pathology as outcome measure and antecedent head injury associated with loss of consciousness or requiring hospitalization and age as predictor variables

Variable	Odds Ratio	95% Confidence Interval		p-value
Head injury†	0.86	0.10	7.30	0.89
Age in years at time of autopsy	1.19	1.06	1.34	0.003*

†Head Injury defined here as an event associated with loss of consciousness or requiring hospitalization, occurring > 1 year prior to diagnosis of ALS

significant p-values (<0.05) marked with an asterix (*)

intercept parameter estimate = -12.13

-2 Log L = 39.5