

Summer 8-15-2015

Relationship between Serum Biomarkers and Three-Month Outcomes following Pediatric Traumatic Brain Injury (TBI)

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Relationship between Serum Biomarkers and Three-Month Outcomes

following Pediatric Traumatic Brain Injury (TBI)

by

Alicia Leanne Janos, M.A.

A dissertation presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

August 2015

St. Louis, Missouri

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Acknowledgements

This work represents the culmination of many years of graduate school, which would not have been possible without the love, support, and wisdom of my family, friends, and colleagues.

I would like to express my deepest gratitude to Dr. Desirée A. White, without whom this work would not have been feasible. Thank you for guiding me through research and providing emotional support during challenging times. You have molded me into a more confident clinician and researcher and I will be forever grateful to you.

Thank you to Drs. Michael Strube, Denise Head, and Deanna Barch for your support and guidance over the past five years. I can only hope to be half as brilliant as you.

Special thanks to the Washington University Interface of Psychology, Neuroscience, and Genetics (IPNG) Training Program and the APA Division 40 Society for Clinical Neuropsychology Dissertation Award for funding.

Many thanks to Suzin Blankenship, our incredible lab manager and guru of data. I promise to never again ask you a word generation scoring question. Thank you to Dr. Jose A. Pineda and Tina Day for help with data collection.

A warm thank you to Sydney Ariagno, an exceptional undergraduate student who provided timely help with data collection and entry. Best of luck in medical school and with all of your future endeavors.

My sincerest gratitude to Bobby Middleton for his unwavering love and support when I needed it most. Thank you for standing by me for seven years, delighting in my accomplishments and consoling me during hardships. You have been instrumental in guiding me through my graduate school.

Thank you, Dad, for urging me to transfer to Cornell University where I discovered my passion for neurobiology and psychology. Through baking soda volcanos, in-depth physics conversations, and “take your daughter to work” days, you taught me the joys of science and the importance of hard work. I look forward to poking you at future conferences!

What to say to the woman who inspires me to be strong, independent, and always curious. Thank you to my #1 fan, my mother, whom I can always rely on for guidance and comfort. I continue to be amazed by your unending knowledge base and your ability to help me through any situation. Thank you for editing countless reports, manuscripts, and internship essays. I owe you everything.

Mom, Dad... I love you both and dedicate this dissertation to you.

Abstract of the Dissertation

Relationship between Serum Biomarkers and Three-Month Outcomes
following Pediatric Traumatic Brain Injury (TBI)

by

Alicia Leanne Janos

Doctor of Philosophy in Psychology

Washington University in St. Louis, 2015

Professor Desirée A. White, Chair

With more than 475,000 cases annually, traumatic brain injury (TBI) is the leading cause of morbidity and mortality in children (Langlois, Rutland-Brown, & Thomas, 2005). Promising new tools for the prediction of functional outcomes following pediatric TBI are biomarkers of brain injury that can be detected in blood serum. The most commonly studied biomarkers, S100 β , neuron-specific enolase (NSE), and myelin basic protein (MBP), have myriad limitations which preclude their use in clinical care (Geyer, Ulrich, Gräfe, Stach, & Till, 2009; Giacoppo et al., 2012; Savola et al., 2003). In the present study, serum concentrations of two novel biomarkers of brain injury (i.e., ubiquitin carboxy-terminal hydrolase-L1, UCH-L1; glial fibrillary acidic protein, GFAP) were collected 24 hours following severe TBI in 30 children aged 1 month to 17 years. These 24-hour biomarkers were examined in relation to functional outcomes 3 months following TBI. Functional outcomes reflected global, intellectual (IQ), and neuropsychological (processing speed, working memory, episodic memory, executive function) function. Results indicated that 24-hour GFAP was significantly and negatively related to global outcome, whereas 24-hour UCH-L1 was significantly and negatively related to intellectual

function and processing speed. Although not statistically significant, relationships with medium effects sizes were identified between UCH-L1 and executive function, as well as between GFAP and working memory. These results indicate that 24-hour serum UCH-L1 and GFAP are of value in predicting functional outcomes 3 months following severe pediatric TBI.

Introduction

Pediatric TBI

Traumatic brain injury (TBI), broadly defined as a non-congenital, non-degenerative, acquired brain injury, is a significant public health concern. Data collected from hospital admissions between 1995 and 2001 indicate that approximately 475,000 children are treated annually for TBI, with 2,685 cases resulting in death, 37,000 requiring hospitalization, and 435,000 involving emergency department visits (Langlois et al., 2005). Due to an underreporting of symptoms and the difficulty in determining the number of children seeking treatment outside of hospital settings, the sum of these figures is likely an underestimate of total pediatric TBI.

In addition to associated medical sequelae, TBI may profoundly affect outcomes such as cognitive function (Allen et al., 2010; Crowe, Catroppa, Babl, & Anderson, 2012), social, emotional, and behavioral function (Ganesalingam et al., 2011), and overall quality of life (Limond, Dorris, & McMillan, 2009). In the past it was believed that TBI in children was associated with better functional outcomes than in adults due to greater brain plasticity and resilience, but it is now recognized that younger age at injury is associated with poorer outcomes (Anderson, Catroppa, Godfrey, & Rosenfeld, 2012; Spinella et al., 2003). Skills that are not fully developed at the time of injury are at greatest risk of disruption (Catroppa & Anderson, 2011), whereas skills that are established prior to injury are relatively spared (Anderson & Catroppa, 2005; Nadebaum, Anderson, & Catroppa, 2007). In addition, stronger pre-injury cognitive function (e.g., higher IQ), higher socioeconomic status, and healthier family function have been associated with better functional outcomes following pediatric TBI (Anderson & Catroppa, 2005; Anderson et al., 2012).

Rapid and accurate assessment of children with TBI is essential for diagnosis, classification, prognostication, and treatment. At present, a combination of findings from medical history, neurological examination, clinical scales (e.g., Glasgow Comma Scale, GCS), and neuroimaging (Bettermann & Slocomb, 2012) is used in clinical assessment. There are, however, limitations to this approach, especially in terms of predicting functional outcomes (Berger et al., 2002). In addition, prediction of functional outcomes in children with TBI is particularly challenging because ongoing developmental changes are occurring within the context of disrupted brain structure and function.

Biomarkers of brain injury are promising tools for improving the prediction of functional outcomes. As defined by the National Institutes of Health (Biomarkers Definitions Working Group, 2001), a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Ideal biomarkers of brain injury should be brain-specific and released soon after brain damage, with predictable relationships between biomarker concentration and degree of brain injury (Bakay et al., 1983).

Biomarkers can be found in biofluids such as urine, cerebrospinal fluid (CSF), and blood serum. Serum biomarkers have been studied most often in pediatric TBI due to their availability and ease of collection (Friess, Kilbaugh, & Huh, 2012). Serum analyses can be completed within 45 minutes using commercially available assays that require only 0.25 mL of blood. Therefore, serum biomarkers are relatively rapid and inexpensive tools with potential as sensitive and specific predictors of functional outcomes (Berger et al., 2002).

Serum Biomarkers of Brain Injury

Studies of biomarkers of brain injury have examined a number of proteins, enzymes, protein degradation products, cytokines, and micro RNAs (for a review, see Bettermann & Slocomb, 2012). Research investigating such biomarkers in pediatric populations, of which there is a great paucity, is needed for a number of reasons. For example, the developmental changes that occur in these biomarkers are very poorly delineated, and there is no information regarding developmental changes in serum biomarkers of brain injury following pediatric TBI. In addition, as detailed below, the three most commonly-studied biomarkers, S100 β , neuron specific enolase (NSE), and myelin basic protein (MBP), all have limitations precluding their use in clinical care. Given the limitations of these previously investigated biomarkers, the present study focused on two novel biomarkers, ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), which show great promise in terms of sensitivity, specificity, and prognostication of outcomes following pediatric TBI.

S100 β . The most extensively studied biomarker, S100 β , is a calcium-binding protein with a low molecular weight that is produced and released primarily by astrocytes in the central nervous system (CNS). Serum S100 β concentrations do not vary in healthy adults after the age of 20 years (Portela et al., 2002). In healthy children, however, age- and sex-dependent changes in S100 β are characterized by a rapid decrease from birth to 7 years, an increase from 7 to 13 years, and a subsequent decrease from 14 to 15 years, with generally higher concentrations in females (Gazzolo et al., 2003). As these findings demonstrate, extrapolating from adult populations precludes a thorough understanding of serum biomarkers in children (Berger, Beers, Papa, & Bell, 2012a).

With regard to TBI, increases in serum S100 β have been identified in adults (Kovesdi et al., 2010) and children (Babcock, Byczkowski, Mookerjee, & Bazarian, 2012; Piazza et al., 2007) following TBI, and higher concentrations have been associated with more severe TBI. Serum S100 β , however, is not a reliable diagnostic indicator of TBI due to a number of limitations, including inadequate specificity. For example, elevations in S100 β can occur following extracranial trauma such as abdominal injury or long bone fracture, which often co-occur with TBI (Pelinka et al., 2003; Savola et al., 2003). In addition, because S100 β has a serum half-life of only 60 to 120 minutes, increases in S100 β are transient, with only severe cases exhibiting detectable concentrations 12 hours after injury (Berger et al., 2002).

Neuron-Specific Enolase. NSE, the γ - γ and α - γ dimers of enolase, is a stable glycolytic enzyme primarily located in the cytoplasm of neurons. Studies have reported increases in NSE following TBI in adults (Kovesdi et al., 2010) and children (Bandyopadhyay, Hennes, Gorelick, Wells, & Walsh-Kelly, 2005; Beers, Berger, & Adelson, 2007), with higher concentrations associated with more severe TBI. Similar to S100 β , there are several limitations which preclude the use of NSE as a brain-specific biomarker. Although NSE indicates functional damage to neurons, it is also found in adipose tissue, smooth muscle, platelets, erythrocytes, and all peripheral and central neuroendocrine cells. Thus, increases in NSE can be indicative not only of brain damage but also damage to other types of tissue.

Myelin Basic Protein. MBP is a lesser studied brain biomarker that plays an important role in the myelination of neurons in the CNS. Unlike S100 β and NSE, MBP rarely increases immediately following brain injury, as serum concentrations peak 48 to 72 hours after injury and can remain elevated for up to 2 weeks (Giacoppo et al., 2012; Menascu, Brezner, Tshechmer, & Rumeny, 2010). As such, this biomarker is of limited use in the acute stages of brain injury

(Beers et al., 2007; Berger et al., 2007). In addition, the use of MBP as a sole marker of TBI is limited by its lack of specificity; as a marker of demyelination, elevations in MBP can reflect other disease processes such as Alzheimer's disease and multiple sclerosis (Bettermann & Slocumb, 2012).

Ubiquitin Carboxy-Terminal Hydrolase-L1. UCH-L1 is a novel candidate biomarker of neuronal injury which, unlike S100 β , NSE, and MBP, is highly abundant in and specific to brain tissue, with only minor expression in kidney, skeletal muscle, large intestine, and testes (Brophy et al., 2011). Because of its small, globular shape and low molecular weight, UCH-L1 passes through the blood-brain barrier and into biofluid as an intact protein with no detectable breakdown product, thus allowing for rapid detection in blood serum. Whereas serum MBP peaks 48 to 72 hours post-TBI, UCH-L1 increases within 6 hours in the CSF of adults following severe TBI and remains significantly elevated for at least 168 hours after injury (Papa et al., 2010). Studies have also shown that UCH-L1 is significantly elevated in children with moderate and severe TBI, although children with mild TBI did not exhibit increased UCH-L1, perhaps reflecting a lack of neuronal or axonal injury or insensitivity of the assay to mild trauma (Berger et al., 2012b).

Glial Fibrillary Acidic Protein. GFAP is a small monomeric intermediate filament protein found in the astroglial skeleton. It is located in both the white and gray matter of the brain and is strongly upregulated during astrogliosis (Pelinka et al., 2004). GFAP is not found outside the CNS and is believed to indicate cell destruction. CSF (0.016-0.163 ng/mL; Rosengren et al., 1992) and serum (0.07 ng/mL; Savage et al., 2011) concentrations of GFAP in healthy children have been found to be low. The first study to examine GFAP in children with

severe TBI reported elevated serum and CSF GFAP within 24 hours of hospital admission, with gradually decreasing concentrations over 7 and 10 days, respectively (Fraser et al., 2011).

Serum Biomarkers as Predictors of Outcomes following Adult TBI

There is a general paucity of information regarding relationships between biomarkers of brain injury and functional outcomes (Kovesdi et al., 2010) following TBI. That said, S100 β , the most extensively studied biomarker, appears to reliably predict global outcome in adults with severe TBI (Berger, Adelson, Richichi, & Kochanek, 2006a), with increased serum concentrations associated with poorer scores on the Glasgow Outcome Scale (GOS; see Appendix A for GOS ratings; for a review, see Kovesdi et al., 2010). Findings in mild TBI have been mixed, with some studies reporting associations between increased S100 β and poorer neuropsychological and return to work outcomes (Herrmann et al., 2001; Stranjalis et al., 2004; Waterloo, Ingebrigsten, & Romner, 1997) and other studies failing to identify relationships with outcomes (de Bousard et al., 2005; Stapert et al., 2005). Studies of other common biomarkers of brain injury have had conflicting results that are most likely due to differences in participant inclusion and exclusion criteria and sample sizes.

Only three studies have investigated the novel biomarkers UCH-L1 and GFAP in relation to functional outcomes in adults. In the first study, which included a sample of 81 adults with severe TBI, higher 12-hour serum concentrations of UCH-L1 and GFAP were associated with more severe injury as assessed by the GCS (Mondello et al., 2011; see Appendix B for GCS ratings). In the second study of 41 adults with severe TBI, higher CSF concentrations of UCH-L1 were associated with greater injury severity, greater 6-week mortality, and poorer 6-month outcome on the GOS (Papa et al., 2010). Finally, an investigation of 92 adults with severe TBI showed that higher GFAP was related to poorer 3-month outcome on the GOS (Pelinka et al.,

2004). However, none of these studies examined relationships between either UCH-L1 or GFAP and more refined measures of outcome (e.g., neuropsychological function) that may be of greater relevance to rehabilitation and long-term function following TBI.

Serum Biomarkers as Predictors of Outcomes following Pediatric TBI

Research investigating biomarkers of brain injury as predictors of functional outcomes following pediatric TBI is even more limited than the research conducted with adults. Investigations of the relationships between elevated serum S100 β and outcomes after pediatric TBI have produced conflicting findings (Berger, Beers, Richichi, Wiesman, & Adelson, 2007; Piazza et al., 2007; Spinella et al., 2003). For NSE, post-traumatic elevations have been associated with poorer global (GOS) (Bandyopadhyay, Hennes, Gorelick, Wells, & Walsh-Kelly, 2005; Beers, Berger, & Adelson, 2007) and intellectual (Bayley Scales of Infant Development or 2nd Edition and Stanford-Binet Intelligence Scale-IV) (Beers et al., 2007) outcomes. Higher peak MBP has also been correlated with poorer global outcome (GOS; Glasgow Outcome Scale - Extended Version, GOS-E; see Appendix C for GOS-E ratings), whereas higher peak and longer time-to-peak MBP have been associated with poorer intellectual function (Bayley Scales of Infant Development, 2nd Edition or Stanford-Binet Intelligence Scale-IV) (Beers et al., 2007; Berger et al., 2007).

Only two studies have been published in which UCH-L1 (Berger, Hayes, Richichi, Beers, & Wang, 2012b) and GFAP (Fraser et al., 2011), the novel biomarkers of interest in this study, have been examined in relation to global outcomes following pediatric TBI. Turning first to UCH-L1, Berger and colleagues (2012b) collected serum UCH-L1 as soon as possible after hospital arrival (median of 3.9 hours post-injury) from 39 children younger than 15 years of age who had sustained TBI. UCH-L1 concentrations were also obtained from 10 control children who presented to the hospital for a well-child examination or evaluation of an acute injury

without head trauma. The predictive validity of UCH-L1 was compared with that of S100 β , NSE, and MBP using concentrations that were previously published by the authors (Berger et al., 2005; Berger et al., 2006b). Outcome was assessed in the TBI group at hospital discharge and three to eight months after discharge using a dichotomized GOS (i.e., good outcome = GOS 1-2, poor outcome = GOS 3-5). Results revealed that higher UCH-L1 was associated with poorer global outcome.

Despite limitations stemming from the single measurement of UCH-L1 and dichotomization of the GOS, this study provides support for the use of UCH-L1 in the prediction of global outcome following pediatric TBI. Relationships between UCH-L1 and both injury severity and outcome were stronger than those for S100 β , NSE, and MBP, all of which are of limited clinical use. UCH-L1 is an especially promising candidate biomarker of brain injury given that it distinguished individuals with TBI from controls soon after injury, an acute stage during which mental status can be influenced by alcohol, drugs, and sedation (Papa et al., 2010).

With regard to GFAP, in children with severe TBI aged 2 to 17 years, Fraser and colleagues (2011) reported that higher serum GFAP obtained on the first day of hospital admission was correlated with poorer six month global outcome on the Pediatric Cerebral Performance Category Scale (PCPC; see Appendix D for PCPC ratings). Furthermore, a serum GFAP cutoff of 0.6 ng/mL predicted normal function to moderate disability (PCPC score 1-3) with 88% sensitivity and 71% specificity. Although this study was limited to one global outcome measure in children with severe TBI, the results clearly indicate that further study is warranted.

Limitations to Outcome Measures Studied

As is apparent from the discussion of the aforementioned studies, research on serum biomarkers as predictors of outcomes following pediatric TBI has largely employed global outcome

measures such as the GOS, GOS-E, Glasgow Outcome Scale – Extended, Pediatric Version (GOS-E Peds; see Appendix E for GOS-E Peds ratings), and PCPC. These measures are of limited utility because the ratings used are categorical, and in some studies the range of ratings has been further restricted through dichotomization. Many studies have also focused on mortality as the primary outcome, which has limited utility because it does not provide information to families or health care providers regarding recovery or intervention strategies. Overall, there is a great need for studies in which biomarkers are examined in relation to more refined outcomes based on continuous intellectual and neuropsychological scores rather than categorical global ratings.

At present, there are no studies in which biomarker concentrations have been related to neuropsychological function following pediatric TBI. This dearth of information is especially surprising given that there are many neuropsychological deficits associated with pediatric TBI. Pediatric TBI is associated with myriad impairments in social (Ganesalingam et al., 2011), emotional, behavioral, intellectual (Anderson & Catroppa, 2005; Crowe et al., 2012), academic (Kinsella et al., 1995), and cognitive (Catroppa & Anderson, 2011) function, the extent and recovery of which are heavily influenced by the severity of injury and age at injury. The most common cognitive sequelae following pediatric TBI include problems in attention (Robin, Max, Stier, Guenzer, & Lindgren, 1999), memory (Kinsella et al., 1995), processing speed (Kinsella et al., 1995), and executive function (Catroppa & Anderson, 2011).

Specific Aims of the Present Study

Given the paucity of information available regarding relationships between novel serum biomarker concentrations and functional outcomes in children with TBI, the current study was conducted with the following specific aims.

Specific Aim 1. The first aim was to examine the relationships between 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations and global outcome (i.e., GOS-E Peds) three months following pediatric TBI.

Specific Aim 2. The second aim was to examine the relationships between 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations and intellectual function as assessed by IQ (i.e., Wechsler Abbreviated Scale of Intelligence, WASI), as well as Verbal and Performance IQ, three months following pediatric TBI.

Specific Aim 3. The third aim was to examine the relationships between 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations and indices of neuropsychological function (i.e., processing speed, working memory, episodic memory, executive function) three months following pediatric TBI.

Specific Aim 4. The fourth aim was to conduct exploratory analyses to examine the possible interaction between age and 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations in relation to outcomes (i.e., GOS-E Peds, IQ indices, neuropsychological indices) three months following pediatric TBI.

Significance

This research will enhance our knowledge of pediatric TBI in several crucial ways. First, it is of importance to further our understanding of the relationships between 24-hour serum UCH-L1 and GFAP and global outcome three months following pediatric TBI. Data collected from hospital admissions between 1995 and 2001 indicate that approximately 475,000 children are treated annually for TBI (Langlois et al., 2005). Current approaches for the diagnosis and classification of TBI (e.g., physical exam, CT scan, GCS) suffer from a number of limitations, including insufficient prediction of outcome (Berger et al., 2002). A better understanding of the

relationships between novel serum biomarker concentrations and global outcome may aid in the development of more objective, reliable methods for predicting global outcome.

Second, this research will facilitate a better understanding of the relationships between 24-hour serum UCH-L1 and GFAP concentrations and intellectual and neuropsychological function three months following pediatric TBI. Serum biomarkers may be of utility in predicting impairments in general intellect, processing speed, working memory, episodic memory, and executive function, thus aiding families and health care providers in making better-informed decisions in terms of rehabilitation, education, and occupational planning for children with TBI.

Finally, this research will provide important information regarding the possible interactions between age and 24-hour serum UCH-L1 and GFAP concentrations in predicting global, intellectual, and neuropsychological outcomes three months following pediatric TBI. Age at injury has been identified as a strong prognostic indicator, with younger injury age associated with poorer global outcome (Spinella et al., 2003). In addition, recent research indicates that cognitive abilities which are not fully developed are at greatest risk of disruption following brain injury (Catroppa & Anderson, 2011), whereas abilities that have reached maturity prior to injury tend to remain relatively intact (Anderson & Catroppa, 2005; Nadebaum et al., 2007). However, it remains to be determined whether age interacts with 24-hour serum UCH-L1 and GFAP concentrations to predict global, intellectual, or neuropsychological outcomes in children. This study will provide insight into the value of serum biomarkers as predictors of outcomes in children aged 1 month to 17 years and determine whether age and biomarker concentrations interact to predict outcomes.

Research Design and Methods

Participants

A total of 37 children were included in preliminary analyses for the study, all of whom were admitted to St. Louis Children's Hospital with a diagnosis of TBI. 24-hour serum biomarker concentrations (i.e., UCH-L1 and GFAP) were available for these 37 children, 33 of whom had severe TBI (defined as a GCS score < 9) and 4 of whom had mild TBI (defined as a GCS score > 12). For three children with mild TBI and three children with severe TBI, no functional outcome data were available three months post-injury due to failure to return for assessment; as such, biomarker data from these children were not included in final analyses. In addition, because the majority of children had severe TBI, only data from children with severe TBI were included in final analyses.

The final sample for data analyses included 30 children. Sample size varied across outcome measures due to factors such as participant refusal and physical limitations that precluded the completion of some measures. Sample size also varied because intellectual and neuropsychological assessments were conducted only with children between 6 and 17 years of age. Sample size ranged from 30 children for GOS-E Peds analyses to 11 children for executive function analyses. The sample size for GOS-E Peds analyses was consistent with that of pediatric TBI studies reporting medium to large effect sizes for correlations between biomarker concentrations and global outcomes. No studies have been published in which serum biomarkers have been examined in relation to intellectual and neuropsychological outcomes in children across the age range of the present study.

Demographic characteristics of the 30 children in the sample are presented in Table 1. Age at injury ranged from 1 to 214 months ($M = 125.5$, $SD = 73.5$). The sample comprised 60%

male and 20% non-Caucasian children. Regarding injury mechanism, 57% were motor vehicle accidents, 20% inflicted injuries, 13% pedestrian accidents, 7% falls, and 3% other injury mechanisms. Post-resuscitation GCS score ranged from 3 to 7 ($M = 4.4$, $SD = 1.6$). No child had a history of intellectual disability, learning disability, CNS disorder (e.g., cerebral palsy), or major medical disorder prior to TBI.

Table 1. Participant demographics (N=30).

Injury Age (mo)	Injury Mechanism	GCS	GOS-E Peds (3 mo)	Sex	Race
125	mva	3	4	male	white
54	mva	3	6	female	black
17	assault	6	1	female	white
183	mva	3	4	female	white
1	assault	4	6	male	white
175	mva	4	3	female	white
7	assault	5	1	male	white
134	fall	3	6	male	white
56	mva	6	4	male	black
149	pedestrian	3	5	female	black
214	mva	3	4	male	white
206	mva	6	6	female	white
160	pedestrian	3	3	male	black
119	pedestrian	3	2	male	black
1	assault	7	8	male	white
199	mva	5	6	female	white
39	assault	7	1	male	white
41	mva	3	2	female	white
139	mva	5	8	female	asian
117	mva	6	6	male	white
191	pedestrian	3	4	male	white
171	fall	3	6	male	white
191	mva	7	8	male	white
203	mva	3	1	female	white
202	mva	7	5	female	white
4	assault	3	1	male	white
204	mva	6	6	male	white
136	mva	3	6	male	white
138	other	7	8	male	white
190	mva	3	6	female	white

Notes: mo = months; GCS = Glasgow Coma Scale; GOS-E Peds = Glasgow Outcome Scale, Extended Pediatric Version; mva = motor vehicle accident.

Study Measures and Procedures

Approval to conduct this study was obtained from the Institutional Review Board for the Protection of Human Subjects at Washington University in St. Louis. 24-hour serum biomarker concentrations were determined and related to functional outcomes three months following pediatric TBI. Global outcome was assessed using the GOS-E Peds. Intellectual function (i.e., IQ) was assessed using the WASI or WASI-II. Neuropsychological function was measured using four indices reflecting the specific cognitive domains of processing speed, working memory, episodic memory, and executive function. Intellectual and neuropsychological evaluation required approximately three hours for completion.

Biomarker concentrations. The medical management of children enrolled in the study was in accordance with standard clinical care at St. Louis Children's Hospital, with blood samples for biomarker analyses collected within the first 6 hours post-injury and every 24 hours thereafter for a maximum of 7 days. Blood samples were processed immediately and stored at -80°C until the time of biomarker analysis, at which point UCH-L1 and GFAP concentrations were measured in collaboration with Banyan Biomarkers, Inc.

Global outcome. Children underwent evaluations of global outcome three months following pediatric TBI using the GOS-E Peds (see Table 2 and Appendix E). The GOS-E Peds is a developmentally appropriate, structured scale used to classify younger patients, with categories ranging from death (score of 1) to upper good recovery (score of 8). The GOS-E Peds is sensitive to severity of injury and recovery over time as measured by parent ratings of daily living skills, intellectual function (Bayley Scales of Infant Development, 2nd Edition or Stanford-Binet-IV), and processing speed (Beers et al., 2012).

Table 2. Scores and category labels for the GOS-E Peds.

Score	Category
1	Death
2	Vegetative State
3	Lower Severe Disability
4	Upper Severe Disability
5	Lower Moderate Disability
6	Upper Moderate Disability
7	Lower Good Recovery
8	Upper Good Recovery

Intellectual function. The WASI and WASI-II are brief and reliable batteries comprising subtests designed to estimate intelligence in individuals aged 6 to 89 years and 6 to 90 years, respectively (Wechsler, 1999; Wechsler, 2011). Administration of two subtests (i.e., Vocabulary and Matrix Reasoning) permits estimation of Full Scale IQ, which was used to investigate relationships between 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations and general intellectual function three months following pediatric TBI. Administration of four subtests permits estimation of an individual’s Verbal and Performance IQs, which were used to investigate relationships between 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations and Verbal and Performance IQs three months following pediatric TBI.

Vocabulary. The Vocabulary subtest is a measure of expressive vocabulary knowledge (Wechsler, 1999). Children named pictures or provided oral definitions of words (e.g., bird, tradition, formidable). For all children, the examiner stated the following: “Now, I am going to ask you to tell me the meanings of some words. Listen carefully and tell me what each word means. Are you ready?” For children aged nine years and older, the examiner pointed to each word in a stimulus booklet while pronouncing it so that the child could read along. For children aged six to eight years, the stimulus booklet listing each word was not presented. There were a

total of 4 picture items and 38 word items. Testing was discontinued after five consecutive incorrect responses.

Similarities. The Similarities subtest is a measure of verbal concept formation and abstract verbal reasoning (Wechsler, 1999). Each child's task was to indicate how objects or concepts were alike (e.g., red versus blue, capitalism versus socialism). For children aged six to eight years, the examiner stated the following: "Ok, let's go on. I am going to show you some groups of pictures. For each group, I want you to tell me which picture in the bottom row is most like the pictures in the top row. Look at these pictures. Which one here is like these? Show me." For children aged nine years and older, the examiner stated the following: "Okay, let's go on. In this next section, I am going to read two words to you and I want you to tell me how they are alike. For example, if I ask, 'How are cookies and candy alike?' you would say, 'They are both snacks or food.'" Testing was discontinued after four consecutive incorrect responses.

Block design. The Block Design subtest is a measure of spatial visualization and abstract nonverbal reasoning (Wechsler, 1999). Each child used blocks to replicate two-color designs within a specified time limit, with the designs increasing in difficulty from simple designs requiring two blocks to more complicated designs requiring nine blocks. For all children, the examiner stated the following: "Now, I am going to ask you to make some designs. You see these blocks? They are all alike. On some sides they are all red; on some, all white; and on some, half red and half white." Testing was discontinued after three consecutive incorrect responses.

Matrix reasoning. The Matrix Reasoning subtest is a measure of nonverbal reasoning (Wechsler, 1999). Each child viewed a matrix from which a section was missing and completed it by indicating one of five response options. For all children, the examiner stated the following:

“Now we are going to do something different. I am going to show you some pictures. In each picture, there is piece missing. Look carefully at all the pieces of each picture and choose the missing piece from the five choices at the bottom of the page. There is only one correct answer to each problem. If you believe that more than one answer is right, choose the best one.” The examiner then administered two sample items and proceeded to the age-appropriate starting point. Testing was discontinued after four consecutive incorrect responses or four incorrect responses during five consecutive items.

Neuropsychological function. Neuropsychological testing included the Wechsler Intelligence Scale for Children – 4th Edition (WISC): Digit Span, Coding, and Symbol Search subtests; Wechsler Adult Intelligence Scale – 3rd Edition (WAIS): Digit Span, Digit Symbol-Coding, and Symbol Search subtests; Test of Memory and Learning – 2nd Edition (TOMAL): Digits Forward, Digits Backward, Object Recall, and Facial Memory subtests; California Verbal Learning Test – Children’s Version (CVLT-C); Developmental NEUROPSYCHOLOGICAL Assessment – 2nd Edition (NEPSY): Word Generation subtest; Clinical Evaluation of Language Fundamentals (CELF) – 3rd or 4th Edition: Concepts & Following Directions subtest; Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI); Simple Reaction Time, Go/No-Go, and Recognition Span computerized tasks. Parents completed the Behavior Rating Inventory of Executive Function (BRIEF) and the Conners Parent Rating Scale – Revised, Long Version questionnaires. Tests and questionnaires were age-specific such that children of different ages may have received different versions.

A subset of the tests listed above was used for the present study for several reasons. First, as shown in Table 3, combinations of variables from these tests comprised indices reflecting the neuropsychological domains of interest (i.e., processing speed, working memory, episodic

memory, executive function). For example, the CVLT-C and Facial Memory are clearly tests of episodic memory, representing verbal and non-verbal memory, respectively. Second, only for a subtest of the tests administered could the performance of children with TBI be compared with normative data. For example, for the working memory index, Digit Span Forward and Backward were selected because these subtests have normative data, whereas there are no normative data for experimental tasks such as Recognition Span. Third, more data were available for some tests due to the prioritization of tests within the battery; tests were prioritized because it was expected that some children would be unable to complete the entire test session. For example, for the episodic memory index, Facial Memory was selected over Object Recall because more children completed this test.

Table 3. Summary of neuropsychological indices.

Index	Tests Comprising Index	
Processing Speed	WISC or WAIS Symbol Search	WISC or WAIS Coding
Working Memory	WISC, WAIS, or TOMAL Digit Span Forward	WISC, WAIS, or TOMAL Digit Span Backward
Episodic Memory	CVLT-C List A total trials 1-5	TOMAL Facial Memory
Executive Function	CVLT-C Semantic Cluster Ratio	NEPSY Word Generation Semantic Category Words

Processing Speed Index. The Processing Speed Index from the WISC or WAIS, comprising summary scores from the Coding and Symbol Search subtests, was used to assess processing speed (Wechsler, 1997; Wechsler, 2003b). Preliminary analyses with data from our sample of 30 children with severe TBI showed that standard scores from Coding and Symbol Search were significantly correlated ($r = .70, p < .01$), justifying their aggregation as indicators of processing speed. In a study of 43 children aged 6 to 16 years with a history of moderate or severe TBI, the Processing Speed Index group mean difference produced the largest effect size,

with poorer performance in children with TBI than a healthy control group (Wechsler, 2003b). The variable of interest was the Processing Speed Index standard score.

WISC Coding. Coding is a core processing speed task which involves visual perception, visual scanning, and visual-motor coordination (Wechsler, 2003b). Each child copied symbols that were paired with simple geometric shapes (if aged six to seven years) or numbers (if aged eight years and older) within a specified time limit (Wechsler, 2003a). Using a key, the child drew each symbol in its corresponding shape or box. After an instruction and training phase, the examiner stated: “When I say go, do these the same way. Start here, go in order, and don’t skip any. Work as fast as you can without making mistakes until I tell you to stop. Are you ready?” Testing was discontinued when a child completed all of the rows or after 120 seconds, whichever came first. The variable of interest was the Coding standard score.

WAIS Digit Symbol-Coding. Digit Symbol-Coding is a core processing speed task in which children copied symbols that are paired with numbers. Using a key, children drew each symbol under its corresponding number. After an instruction and training phase, the examiner stated: “Now you know how to do them. When I tell you to start, you do the rest of them. Begin here and fill in as many squares as you can, one after the other without skipping any. Keep working until I tell you to stop. Work as quickly as you can without making mistakes. When you finish this line, go on to this one. Go ahead.” Testing was discontinued when a child completed all of the rows or after 120 seconds, whichever came first. The variable of interest was the Digit Symbol-Coding standard score.

WISC Symbol Search. Symbol Search is also a core processing speed task which involves visual discrimination and visual-motor coordination (Wechsler, 2003b). Children scanned a search group and indicated whether a target symbol (if aged six to seven years) or symbols (if

aged eight years and older) matched any of the symbols in the search group within a specified time limit. After an instruction and training phase, the examiner stated: “When I say go, do these the same way. Start here, go in order, and don’t skip any. Work as quickly as you can without making mistakes. When you finish the first page, go to the second page and the following page. Are you ready?” Testing was discontinued when a child completed all of the items or after 120 seconds, whichever came first. The variable of interest was the Symbol Search standard score.

WAIS Symbol Search. The Symbol Search subtest is a core processing speed task in which children visually scanned two groups of symbols (a target group and a search group) and indicated whether either of the target symbols matched any of the symbols in the search group. After an instruction and training phase, the examiner stated: “When I tell you to start, you do these the same way. Begin here and do as many as you can. When you finish the first page, go on to the next page and so on. Most people don’t do all of them. Work as quickly as you can without changing your answers. Don’t skip any items and don’t stop until I tell you to do so. Any questions? Okay. Ready? Begin.” Testing was discontinued when a child completed all of the items or after 120 seconds, whichever came first. The variable of interest was the Symbol Search standard score.

Working Memory Index. The working memory index was assessed using the Digit Span subtest (Digit Span total standard score) from the WISC or WAIS, comprising Digit Span Forward and Digit Span Backward tasks, or from the TOMAL Digits Forward and Digits Backward tasks. Preliminary analyses showed that standard scores from Digits Forward and Backward were significantly correlated ($r = .70, p < .01$). The variable of interest was the average of the standard scores from WISC or WAIS Digit Span Forward and Backward or TOMAL Digits Forward and Backward. Working memory has been shown to be impaired in

children with moderate to severe TBI compared to normative samples using the Digit Span Backward task (Conklin, Salorio, & Slomine, 2008).

WISC Digit Span Forward. Digit Span Forward is a measure of auditory short-term memory, attention, concentration, and sequencing skills (Wechsler, 2003b). Each child was instructed to repeat numbers in the same order as read aloud by the examiner (e.g., Examiner: 3-8-2; Child: 3-8-2). For all children, the examiner stated: “I am going to say some numbers. Listen carefully, and when I am through, say them right after me. Just say what I say” (Wechsler, 2003a). Digit Span Forward consists of eight items, each of which is divided into two trials of equal span. Testing was discontinued after incorrect responses on both trials of an item. The variable of interest was the Digit Span Forward standard score.

WAIS Digit Span Forward. For all children, the examiner stated: “I am going to say some numbers. Listen carefully, and when I am through, I want you to say them right after me. Just say what I say” (Wechsler, 1997). Digit Span Forward consists of eight items, each of which is divided into two trials of equal span. Testing was discontinued after incorrect responses on both trials of an item. The variable of interest was the Digit Span Forward standard score.

TOMAL Digits Forward. For all children, the examiner stated: “I’m going to say some numbers. Listen carefully, because when I’m done, I want you to say them just like I did” (Reynolds & Voress, 2007). Digits Forward consists of 15 items. Testing was discontinued when a child earned three or fewer points on each of two consecutive items after administration of items one through four. The variable of interest was the Digits Forward standard score.

WISC Digit Span Backward. Digit Span Backward is a measure of auditory short-term memory, attention, concentration, sequencing skills, and mental manipulation of information (Wechsler, 2003b). Each child was instructed to repeat numbers in the reverse order of that

presented by the examiner (e.g., Examiner: 3-8-2; Child: 2-8-3). For all children, the examiner stated: “Now I am going to say some more numbers, but this time when I stop, I want you to say them backward. If I say 8-2, what would you say?” (Wechsler, 2003a). The examiner administered an additional practice trial before proceeding to test items. Digit Span Backward consists of eight items, each of which is divided into two trials of equal span. Testing was discontinued after incorrect responses on both trials of an item. The variable of interest was the Digit Span Backward standard score.

WAIS Digit Span Backward. For all children, the examiner stated: “Now I am going to say some more numbers. But this time when I stop, I want you to say them backward. For example, if I say 7-1-8, what would you say?” (Wechsler, 1997). Digit Span Backward consists of seven items, each of which is divided into two trials of equal span. Testing was discontinued after incorrect responses on both trials of an item. The variable of interest was the Digit Span Backward standard score.

TOMAL Digits Backward. For all children, the examiner stated: “I’m going to say some numbers again, but this time when I finish, I want you to say the numbers backward. So if I said 1-2, what would you say?” (Reynolds & Voress, 2007). Digits Backward consists of 13 items. Testing was discontinued after a child earned three or fewer points on each of two consecutive items after administration of items one through four. The variable of interest was the Digits Backward standard score.

Episodic Memory Index. The episodic memory index was assessed using a measure of immediate verbal recall and a measure of immediate visual recognition memory. The variable of interest was the average of standard scores from CVLT-C recall for trials 1-5 and TOMAL Facial Memory. Preliminary analyses showed that standard scores from CVLT-C recall and

TOMAL Facial Memory were significantly correlated ($r = .53, p < .05$). Pediatric TBI has been associated with poorer verbal memory, as measured by recall on trials 1-5 of the CVLT-C (Warschawsky, Kay, Chi, & Donders, 2005), as well as poorer nonverbal visual memory (Allen et al., 2010).

CVLT-C trials 1-5. The immediate free recall portion of the CVLT-C was administered following standard administration procedures (Delis, Kramer, Kaplan, & Ober, 1994). Children were read the directions: “Let’s pretend you are going shopping on Monday. I’m going to read a list of things for you to buy. Listen carefully, because when I’m through, I want you to tell me as many of the things as you can. You can say them in any order – just say as many of them as you can. Are you ready?” Children then listened as the examiner read a list of 15 words (bananas, sweater, puzzle, jacket, grapes, blocks, watermelon, shorts, crayons, peaches, balloons, hat, strawberries, belt, marbles) aloud over 5 learning trials, with the words presented in the same order for each trial. After each trial, children were asked to freely recall as many words as possible. The variable of interest was the standard score for the total number of words correctly recalled across all five trials.

TOMAL Facial Memory. The Facial Memory subtest measures nonverbal, visual memory (Reynolds & Voress, 2007). Children were required to recognize and identify faces from a set of distracters comprising gray-scale photographs of faces of individuals of various ages, both sexes, and various ethnic backgrounds. The examiner began with a practice item, pointing to a picture and stating: “See this face?” After a five-second viewing period, the examiner turned the page and stated: “Put the chip on the person you saw.” For items with more than one face, instructions were modified by saying: “See these faces? Put the chips on the faces you saw.” Children were shown 7 pictures of faces and were allowed 5 seconds to view the first 4 stimulus pictures, 10

seconds for item 5, 15 seconds for item 6, and 20 seconds for item 7. The variable of interest was the Facial Memory standard score.

Executive Function Index. The executive function index was assessed by averaging standard scores from the CVLT-C semantic clustering variable and the NEPSY Word Generation total number of words correctly generated. Preliminary analyses showed that standard scores from the CVLT-C and NEPSY Word Generation were not significantly correlated, but the effect size for the correlation was medium ($r = .39, p < .12$). It is likely that small sample size (11 children with CVLT-C and Word Generation scores) prevented the correlation with medium effect size from reaching statistical significance. As such, the aggregate executive function variable was retained for further analyses. Executive function, as measured using a word fluency task, has been shown to be more impaired in children with severe TBI than in children with mild TBI or healthy controls (Levin, Song, Ewing-Cobbs, Chapman, & Mendelsohn, 2001).

CVLT-C semantic clustering. Semantic clustering is a measure of the extent to which a child has “actively imposed an organization on the list of words according to shared semantic features. . . a kind of ‘mental filing system’” (Delis et al., 1994, p. 32). The semantic cluster index refers to the ratio of observed to expected correct cluster scores based on the clustering of words from the same semantic categories on Trials 1-5 of the CVLT-C. A score of 1 indicates chance clustering performance, whereas scores above and below 1 indicate above-chance or below-chance clustering performance, respectively. The observed correct semantic cluster score refers to the degree to which the child utilizes a semantic strategy (e.g., consecutively recalling grapes and bananas from the semantic category fruits) in recalling the list during each of the five free-recall trials. The expected correct semantic cluster score refers to the chance value of semantic clustering given the total number of words and number of different categories

represented in the child's recall during each of the five free-recall trials. The variable of interest was the chance-adjusted semantic clustering standard score for Trials 1-5.

NEPSY Word Generation semantic category total correct. Word Generation is a subtest that measures verbal productivity through the ability to generate words within specific categories. Because successful performance requires that children sustain attention, establish, maintain, and change response set based on semantic memory, and engage in monitoring and self-regulation to avoid repetitive responses, this task is considered a measure of executive function. Children were given semantic categories (i.e., animals, food and drinks) and asked to name as many items as possible in 60 seconds. Children were read the following directions for the animal category: "We want to see how many different animals you can name, like cat or dog. Say them as quickly as you can. Are you ready? Go." Children were read the following directions for the food and drink category: "Now, see if you can name some things you can eat or drink. Say as many different ones as you can, like pizza or milk. Do it quickly. Ready? Go." The examiner recorded the words in the order produced by children. The variable of interest was the semantic category standard score.

Data Analyses

For the most part, raw values for biomarker concentrations were used in data analyses. Similarly, raw values were used in analyses involving global outcome (i.e., GOS-E Peds). Standard scores ($M = 100$, $SD = 15$) based on normative data were used in analyses involving IQ indices, neuropsychological indices, and individual neuropsychological tests.

SPSS 22.0 Software (Chicago, IL) was used to conduct all analyses. Pearson correlation was the primary method used to examine the first three aims of the study, in which relationships between biomarker concentrations and functional outcomes were examined. Given the a priori hypotheses, one-tailed tests were used. Effect sizes were determined using the Pearson correlation coefficient, with 0.1 considered small, 0.3 considered medium, and 0.5 considered large (Cohen, 1988). Statistical rigor was increased by considering results significant only if $p < .05$ and effect size was either medium or large. Results were considered to represent notable trends if effect size was either medium or large.

For the fourth aim of the study, in which the possible interaction between age and biomarker concentrations was examined in relation to outcomes, hierarchical linear regression was used. The GOS-E Peds score, IQ, Verbal and Performance IQ, and four indices of neuropsychological function (i.e., processing speed, working memory, episodic memory, executive function) served as dependent variables in separate analyses for each biomarker. In all analyses, age at injury was entered in the first step as an independent variable, biomarker (UCH-L1 or GFAP) concentrations were entered in the second step, and the interaction between age at injury and biomarker concentrations (age at injury X UCH-L1 or age at injury X GFAP) was entered in the final step. To reduce multicollinearity, age at injury and biomarker concentrations were centered around the mean before creating the interaction terms.

Data were examined carefully in preparation for statistical analyses. For 4 of the 30 children in the study, the 24-hour serum GFAP concentration was above the range of the assay. As such, these four biomarker concentrations were recorded as 50 ng/mL, the upper limit of quantification for the GFAP assay. For one child, the 24-hour serum GFAP concentration was below the range of the assay. As such, this biomarker concentration was recorded as 0.03 ng/mL, the lower limit of quantification for the GFAP assay.

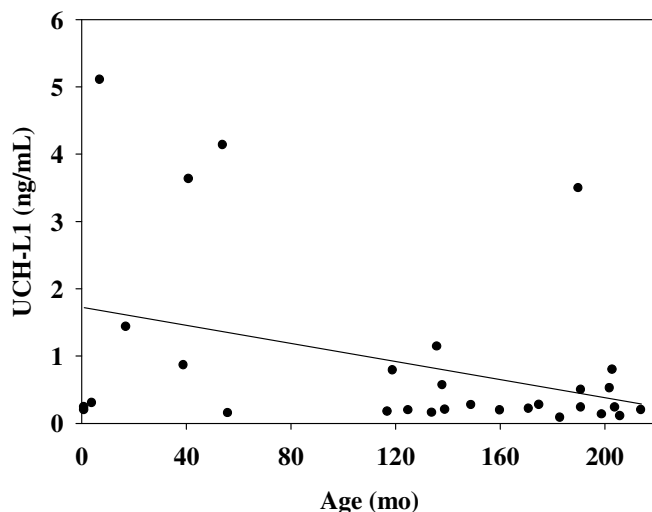
Results

Biomarker Concentrations

24-hour serum biomarker concentrations of UCH-L1 and GFAP were available for all 30 children in the study. UCH-L1 ranged from 0.08 ng/mL to 5.10 ng/mL ($M = 0.88$, $SD = 1.34$), whereas GFAP ranged from 0.03 ng/mL to 50.00 ng/mL ($M = 13.37$, $SD = 16.55$). As a group, biomarker concentrations were elevated in our sample of children with severe TBI compared with concentrations observed in typically developing children (Berger et al., 2012b; Fraser et al., 2011). The correlation between concentrations of UCH-L1 and GFAP was statistically significant, with a large effect size ($r = .54$, $p < .01$), indicating that higher UCH-L1 was associated with higher GFAP.

In addition, as shown in Figure 1, UCH-L1 was significantly correlated with age ($r = -.37$, $p < .05$), indicating that UCH-L1 decreased as age increased. It appears that the primary reason for this age-related finding is that some younger children have dramatically elevated UCH-L1 levels in comparison with older children. This is likely due to differences in injury mechanism, as the majority of younger children sustained inflicted injury (6/9), whereas the majority of older children sustained injury due to motor vehicle accidents (14/21). The correlation between GFAP and age ($r = -.29$, $p < .06$) was not significant.

Figure 1. UCH-L1 as a function of age.



Outcomes

The range, M , and SD for all functional outcome scores (as well as individual test scores that form outcome scores) are presented in Table 4. In terms of global outcome, GOS-E Peds scores ranged from 1 to 8 ($M = 4.6$, $SD = 2.3$). More specifically, 13% of the children had good recovery (GOS-E Peds = 7-8), 39% had moderate disability (GOS-E Peds = 5-6), 24% had severe disability (GOS-E Peds = 3-4), 7% were in a vegetative state (GOS-E Peds = 2), and 17% died (GOS-E Peds = 1).

Turning to outcomes indicative of intelligence, IQ ranged from 63 to 111 ($M = 88.9$, $SD = 14.3$), Verbal IQ ranged from 64 to 106 ($M = 87.4$, $SD = 13.1$), and Performance IQ ranged from 57 to 116 ($M = 89.0$, $SD = 20.0$). In comparison with normative samples, these standard scores reflect a broad range of ability across individual children, varying from extremely low to high average. At the group level, IQ, Verbal IQ, and Performance IQ all fell within the low average range.

With regard to neuropsychological outcome indices, standard scores for processing speed ranged from 53 to 100 ($M = 78.3$, $SD = 16.0$), working memory ranged from 55 to 110 ($M = 86.1$, $SD = 16.1$), episodic memory ranged from 63 to 114 ($M = 82.3$, $SD = 15.8$), and executive

function ranged from 65 to 118 ($M = 89.5$, $SD = 18.4$). As was the case for the IQ indices, these standard scores reflect a broad range of ability, varying from extremely low to high average. At the group level, working memory, episodic memory, and executive function fell within the low average range. Processing speed, however, was borderline, suggesting somewhat greater difficulty within this neuropsychological domain.

Table 4. Range, mean, and standard deviation for GOS-E Peds, IQ, Verbal and Performance IQ, neuropsychological indices, and neuropsychological test scores.

Outcome	Range	<i>M</i>	<i>SD</i>
GOS-E Peds (N=30)	1 – 8	4.6	2.3
IQ (N=15)	63 – 111	88.9	14.3
Vocabulary (n=15)	66 – 114	89.4	15.1
Matrix Reasoning (n=15)	55 – 117	88.7	19.6
Verbal IQ (N=13)	64 – 106	87.4	13.1
Vocabulary (n=15)	66 – 114	89.4	15.1
Similarities (n=13)	58 – 114	83.7	15.5
Performance IQ (N=13)	57 – 116	89.0	20.0
Matrix Reasoning (n=15)	55 – 117	88.7	19.6
Block Design (n=13)	58 – 123	88.7	20.4
Processing Speed (N=12)	53 – 100	78.3	16.0
Coding (n=12)	55 – 95	77.1	13.4
Symbol Search (n=13)	55 – 115	81.2	19.5
Working Memory (N=16)	55 – 110	86.1	16.1
Digit Span Forward (n=14)	65 – 115	86.1	17.1
Digit Span Backward (n=14)	65 – 110	88.6	14.5
Episodic Memory (N=12)	63 – 114	82.3	15.8
CVLT-C Trials 1-5 Recall (n=14)	55 – 112	77.0	21.8
Facial Memory (n=14)	70 – 115	88.6	14.1
Executive Function (N=11)	65 – 118	89.5	18.4
CVLT-C Semantic Cluster Ratio (n=14)	70 – 115	89.3	16.0
Word Generation (n=11)	55 – 120	87.3	26.7

Notes: Sample size for the working memory index was larger than sample sizes for the constituent tests because, for the two children who completed Digit Span from the WAIS-III, normative data were not available that separately reflected Digit Span Forward and Backward standard scores. Sample size for the episodic memory index was smaller than sample sizes for the constituent tests because two children completed CVLT-C recall but not Facial Memory and two children completed Facial Memory but not CVLT-C recall.

There were no significant relationships between age and functional outcome scores. There were, however, trends with medium effect sizes between age and Performance IQ ($r = -.45, p < .10$) and processing speed ($r = -.43, p < .10$). As shown in Figures 2 and 3, in each instance, outcome scores decreased as age increased.

Figure 2. Performance IQ as a function of age.

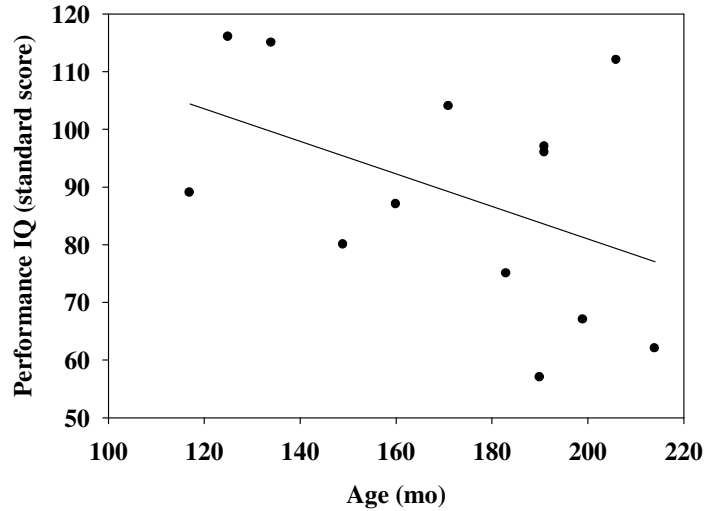
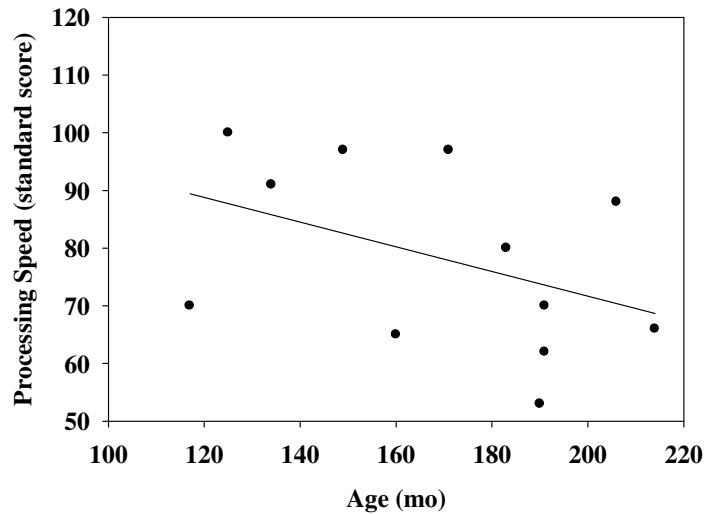


Figure 3. Processing speed as a function of age.



Specific Aims

For each specific aim, findings related to UCH-L1 are presented first, followed by findings related to GFAP.

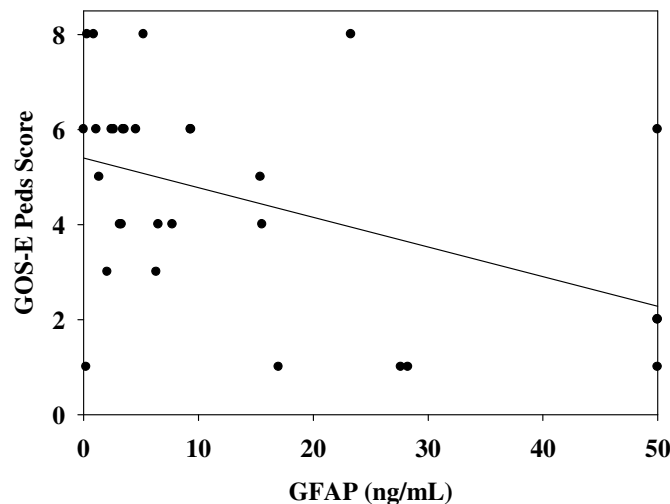
Specific Aim 1. As described earlier, the first aim of this study was to examine the relationships between 24-hour serum UCH-L1 and GFAP concentrations and global outcome (i.e., GOS-E Peds) three months following pediatric TBI. As shown in Table 5, the correlation between UCH-L1 and GOS-E Peds at three months post-injury ($r = -.27, p < .08$) was not statistically significant. The correlation between GFAP and GOS-E Peds at three months post-injury, however, was statistically significant with a large effect size ($r = -.53, p < .001$); as shown in Figure 4, GOS-E Peds decreased as GFAP increased.

Table 5. Correlations between 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations and outcomes.

<i>Outcome</i>	Biomarker	
	UCH-L1	GFAP
GOS-E Peds	-.27	-.53*
IQ	-.59*	-.13
Verbal IQ	-.38	-.16
Performance IQ	-.47	-.12
Processing Speed	-.53*	-.22
Working Memory	-.12	-.34
Episodic Memory	-.29	.16
Executive Function	-.47	-.24

Note: * = significant at $p < .05$ with medium or large effect size.

Figure 4. GOS-E Peds as a function of GFAP.



Hierarchical regression analyses were used to determine the degree to which GFAP predicted losses in GOS-E Peds. Specifically, unstandardized regression coefficients (B) showed that for every 1 ng/mL increase in GFAP, GOS-E Peds decreased by 0.073. Extrapolating from the mean GFAP concentration of children in our sample, GOS-E Peds decreased by 0.98 in relation to increased GFAP, which represents a downward shift of 1 GOS-E Peds category.

Specific Aim 2. The second aim of the study was to examine the relationships between 24-hour serum UCH-L1 and GFAP concentrations and IQ, as well as Verbal and Performance IQ, three months following pediatric TBI. As shown in Table 5, there was a significant correlation between UCH-L1 and IQ, with a large effect size ($r = -.59, p < .01$; see Figure 5); although not statistically significant, correlations between UCH-L1 and both Verbal ($r = -.38, p < .11$; see Figure 6) and Performance ($r = -.47, p < .06$; see Figure 7) IQ had medium effect sizes. In all instances, intellectual function was poorer as UCH-L1 increased.

In examining Figures 5 through 7, the UCH-L1 concentration of 3.49 ng/mL appears to be an outlier, but this is not the case when considered within the context of the entire sample of 30 children in the study. Recall that the mean and standard deviation across the entire sample were 0.88 and 1.34, respectively. As such, UCH-L1 concentrations would be considered outliers when greater than 4.90 ng/mL (i.e., 3 standard deviations from the group mean). In the sample, there were four children with UCH-L1 concentrations greater than 3.0 ng/mL. Of these children, one had died, one was in a vegetative state, and two had moderate disability; only one of the children with moderate disability was able to complete IQ assessment. We elected to retain data for this child because exclusion dramatically restricted the range of UCH-L1 and it was of interest to evaluate the influence of higher UCH-L1 values on the IQ indices.

Turning to GFAP, the correlations with IQ ($r = -.13, p < .33$), Verbal IQ ($r = -.16, p < .30$), and Performance IQ ($r = -.12, p < .36$) were not statistically significant.

Figure 5. IQ as a function of UCH-L1.

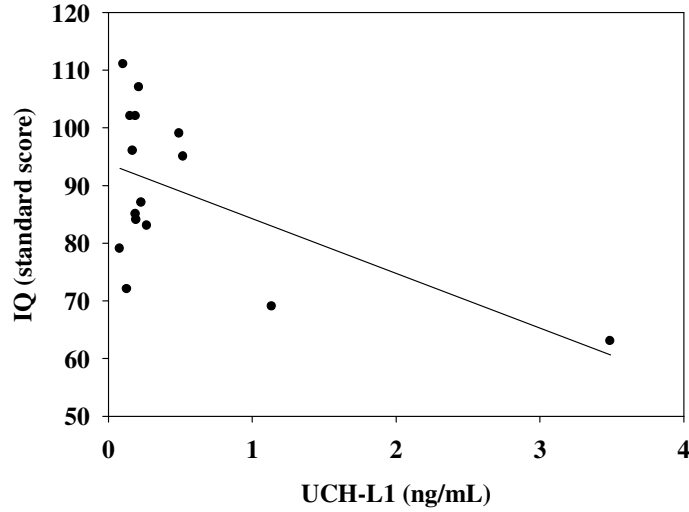


Figure 6. Verbal IQ as a function of UCH-L1.

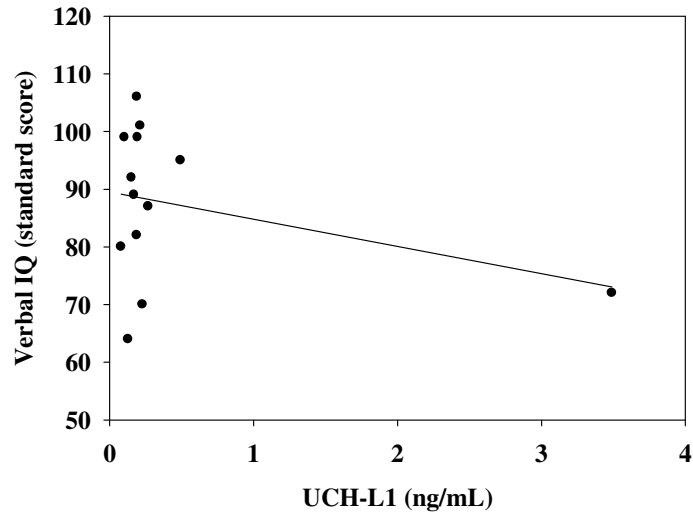
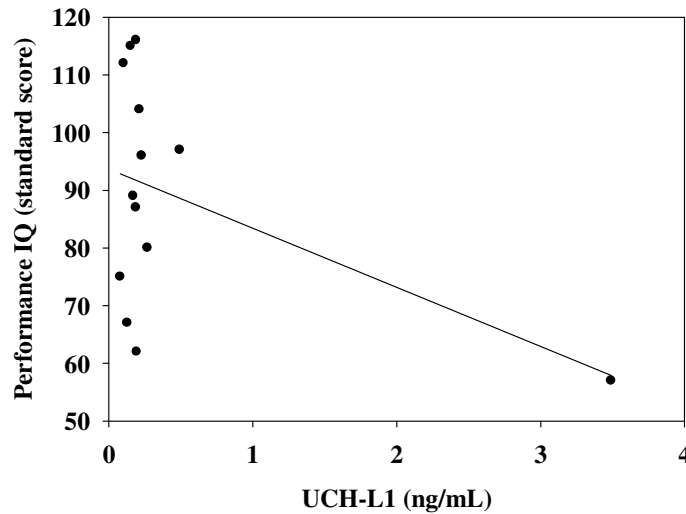


Figure 7. Performance IQ as a function of UCH-L1.



Hierarchical regression analyses were used to determine the degree to which UCH-L1 predicted losses in standard score points in IQ indices. Specifically, unstandardized regression coefficients (B) showed that for every 1 ng/mL increase in UCH-L1, standard scores for IQ, Verbal IQ, and Performance IQ decreased by 9.78, 5.38, and 10.23 points, respectively. Extrapolating from the mean UCH-L1 concentrations of children in our sample who received intellectual evaluation, standard scores for IQ, Verbal IQ, and Performance IQ decreased by 4.94, 2.45, and 4.65 points in relation to increased UCH-L1.

Specific Aim 3. The third aim was to examine the relationships between 24-hour serum UCH-L1 and GFAP concentrations and indices of neuropsychological function (i.e., processing speed, working memory, episodic memory, executive function) three months following pediatric TBI. As shown in Table 5, there was a significant correlation between UCH-L1 and processing speed, with a large effect size ($r = -.53, p < .05$; see Figure 8). Given that earlier analyses revealed a significant relationship between UCH-L1 and age and a trend for a relationship between processing speed and age, a post-hoc regression analysis was conducted in which processing speed was entered as the dependent variable, with age followed by UCH-L1 entered

as independent variables. After accounting for the contribution of age, although not statistically significant, a trend with a medium effect size remained for the relationship between UCH-L1 and processing speed ($r = -.44, p < .12$). In addition, although not statistically significant, the correlation between UCH-L1 and executive function had a medium effect size ($r = -.47, p < .08$; see Figure 9). Correlations between UCH-L1 and working memory ($r = -.12, p < .33$) and episodic memory ($r = -.29, p < .19$) were not significant.

Figure 8. Processing speed as a function of UCH-L1.

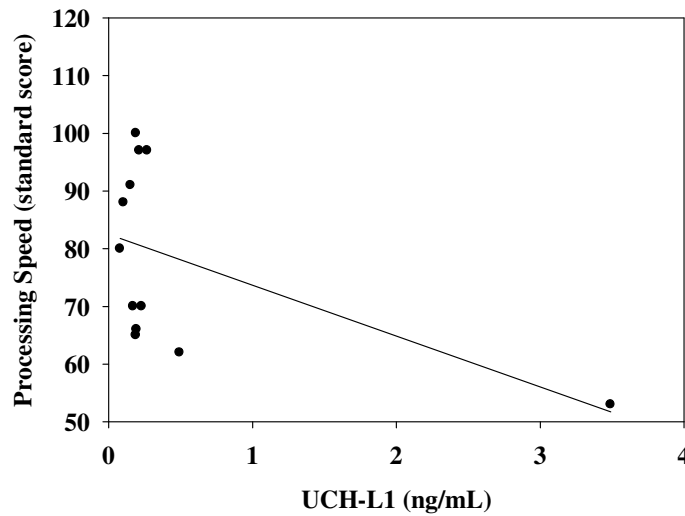
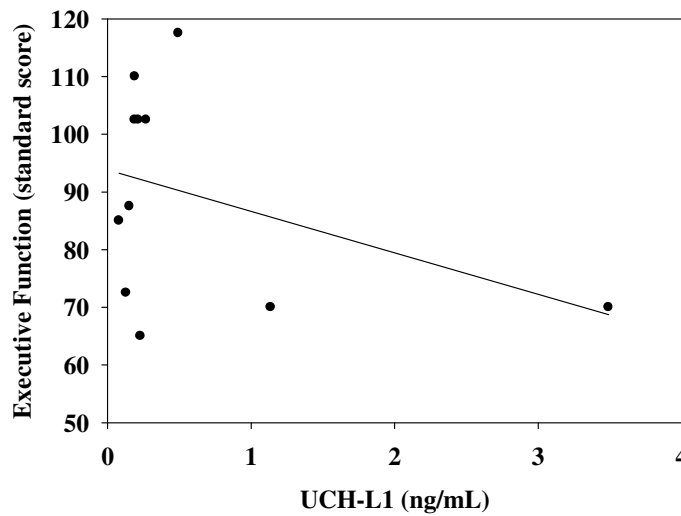
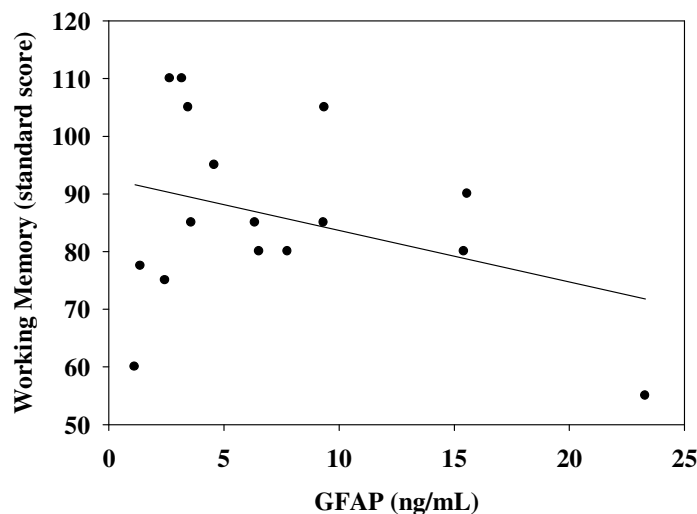


Figure 9. Executive function as a function of UCH-L1.



With regard to GFAP, although not statistically significant, the correlation between GFAP and working memory had a medium effect size ($r = -.34, p < .10$; see Figure 10). Correlations between GFAP and processing speed ($r = -.22, p < .25$), episodic memory ($r = .16, p < .32$), and executive function ($r = -.24, p < .25$) were not significant. For all findings with medium and large effect sizes, neuropsychological function was poorer as biomarker concentrations increased.

Figure 10. Working memory as a function of GFAP.



Hierarchical regression analyses were used to determine the degree to which UCH-L1 and GFAP predicted losses in standard score points in neuropsychological indices. Unstandardized regression coefficients (B) showed that for every 1 ng/mL increase in UCH-L1, standard scores for processing speed and executive function decreased by 8.81 and 8.57 points, respectively. Extrapolating from the mean UCH-L1 concentrations of children in our sample who received neuropsychological evaluation, standard scores for processing speed and executive function decreased by 4.24 and 5.13 points, respectively, in relation to increased UCH-L1. With regard to GFAP, unstandardized regression coefficient (B) showed that for every 1 ng/mL increase in GFAP, the standard score for working memory decreased by 0.9 points. Extrapolating

from the mean GFAP concentration of children in our sample who received neuropsychological evaluation, the standard score for working memory decreased by 6.49 points in relation to increased GFAP.

Additional analyses were conducted to examine relationships between individual neuropsychological test scores and 24-hour serum UCH-L1 and GFAP concentrations (see Table 6). Findings revealed significant correlations between UCH-L1 and Vocabulary ($r = -.50, p < .05$), Matrix Reasoning ($r = -.51, p < .05$), and Word Generation ($r = -.53, p < .05$), with large effect sizes; although not statistically significant, correlations between UCH-L1 and Block Design ($r = -.40, p < .09$), Coding ($r = -.45, p < .08$), Symbol Search ($r = -.40, p < .09$), Digit Span Backward ($r = -.32, p < .14$), and CVLT-C trial 1-5 recall ($r = -.37, p < .10$) had medium effect sizes. Correlations between UCH-L1 and Similarities ($r = -.27, p < .19$), Digit Span Forward ($r = .08, p < .40$), Facial Memory ($r = -.07, p < .41$), and CVLT-C semantic cluster ratio ($r = -.10, p < .37$) were not significant. Although no correlations between GFAP and neuropsychological test scores were statistically significant, correlations between GFAP and Coding ($r = -.37, p < .12$) and Digit Span Backward ($r = -.38, p < .10$) had medium effect sizes. For all findings with medium and large effect sizes, neuropsychological test performance was poorer as biomarker concentrations increased.

Table 6. Correlations between 24-hour serum biomarker (i.e., UCH-L1 and GFAP) concentrations and neuropsychological test scores.

Test	Biomarker	
	UCH-L1	GFAP
Vocabulary	-.50*	-.11
Matrix Reasoning	-.51*	-.10
Similarities	-.27	-.18
Block Design	-.40	-.09
Coding	-.45	-.37
Symbol Search	-.40	.00
Digit Span Forward	.08	-.20
Digit Span Backward	-.32	-.38
CVLT-C Trials 1-5 Recall	-.37	-.07
Facial Memory	-.07	.04
CVLT-C Semantic Cluster Ratio	-.10	-.12
Word Generation	-.53*	-.19

Note: * = significant at $p < .05$ with medium or large effect size.

Finally, Fisher's z transformation for dependent overlapping correlations was used to determine whether the significant correlations related to aims 1 through 3 (i.e., UCH-L1 and IQ and processing speed; GFAP and GOS-E Peds) were different. No result from these analyses reached statistical significance, suggesting that the strength of the correlations was similar.

Specific Aim 4. The fourth aim was to conduct exploratory regression analyses to examine the possible interaction between age and 24-hour serum UCH-L1 and GFAP concentrations in relation to outcomes (i.e., GOS-E Peds, IQ indices, neuropsychological indices) three months following pediatric TBI. As noted previously, both age at injury and biomarker concentrations were centered before use in regression analyses. Age at injury centered was entered in the first step of all analyses, followed by biomarker concentration centered, followed by the interaction between age at injury centered and biomarker concentration centered.

Because correlations between age at injury and outcomes, as well as correlations between biomarker concentrations and outcomes, were reported earlier, findings from the first two steps of the regression analyses are not reported here.

The interaction between age at injury centered and GFAP centered accounted for a significant proportion of the variance in episodic memory ($\Delta R^2 = .68$, $\Delta F(1, 8) = 19.26$, $\Delta p < .005$). In addition, there was a trend suggesting that the interaction between age at injury centered and GFAP centered accounted for a proportion of the variance in processing speed ($\Delta R^2 = .26$, $\Delta F(1, 8) = 3.91$, $\Delta p < .10$). To elucidate the nature of the interaction, standard scores for episodic memory (see Figure 11) and processing speed (see Figure 12) were plotted as a function of raw GFAP concentrations for older versus younger children (based on a median split on age). For both neuropsychological outcome indices, standard scores for older children decreased as GFAP increased. For younger children, however, standard scores increased as GFAP increased, which seems counterintuitive.

Figure 11. Episodic memory as a function of GFAP for younger and older children.

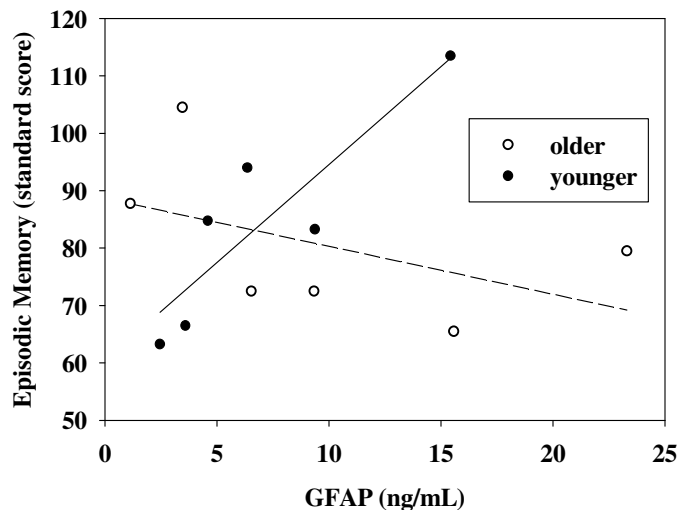
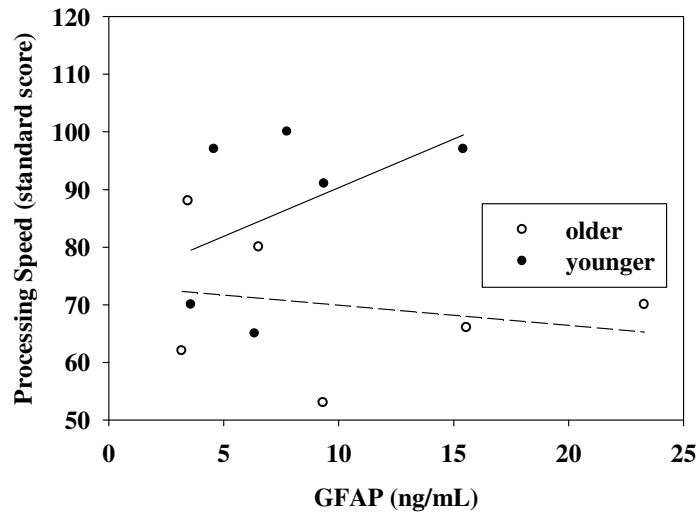


Figure 12. Processing speed as a function of GFAP for younger and older children.



The reason for this pattern of findings is unclear, but it is possible that age at injury and GFAP interact in complex ways to predict functional outcomes. In addition, it should be noted that the range of GFAP was restricted in the subsamples of children with episodic memory and processing speed standard scores. Specifically, GFAP ranged from 1.13 to 15.57 ng/mL for the subsample with episodic memory scores, whereas GFAP ranged from 3.19 to 23.30 ng/mL for the subsample with processing speed scores. Recall that GFAP for the entire sample of 30 children included in the study ranged from 0.03 ng/mL to 50.00 ng/mL. It is possible that the restricted range of GFAP resulted in the unexpected patterns of results across older and younger children.

Discussion

TBI is a significant public health concern that remains the leading cause of morbidity and mortality in children (Langlois et al., 2005). Biomarkers of brain injury that are detectable in blood serum are promising new tools for the prediction of functional outcomes following pediatric TBI. Previous studies have shown that elevations in the most commonly-investigated biomarkers (S100 β , NSE, and MBP) are associated with poorer global outcome (Bandyopadhyay et al., 2005; Beers et al., 2007; Berger et al., 2007). However, a number of limitations, including inadequate specificity to brain injury, preclude the use of these biomarkers in clinical care (Berger et al., 2002; Berger et al., 2007; Bettermann & Slocomb, 2012; Pelinka et al., 2003; Savola et al., 2003).

Unlike S100 β , NSE, and MBP, the novel biomarkers UCH-L1 and GFAP are specific to the brain and exhibit greater sensitivity and specificity in discriminating between adults with TBI and healthy adults (Diaz-Arrastia et al., 2014; Missler, Wiesmann, Wittmann, Magerkurth, & Hagenstrom, 1999). In children, the only study to compare relationships between outcome and UCH-L1, S100 β , NSE, and MBP showed that UCH-L1 was the biomarker most strongly associated with both global outcome and injury severity (Berger et al., 2012b). In the single study investigating GFAP following pediatric TBI, higher GFAP was associated with poorer global outcome (Fraser et al., 2011).

The research conducted to date provides a starting point in determining the utility of UCH-L1 and GFAP in predicting functional outcomes following TBI in children, but the focus of past research has been on global outcome. In no studies have either UCH-L1 or GFAP been examined in relation to intellectual or neuropsychological function. As such, there is no information available regarding these novel biomarkers as predictors of general intellectual

ability or function within specific cognitive domains. Such information is crucial for guiding intervention strategies that may improve cognition and overall quality of life for children with TBI.

The present study was conducted to examine UCH-L1 and GFAP in relation to not only global outcome but also intellectual and neuropsychological function following pediatric TBI. Serum UCH-L1 and GFAP were measured 24 hours after severe TBI in children aged 1 month to 17 years. Global outcome was measured three months post-TBI using the GOS-E Peds, whereas IQ, Performance IQ, and Verbal IQ were measured three months post-injury using subtests from the WASI or WASI-II. Neuropsychological function was measured three months post-injury by creating composite indices of processing speed, working memory, episodic memory, and executive function based on results from a range of standard neuropsychological tests. In addition to investigating relationships between 24-hour biomarker concentrations and the noted 3-month outcomes, possible interactions between age at injury and biomarker concentrations were examined in relation to outcomes.

Results indicated that both UCH-L1 and GFAP were elevated 24 hours following severe pediatric TBI. Consistent with adult research, UCH-L1 was significantly correlated with GFAP in children (Mondello et al., 2011). Outcome findings showed that the majority of children in our study had global outcome scores on the GOS-E Peds indicative of moderate disability. IQ, Performance IQ, and Verbal IQ ranged from extremely low to high average, with group means in the low average range, indicating that general intellectual function was slightly poorer than that of normative samples. Similarly, neuropsychological indices reflecting working memory, episodic memory, and executive function ranged from extremely low to high average, with group means in the low average range. For the processing speed index, scores ranged from extremely

low to average, with the group mean in the borderline range. The finding of relatively poorer processing speed is consistent with reports in the literature of particular impairment in processing speed following severe TBI in children (Anderson et al., 2012; Catroppa, Anderson, Morse, Haritou, & Rosenfeld, 2007; Wozniak et al., 2007). Impairments in working memory (Mandalis, Kinsella, Ong, & Andereson, 2007; Treble et al., 2013), episodic memory (Hawley, Ward, Magnay, & Mychalkiw, 2004), and executive function (Levin & Hanten, 2005; Sesma, Slomine, Ding, McCarthy, & Children's Health After Trauma Study Group, 2008) have also been observed following pediatric TBI, which is consistent with the current findings.

Turning to results regarding UCH-L1 and GFAP as predictors of functional outcomes, higher GFAP was significantly associated with poorer global outcome, which verifies results from the single study of GFAP and global outcome conducted to date (Fraser et al., 2011). In contrast, UCH-L1 was not associated with global outcome ($r = -.27$). In a previous study (Berger et al., 2012b), higher UCH-L1 was associated with poorer global outcome ($r = .42$), which is inconsistent with the current finding. Although further research is needed to definitively determine the reason for the discrepancy between the studies, it is likely that differences in methodology are the cause. For example, Berger et al. examined UCH-L1 4 hours post-injury, whereas we examined UCH-L1 24 hours post-injury. Given that UCH-L1 concentrations are more elevated within the first 6 than 24 hours post-injury in adults (Mondello et al., 2012), it is possible that 4-hour UCH-L1 is a more robust predictor of global outcome than 24-hour UCH-L1. In addition, Berger et al. used a dichotomized five-category GOS to assess global outcome three to eight months post-injury, whereas we used the eight-category GOS-E Peds to assess global outcome three months post-injury. Although unlikely, it is possible that scores from the GOS are better predicted by UCH-L1 than are scores from the GOS-E Peds due to differences in

content. Finally, the sample of children with global outcome data was somewhat larger in the Berger et al. study (N = 39) than in the current study (N = 30), which provided Berger et al. with greater power to detect a statistically significant correlation.

With regard to intellectual and neuropsychological function, higher UCH-L1 was significantly associated with both poorer IQ and processing speed. In addition, although not statistically significant, correlations between UCH-L1 and Verbal IQ, Performance IQ, and executive function had medium effect sizes. There were no significant relationships between GFAP and either IQ or neuropsychological indices, although the correlation between GFAP and working memory had a medium effect size. Overall, these findings suggest that UCH-L1 may be the better predictor of intellectual and neuropsychological outcomes, whereas GFAP may be the better predictor of global outcome.

It should be noted that biomarker concentrations were not predictive of outcomes across all neuropsychological indices. Episodic memory, for example, was predicted by neither UCH-L1 nor GFAP. It is possible that the specific conditions of the tests selected to represent episodic memory were not optimal. For both the CVLT-C and Facial Memory, immediate recall conditions were used, but the more demanding delayed recall conditions may have been better choices. The notion that more demanding tests or conditions of tests should be used is supported by findings from the working memory index. Correlations between Digit Span Forward and both UCH-L1 and GFAP had small effect sizes ($r = .08$ and $r = -.20$, respectively), whereas correlations between the more demanding Digit Span Backward and both UCH-L1 and GFAP had medium effect sizes ($r = -.32$ and $r = -.38$, respectively). In addition, in the executive domain, CVLT-C semantic clustering was not related to biomarker concentrations, although Word Generation (which also has a considerable processing speed component) was related to

UCH-L1 with a large effect size. These findings clearly point to the need for future research to delineate which cognitive domains and neuropsychological tests are best predicted by biomarker concentrations.

The final issue addressed in the current study was the impact of age at injury on biomarker concentrations, outcomes, and the relationships between biomarker concentrations and outcomes. Turning first to the relationship between age and biomarkers concentrations, UCH-L1 decreased significantly as age increased, whereas GFAP was not significantly related to age. The age-related finding for UCH-L1 may have been due to differences in injury mechanism, as the majority of younger children sustained inflicted injury, whereas the majority of older children sustained motor vehicle accidents. In future research it will be important to determine whether UCH-L1 decreases with age regardless of injury mechanism.

Based on the existing literature, it was hypothesized that younger age at injury would be associated with poorer intellectual and neuropsychological outcomes (Ganesalingam et al., 2011; Taylor & Alden, 1997). Results from the present study, however, did not support this hypothesis. In fact, trends with medium effect sizes suggested that that older age at injury was associated with poorer Performance IQ and processing speed. It is possible that the discrepancy in findings between past studies and the current study is due to differences in injury mechanism, TBI severity, or the timing of outcomes evaluation. Studies reporting age-related deficits in intellectual and neuropsychological functions have evaluated outcomes several years post-injury (Verger et al., 2000) and with various injury severities (Kaufmann, Fletcher, Levin, Miner, & Ewing-Cobbs, 1993), which may have resulted in differing patterns of age-related impairment. Unfortunately, examination of this issue is beyond the scope of the current study because only

three-month outcome data were available for children with severe TBI resulting from a variety of injury mechanisms.

Of particular relevance to the current study, there was only one instance in which the interaction between age at injury and biomarker concentration was significantly related to outcome. Specifically, the interaction between age at injury and GFAP was significantly associated with episodic memory. There was also a trend suggesting that the interaction between age at injury and GFAP was associated with processing speed. In both instances, higher GFAP in older children was associated with poorer outcome, whereas lower GFAP in younger children was associated with poorer outcomes. The discrepancy between older and younger children may reflect differences in injury mechanism or small sample size and will require further exploration to clarify.

Overall, findings from the present study suggest that, in general, UCH-L1 may be the better predictor of intellectual and neuropsychological outcomes, whereas GFAP may be the better predictor of global outcome. However, the relationship between GFAP and neuropsychological outcomes may be complex and may need to be considered within the context of age at the time of injury. Further research is clearly warranted to investigate novel biomarkers of brain injury as predictors of functional outcomes in children with TBI.

In future research, it will be important to address the limitations of the current study. First, and of particular concern, was sample size, which was smaller than expected due to factors such as death, withdrawal from the study, and difficulty completing functional outcomes evaluations with children having substantial physical limitations and medical comorbidities. It is possible that a larger sample size would have permitted detection of additional relationships between biomarker concentrations and outcomes. In turn, due to small sample size, it was not

possible to conduct analyses on subgroups of children with different injury mechanisms (e.g., motor vehicle accident versus inflicted injury) or injuries affecting different brain regions (e.g., frontal versus parietal). Second, future studies should consider inclusion of a comparison group of demographically-matched children with injuries other than TBI to verify the specificity of UCH-L1 and GFAP to pediatric brain injury. Third, in the present study relationships were examined only between 24-hour serum biomarker concentrations and 3-month outcomes. It is possible that other biomarker variables, such as peak concentrations or time-to-peak concentrations (Beers et al., 2007), could be better predictors of outcomes. Similarly, it is possible that biomarker concentrations are better predictors of outcomes that are assessed after a longer period of time post-injury. Finally, only children with severe TBI were included in the current study. Future research including children with mild and moderate TBI is needed to determine the value of biomarkers as predictors of outcomes across the range of TBI severity.

Conclusions

This was the first study in which serum UCH-L1 and GFAP were examined in relation to global, intellectual, and neuropsychological outcomes in children with TBI. Results suggested that UCH-L1 was the better predictor of intellectual and neuropsychological outcomes, whereas GFAP was the better predictor of global outcome. GFAP, however, may also be a good predictor of neuropsychological outcomes if considered within the context of age at the time of injury. Additional research will be crucial for translating these findings into clinical care for children with TBI.

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Appendix A

Glasgow Outcome Scale (GOS)

Score	Category
1	Good Recovery
2	Moderate Disability (Able to Live Independently, Unable to Return to Work/School)
3	Severe Disability (Able to Follow Commands, Unable to Live Independently)
4	Persistent Vegetative State (Unable to Interact with Environment, Unresponsive)
5	Death

Appendix B

Glasgow Coma Scale (GCS)

Score	Feature	Responses
1	Eye Opening	None
2		Opens to Pain, Not Applied to Face
3		Opens to Verbal Command, Speech, or Shout
4		Spontaneous, Open with Blinking at Baseline
1	Verbal	None
2		Incomprehensible Speech
3		Inappropriate Responses, Words Discernible
4		Confused Conversation, but Able to Answer Questions
5		Oriented
1	Motor	None
2		Extensor (Rigid) Response, Decerebrate Posture
3		Abnormal (Spastic) Flexion, Decorticate Posture
4		Withdraws from Pain
5		Purposeful Movement to Painful Stimulation
6		Obeys Commands for Movement

Appendix C

Glasgow Outcome Scale, Extended Version (GOS-E)

Score	Category
1	Upper Good Recovery
2	Lower Good Recovery
3	Upper Moderate Disability
4	Lower Moderate Disability
5	Upper Severe Disability
6	Lower Severe Disability
7	Vegetative State
8	Death

Appendix D

Pediatric Cerebral Performance Category Scale (PCPC)

Score	Feature	Responses
1	Normal	Normal, At Age Appropriate Level, School Age Child Attends Regular School Classroom
2	Mild Disability	Conscious, Alert, Able to Interact at Age Appropriate Level School Age Child Attending Regular Classroom, but Grade Inappropriate
3	Moderate Disability	Conscious, Sufficient Cerebral Function for Age Appropriate Independent Activities, School Age Child Attending Special Education Classroom, May Have Learning Disability
4	Severe Disability	Conscious, Dependent for Daily Support Because Impaired Brain Function
5	Coma or Vegetative State	Any Degree of Coma Without Any of the Criteria for Brain Death, Unawareness (Even if Awake) Without Interaction with Environment, Cerebral Unresponsiveness, No Evidence of Cortical Function and Not Aroused by Verbal Stimuli, Reflexive Responses, Spontaneous Eye Opening, Sleep-Wake Cycles
6	Brain Death	Apnea or Areflexia or Electroencephalographic (EEG) Silence

Appendix E

Glasgow Outcome Scale - Extended, Pediatric Version

Glasgow Outcome Scale-Extended Pediatric (GOS-E Peds)

NOTE: Only problems that have **developed or become markedly worse** since the head injury should be considered when completing the GOS-E Peds. That is, the child's premorbid status must be weighed when answering all questions.

Information obtained (select one): In person By phone From records

1. CONSCIOUSNESS

1a) Is the head-injured person able to obey simple commands or say any words?

Or for younger patients...

Can he or she act/react/interact beyond reflexes?

No

Yes (Skip to 2.)



Vegetative State (VS)
Skip to end of form and record GOS-E
Peds Score = 2.

An individual who shows the ability to obey even simple commands or utter any word or communicate specifically in any other way is no longer considered to be in a vegetative state. Eye movements are not reliable evidence of meaningful responsiveness; corroborate with nursing staff and the child's parents when possible. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines. However, for infants, actively following the movement of a parent or people/object with eyes, grasping for objects, making faces, etc. are interactions; breast feeding and crying continuously can be reflexes.

2. INDEPENDENCE IN THE HOME

2a) Is the assistance of another person at home essential every day for some activities of daily living?

Or for younger patients...

Is the child dependent upon a caretaker more so than is expected based on age?

Yes (Go to 2b.)

No (Skip to 3.)

For an older child, complete independence and a 'no' answer should mean that the person can get washed, put on clean clothes without prompting, prepare food for themselves, deal with callers, and handle minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone for an age appropriate period. Young children should be able to accomplish age appropriate developmental milestones without assistance (see Vineland Daily Living Skills). If a child compensates for physical disability to the point where developmental milestones are only mildly compromised, question parents to determine the level of independence (i.e., a child with a hemiparesis who is still able to complete tasks that other children of that age can be rated as independent).

2b) Does the child need frequent help or for someone to be around at home most of the time?

Or for younger patients...

Does the child need frequent help from a caretaker to accomplish tasks that a child this age should be able to accomplish (If child sometimes functions at an age appropriate level, then answer 'yes.')

Yes



Lower Severe Disability
Skip to end of form and record GOS-E
Peds Score = 3.

No



Upper Severe Disability
Skip to end of form and record GOS-E
Peds Score = 4.

3. INDEPENDENCE OUTSIDE THE HOME

3a) Is the child able to shop and travel without assistance?

Or for younger patients...

Does the child behave age appropriately outside the home?

Yes (Skip to 4.)

No



Upper Severe Disability
Skip to end of form and record GOS-E
Peds Score = 4.

This item considers activities such as shopping and traveling, always in the context of age appropriate behaviors. This includes being able to plan what to buy, take care of money, and behave appropriately in public. The individual need not normally shop, but must be able to do so. A younger child must behave age appropriately in public. An older child may drive or use public transit to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and give instruction the driver. Older children who sometimes were allowed to travel independently before the injury should be able to walk to a neighbor's house, take a school bus, ride a bike, or take public transportation.

4. SCHOOL/WORK

4a) Can the child function at work or in school at his or her **previous** capacity?

Yes (Skip to 5.)

No (Go to 4b.)

If an adolescent was working before the injury, then his or her current capacity for work should be at the same level. If the individual was seeking work before, then the injury should not have adversely affected chances of obtaining work or the level of work for which he or she is eligible. If the patient was in preschool or a student before the injury, then capacity for school work and school activities should not be adversely affected.

4b) Level of restriction:

i) Able to work only in a sheltered workshop or non-competitive job, in a school setting for severely impaired children or tutored at home, or currently unable to work or go to school.

Yes

No (Go to 4b ii.)



Lower Moderate Disability
Skip to end of form and record GOS-E
Peds Score = 5.

- ii) Reduced work or school capacity. Yes No (Go to 5.)

Upper Moderate Disability
Skip to end of form and record GOS-E
Peds Score = 6.

5. SOCIAL & LEISURE ACTIVITIES

- 5a) Is the child able to resume regular social and leisure activities?
 Yes (Skip to 6.) No (Go to 5b.)

The individual may not have resumed all previous leisure activities, but should not be prevented from doing so by physical or mental impairment. If he or she has stopped the majority of activities because of loss of interest or motivation, then this is considered a disability. For younger children, social and leisure activities can include games and toys played with caretakers, siblings or other children as well as the ability to interact in a playful manner with others.

- 5b) What is the extent of restrictions on social and leisure activities?

- i) Unable to participate: Rarely, if ever, take part. Yes No (Go to 5b ii.)

Lower Moderate Disability
Skip to end of form and record GOS-E
Peds Score = 5.

- ii) Participate much less: Less than half as often. Yes No (go to 5b iii.)

Upper Moderate Disability
Skip to end of form and record GOS-E
Peds Score = 6.

- iii) Participate a bit less: At least half as often as before injury. Yes No (Skip to 6.)

Lower Good Recovery
Skip to end of form and record GOS-E
Peds Score = 7.

6. FAMILY & FRIENDSHIPS

6a) Are there psychological problems that have resulted in ongoing disruption with respect to either family or friendships?

- Yes (Go to 6b.) No (Skip to 7.)

Typical post-traumatic personality changes: quick temper, irritability, anxiety, aggressive acts, insensitivity to others, mood swings, depression, and unreasonable or childish behavior that is not age appropriate.

6b) What is the extent of disruption or strain?

- Constant – daily and intolerable →

Lower Moderate Disability
Skip to end of form and record GOS-E
Peds Score = 5.

- Frequent – once a week or more, but tolerable →

Upper Moderate Disability
Skip to end of form and record GOS-E
Peds Score = 6.

- Occasional – less than weekly →

Lower Good Recovery
Skip to end of form and record GOS-E
Peds Score = 7.

7. RETURN TO NORMAL LIFE

7a) Are there any other problems relating to the injury that affect daily life?

- Yes

Lower Good Recovery
Skip to end of form and record GOS-E
Peds Score = 7.

- No

Upper Good Recovery
Skip to end of form and record GOS-E
Peds Score = 8.

Typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, concentration problems, or other problems.

Scoring caveat: Remember to consider premorbid status when assigning category scores. To an outcome of injury, problems in functioning should have deteriorated from premorbid level.

- 1 - Death
- 2 - Vegetative State (VS)
- 3 - Lower Severe Disability (Lower SD)
- 4 - Upper Severe Disability (Upper SD)
- 5 - Lower Moderate Disability (Lower MD)
- 6 - Upper Moderate Disability (Upper MD)
- 7 - Lower Good Recovery (Lower GR)
- 8 - Upper Good Recovery (Upper GR)

GOS-E Peds Score: _____