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Elevated cerebrospinal fluid concentrations of N-acetylaspartate correlate with poor outcome in a pilot study of severe brain trauma

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Abstract

Primary objective: Examine the correlation between acute cerebrospinal fluid (CSF) levels of N-acetylaspartate (NAA) and injury severity upon admission in addition to long-term functional outcomes of severe traumatic brain injury (TBI).

Design and rationale: This exploratory study assessed CSF NAA levels in the first four days after severe TBI, and correlated these findings with Glasgow Coma Scale (GCS) score and long-term outcomes at 3-, 6-, 12-, and 24-months post-injury.

Methods: CSF was collected after passive drainage via an indwelling ventriculostomy placed as standard of care in a total of 28 people with severe TBI. NAA levels were assayed using triple quadrupole mass spectrometry. Functional outcomes were assessed using the Glasgow Outcomes Scale (GOS) and Disability Rating Scale (DRS).

Results: In this pilot study, better functional outcomes, assessed using the GOS and DRS, were found in individuals with lower acute CSF NAA levels after TBI. Key findings were that average NAA level was associated with GCS ($p = 0.02$), and GOS at 3- ($p = 0.01$), 6- ($p = 0.04$), 12- ($p = 0.007$), and 24- months ($p = 0.002$).

Implications: The results of this study add to a growing body of neuroimaging evidence that raw NAA values are reduced and variable after TBI, potentially impacting patient outcomes,

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warranting additional exploration into this finding. This line of inquiry could lead to improved diagnosis and prognosis in patients with TBI.

Keywords

Traumatic brain injury (TBI); brain trauma; severe TBI; N-acetylaspartate (NAA); biomarker

Introduction:

Traumatic brain injury (TBI) affects individuals across the lifespan and is a major cause of death and disability worldwide (1,2). Long-term deficits and reduced functional independence can occur after TBI of any severity, but are especially common and often profound in persons with severe TBI (i.e. defined as Glasgow Coma Scale (GCS) score 8) (3–5). A growing body of evidence suggests that acute indicators of central nervous system (CNS) pathology may be useful in predicting long-term TBI outcomes (6,7). However, additional exploration of the acute physiological changes, using indirect neuroimaging techniques, direct biomarker quantification, and other evaluation techniques is needed to enhance predictive efforts and ultimately improve TBI diagnosis and management.

One promising direction involves evaluating acute changes in N-acetylaspartate (NAA), a free amino acid produced by mitochondria during CNS metabolism in various brain regions (8–15). Intracellular NAA can be assessed using neuroimaging and extracellular NAA can be quantified in cerebrospinal fluid (CSF) using various protein analysis methods (16,17). The relative abundance of NAA within the CNS has led researchers to use this metabolite as a marker for neuronal viability (18) and a proxy for overall neuronal density (19). Additionally, because NAA produces a prominent proton signal in magnetic resonance spectroscopy (MRS) it has been included as an outcome in several neuroimaging studies of TBI and other neurological conditions (20–25).

Still, little is known about changes in NAA levels following TBI in humans and how these changes relate to health outcomes. Most published studies use imaging methods, which detect intracellular levels. Reduced levels of intracellular NAA on MRS scans, after pre-clinical and clinical brain trauma, has been associated with increased TBI pathology and functional deficits in several published studies (26–37). Only two published studies to date have measured NAA in extracellular fluid obtained from patients via microdialysis (38,39). There remains a gap in the literature surrounding extracellular NAA levels after TBI with no published brain trauma study to date directly assaying NAA levels in human CSF. Thus, the purpose of this prospective exploratory pilot study is to examine the correlation between acute NAA in CSF, initial extent of injury (assessed using the GCS), and long-term outcomes (assessed using the Glasgow Outcomes Scale (GOS) and Disability Rating Scale (DRS)) in a sample of individuals with severe TBI.

Methods

Sample

Prior to all recruitment and data collection efforts Institutional Review Board approval was obtained. Participants in the present pilot study were drawn from a larger ongoing study that recruited individuals with severe TBI who received treatment at the neurointensive care unit of a university-affiliated Level I Trauma Centre between February and September of 2008. Recruitment was based on the following inclusion criteria: (1) sustained a severe TBI, defined as an admission GCS ≤ 8 ; (2) aged 16–80 years at the time of injury; and (3) equipped with an indwelling ventriculostomy catheter for CSF drainage that enabled biosample collection. Exclusion from the parent sample was based on the presence of: (1) penetrating brain trauma; (2) comorbid cardiac and/or respiratory arrest; and/or (3) a history of any neurological deficit that might obscure outcomes on the chosen measures (e.g. intellectual disability; dementia; stroke). In total, $n = 28$ participants with severe TBI, enrolled into the ongoing larger study with at least 1 CSF sample collected during the first 4 days after injury and at least 1 outcome time point available, were assayed for NAA levels.

Cerebrospinal fluid collection, storage, and NAA quantification

CSF samples were collected from a drainage bag, attached to an indwelling ventriculostomy catheter, that was placed as standard of care as part of clinical management in those patients included in this study. The drainage bag was changed every 12 hours. The CSF was centrifuged to pellet the cellular component from the supernatant. The supernatant was aliquoted into multiple vials and stored frozen at -80°C . On the day of laboratory analysis, CSF samples were thawed and diluted with distilled water before being vortexed. The solution was then combined with acetonitrile and internal standard and briefly vortexed and centrifuged to pellet the cellular component from the clear supernatant. The supernatant was aliquoted into multiple vials and NAA levels were quantified by laboratory personnel blinded to participant phenotype data. Ultra performance liquid chromatography was conducted for separation (Acquity model, Waters, Milford, MA) and detection was conducted using a triple quadrupole mass spectrometer (TSQ Quantum Ultra model, Thermo Fisher Scientific, San Jose, CA). Data acquisition and processing was conducted (XCalibur 3.0 version, ThermoFinnigan, San Jose, CA).

Outcome measures

Initial injury severity was assessed using the GCS. At 3-, 6-, 12-, and 24- months following the TBI; a trained technician assessed long-term functional outcomes using the GOS and DRS. Whenever possible, these long-term outcomes were assessed in-person, but when face-to-face assessment was not feasible, the examination was performed via telephone. All technicians were blinded to participant NAA levels. Due to this pilot study's exploratory nature and small sample size, the measures chosen were analyzed in their original scale and dichotomized versions (GCS= 3–5 vs. 6–8; GOS= 1–2 vs. 3–5; DRS= 0–18 vs. 19–30). On the GCS and GOS lower scores are associated with a greater extent of dysfunction; on the DRS higher scores are associated with a greater extent of dysfunction.

Statistical analysis

Data cleaning and analyses were performed using SPSS version 24 software (IBM, Chicago, IL, USA). For each continuous and ordinal variable, summary statistics (e.g. mean, standard deviation, range) were generated; for categorical variables, frequencies were generated. Graphs were generated to explore the distribution of the data. For outcome variables left in their original (i.e., ordinal) scale, Spearman's rank order correlation (ρ) was used to explore the relationship with continuous variables (e.g. age, NAA levels). For dichotomized outcome variables, the point biserial correlation coefficient (r_{pb}) was used to explore relationships with continuous variables (e.g. NAA levels). For each participant, an average NAA value across all available daily measurements was calculated. Due to the small sample size in this exploratory pilot study, correction for multiple testing was not performed.

Results

Descriptive participant demographics and NAA measures

In total, $n=28$ participants with severe TBI (GCS = 8) were included in this exploratory pilot study. The age of the participants ranged from 16–68 years with an average of 34.0 years (standard deviation [SD]= 16.9 years). The majority ($n=27$) were Caucasian (96.4%) and $n=1$ was African American (3.6%); $n=22$ of the participants were male (79%). Participants were diversified for CT scan findings with 7% having epidural hematoma, 36% having subdural hematoma, 18% having subarachnoid hemorrhage, 25% having intracranial hemorrhage, 7% having intraventricular hemorrhage, and 7% having diffuse axonal injury. Age was neither significantly correlated with admission GCS nor with long-term outcomes assessed using any of the included measures (i.e., GOS and DRS) at 3-, 6-, 12- or 24-months post-injury (all p -values > 0.05).

While all participants had severe TBI, 50% of participants ($n=14$) had a GCS in the range of 3–5 and the remaining 50% of the sample ($n=14$) had a GCS in the range of 6–8.

Dichotomized GCS was significantly *positively* correlated with GOS at 3- ($p=0.005$, $r=0.527$), 6- ($p=0.002$, $r=0.571$), 12- ($p=0.026$, $r=0.427$), and 24- months ($p=0.010$, $r=0.487$), such that individuals with more severe injury on admission were likely to have poorer long-term outcomes (i.e. lower GOS score). Similarly, dichotomized GCS was significantly *negatively* correlated with DRS at 3- ($p=0.003$, $r=-0.554$), 6- ($p=0.003$, $r=-0.566$), 12- ($p=0.006$, $r=-0.513$), and 24-months ($p=0.004$, $r=-0.541$), with more severely injured individuals at baseline having more extensive disability (i.e. higher DRS score).

All 28 participants had NAA data for at least 1-time point. When more than one NAA concentration was available, the data were interrogated as both: (1) daily NAA concentration on days 1, 2, 3, and 4 post-TBI; as well as (2) average NAA concentration across all valid measures. Participants with data for day 1 and day 2 ($n=23$) demonstrated that the majority of participants experienced an increase ($n=16$) in NAA from day 1 to day 2 after injury with a smaller number staying the same ($n=4$) or declining ($n=4$). Participants with data beyond day 2 after injury ($n=16$) demonstrated a decline in NAA after day 2 ($n=8$), no change after day 2 ($n=5$), and an increase after day 2 ($n=3$). Neither age nor sex were significantly

correlated with average NAA concentration (all p -values > 0.05); likewise, neither age nor sex were significantly correlated with NAA concentration on day 1, 2, 3 or 4 following TBI.

Correlation between average NAA levels and long-term outcomes

When analysis was done using the participants average NAA values, there was a significant *negative* correlation with admission GCS ($p = 0.022$, $r = 0.432$) as well as 3-, 6-, 12- and 24-month GOS (all $ps < 0.05$) [Table 1; Figure 1]. In other words, *better* functioning on admission and all four post-injury time points tended to occur in individuals with *lower* average NAA levels in the CSF during the first few days after severe TBI. Similarly, when the GOS was dichotomized, average NAA levels were significantly *inversely* correlated with 3-, 6-, 12-, and 24-month GOS (all $ps < 0.05$) but not the dichotomized GCS ($p = 0.152$, $r = -0.278$) [Table 2]. Likewise, average NAA levels were significantly *positively* correlated with DRS, both when it was left in its original ordinal scale [Table 3; Figure 2] and also when dichotomized [Table 4]; that is, a *greater extent* of disability tended to occur in individuals with *higher* average NAA levels early after injury.

Correlation between NAA levels on days 1, 2, 3, and 4 post-injury and ordinal long-term outcomes

NAA concentration on each of the first 4 days after TBI *negatively* correlated with GCS [Table 1] and GOS [Table 1], but *positively* correlated with DRS [Table 3]; in other words, *better* functioning on the GCS, GOS, and DRS tended to occur in individuals with *lower* NAA levels during the first 4 days after severe TBI. NAA concentration on the first day after TBI was significantly *negatively* correlated with 24-month GOS ($p = 0.026$, $r = -0.567$), with non-significant negative correlations between day 1 NAA and admission GCS as well as GOS at 3-, 6-, or 12-months (all $ps > 0.05$). At 2 days post-injury, NAA concentration was not correlated with GCS ($p = 0.146$, $r = -0.368$), but it was significantly *negatively* correlated with GOS at 3- ($p = 0.022$, $r = -0.551$), 6- ($p = 0.044$, $r = -0.493$), 12- ($p = 0.030$, $r = -0.526$), and 24- months ($p = 0.030$, $r = -0.526$). NAA values 3 days after TBI were significantly *negatively* correlated with admission GCS ($p = 0.002$, $r = -0.669$) but not GOS at any time point examined (all $ps > 0.05$, all $rs > -0.3$). Finally, at 4 days post TBI, NAA concentration was not correlated with GCS ($p = 0.412$, $r = -0.213$), but was significantly correlated with GOS at 3- ($p = 0.015$, $r = -0.597$), 6- ($p = 0.035$, $r = -0.530$), 12- ($p = 0.004$, $r = -0.674$), and 24-months ($p = 0.005$, $r = -0.666$).

Day 1 and day 3 NAA levels were not associated with DRS at any time point examined (all $ps > 0.05$). Day 2 NAA levels, however, were significantly *positively* correlated with DRS at 3- ($p = 0.029$, $r = 0.529$), 6- ($p = 0.036$, $r = 0.510$), 12- ($p = 0.041$, $r = 0.501$), and 24- months ($p = 0.023$, $r = 0.546$). Likewise, NAA levels on the fourth day after severe TBI were significantly *positively* correlated with DRS at 3- ($p = 0.015$, $r = 0.595$), 6- ($p = 0.032$, $r = 0.536$), 12- ($p = 0.007$, $r = 0.644$), and 24- months ($p = 0.007$, $r = 0.643$).

Association between NAA levels on days 1, 2, 3, and 4 post-injury and dichotomized long-term outcomes

NAA concentration on each of the first 4 days after TBI were correlated with dichotomized GCS [Table 2], GOS [Table 2], and DRS [Table 4]. Dichotomized GCS was significantly

negatively correlated with NAA levels at 3 days post-severe TBI ($p=0.028$, $r=-0.517$), but not with day 1-, 2-, or 4- post-injury NAA levels. NAA levels 1 day after severe TBI were significantly *negatively* correlated with dichotomized GOS at 6- ($p=0.042$, $r=-0.514$) and 24- months ($p=0.047$, $r=-0.487$). The same pattern emerged with a *negative* correlation between NAA levels at days 3 and 4 post-TBI, and dichotomized GOS at 6- and 24- months (all $ps < 0.05$). For day 2 post-TBI levels of NAA, a significant *negative* correlation with 3- ($p=0.025$, $r=-0.540$) and 6- month GOS ($p=0.033$, $r=-0.518$) was found.

When DRS was dichotomized, no significant associations with day 1 or day 3 NAA levels were detected (all $p's > 0.05$). On day 2 after TBI, NAA levels were significantly *positively* correlated with dichotomized DRS at 6- ($p=0.025$, $r=0.540$) and 12- months ($p=0.025$, $r=0.025$). On day 4 post-TBI, NAA levels were significantly *positively* with DRS at 3- ($p=0.035$, $r=0.529$), 6- ($p=0.021$, $r=0.571$), 12- ($p=0.021$, $r=0.571$), and 24-months ($p=0.031$, $r=0.031$). These findings suggest that the dichotomization of the GCS, GOS, and DRS scores resulted in an overall fewer number of significant associations with NAA levels than when scores were kept in their original form.

Discussion

Summary of the Study and Relationship to Published Evidence

The results of this exploratory study contribute to the existing literature by measuring extracellular NAA in the CSF of patients with TBI for the first time. *Better* functioning on the GCS (i.e. higher score), GOS (i.e. higher score), and DRS (i.e. lower score) tended to occur in individuals with *lower* NAA levels in the CSF during the acute post-injury period. In most cases there was a moderately strong negative correlation between NAA levels and the GCS and the GOS and a moderately strong positive correlation between NAA levels and the DRS.

This finding of the moderately strong association with *extracellular* NAA in CSF after more severe injuries corroborates past reports of lower *intracellular* NAA after TBI in several neuroimaging studies (27,32,40,41). However, not all published neuroimaging studies reported robust changes in NAA levels after trauma (42,43); for example, one study failed to find meaningful differences in NAA neuroimaging between athletes with repetitive TBI and controls (44). Another study reported a trend toward increasing ratios of NAA to choline (Cho) and creatinine (Cr) (i.e. NAA:Cho and NAA:Cr) with an increasing number of mild TBIs (45). However, it is possible that the less severe nature of the injuries in these studies (44,45) contributed to the lack of a significant difference in NAA levels.

Interesting, this finding contradicts the only published study in humans associating NAA measured in extracellular fluid obtained via microdialysis, which found lower NAA levels were associated with death after injury (39). However, a published study investigating extracellular levels of NAA via microdialysis in a rat study found NAA levels were modestly increased after isolated TBI and considerably and persistently elevated in instances of TBI with secondary hypoxia-ischemia (46), findings consistent with the present study. A second rat study used high-performance liquid chromatography (HPLC) to quantify intracellular NAA in homogenized brain tissue and the results were similar to past human neuroimaging

studies; when comparing rats exposed to either a sham control procedure or mild-, moderate-, or severe TBI, the authors found that 48 hours post-injury NAA reduction is graded according to the extent of injury (26). Curiously, a third rat study looked at intracellular levels of NAA using 1H-MR spectroscopic monitoring and found levels abruptly spiked ipsilateral to the contusion with a simultaneous reduction in NAA on the contralateral side; this suggests that NAA changes may differ by location and proximity to the injury site, warranting further evaluation in humans (47).

While reductions in *intracellular* NAA assessed using neuroimaging are well-established, as summarized in a recent review (48), there remains a gap in the knowledge surrounding the mechanism and meaning of reduced NAA levels in neuroimaging after TBI (42,46). The present study represents an early attempt at addressing these knowledge gaps, as these findings of elevated extracellular NAA measured in CSF being inversely correlated with GOS and positively correlated with DRS. Though the relationship remains to be clarified, it is plausible that severely damaged neurons may release NAA *extracellularly* into the CSF; these findings warrant follow up in future studies. For example, any consequences of extracellular NAA remain to be determined. Moreover, there remains a need to examine the concordance of changes in NAA compared, using ratios, to other brain metabolites (e.g. lactate, choline, creatinine) disrupted in neuroimaging studies (34,49–54) with CSF levels.

Another factor that may contribute to NAA changes after injury is the time point at which levels are evaluated. In the present study, all NAA levels were evaluated acutely within the first week of injury. A past clinical study found NAA in extracellular fluid spiked early after injury and were lower than non-TBI controls by day 4 (38). In this exploratory pilot study, different patterns of NAA levels emerged over time, within individuals, including some that stabilized over time, but sample sizes were too low to perform formal trajectory analyses.

Several past studies that used neuroimaging to evaluate NAA levels acutely (i.e. during the first week of TBI), found reduced levels (37,54–56). In one long-term study, lower concentrations of NAA and other brain metabolites at 1–3 years post-injury were seen in individuals with more severe TBI (i.e. lower GCS) at the time of initial injury, and levels were lower in TBI individuals when compared to orthopedically-injured controls (53). In this study, long-term NAA levels in the medial frontal gray matter were also positively correlated with skills related to school readiness and spelling (53). Interestingly, one study found that during the semi-acute post-TBI period partial normalization of NAA levels occurred (57).

Overall, there remains a need for additional exploration of how NAA levels change in response to TBI and the relationship between levels and clinical outcome. This study makes a novel contribution to the literature by studying the relationship between CSF levels and functional outcomes. Better functional outcomes, assessed using the GOS and DRS, was found in individuals with lower acute CSF NAA levels after TBI.

Limitations of This Study

This exploratory pilot study is limited by a small sample size. The sample excluded pediatric patients and was predominately comprised of male Caucasians recruited from a single

geographic region; thus, the generalizability of these findings is limited. Replication in independent samples drawn from different geographic regions is needed. Moreover, the small sample may have been underpowered to detect additional relationships that may have been significant in a larger sample. It is unlikely that the results would have remained significant after correction for multiple testing; larger samples with sufficient power are needed to confirm the associations reported here after the application of post hoc corrections as well as determine if NAA levels provide additional prognostic value beyond information provided by GCS or CT scan.

The present sample is also restricted to only severe TBI; thus, the relationship between NAA levels and outcomes after mild and moderate TBI remain to be explored. Likewise, the extensive functional deficits characteristic of severe TBI limit the nature of outcome measures that can be assessed to gross functional outcomes. Evaluating patients with mild- and moderate- TBI for NAA levels would afford an opportunity to include additional experimental endpoints (e.g. performance-based measures of cognition, memory, mood). Further clarification of the mechanism of the increased CSF levels reported here is also needed, as is formal evaluation of how CSF levels relate to neuroimaging findings. Still, this pilot study represents an important contribution to our understanding of the relationship between NAA levels in CSF and patient outcomes after severe TBI and adds to the evidence that can be built upon in future studies.

Conclusion

This exploratory pilot study suggests that lower NAA in CSF was found in individuals with better functional outcomes, assessed using the GOS and DRS, out to 24 months post-injury. These findings add to a growing body of neuroimaging evidence that NAA levels and ratios of NAA to other metabolites are reduced both acutely and chronically after TBI. Still considering the small sample size and lack of statistical control, these findings remain to be replicated in larger studies that are adequately powered to detect associations between NAA levels and other performance-based neuropsychological measures, and evaluate concordance with neuroimaging findings. This line of inquiry may be useful to predicting prognosis in patients with TBI so that targeted interventions can be pursued.

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Declarations of interest

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Figure 1. Inverse correlation between concentration of NAA in the CSF and score on the GOS suggesting greater disability at 3-, 6-, 12- and 24- months post-TBI in participants with higher acute extracellular NAA levels.

Figure 2. Positive correlation between concentration of NAA in the CSF and score on the DRS suggesting greater disability at 3-, 6-, 12- and 24- months post-TBI in participants with higher acute extracellular NAA levels.

Table 1

Correlation between NAA concentrations in the CSF and scores on the Glasgow Coma Scale (GCS) and Glasgow Outcomes Scale (GOS).

Variable	GCS		3 mo GOS		6 mo GOS		12 mo GOS		24 mo GOS	
	rho	p	rho	p	rho	p	rho	p	rho	p
Average [NAA] (<i>n</i> =26–28)	−0.432	0.022 *	−0.488	0.010 *	−0.403	0.041 *	−0.504	0.007 **	−0.567	0.002 **
1 day post-TBI [NAA] (<i>n</i> =16–17)	−0.217	0.404	−0.383	0.129	−0.319	0.228	−0.382	0.130	−0.537	0.026 *
2 days post-TBI [NAA] (<i>n</i> =17)	−0.368	0.146	−0.551	0.022 *	−0.493	0.044 *	−0.526	0.030 *	−0.526	0.030 *
3 days post-TBI [NAA] (<i>n</i> =17–18)	−0.669	0.002 **	−0.412	0.089	−0.331	0.194	−0.392	0.107	−0.427	0.077
4 days post-TBI [NAA] (<i>n</i> =16–17)	−0.213	0.412	−0.597	0.015 *	−0.530	0.035 *	−0.674	0.004 **	−0.666	0.005 **

* $p < 0.05$

** $p < 0.01$

Correlation between NAA concentrations in the CSF and dichotomized scores on the Glasgow Coma Scale (GCS= 3–5 vs. 6–8) and Glasgow Outcomes Scale (GOS= 1–2 vs. 3–5).

Table 2

Variable	GCS = 3–5 vs. 6–8		3 mo GOS = 1–2 vs. 3–5		6 mo GOS = 1–2 vs. 3–5		12 mo GOS = 1–2 vs. 3–5		24 mo GOS = 1–2 vs. 3–5	
	r _{pb}	p	r _{pb}	p	r _{pb}	p	r _{pb}	p	r _{pb}	p
Average [NAA] (n=27–28)	–0.278	0.152	–0.521	0.005***	–0.532	0.005***	–0.473	0.013*	–0.506	0.007***
1 day post-TBI [NAA] (n=16–17)	–0.217	0.402	–0.465	0.060	–0.514	0.042*	–0.409	0.103	–0.487	0.047*
2 days post-TBI [NAA] (n=17)	–0.212	0.413	–0.540	0.025*	–0.518	0.033*	–0.428	0.087	–0.411	0.101
3 days post-TBI [NAA] (n=17–18)	–0.517	0.028*	–0.437	0.070	–0.487	0.047*	–0.389	0.111	–0.475	0.046*
4 days post-TBI [NAA] (n=16–17)	0.064	0.809	–0.571	0.021	–0.617	0.011*	–0.539	0.031*	–0.594	0.015*

* p<0.05

** p<0.01

Table 3

Correlation between NAA concentrations in the CSF and scores on the Disability Rating Scale (DRS).

Variable	3 mo DRS		6 mo DRS		12 mo DRS		24 mo DRS	
	rho	p	rho	p	rho	p	rho	p
Average [NAA] (<i>n</i> =26–27)	0.438	0.022 *	0.424	0.031 *	0.507	0.007 *	0.549	.003 **
1 day post-TBI [NAA] (<i>n</i> =16–17)	0.331	0.195	0.227	0.398	0.444	0.074	0.478	0.052
2 days post-TBI [NAA] (<i>n</i> =17)	0.529	0.029 *	0.510	0.036 *	0.501	0.041 *	0.546	0.023 *
3 days post-TBI [NAA] (<i>n</i> =17–18)	0.352	0.152	0.362	0.153	0.379	0.120	0.427	0.077
4 days post-TBI [NAA] (<i>n</i> =16)	0.595	0.015 *	0.536	0.032 *	0.644	0.007 **	0.643	0.007 **

* $p < 0.05$

** $p < 0.01$

Table 4

Correlation between NAA concentrations in the CSF and dichotomized scores on the Disability Rating Scale (DRS= 0–18 vs. 19–30).

Variable	3 mo DRS = 0–18 vs. 19–30		6 mo DRS = 0–18 vs. 19–30		12 mo DRS = 0–18 vs. 19–30		24 mo DRS = 0–18 vs. 19–30	
	r _{pb}	p	r _{pb}	p	r _{pb}	p	r _{pb}	p
Average [NAA] (<i>n</i> =26–27)	0.454	0.017 *	0.500	0.009 **	0.521	0.005 **	0.473	0.013 *
1 day post-TBI [NAA] (<i>n</i> =16–17)	0.465	0.060	0.436	0.091	0.465	0.060	0.409	0.103
2 days post-TBI [NAA] (<i>n</i> =17)	0.438	0.079	0.540	0.025 *	0.540	0.025 *	0.428	0.087
3 days post-TBI [NAA] (<i>n</i> =17–18)	0.283	0.255	0.397	0.115	0.437	0.070	0.389	0.111
4 days post-TBI [NAA] (<i>n</i> =16)	0.529	0.035 *	0.571	0.021 *	0.571	0.021 *	0.539	0.031 *

*
p<0.05

**
p<0.01