Scientific Advances in TBI: Toward Realizing a Neurobiopsychosocial Model of Injury and Recovery

Michael McCrea, PhD, ABPP
Professor and Eminent Scholar
Vice Chair of Research
Director of Brain Injury Research
Departments of Neurosurgery, Neurology & Psychiatry
Medical College of Wisconsin
Clement Zablocki VA Medical Center
Neuropsychology Consultant, Green Bay Packers
Anybody Drinkin’ What I’m Pourin’?
Without Reinventing the Wheel:

Replicable Paradigms in Medical Research

About Disease and Who Comes to Disease
Toward an Integrated Understanding of Injury, Recovery, Outcome and Risk in TBI

About Injury and Who Comes to Injury
Predicting Mortality after TBI

Sources: Jane & Rimel, 1982;
Recovery & Outcome:

Injury Severity Matters (a lot)

From Dikmen et al., 1995

---

GLASGOW COMA SCALE SCORE

- TC (n=120)
- 13-15 (n=243)
- 9-12 (n=73)
- 6-8 (n=77)
- 3-5 (n=35)

---

GOS Score

- Good
- Moderate
- Severe
- Veg/Dead

---

Time to Follow Commands

- TC < 1 Hr
- 1-24 Hr
- 1-6 Days
- 7-13 Days
- 14-28 Days
- 29+ Days

From Dikmen et al., 1995
Beyond Neurobiology of Injury

Preinjury family environment as a determinant of recovery from traumatic brain injuries in school-age children

Family Support

Socioeconomics

Socioenvironment

Long-Term Behavior Problems Following Pediatric Traumatic Brain Injury: Prevalence, Predictors, and Correlates

Lisa Schwartz, MA, H. Gerry Taylor, JD, PhD, Dennis Drotar, MD, PhD, Keith Owen Yeeates, PhD, Shari L. Wade, PhD, and Terry Stancin, PhD

Objective To study identified rates of long-term behavior problems in children with traumatic brain injury (TBI) compared to children with only orthopedic injuries and risk factors and common

Socioenvironmental

Social Environmental Moderators of Long-term Functional Outcomes of Early Childhood Brain Injury

Participants, Methods, and Findings

Social Environment

Socioenvironment

Social Environment
Recovery & Outcome after Mild TBI (Concussion)
Predicting Outcome after mTBI

<table>
<thead>
<tr>
<th>Early Predictor</th>
<th>Productivity</th>
<th>Global Outcome</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOC</td>
<td>0.23</td>
<td>0.23</td>
<td>0.06</td>
</tr>
<tr>
<td>PTA</td>
<td>0.27</td>
<td>0.43</td>
<td>ns</td>
</tr>
<tr>
<td>GCS</td>
<td>0.19</td>
<td>0.38</td>
<td>0.18</td>
</tr>
<tr>
<td>LOStay</td>
<td>0.35</td>
<td>0.14</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Effect Sizes: 0.2 Small, 0.5 Medium, 0.8 Large

< 0.3 Difficult to detect in individual patients; large overlap b/n patients and control group

Cappa et al, 2011, Meta-Anal of head injury Outcome, Health Psychol, V3, 542
Recovery & Outcome After mTBI

Clinical and scientific communications

Disability Caused by Minor Head Injury

Rebecca W. Rimel, R.N., N.P., Bruno Giordani, M.A., Jeffrey T. Barth, Ph.D., Thomas J. Boll, Ph.D., and John A. Jane, M.D., Ph.D.

Departments of Neurosurgery (R.W.R., J.A.J.), Neurology (B.G.), and Psychiatry (J.T.B.), University of Virginia Medical Center, Charlottesville, Virginia, and Department of Psychiatry (T.J.B.), University of Health Sciences—The Chicago Medical School, Chicago, Illinois

The authors studied 538 patients who had sustained minor head trauma, which was defined as a history of unconsciousness of 20 minutes or less, a Glasgow Coma Scale score of 13 to 15, and hospitalization not exceeding 48 hours. Of these patients, 424 were evaluated 3 months after injury. The follow-up evaluation included a history of events since the accident, assessment of subjective complaints and objective measures such as employment status, a neurological examination, a psychosocial assessment designed for estimating life stress, and a neuropsychological test battery to measure higher cortical function. Of these 424 patients, 79% complained of persistent headaches, and 59% described problems with memory. Of the patients who had been gainfully employed before the accident, 34% were unemployed 3 months later. Comparisons were then made between the employed and the unemployed groups. Three explanations for the high rate of unemployment were examined. (a) Evidence of organic brain damage: Although the neurological examination was completely normal in nearly all patients, neuropsychological testing demonstrated some problems with attention, concentration, memory, or judgment in most of the 69 patients evaluated. (b) Psychological responses to the injury: Emotional stress caused by persistent symptoms seems to be a significant factor in the long term disability of these patients. (c) Litigation and compensation: These factors have a minimal role in determining outcome after minor head injury. In conclusion, the most striking observations of these studies are the high rates of morbidity and unemployment in patients 3 months after a seemingly insignificant head injury and the evidence that many of these patients may have, in fact, suffered organic brain damage. (Neurosurgery 9:221–228, 1981)

Where Have We Been for 30 Years?

• Neurobiological: Evidence of organic brain damage

• Psychological: Response to injury

• Social/Environmental Litigation & compensation
War of the Worlds in mTBI

Myths and Mild Traumatic Brain Injury

Ronald M. Ruff • Christina Weyer Jamora

Desperate for a Singular Answer
Who Comes to Injury?

Frequency of factors that complicate the identification of mild traumatic brain injury in level I trauma center patients

Aim: Determine the frequency of factors that complicate identification of mild traumatic brain injury (mTBI) in emergency department patients. Setting: Chart review. Materials & methods: Records of 3042 patients (age 18–45 years) exposed to a potential mechanism of mTBI were reviewed for five common complicating factors and signs of mTBI. Results: Most patients (65.1%) had at least one complicating factor: given narcotics in the emergency department (43.7%), on psychotropic medication (18.4%), psychiatric diagnosis (15.3%), alcohol consumption near time of admission (14.2%) and preadmission narcotic prescription (8.9%). Conclusion: Our findings highlight the frequency of these confounding factors in this population. Future research should identify how these factors interact with performance on assessment measures to improve evidence-based mTBI assessment in this population.

Keywords: • assessment • comorbidities • concussion • confounding variables • emergency department

Figure 1. Frequency of complicating factors in patients presenting with a common mechanism of mild traumatic brain injury (n = 3042).
Challenges in mTBI

Clinical Study

Outcome from Complicated versus Uncomplicated Mild Traumatic Brain Injury

Grant L. Iverson,1 Rael T. Lange,2,3 Minna Wiljas,4 Suli Liimatainen,4 Prasun Dastidar,5 Kaisa M. Hartikainen,5 Seppo Soimakallio,5 and Juha Ohman5

1Department of Psychiatry, University of British Columbia, 2251 Wesbrook Mall, Vancouver, BC, Canada V6T 2A1
2Department of Orthopaedics and Rehabilitation, Walter Reed National Military Medical Center and Defense and Veteran Brain Injury Center, 11300 Rockville Pike, Suite 100, North Bethesda, MD 20852, USA
3Department of Neuroscience and Rehabilitation, Temple University Hospital and University of Temple Medical School, Philadelphia, PA 19122, USA
4Department of Neuroscience and Rehabilitation and Emergency Department Acute, Temple University Hospital, Philadelphia, PA 19122, USA
5Medical Imaging Centre of Parkinson’s Hospital District and University of Temple Medical School, Philadelphia, PA 19122, Temple, Philadelphia, PA

Correspondence should be addressed to Grant L. Iverson, giverson@interchange.mcgill.ca

Received 4 November 2011; Revised 3 February 2012; Accepted 27 February 2012

Academic Editor: Anne Felicia Ambrose

Copyright © 2012 Grant L. Iverson et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. To compare acute outcome following complicated versus uncomplicated mild traumatic brain injury (mTBI) using neuropsychological and self-report measures. Methods. Participants were 47 patients who presented to the emergency department of Temple University Hospital, Philadelphia. All completed MRI scanning, self-report measures, and neuropsychological testing at 3-4 weeks after injury. Participants were classified into the complicated or uncomplicated mTBI group based on the presence or absence of intracranial abnormalities on day-of-injury CT scan or on 3-4 week MRI scan. Results. There was a large statistically significant difference in time to return to work between groups. The patients with uncomplicated mTBIs had a median of 60 days (IQ95% 14–57 range 8–77) off work compared to a median of 36 days (IQ95% 13–53 range 4–315) for the complicated group. There were no significant differences between groups for any of the neuropsychological or self-report measures. There were no differences in the proportion of patients who (a) met criteria for PTSD-10 postconcussional disorder or (b) had multiple low scores on the neuropsychological measures. Conclusion. Patients with complicated mTBIs took considerably longer to return to work. They did not perform more poorly on neuropsychological measures or report more symptoms, at 3-4 weeks after injury compared to patients with uncomplicated mTBIs.

Predicting Recovery & Outcome

Predictors of Postconcussive Symptoms 3 Months After Mild Traumatic Brain Injury

Jennie Posnford
Monash University; Monash-Epworth Rehabilitation Research Centre, Epworth Hospital, and National Trauma Research Institute, Melbourne, Australia

Michele Grant
Monash University; Monash-Epworth Rehabilitation Research Centre, Epworth Hospital, and National Trauma Research Institute, Melbourne, Australia

Peter Cameron and Mark Fitzgerald
Monash University; Alfred Hospital; and National Trauma Research Institute, Melbourne, Australia

Antonina Mikocka-Wallace
Monash University, National Trauma Research Institute and University of South Australia

Michael Schlüerberger
Monash University; Monash-Epworth Rehabilitation Research Centre, Epworth Hospital, and University of Freiburg

Objective: There is continuing controversy regarding predictors of poor outcome following mild traumatic brain injury (mTBI). This study aimed to prospectively examine the influence of primary factors, injury-related factors, and postinjury factors on outcome following mTBI. Methods: Participants were 125 patients with mTBI and 500 trauma patient controls recruited and assessed in the emergency department and followed up 1 week and 3 months postinjury. Outcome was measured in terms of reported postconcussional symptoms. Measures included the InPAT Post-Concussional Symptom Scale and cognitive concussion history, including Attention, Verbal and Visual memory, Processing Speed and Reaction Time modules, pre- and postinjury SF-36 and MINI psychiatric status ratings, VAS Pain Inventory, Hospital Anxiety and Depression Scale, PTSD Checklist-Specific, and Revised Social Readjustment Scale. Results: Presence of mTBI predicted postconcussional symptoms 1 week postinjury, along with biologic, female, and psycho-social factors, by elevated HADS anxiety as a concurrent indicator. However, at 3 months, only physical or psychiatric problems but not mTBI most strongly predicted continuing symptoms, with concurrent indicators including HADS anxiety, PSSD symptoms, other life stressors and pain. HADS anxiety and age predicted 3-month PCS in the mTBI group, whereas PSSD symptoms and other life stressors were most significant for the controls. Cognitive measures were not predictive of PCS at 1 week or 3 months. Conclusions: Given the evident influence of both biologic and concurrent psychiatric problems, especially anxiety, on postinjury symptoms, managing the anxiety response in vulnerable individuals with mTBI may be important to minimize ongoing sequelae.

Keywords: traumatic brain injury, concussion, outcome assessment
Neurobiopsychosocial Model of TBI: Multidimensional Prediction of Recovery, Outcome & Risk

Multi-Domain Predictor Variables

Neurobiological
- Pre-Injury Factors
  - Genetics
  - Neurologic Vulnerabilities
- Trauma Burden
  - Injury Severity
  - Repetitive Exposure
  - Polytrauma
- Biomarkers
  - Structural/Functional Imaging
  - Blood Biomarkers

Psychosocial
- Psychological Function
  - Premorbid
  - Post-injury Comorbidities
- Environmental Factors
  - Social Support
  - Life Stressors
  - Iatrogenesis
- Motivational Factors
  - Expectation
  - Secondary Gain

Multi-Dimensional Outcome
- Neurologic Health
- Neurocognitive Function
- Neurobehavioral Function
- Psychological Health and Wellness
- Life Function & Quality

Implications for Translational Research
Translational Research in TBI

Informing the Broader Science of TBI
Building Translational Bridges

**FUNDAMENTAL PRINCIPLES**

The New Neurometabolic Cascade of Concussion

Since the original descriptions of postconcussive pathophysiology, there has been a significant increase in interest and ongoing research to study the biological underpinnings of concussion. The initial ionic flux and glutamate release result in significant energy demands and a period of metabolic crisis for the injured brain. These physiological perturbations can now be linked to clinical characteristics of concussion, including migrainous symptoms, vulnerability to repeat injury, and cognitive impairment. Furthermore, advanced neuroimaging now allows a research window to monitor postconcussion pathophysiology in humans noninvasively. There is also increasing concern about the risk for chronic or even progressive neurobehavioral impairment after concussion/mild traumatic brain injury. Critical studies are underway to better link the acute pathobiology of concussion with potential mechanisms of chronic cell death, dysfunction, and neurodegeneration. This "new and improved" article summarizes in a translational fashion and updates what is known about the acute neurometabolic changes after concussive brain injury. Furthermore, new connections are proposed between this neurobiology and early clinical symptoms as well as to cellular processes that may underlie long-term impairment.

**Neurometabolic Cascade Following Cerebral Conussion/mTBI**

**Vulnerability: Metabolism & Timing**

2nd concussion during metabolic impairment results in worse metabolic disruption and cognition

Translation: Pathophysiology in Humans
Big Science in TBI

Impact on Research & Clinical Care in all Populations at Risk

A Collaborative for Advancing Diagnosis and Treatment of TBI

A Public-Private Partnership to Advance the Science of Concussion in Sports & Military
How Long Does it Take for the Brain to Recover?

1. How does the time course of physiological recovery compare to clinical recovery?
2. Should there be a minimum stand-down period following SRC?
3. Is the duration or content of graded return to play progression appropriate?
NCAA-DoD CARE Consortium:
Sponsored by U.S. Dept. of Defense (DoD) & NCAA
Principal Investigators: S. Broglio, PhD, Thomas McAllister, MD, Michael McCrea, PhD
NCAA-DoD CARE Consortium

Clinical Study Core (CSC)
- Multi-center: 30 Sites
- MSA Cadets (all cadets), NCAA Athletes (all sports)
- \( N = > 40,000 \) enrolled
- \( N = > 3,000 \) concussions
- \( \sim \frac{1}{2} \) NCAA, \( \frac{1}{2} \) MSA
- \( \sim \frac{1}{3} \) female
- >70 million data points

Studying Natural History of Injury & Recovery
CARE Consortium investigators and SSAP members engaged with respective ARC Scientific Concentrations.
## CARE ARC ASSESSMENT PROTOCOL

<table>
<thead>
<tr>
<th>Pre-Season</th>
<th>Acute Concussion</th>
<th>Sub-Acute Concussion</th>
<th>Post-Concussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>&lt;6hrs Post-Injury</td>
<td>24-3 Days Post-Injury</td>
<td>Asymptomatic / Cleared for Return to Play Progression</td>
</tr>
<tr>
<td>Neurocognitive and Behavioral Testing</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood Biomarker &amp; DNA Collection</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Multi-modal MRI Studies*</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Head Impact Measurement</td>
<td>Football athletes instruments with HITS, non-helmeted sensors to measure biomechanics of injury &amp; exposure under laboratory and field validation studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARC Sports: Football, M/W Soccer, M/W LaCrosse, M/W Ice Hockey, Rugby

*MRI at NCAA sites only
Differentiating Effects of Injury & Repetitive Exposure

Is it about “How Many” vs. “How Much”?

Concussed Cadets/Athletes (Injured & Exposure)

Contact Sport Controls (Exposure Without Injury)

Non-Contact Controls (No Exposure, No Injury)

Innovative Study Design

Concussions in a Required Class: Boxing at Military Academies

By DAVE PHILIPPS
SEPT. 29, 2015

WEST POINT, N.Y. — A bell clanged and two cadets in boxing gloves surged from their corners in a gym at the For more than a century, boxing for male freshmen here has been a rite of passage and an academic requirement — one they share with male cadets at the academy than in Iraq or Afghanistan.” But data obtained by The New York Times shows that the lesson comes at considerable cost.
Advanced Research Core: Comprehensive, Integrated Approach

**Premorbid Individual Factors**
- Role of genomics, proteomics
- Influence of pre- & comorbid factors

**Biomechanics of Injury and Exposure**

**Acute Effects & Recovery: Brain Structure & Function**

**Clinical / Functional**

**Neurobiological**

**Outcome, Intervention & Risk Prevention**
- Prevention
- Rehabilitation
- Return to Activity
- Academic Function
- Targeted Therapies

Understanding neurobiological effects and recovery
Neurobiological Effects and Recovery

**Acute White Matter Changes following Sport-Related Concussion: A Serial Diffusion Tensor and Diffusion Kurtosis Tensor Imaging Study**

Melissa A. Lancaster, 1,2 Daniel V. Olson, 3 Michael A. McCrea, 1,2 Lindsay D. Nelson, 1,2 Ashley A. LaRoche, 2 and L. Tugan Muftuler 1,2

1Department of Neurology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin, 53226
2Department of Neurosurgery, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin, 53226
3Department of Biophysics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin, 53226

**Acute and Subacute Changes in Neural Activation during the Recovery from Sport-Related Concussion**

Thomas A. Hammeke, 1 Michael McCrea, 2 Sarah M. Coats, 3 Matthew D. Verber, 4 Sally Duggerian, 3 Kristin Flocum, 5 Gary S. Olsen, 6 Peter D. Leo, 2 Thomas A. Gemmelelll, 2 and Stephen M. Rao 7

**Cerebral Blood Flow Alterations in Acute Sport-Related Concussion**

Yang Wang, 1,2 Lindsay D. Nelson, 3,4 Ashley A. LaRoche, 3 Adam Y. Pfaller, 4 Andrew S. Nenoka, 2 Kevin M. Koch, 1,2 and Michael A. McCrea, 3,4

**Recovery of Cerebral Blood Flow Following Sports-Related Concussion**

Timothy B. Meier, PhD; Patrick S. F. Bellgowan, PhD; Rashmi Singh, PhD; Rayus Kuplicki, PhD; David W. Polanski, MS, ATC, LAT; Andrew R. Mayer, PhD

**Correlation with Clinical Recovery**
Acute Changes in Brain Structure & Function

White Matter Integrity (DTI/DKI)
Decreased mean diffusivity & increased axial kurtosis at 24 hour injury time point

Functional Connectivity (rs-fMRI)
Increased connectivity compared to controls

Cerebral Blood Flow (ASL)
Decreased cerebral blood flow acutely

Susceptibility (QSM)
Regions of increased susceptibility at 24 hours postinjury

Quantifying Effects of Injury, Recovery & Exposure using Advanced Imaging
Biomarkers of Injury & Recovery

**Acute markers**
- UCH-L1
- GFAP (Banyan)
- SBDP150
- SBDP120
- CNPase

**Subacute markers**
- MAP2
- BA-0293

**Chronic markers**
- Demyelination
- Neuronal cell body damage
- Dendritic injury

**Markers of Neuronal Injury & Recovery**
- Acute markers: UCH-L1, GFAP, SBDP150
- Subacute/Chronic markers: MAP2, SBDP120, MBP, CNPase, GFAP autoantibodies

**Markers of Gliosis/Glial Injury**
- Neuronal cell body damage
- Axonal injury
- Gliosis/Glial injury

**Markers of Vascular Injury**
- Demyelination
- Microgliosis
- Chronic inflammatory responses to blood vessels and neurons

**Markers of Dendritic Injury**
- Demyelination

**With permission, Banyan Biomarkers**
Integrated Recovery Model

**What Factors Influence Recovery?**

**PRE-INJURY:**
Normal Cerebral Function

**CONCUSSIVE EVENT**

**ACUTE**
IMPARED: Elevated symptoms, functional impairment, physiological dysfunction

**Window of Cerebral Vulnerability**

**POST-ACUTE**
COMPENSATORY: Full clinical recovery, but persistent physiological dysfunction

**Clinical Recovery**
(Common Time Point for Return to Play)

**Physiological Recovery**

**FULL**
COMPLETE: Full clinical recovery, normal physiological function

**Prevention-based Return to Activity**

**FULL COMPLETE:**
Full clinical recovery, normal physiological function
Benefits of Strict Rest After Acute Concussion: A Randomized Controlled Trial

Danny George Thomas, MD, MPH\textsuperscript{a}, Jennifer N. Apps, PhD\textsuperscript{b}, Raymond G. Hoffmann, PhD\textsuperscript{b}, Michael McCrea, PhD\textsuperscript{b}, Thomas Hammeke, PhD\textsuperscript{b}

OBJECTIVES: To determine if recommending strict rest improved concussion recovery and outcome after discharge from the pediatric emergency department (ED).

METHODS: Patients aged 11 to 22 years presenting to a pediatric ED within 24 hours of concussion were recruited. Participants underwent neurocognitive, balance, and symptom assessment in the ED and were randomized to strict rest for 5 days versus usual care (1-2 days rest, followed by stepwise return to activity). Patients completed a diary used to record physical and mental activity level, calculate energy exertion, and record daily postconcussive symptoms. Neurocognitive and balance assessments were performed at 3 and 10 days postinjury. Sample size calculations were powered to detect clinically meaningful differences in postconcussive symptom, neurocognitive, and balance scores between treatment groups. Linear mixed modeling was used to detect contributions of group assignment to individual recovery trajectory.

RESULTS: Ninety-nine patients were enrolled; 88 completed all study procedures (45 intervention, 43 control). Postdischarge, both groups reported a 20% decrease in energy exertion and physical activity levels. As expected, the intervention group reported less school and after-school attendance for days 2 to 5 postconcussion (3.8 vs 6.7 hours total, \( P < .05 \)). There was no clinically significant difference in neurocognitive or balance outcomes. However, the intervention group reported more daily postconcussive symptoms (total symptom score over 10 days, 187.9 vs 131.9, \( P < .03 \)) and slower symptom resolution.

CONCLUSIONS: Recommending strict rest for adolescents immediately after concussion offered no added benefit over the usual care. Adolescents’ symptom reporting was influenced by recommending strict rest.
Not All “Mild TBI” Created Equal

mTBI Symptom Duration by Patient Population

- Community Athlete
- Emergency Department
- Inpatient

L. Nelson et al., 2018
Big Science: Civilian TBI

Geoff Manley, MD, PhD (PI)

TBI
Endpoints
Development

A Collaborative for Advancing Diagnosis and Treatment of TBI

Prospective longitudinal Observational Study
3000 subjects, including Controls
Across the spectrum from concussion to coma
TRACK-TBI: Precision Medicine

Patient Population
Incidence, Clinical Course, and Predictors of Prolonged Recovery Time Following Sport-Related Concussion in High School and College Athletes

Michael McCrea,1 Kevin Guszkiewicz,2,3,4 Christopher Randolph,5 William B. Barr,6 Thomas A. Hammeke,7 Stephen W. Marshall,3,8 Matthew R. Powell,9 Kwang Woo Ahn,10 Yanzhi Wang,10 and James P. Kelly11

1Departments of Neurosurgery and Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin
2Department of Exercise and Sport Science, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
3Department of Orthopedics; University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
4Injury Prevention Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
5Department of Neurology, Loyola University Medical School, Maywood, Illinois
6Departments of Neurology and Psychiatry, New York University School of Medicine, New York, New York
7Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin
8Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
9Department of Neuropsychology, Marshfield Clinic – Minocqua Center, Minocqua, Wisconsin
10Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin
11U.S. Department of Defense, National Intrepid Center of Excellence, Bethesda, Maryland

(Rceived September 21, 2011; Final Revision June 7, 2012; Accepted June 7, 2012)
# Measuring TBI Outcome

## Glasgow Outcome Scale – Extended (GOSE)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dead</td>
<td>Condition of unawareness with only reflex responses but with periods of spontaneous eye opening</td>
</tr>
<tr>
<td>2</td>
<td>Vegetative State (VS)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe Disability – Lower (SD–)</td>
<td>Dependence on daily support for mental or physical disability or both. If the patient can be left alone for more than 8 hours at home, it is upper level of SD; if not, then it is low level of SD</td>
</tr>
<tr>
<td>4</td>
<td>Severe Disability – Upper (SD+)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Moderate Disability – Lower (MD–)</td>
<td>Patients have some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality but are able to look after themselves. They are independent at home but dependent outside. If they are able to return to work event with special arrangement it is upper level of MD; if not then it is low level of MD</td>
</tr>
<tr>
<td>6</td>
<td>Moderate Disability – Upper (MD+)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Good Recovery – Lower (GR–)</td>
<td>Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some patients have minor neurological or psychological deficits. If these deficits are not disabling then it is upper level of GR; if disabling, then it is lower level of GR</td>
</tr>
<tr>
<td>8</td>
<td>Good Recovery – Upper (GR+)</td>
<td></td>
</tr>
</tbody>
</table>
Good vs. Not So Good Outcome

6 Month Symptom Reporting in Good Outcomes (GOSE 7 & 8)

Percentage of TBI Patients Endorsing Symptoms on RPQ

Nelson et al, 2017
6 Month CDE Performance in Good Outcomes (GOSE 7 & 8)

Percentage of TBI Patients Impaired on CDEs

Good vs. Not So Good Outcome after TBI

Nelson et al, 2017
Magnetic Resonance Imaging Improves 3-Month Outcome Prediction in Mild Traumatic Brain Injury

Esther L. Yuh, MD, PhD,1,2 Pratik Mukherjee, MD, PhD,1,2 Hester F. Lingsma, PhD,3 John K. Yue, BS,1,4 Adam R. Ferguson, PhD,1,4 Wayne A. Gordon, PhD,5 Alex B. Valadka, MD,6 David M. Schnyer, PhD,7 David O. Okonkwo, MD, PhD,8 Andrew I. R. Maas, MD, PhD,9 Geoffrey T. Manley, MD, PhD,1,4 and the TRACK-TBI Investigators

Objective: To determine the clinical relevance, if any, of traumatic intracranial findings on early head computed tomography (CT) and brain magnetic resonance imaging (MRI) to 3-month outcome in mild traumatic brain injury (MTBI).

Methods: One hundred thirty-five MTBI patients evaluated for acute head injury in emergency departments of 3 LEVEL I trauma centers were enrolled prospectively. In addition to admission head CT, early brain MRI was performed 12 ± 3.9 days after injury. Univariate and multivariate logistic regression were used to assess for demographic, clinical, socioeconomic, CT, and MRI features that were predictive of Extended Glasgow Outcome Scale (GOS-E) at 3 months postinjury.

Results: Twenty-seven percent of MTBI patients with normal admission head CT had abnormal early brain MRI. CT evidence of subarachnoid hemorrhage was associated with a multivariate odds ratio of 3.5 (p = 0.01) for poorer 3-month outcome, after adjusting for demographic, clinical, and socioeconomic factors. One or more brain contusions on MRI, and ≥4 foci of hemorrhagic axonal injury on MRI, were each independently associated with poorer 3-month outcome, with multivariate odds ratios of 4.5 (p = 0.01) and 3.2 (p = 0.03), respectively, after adjusting for head CT findings and demographic, clinical, and socioeconomic factors.

Interpretation: In this prospective multicenter observational study, the clinical relevance of abnormal findings on early brain imaging after MTBI is demonstrated. The addition of early CT and MRI markers to a prognostic model based on previously known demographic, clinical, and socioeconomic predictors resulted in a >2-fold increase in the explained variance in 3-month GOS-E.

ANN NEUROL 2013;73:224–235

FIGURE 1: Incidence of computed tomography (CT) versus magnetic resonance imaging (MRI) traumatic brain injury common data element (CDE) abnormalities in 135 study participants. For MRI evidence of contusion and MRI evidence of hemorrhagic axonal injury, progressively darker shades of red indicate larger numbers of lesions (gray legend). Study participants with CT evidence of brain contusion had, in most cases, evidence of 1 or 2 hemorrhagic contusions, with no CT demonstrating >3 convincing brain contusions. CT showed evidence of hemorrhagic axonal injury in 3 of 135 study participants, all with 1 to 3 foci of injury. [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]
Complicated Mild TBI

- When clinical neuroimaging findings are present following a mTBI, the classification changes to “complicated mTBI,” which has a 6-month outcome more similar to moderate TBI\(^1,2\)


From Belanger, 2009
Biological Markers of Injury & Recovery

**Acute Biomarkers**
- UCH-L1
- GFAP
- SBDP150

**Subacute/Chronic Biomarkers**
- MAP2
- SBDP120
- MBP
- CNPase
- GFAP autoantibodies

**Protein Biomarker**
- Injury
- Necrosis
- Axonal Injury
- Glial Damage
- Apoptosis
- Demyelination
- Microgliosis

**Chronic Inflammatory responses to blood vessels and neurons**
- CTE, PD, AD
Clinical Utility of Biomarkers

Measurement of the Glial Fibrillary Acidic Protein and Its Breakdown Products GFAP-BDP Biomarker for the Detection of Traumatic Brain Injury Compared to Computed Tomography and Magnetic Resonance Imaging


Abstract

Gliial fibrillary acidic protein and its breakdown products (GFAP-BDP) are brain-specific proteins released into serum as part of the pathophysiological response after traumatic brain injury (TBI). We performed a multi-center trial to validate and characterize the use of GFAP-BDP levels in the diagnosis of intracranial injury in a broad population of patients with a positive clinical screen for head injury. This multi-center, prospective, cohort study included patients 16–93 years of age presenting to three level 1 trauma centers with suspected TBI (loss of consciousness, post-trauma amnesia, and so on). Serum GFAP-BDP levels were drawn within 24h and analyzed, in a blinded fashion, using sandwich enzyme-linked immunosorbent assay. The ability of GFAP-BDP to predict intracranial injury on admission computed tomography (CT) as well as delayed magnetic resonance imaging was analyzed by multiple regression and assessed by the area under the receiver operating characteristic curve (AUC). Utility of GFAP-BDP to predict injury and reduce unnecessary CT scans was assessed utilizing decision curve analysis. A total of 215 patients were included, of which 83% suffered mild TBI, 4% moderate, and 12% severe; mean age was 42.1 ± 18 years. Evidence of intracranial injury was present in 51% of the sample (median Rotterdam Score, 2; interquartile range, 2). GFAP-BDP demonstrated very good predictive ability (AUC = 0.87) and demonstrated significant discrimination of injury severity (odds ratio, 1.45; 95% confidence interval, 1.29–1.64). Use of GFAP-BDP yielded a net benefit above clinical screening alone and a net reduction in unnecessary scans by 12–30%. Used in conjunction with other clinical information, rapid measurement of GFAP-BDP is useful in establishing or excluding the diagnosis of radiographically apparent intracranial injury throughout the spectrum of TBI. As an adjunct to current screening practices, GFAP-BDP may help avoid unnecessary CT scans without sacrificing sensitivity (Registry: ClinicalTrials.gov Identifier: NCT01565551).

FIG. 1. Box plots showing median levels of GFAP-BDP measured on admission in two groups of patients. Boxes show interquartile ranges, and I bars represent highest and lowest values. CT, computed tomography. GFAP-BDP, glial fibrillary acidic protein and its breakdown products.

FIG. 3. Receiver-operating-characteristic curves for various cutoff levels of GFAP-BDP in differentiating presence or absence of intracranial injury on CT. Curves for GFAP-BDP alone and after adjustment for known predictors of injury and severity (age, GCS, pupillary reactivity, and ISS). AUC, area under the receiver operating characteristic curve; CI, confidence interval; CT, computed tomography; GCS, Glasgow Coma Scale; GFAP-BDP, glial fibrillary acidic protein and its breakdown products; ISS, Injury Severity Scale.
The personal experience and reporting of post-concussion symptoms is likely individualized, representing the cumulative effect of multiple variables, such as genetics, mental health history, current life stress, medical problems, chronic pain, depression, personality factors, and other psychosocial and environmental factors.

The extent to which damage to the structure of the brain contributes to the persistence of post-concussion symptoms remains unclear.
Several injury-related and neuropsychological variables assessed acutely (< 72 hours) post-injury predicted symptom duration, particularly loss of consciousness (mTBI group), acute somatic symptom burden (both groups), and acute reaction time (both groups), with reasonably good model fit when including all of these variables.
Outcome Prediction after Mild and Complicated Mild Traumatic Brain Injury: External Validation of Existing Models and Identification of New Predictors Using the TRACK-TBI Pilot Study


Abstract

Although the majority of patients with mild traumatic brain injury (mTBI) recover completely, some still suffer from disabling ailments at 3 or 6 months. We validated existing prognostic models for mTBI and explored predictors of poor outcome after mTBI. We selected patients with mTBI from TRACK-TBI Pilot, an unselected observational cohort of TBI patients from three centers in the United States. We validated two prognostic models for the Glasgow Outcome Scale Extended (GOS-E) at 6 months after injury. One model was based on the CRASH study data and another from Nijmegen, The Netherlands. Possible predictors of 3- and 6-month GOS-E were analyzed with univariate and multi-variable proportional odds regression models. Of the 386 of 485 patients included in the study (median age, 44 years; interquartile range, 27-58; 75% (n=290) presented with a Glasgow Coma Score (GCS) of 15. In this mTBI population, both previously developed models had a poor performance (area under the receiver operating characteristic curve, 0.49-0.56). In multivariable analyses, the strongest predictors of lower 3- and 6-month GOS-E were older age, pre-existing psychiatric conditions, and lower education. Injury caused by assault, extracranial injuries, and lower GCS were also predictive of lower GOS-E. Existing models for mTBI performed unsatisfactorily. Our study shows that, for mTBI, different predictors are relevant as for moderate and severe TBI. These include age, pre-existing psychiatric conditions, and lower education. Development of a valid prediction model for mTBI patients requires further research efforts.
Acute severity predicts subacute recovery (LOC, PTA, 24 hr GSC)
Toward an Integrated Understanding of Injury, Recovery, Outcome and Risk in TBI

About Injury, Who Comes to Injury, and Response to Injury
Factors Influencing TBI Outcome

L. Nelson et al., 2018

- Personality Traits
- Psychiatric Symptoms
- Cognitive Reserve
- Medical Comorbidities
- Neurophysiology
- Genetics
- Cause of Injury
- TBI Characteristics
- Polytrauma
- Complications
- Pre-Injury Risk/Resilience
- Treatment
- Environment
- Injury Characteristics
- Injury Response
- Attributions/Expectancies
- Cognitive Sequelae
- Neurophysiologic Response
- Epigenetics
- Repeated Trauma Exposure
- Secondary Gain
- Financial Resources
- Social Support

About Injury, Who Comes to Injury, & Response to Injury
Evidence-based mTBI Care

- Early intervention at point of entry (ED)
- Patients with acute/subacute TBI or concussion
  - Before point of contamination
- Inter-disciplinary
  - PM&R, Sports Medicine
  - Neuropsychology
  - Nurse Practitioner
- Systematic Follow-up
- Focus on restoring function, maximizing outcome