Neurobehavioral Sequelae of Concussion/mTBI

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New York, NY

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Disclosures

- This speaker program is sponsored by and on behalf of Abbott and the content of this presentation is consistent with all applicable FDA requirements. The speaker is presenting at the request of Abbott
- Abbott
- NFL Player Disability Plans - consultant, MAP reviewer.

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OBJECTIVES

- Talk about the clinical manifestations
- Discuss challenges in the evaluation of Neurobehavioral Sequelae (NBS) of concussion/mTBI
- Discuss the importance of a comprehensive approach in the evaluation of concussion/mTBI patients
- Discuss management options

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Key Points

- A concussion is a mTBI; not all mTBI are a concussion
- An mTBI defines a patient who has had trauma to the brain but is awake (GCS 13-15)
  - It does not exclude patients with traumatic lesions identified on CT (E.g., traumatic subdural patient may be alert GCS 15)
  - It does not exclude patients who are at risk of deterioration
- A functional definition of concussion is emerging that is based on objective measures of neurologic or cognitive function
- Future research needs to focus on establishing diagnostic criteria for concussion
  - Once diagnostic criteria are established, prognosis and treatment studies can be done

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BTF / CDC / DoD
Concussion Definition Consortium

- Multidisciplinary task force
- Goal to develop an evidence-based definition of concussion
- Key questions:
  - What are the most common signs, symptoms, and neurologic and cognitive deficits after a PCE
  - What is the association between signs, symptoms, and deficits
  - What is the relationship between signs, symptoms, and deficits with imaging and biomarkers

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Concussion Definition Consortium

- 5545 abstracts: 1336 full text articles
- 56 were rated medium potential for bias
- 24 had inclusive case definitions and reported data at fixed time points

New Jersey Least Corrupt? Ha, Ha

By Paul Sherman
And David M. Primo

Exaggerated claims about political corruption from self-styled good-government groups are nothing new. Often they're made with no data to back them up. Perhaps more dangerous is when the claims are supported with bad data, yet reported faithfully by the media with little scrutiny.

So it is with the study released last month by a consortium led by the Center for Public Integrity, which concludes that of all 50 states, the one with the lowest risk of political corruption is . . . New Jersey.

Because other groups such as Common Cause and newspaper editorial boards including the New York Times and the Washington Post are already pointing to the "State Integrity Investigation" as evidence that more regulation of lobbying and campaign finance is needed, it's worth taking a critical look. The Garden State has many virtues, but a reputation for political integrity is not among them.

New Jersey's place at the top of the heap isn't the only curious conclusion reached in the study. Virginia—which in 2008 by the Pew Center on the States—earned an F grade, placing it with seven other states, including North and South Dakota, that allegedly have the greatest risk of political corruption.

The flawed methodology behind the recent 'State Integrity Investigation.'

These sorts of findings admit of only two explanations: Either New Jersey has gotten a bum rap in the past or something is very wrong with the State Integrity Investigation.

For starters, the study never actually defines what it means by corruption. Instead, the risk of corruption is defined by the presence or absence of certain laws—such as strict campaign-finance limits and lobbying disclosure—that good-government groups promote. But without a working definition of corruption, it is impossible to determine whether these sorts of reforms are the appropriate remedy.

Is regulation of state insurance commissions, for example, as important as lobbying disclo- gives equal weight to both. Yet that's like assuming aspirin is as good as a herbal supplement because some people think both can cure headaches.

All of which leads to the biggest problem with the State Integrity Investigation—the dearth of evidence demonstrating that many of the promoted reforms, such as public input into legislative redistricting and registration of lobbyists, actually prevent corruption.

Despite years of effort by proponents of strict campaign-finance laws, there's no strong evidence that such laws affect either actual corruption or the public perception of corruption. Despite this absence of evidence, Virginia is penalized in the State Integrity Investigation because it has no campaign-finance limits (nor, it should be noted, any meaningful history of corruption).

The conclusions of the State Integrity Investigation are in conflict with other studies that have attempted to measure how well the states are governed. For example, the Pew study mentioned earlier, "Grading the States 2008," concluded that Utah, Virginia and Washington were the best-governed states in the country. The State Integ- tively.

The Pew methodologic own, but if grades for a emphasizes a (such as wh cost-benefit a tions, or enga spending prac that measure have laws that might do som ruption—we'll ernance meas

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Concussion Definition Consortium

- Insufficient evidence is available to derive diagnostic criteria for a concussion from symptoms
- Neither loss of consciousness nor post traumatic amnesia are pre-requisite for the diagnosis of concussion
- Objective measures that may be indicators of concussion include deficits in balance; and deficits in concentration, memory, recall, processing speed, verbal memory, memory composite
- Limited evidence links signs, symptoms, and cognitive deficits
- There is insufficient evidence linking biomarkers and / or brain imaging with signs, symptoms, neurologic and or cognitive deficits

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NBS

- The majority of concussion patients will have resolution of symptoms within days to 3 months.
- Most studies indicate that complete recovery is the norm
- In approximately 15-20% of post concussion patients who seek care, NBS may persist beyond 3 months (these pts will either return to the ED or will see psych or neuro care)

Carroll LJ et al. J Rehab Med. 2004;43 suppl: 84-105

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NBS

- NBS can include
  - Cognitive:
    - Attention/concentration problems, memory problems, executive dysfunction (Impairment of Attention, has been described as one of the most prevalent indicators of concussion)
  - Affective
    - Irritability/anxiety, apathy/depression, impulsivity/aggression, emotional liability
  - Somatic
    - Headache, dizziness/vertigo, impairment of balance/ vestibular dysfunction, sleep disturbance, nausea, disturbance of vision, sensitivity to light/sound, fatigue, seizures.

Carney N.et al Neurosurg.2014;75:S1-S2

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NBS

- Well designed, retrospective study by Voormolen et al:
  - 1000 mTBI pts were compared to 1000 patients without TBI;
  - Results indicated that the symptoms that we see in mTBI are also prominent in the general population and thus not unique to a mTBI injury, emphasizing the importance of a comprehensive approach and of a detailed history and differential diagnosis

Voormolen DC. Brain Inj.2019;33 (8):1078-1086

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NBS

- Evaluating the NBS of concussion requires a detailed understanding of a patient's neurological, psychiatric, and primary illnesses both pre-and post-injury and includes a careful assessment of potential contributory factors.(sx alone are not dx but often multifactorial)
- Provide education and reassurance that recovery is the norm
- Normalized the experience

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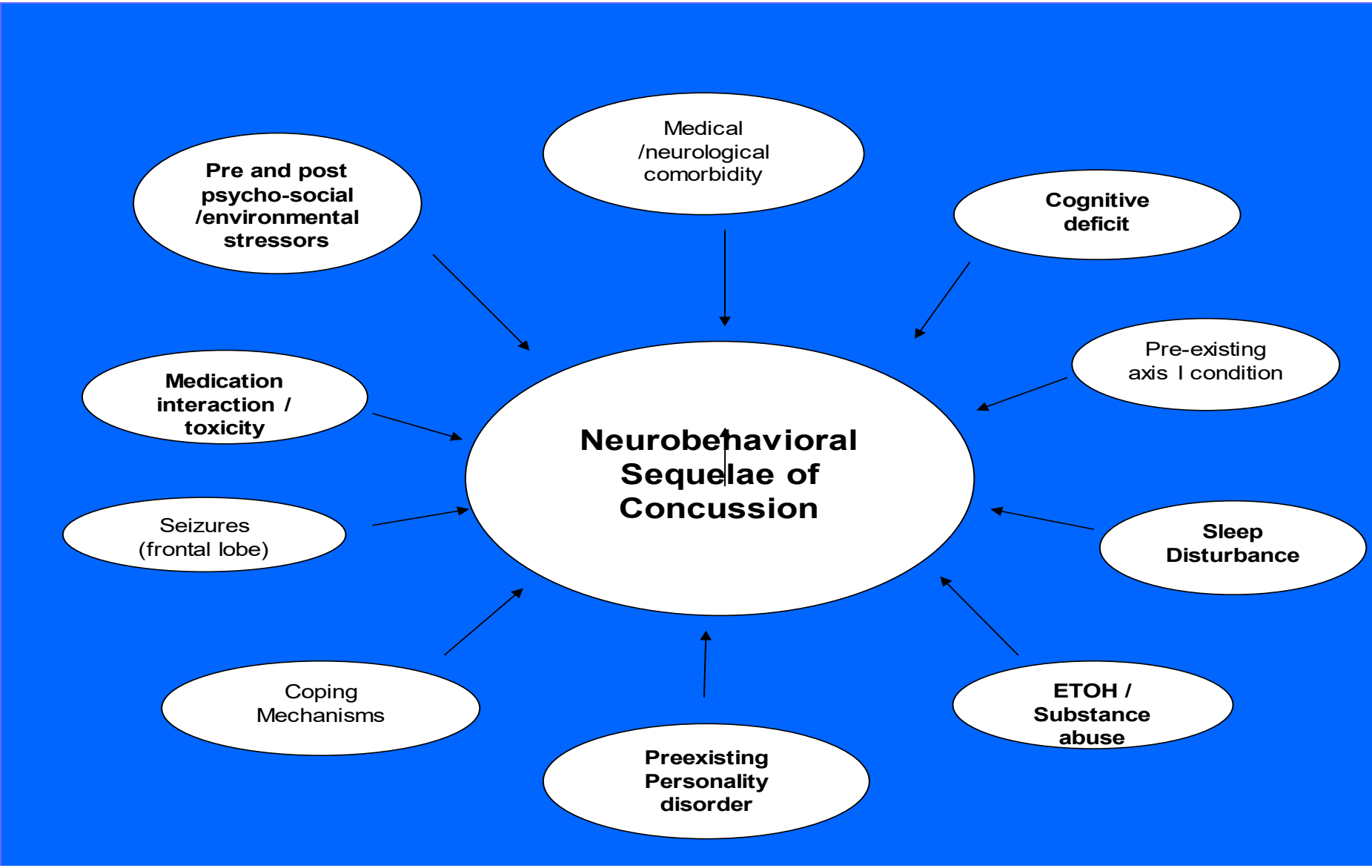
Comprehensive History

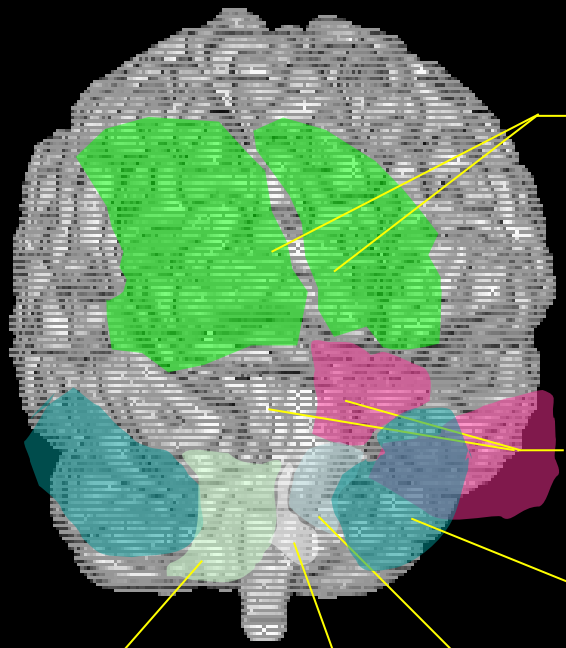


NBS

- Sx vary in:
  - Severity
  - Duration

  Depending on:
  - Medical, Psychiatric/ Neurologic comorbidities
  - Possible concomitant side effects of medications
  - Pre and Post Psychosocial factors
  - Individual coping mechanisms
  - Social and economic support
  - Extent of the injury and type of injury
  - Localization
  - Lateralization

  - Misdiagnosis can occur in case of FLE



Dorsolateral cortex: executive function : (Difficulty with planning, organizational skills , shifting parameters,)

Orbitofrontal cortex (Characterized by prominent personality changes emotional liability, irritability, impulsivity, aggression, disinhibition, bizarre behavior)

Mesial Frontal: decreased spontaneous activity that ranges from akinetic mutism to transient abulic hypokinesia (can be mistaken for major depression)

Anterior temporal cortex (memory , language)

Amygdala (emotional learning and conditioning, including fear/anxiety)

Ventral brainstem (arousal, ascending activation of diencephalic, subcortical, and cortical structures)

Hippocampus (memory)

Assessing Neurocognitive Function

- In the acute phase (e.g. on the sidelines) cognition is often assessed using a standardized evaluation form such as the SCAT 5
- In the subacute and chronic periods either pencil and paper or computer based testing can be done
- A challenge of interpreting the findings of cognitive tests may be the lack of a baseline comparison

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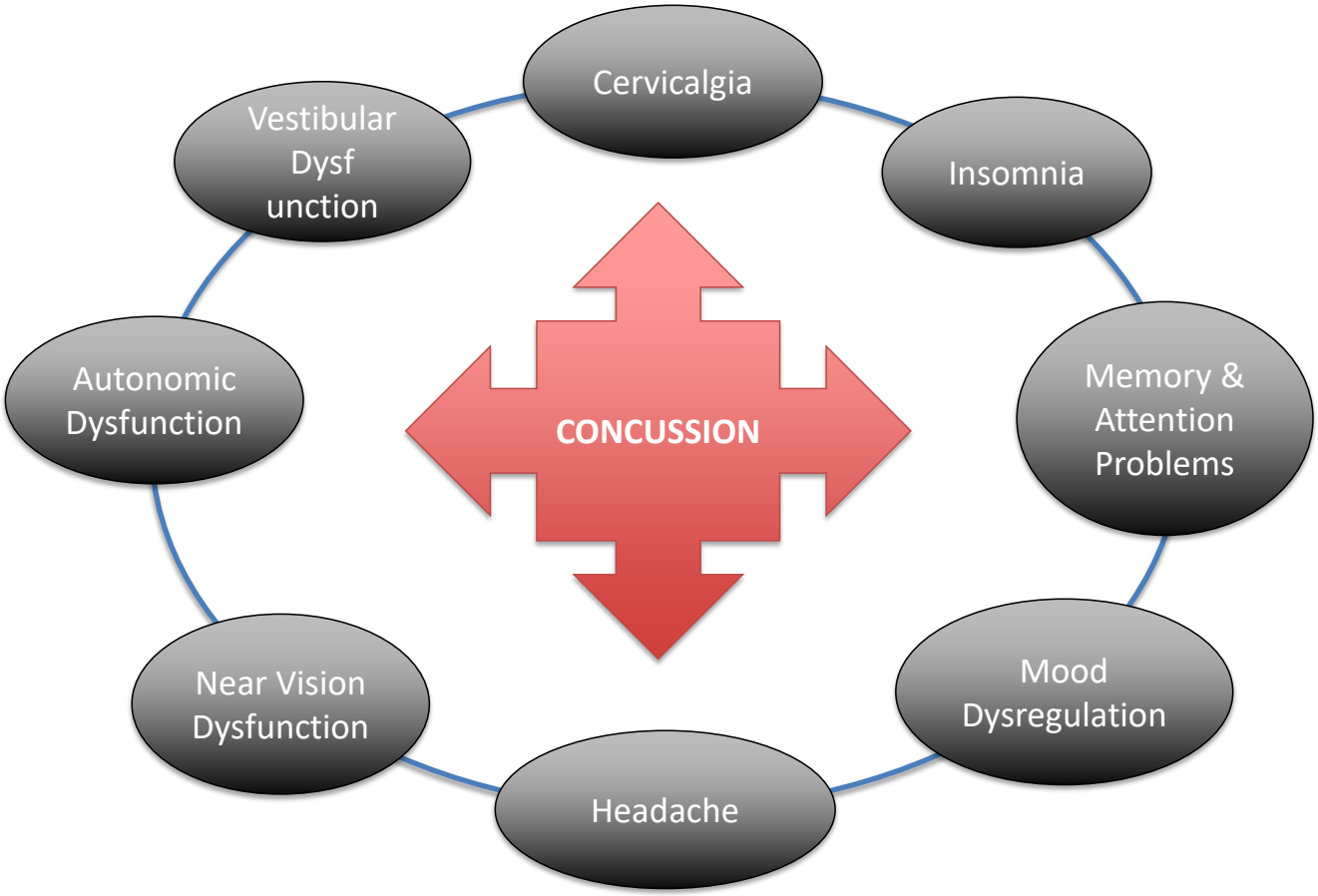
NBS Clusters



NBS: Cognition

- Impairment of attention/memory and balance are the hallmarks of concussion in the acute phase
- Cognitive Dysfunction is a prevalent finding associated with mTBI (as evidenced by increased reaction time, impaired verbal learning and memory)
- Clinicians must determine if the cause is due to the CNS injury itself or to some other confounding condition (e.g. pain, poor sleep, medication, pre-existing medical comorbidities/ psychiatric disorders)
  - If the pt has an underlying affective disorder and or psychotic disorder, attention can also be impaired
  - Mood Sx post mTBI (due to fear of loosing their job, fear of disability or other possible consequences of the mTBI, poor social support, weak defense mechanisms, ETOH, drug use and others)
- Neither LOC nor PTA reliably stratifies those patients at greater risks for cognitive deficit

Carney N. et al. Neurosurgery.2014:75:S1-S2
Lumba-Brown A,. Neurosurgery/ 2020;86 (1): 2-13

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NBS: Aggression

- Aggression is more commonly reported after a moderate TBI than after mTBI
- Risks factors for aggression after mTBI include frontal lobe injury, premorbid affective disorder, personality disorder, alcohol and/or substance use.
- Aggressive behavior in mTBI patient has been identified as a precursor to depression and suicide risk, suggesting that clinical interventions treating anger may inhibit the pathway to suicide risk in this group

Stanley IH et all. J. Psychiatric Res. 2017;84;161-168

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NBS: Substance Abuse

- Many studies have cited substance abuse as a risk factor for TBI
- Premorbid substance use has been found to be strongly associated with post-TBI drug use
- A 30 year longitudinal study by Koponen et al showed that 71% of mTBI pts who were using drugs currently also did so pre-TBI

KoponenS et all. Am. J Psychiatry.2202;159:1315-1321

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NBS: Depression

- Depression: is one of the most frequent reported NBS of mTBI
- Prevalence has generally been reported to be significantly higher than the 17% reported in the general population (though varies from study to study based on the methodology)
- The degree to which premorbid psychiatric disorder increases the risk for NBS after mTBI is unclear though studies suggests that there is a positive correlation
- Risks factors for developing major depression after mTBI fall into two categories
  - Pre-morbid psychiatric pathology
  - Low socioeconomic status

Barker- Collo et al.Brain Injury . 2015; 29 (7-8); 859-865

Roy D et al. Brain Injury . 2019; 33 (8) : 1064-1069

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NBS: Anxiety

- Some studies suggest:
  - an association between anxiety and mTBI
  - and that an acute stress disorder may predispose mTBI patients to develop PTSD but cause and effect relationship is unclear
- It has been hypothesized that LOC and or post traumatic amnesia may be protective against the development of PTSD by inhibiting assess to traumatic memories
- The best available evidence on the relationship between mTBI and PTSD comes from a military study by Hoge et al.
  - After adjusting for PTSD and depression they reported that mTBI was not significantly associated with PTSD

Hoge CW et all. New England J. Med 2008;358:453-463

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NBS: Somatic Sx

- H/A is the most commonly reported somatic sx after mTBI (this may cause people to become anxious or depressed)
- A hx of H/A increases the risk of having a headaches after mTBI though the majority resolve within 3 months.
- H/A normally co-occurs with other NBS
- Baandrup and Jensen reported that:
  - 53% of patients had at least one other somatic complaint
  - 49% had at least one cognitive complaint
  - 26% had at least one psychiatric complaint
  - 17% had all 3 types of complaints
  - 17% had none

Sufrinko A. J. Head Trauma Rehab. 2018;131:17-24
Baandrup L. Cephalgia .2005; 25;132-138

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NBS: Dizziness

- Is the second most commonly reported somatic complaints after head injury.
- Most studies do not separate the complaint of dizziness from that of vertigo.
- Dizziness/Vertigo can have a major impact on the overall well being and may contribute to anxiety and other NBS.

Lumba-BrowN a. Neurosurgery. 2020; 86 (1): 2-13

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NBS: Sleep Disturbance

- Is a frequently reported NBS
- Veterans who sustained an mTBI during deployment indicated a increased incidence of poor sleep quality compared to Veterans without a history of mTBI even when combat exposure and behavioral health issues were taken into consideration.
- Key to managing sleep disorders is identifying the factors contributing to the presentation
- Sleep disturbance may contribute to neurocognitive and neurobehavioral deficits and increase recovery time following mTBI
- Early intervention may improve patient's outcome and reduce secondary effect of mTBI

Rao V et al. Curr Treat Options Neurol. 3003; 4:77-87

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NBS: Fatigue

- Fatigue occurs in up to 70% of mTBI pts and may complicate the assessment of depression in these patients
- Like other sx it typically improves within 3 months
- It can be disabling and its etiology / can be multifactorial:
  - Sleep disorder
  - Pain
  - Cognitive Deficits
  - Mood Disorders
  - Medical co-morbidities
  - Lack of physical exercise
  - Medications
- It can be associated with poor social integration, decreased level of productive activities, decreased overall quality of life

Cantor J.B. et all. J. Head Trauma Rehab. 2008;23:41-51

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FLE after mTBI

- Seizures of Frontal Lobe Origin can be difficult to diagnose because they can present with a wide variety of clinical manifestations, frequently mimicking psychiatric disorders
- FLE can be characterized by RMA and bizarre behavior
- Because of the lack of tonic–clonic activity and or LOC and at times lack of post ictal confusion they can be frequently misdiagnosed to be psychiatric in origin.
- The episodes are usually stereotypic, brief in duration with a variable post ictal phase (32 sec from EEG onset and lasting 35 sec)
- EEG: in our series of 21 pts with FLE who underwent surgery
  - 14% Had a NL EEG
  - 14% Had a strict frontal focus
  - 29% showed a bilateral spike-slow
  - 43% Focal temporal focus

Riggio S. Harner RN. Epilepsy and the Functional Anatomy of the Frontal Lobe. Raven Press:1995:153-166

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Return to work or play

- Deficits in attention and information processing may interfere with the performance of pre-injury tasks.
- Patients should be symptom free at rest and with exertion (in order to avoid re-injury)
- Little is known regarding the incidence of recurrent concussion or whether repetitive concussion or head impact exposure leads to cognitive impairment directly or indirectly
- Ideally patients should be determined to be cognitively at their baseline prior to returning to full activities

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Acute Concussion Evaluation - Summary

- Based on the best available evidence, acute assessment of concussion should include:
  - Documentation of LOC / PTA
  - Symptom checklist that includes; headache, nausea, dizziness, fogginess, difficulty with vision, concentration, balance, seizures.
  - Assessment of orientation, attention, memory
  - Assessment of reaction time
  - Assessment of balance
- Discharge instructions should include education on return to work, NBS; guidance on when and where to follow-up; appropriate time off

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NBS: Treatment Options

- Understanding of the underlying mechanisms of the various symptoms can have marked implications on:
  - When do we treat
  - On the treatment we choose
  - Which modality we choose (pharmacotherapy vs psychotherapy)
  - Decrease risks for disability

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Summary

- Individuals with concussion may present with common cluster of cognitive, somatic, behavioral changes
- Neurobehavioral sequelae may be multifactorial in origin
- Comprehensive evaluation is key
- Therapy needs to be individualized to the pt
- Early treatment education and reassurance are fundamental to good outcome

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4224.REV1 05/22

Biomarker Use for Evaluating mTBI: A Game-changing New Technology

Chris Davlantes, MD, FACEP
Sr. Director, Global Medical Affairs

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- The speaker is employed by Abbott Point of Care
  - Sr. Director of Global Medical Affairs

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Background

- Board-certified in Emergency Medicine >25 years
- Assistant Professor, Dept. of Emergency Medicine University of Kansas Medical Center (Kansas City, KS)
- Attending Physician, Lenox Health Greenwich Village (Manhattan, New York City, NY)

Thinking Outside the Box

4079.REV2

Demographics

~69 million

Global annual estimate, sustain a TBI[1,2]

>80%

Have mTBI with a Glasgow Coma Scale (GCS) score of 13-15[1,3]

~5 million

US Patients present to an ED with TBI[4]
(~6% of ED patients)

94.5%

Are mTBI (GCS 13-15)[4]

82%

Get a CT Scan[4]

90%

CT Scans show no evidence of traumatic abnormality[4]

REFERENCES: 1. Dewan MC et al. *J Neurosurg*. 2004;43(suppl):113-125. **2.** Centers for Disease Control and Prevention. Updated March 29, 2019. Accessed January 20, 2021. https://www.cdc.gov/traumaticbraininjury/data/tbi-ed-visits.html. **3.** Brainline. What is the Glasgow Coma Scale? Published February 13, 2018. Accessed November 13, 2020. https://www.brainline.org/article/what-glasgow-coma-scale. **4.** Korley FK et al. *J Head Trauma Rehabil*. 2016;31(6):379-387.

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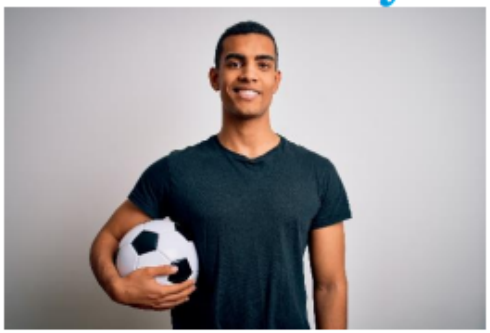
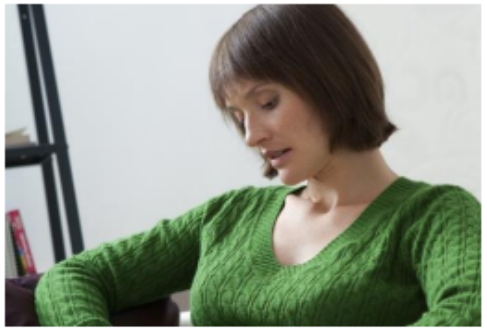
mTBI can present in various ways





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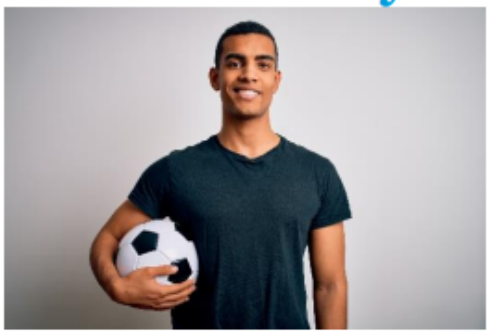

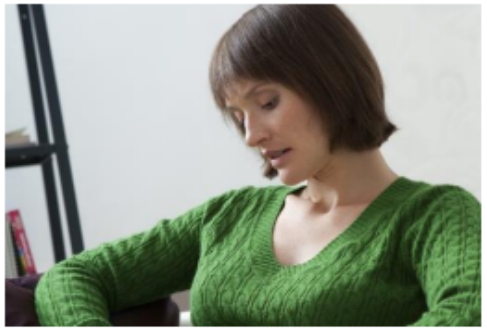

- 75-year-old female
- Found on the floor next to her bed; Fall suspected
- Unable to give accurate history due to dementia
- Not taking any oral anticoagulants
- GCS = 14

Clinical Decision Rules

Canadian CT Head Rule

- **Inclusion Criteria**
  - GCS 13-15 w/ ONE of the following:
    - Loss of consciousness
    - Amnesia to the head injury event
    - Witnessed disorientation
- **Exclusion Criteria**
  - Age < 16 years
  - Blood thinners
  - Seizure after injury

Consider CT if:

- **High Risk Criteria**
  - GCS < 15 at 2 hours post-injury
  - Suspected open/depressed skull fracture
  - Signs of basilar skull fracture
  - $\geq$ 2 episodes of vomiting
  - Age $\geq$ 65 years
- **Medium Risk Criteria**
  - Retrograde amnesia $\geq$ 30 min
  - “Dangerous Mechanism”

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  - Retrograde amnesia ≥ 30 min
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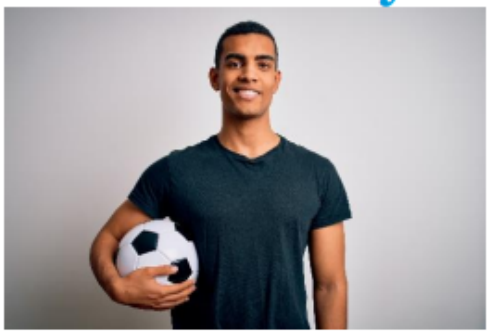
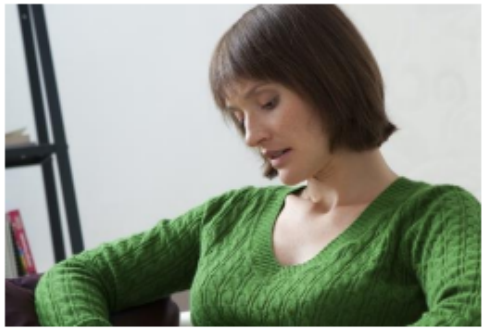


- 20-year-old male
- Head-on collision during soccer game
- No LOC, but briefly disoriented on the field
- Retrograde amnesia
- Hx of 3 previous TBIs in past 12 months and negative CT



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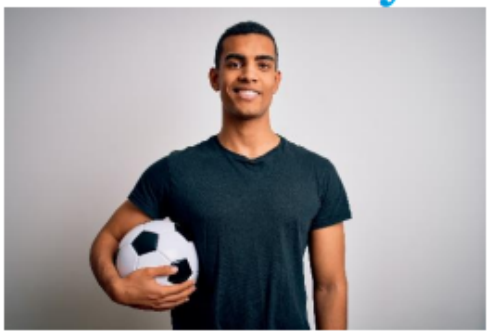

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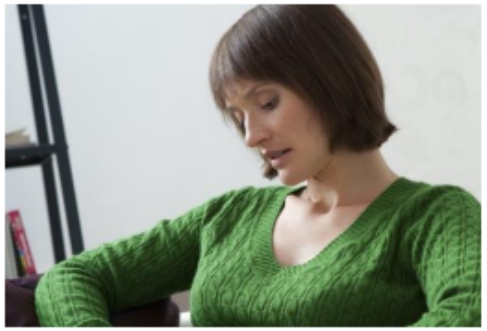

- 30-year-old female brought to the ED by ambulance due to altered mental status
- Friends found her vomiting in ladies' room, ? fall
- Brief LOC at scene per EMS
- Odor suggestive of ETOH on breath, likely intoxicated
- GCS = 15

Clinical Decision Rules

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Clinical Decision Rules

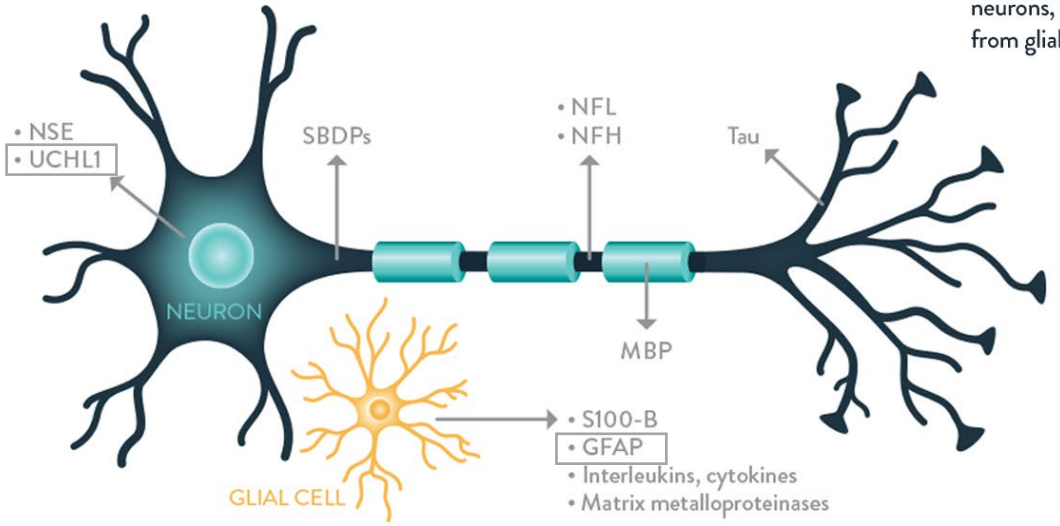
New Orleans Head CT Rule

- **Inclusion Criteria**
  - LOC
  - GCS 15
  - Normal brief neuro exam
- **CT necessary if any ONE of the following:**
  - Headache
  - Vomiting
  - Age > 60 years
  - Drug or alcohol intoxication
  - Short-term memory deficit
  - Visible trauma above the clavicles
  - Seizure

Cellular Origins of TBI Biomarkers

Following TBI, there is increased permeability and leakage of molecules across the blood-brain barrier

Biomarkers differ in their cellular origins—some are derived from the cell body, axon, or dendrite of neurons, while others are derived from glial cells.[6]



Reprinted from Nature Reviews Neurology, 12, Zetterberg K, & Blennow K, Fluid biomarkers for mild traumatic brain injury and related conditions, Page 574, 2016. Reproduced with permission from copyright holder.[6]

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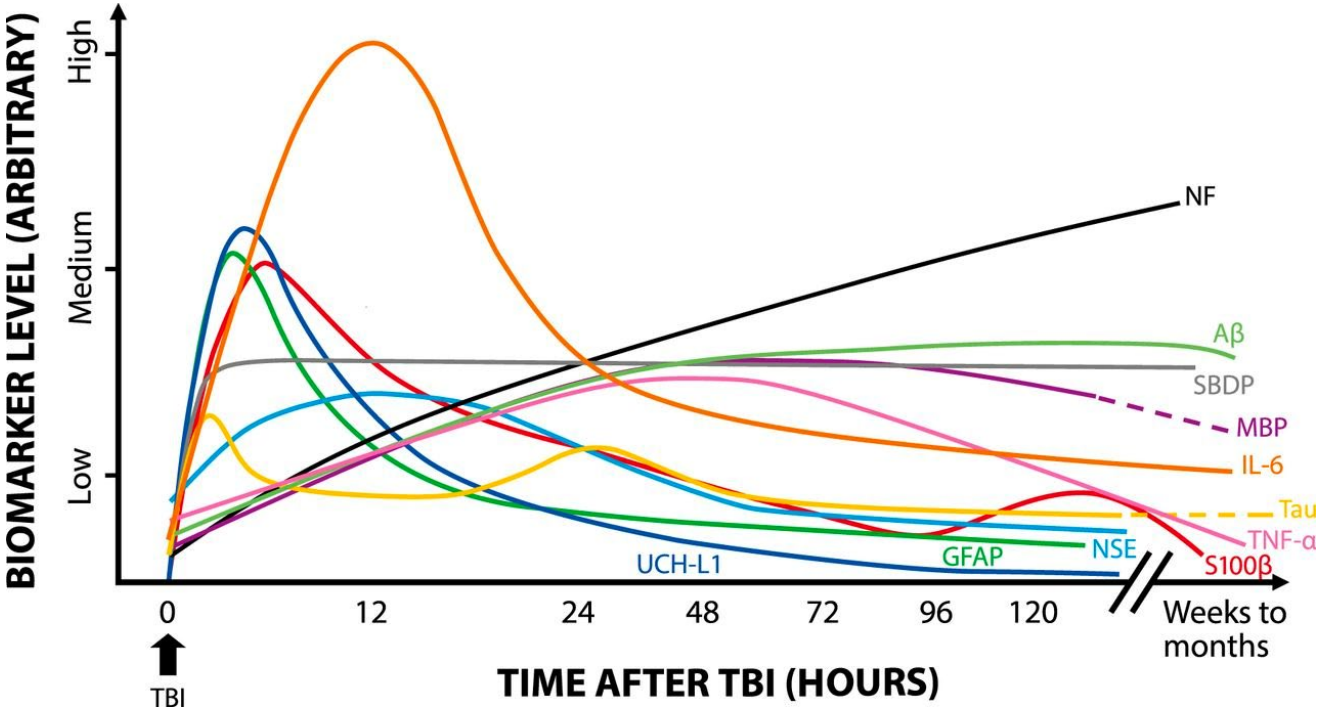
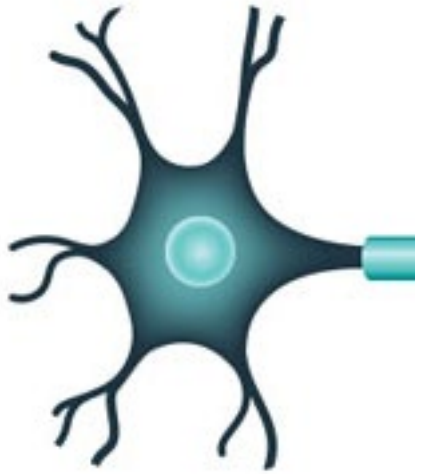
Levels must be measurable in peripheral blood shortly after the onset of injury



References: 1. Wang K, Yang Z, Zhu T, Shi Y, Rubenstein R (2018): An update on diagnostic and prognostic biomarkers for traumatic brain injury, Expert Review of Molecular Diagnostics

Ubiquitin C-terminal hydrolase-L1 (UCH-L1)[1]

- **EVIDENCE DEMONSTRATES:**
  - Ability to discriminate between mTBI patients and patients without head injuries.
  - Significantly elevated levels in patients with TBI lesions on CT
  - Higher levels in patients who required neurosurgical intervention.



NEURONAL BIOMARKER
Protein involved in the metabolism of ubiquitin

Classification performance for detecting intracranial lesions on CT* :

100% sensitivity (95%CI 88–100) • 21% specificity (95%CI 13–32)
100% negative predictive value (95%CI 76–100)

*UCH-L1 cutoff level of 0.09 ng/mL

Reference: **1**. Papa L, Lewis LM, Silvestri S, et al. Serum levels of Ubiquitin C-terminal Hydrolase (UCH-L1) distinguish mild traumatic brain injury (TBI) from trauma controls and are elevated in mild and moderate TBI patients with intracranial lesions and neurosurgical intervention. *J Trauma Acute Care Surg*. 2012;72(5):1335-1344.

Glial fibrillary acidic protein (GFAP)[1]

- **EVIDENCE DEMONSTRATES:**
  - Reliably distinguishes between trauma patients with mTBI and those without head injury
  - Levels elevated in patients with traumatic intracranial abnormalities on CT compared to patients without lesions
  - Potential to be used to predict those patients who require neurosurgical intervention

Classification performance for detecting intracranial lesions on CT* :

97% sensitivity (95%CI 82–100) • 18% specificity (95%CI 11–28)
94% negative predictive value (95%CI 68–100)[10]

ASTROCYTE BIOMARKER
A structural protein

*GFAP-BDP cutoff level of 0.035 ng/mL

Reference: Papa L, Lewis LM, Falk JL, et al. Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. *Ann Emerg Med*. 2012;59(6):471-483.

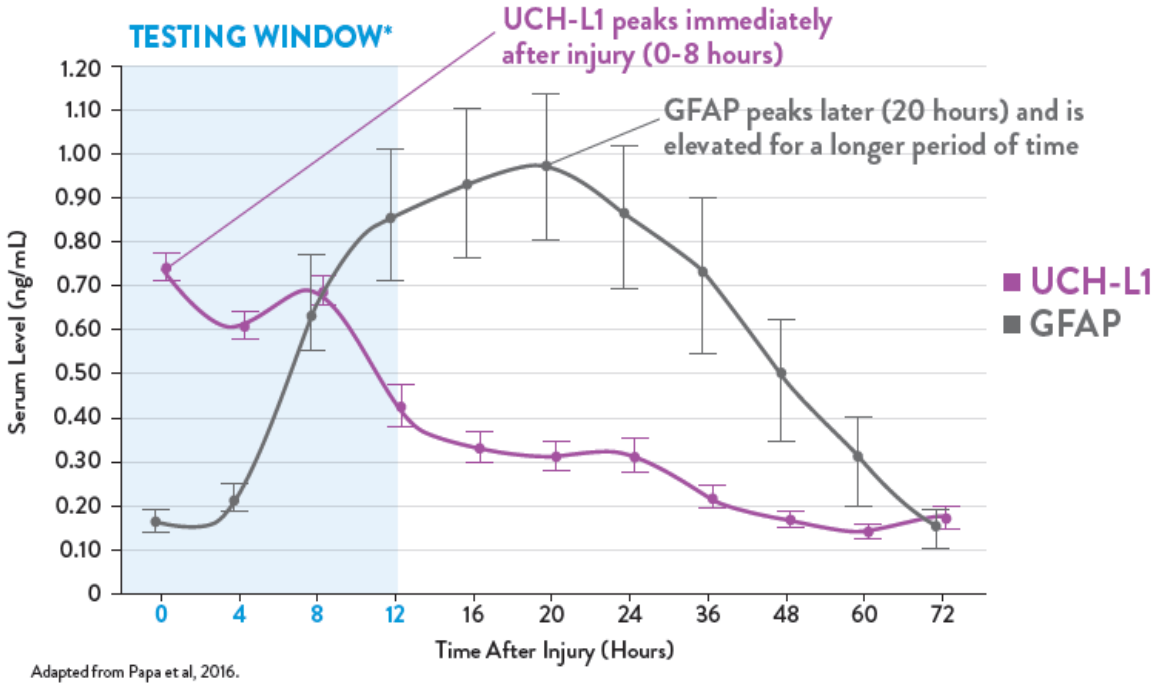
Comparing available mTBI biomarkers

Essential Characteristics	UCH-L1	GFAP	S100β
Levels must be measurable in peripheral blood shortly after the onset of injury[1-3]	✓ Elevated up to **24 hours** after injury	✓ Elevated up to **72 hours** after injury	✓ Elevated up to **6 hours** after injury
The test should have sufficient sensitivity to be able to diagnose mTBI[2-4]	✓ **100%**	✓ **97%**	✗ **61%**
Levels are unaffected by non-head trauma[5-7]	✓	✓	✗ **Elevated in non-CNS trauma conditions, e.g. melanoma, fractures, extracranial injuries**

References: 1. Papa L, Lewis LM, Silvestri S, et al. Serum levels of Ubiquitin C-terminal Hydrolase (UCH-L1) distinguish mild traumatic brain injury (TBI) from trauma controls and are elevated in mild and moderate TBI patients with intracranial lesions and neurosurgical intervention. *J Trauma Acute Care Surg*. 2012;72(5):1335-1344. **2**. Papa L, Lewis LM, Falk JL, et al. Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. *Ann Emerg Med*. 2012;59(6):471-483. **3**. Chabok SY, Moghadam AD, Saneei Z, et al. Neuron-specific enolase and S100BB as outcome predictors in severe diffuse axonal injury. *J Trauma Acute Care Surg*. 2012;72(6):1654-1657. **4.** Nygren de boussard C, Fredman P, Lundin A, et al. S100 in mild traumatic brain injury. *Brain Inj*. 2004;18(7):671-683. **5**. Anderson RE, Hansson LO, Nilsson O, et al. High serum S100B levels for trauma patients without head injuries. *Neurosurgery*. 2001;48(6):1255-1260. **6**. Unden J, Bellner J, Eneroth M, et al. Raised serum S100B levels after acute bone fractures without cerebral injury. *J Trauma*. 2005;58:59-61. **7**. Andres R, Mayordomo JI, Zaballos P, et al. Prognostic value of serum S-100B in malignant melanoma. *Tumori*. 2004;90:607-610.

“Rule-Out CT test” for mTBI

The i-Stat TBI Plasma test combines two complementary, brain specific biomarkers (GFAP and UCH-L1) in a single test designed to optimize sensitivity and Negative Predictive Value (NPV) to help determine the need for CT



Adapted from Papa et al, 2016.

4079.REV2

Accuracy of a rapid glial fibrillary acidic protein/ubiquitin carboxyl-terminal hydrolase L1 test for the prediction of intracranial injuries on head computed tomography after mild traumatic brain injury

Jeffrey J. Bazarian MD, MPH[1] | Robert D. Welch MD, MS[2,3] | Krista Caudle PhD[4] | Craig A. Jeffrey PhD[5] | James Y. Chen MD[6,7] | Raj Chandran PhD[8] | Tamara McCaw[5] | Saul A. Datwyler PhD[8] | Hongwei Zhang PhD[5] | Beth McQuiston MD[8]

- ALERT-TBI Study data (2012-14), 22 sites in US and Europe
- > or = 18 years, head injury, GCS 9-15, all underwent HCT + testing (<12 h of injury)
- Used i-STAT Alinity and TBI Cartridges
- Outcome was traumatic intracranial injury
- Test: Either GFAP or UCH-L1 “elevated” was a positive test
- 1901 subjects with mTBI (GCS 13-15)
- Sensitivity: 95.8% (CI 90.6-98.2%); Specificity: 40.4% (CI 38.2-42.7%)
- NPV: 99.3% (CI 98.5-99.7%); PPV: 9.8% (8.2-11.6%)

Academic Emergency Medicine, 2021 Epub

Results of Pivotal Study established NPV & Clinical Sensitivity for Rule-Out CT Claim

i-STAT TBI PLASMA TEST	ADJUDICATED CT RESULT		TOTAL
Test Interpretation	**Positive**	**Negative**	
Elevated	115	1061	1176
Not Elevated	5	**720**	725
Total	120	1781	1901

95.8% Sensitivity

40.4% Specificity

9.7% PPV

99.3% NPV

4079.REV2

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4079.REV2

Hot Off the Press:
CDRs + TBI Biomarkers

JAMA Network Open.

Original Investigation | Emergency Medicine

Evaluation of Glial and Neuronal Blood Biomarkers Compared With Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients With Mild Traumatic Brain Injury

Linda Papa, MDCM, MSc; Jay G. Ladde, MD; John F. O'Brien, MD; Josef G. Thundiyil, MD; James Tesar, MD; Stephen Leech, MD; David D. Cassidy, MD; Jesus Roa, MD; Christopher Hunter, MD, PhD; Susan Miller, MD; Sara Baker, MD; Gary A. Parrish, MD; Jillian Davison, MD; Christine Van Dillen, MD; George A. Ralls, MD; Joshua Briscoe, MD; Jay L. Falk, MD; Kurt Weber, MD; Philip A. Giordano, MD

Abstract

IMPORTANCE In 2018, the combination of glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase (UCH-L1) levels became the first US Food and Drug Administration–approved blood test to detect intracranial lesions after mild to moderate traumatic brain injury (MTBI). How this blood test compares with validated clinical decision rules remains unknown.

OBJECTIVES To compare the performance of GFAP and UCH-L1 levels vs 3 validated clinical decision rules for detecting traumatic intracranial lesions on computed tomography (CT) in patients with MTBI and to evaluate combining biomarkers with clinical decision rules.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study from a level I trauma center enrolled adults with suspected MTBI presenting within 4 hours of injury. The clinical decision rules included the Canadian CT Head Rule (CCHR), New Orleans Criteria (NOC), and National Emergency X-Radiography Utilization Study II (NEXUS II) criteria. Emergency physicians prospectively completed data forms for each clinical decision rule before the patients' CT scans. Blood samples for measuring GFAP and UCH-L1 levels were drawn, but laboratory personnel were blinded to clinical results. Of 2274 potential patients screened, 697 met eligibility criteria, 320 declined to participate, and 377 were enrolled. Data were collected from March 16, 2010, to March 5, 2014, and analyzed on August 11, 2021.

MAIN OUTCOMES AND MEASURES The presence of acute traumatic intracranial lesions on head CT scan (positive CT finding).

RESULTS Among enrolled patients, 349 (93%) had a CT scan performed and were included in the analysis. The mean (SD) age was 40 (16) years; 230 patients (66%) were men, 314 (90%) had a Glasgow Coma Scale score of 15, and 23 (7%) had positive CT findings. For the CCHR, sensitivity was 100% (95% CI, 82%-100%), specificity was 33% (95% CI, 28%-39%), and negative predictive value (NPV) was 100% (95% CI, 96%-100%). For the NOC, sensitivity was 100% (95% CI, 82%-100%), specificity was 16% (95% CI, 12%-20%), and NPV was 100% (95% CI, 91%-100%). For NEXUS II, sensitivity was 83% (95% CI, 60%-94%), specificity was 52% (95% CI, 47%-58%), and NPV was 98% (95% CI, 94%-99%). For GFAP and UCH-L1 levels combined with cutoffs at 67 and 189 pg/mL, respectively, sensitivity was 100% (95% CI, 82%-100%), specificity was 25% (95% CI, 20%-30%), and NPV was 100%; with cutoffs at 30 and 327 pg/mL, respectively, sensitivity was 91% (95% CI, 70%-98%), specificity was 20% (95% CI, 16%-24%), and NPV was 97%. The area under the receiver operating characteristic curve (AUROC) for GFAP alone was 0.83; for GFAP plus NEXUS II, 0.83; for GFAP plus NOC, 0.85; and for GFAP plus CCHR, 0.88. The AUROC for UCH-L1 alone was 0.72; for

(continued)

Key Points

Question How does the diagnostic performance of serum glial fibrillary acidic protein (GFAP) and neuronal ubiquitin C-terminal hydrolase (UCH-L1) biomarkers compare with that of validated clinical decision rules for detecting intracranial lesions on computed tomography (CT) of the head in patients with mild traumatic brain injury, and is a combination of biomarkers and clinical decision rules associated with improved performance?

Findings In this cohort of 349 patients with mild traumatic brain injury, the Canadian CT Head Rule (CCHR), the New Orleans Criteria (NOC), and GFAP plus UCH-L1 had 100% sensitivity for detecting lesions on CT, but the CCHR had the highest specificity (33%), followed by GFAP plus UCH-L1 (25%) and the NOC (16%). The combination of GFAP level and the CCHR yielded the highest diagnostic performance.

Meaning These findings suggest that although GFAP plus UCH-L1 and the clinical decision rules performed similarly in detecting intracranial lesions on CT scans, the diagnostic performance was improved when biomarkers were combined with rules, specifically GFAP with the CCHR.

Supplemental content

Author affiliations and article information are listed at the end of this article.

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JAMA Network Open. 2022;5(3):e221302. doi:10.1001/jamanetworkopen.2022.1302 March 14, 2022 1/13

- Prospective cohort study of 349 patients with mTBI conducted at a level I trauma center
- Evaluated validated clinical decision rules, completed in real time by ED physicians during their clinical evaluations, against serum biomarkers GFAP and UCH-L1 in patients with suspected mTBI to detect intracranial lesions on CT scans
- 93% of patients had a CT done; 90% had GCS of 15

Reference: Papa L, Ladde JG, O'Brien JF, et al. Evaluation of Glial and Neuronal Blood Biomarkers Compared With Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients With Mild Traumatic Brain Injury. *JAMA Netw Open.* 2022;5(3):e221302. doi:10.1001/jamanetworkopen.2022.1302

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Original Investigation | Emergency Medicine

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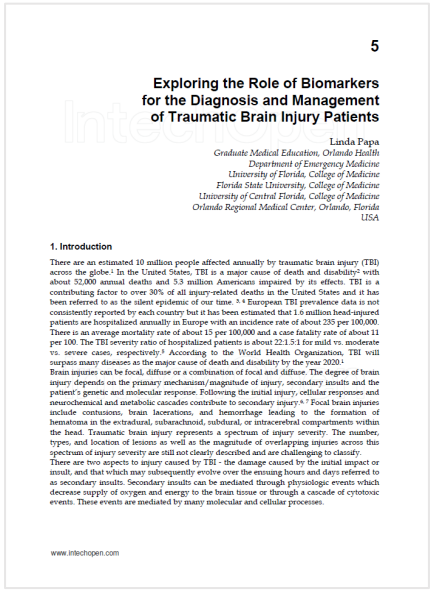
JAMA Network Open. 2022;5(3):e221302. doi:10.1001/jamanetworkopen.2022.1302 March 14, 2022 1/13

- CCHR: Sensitivity 100%, Specificity 33%, NPV 100%
- NEXUS II: Sensitivity 83%, Specificity 52%, NPV 98%
- NOC: Sensitivity 100%, Specificity 16%, NPV 100%
- The combination of the Canadian CCHR and GFAP had the best performance for detecting traumatic intracranial lesions on CT
- 86% would consider a blood test useful compared with the 56% to 61% comfort levels with the decision rules

Reference: Papa L, Ladde JG, O'Brien JF, et al. Evaluation of Glial and Neuronal Blood Biomarkers Compared With Clinical Decision Rules in Assessing the Need for Computed Tomography in Patients With Mild Traumatic Brain Injury. *JAMA Netw Open.* 2022;5(3):e221302. doi:10.1001/jamanetworkopen.2022.1302

The potential gains of biomarkers for TBI assessment in the Emergency Department[1]



5

Exploring the Role of Biomarkers for the Diagnosis and Management of Traumatic Brain Injury Patients

Linda Papa
Graduate Medical Education, Orlando Health
Department of Emergency Medicine
University of Florida, College of Medicine
Florida State University, College of Medicine
University of Central Florida, College of Medicine
Orlando Regional Medical Center, Orlando, Florida
USA

1. Introduction

There are an estimated 10 million people affected annually by traumatic brain injury (TBI) across the globe.[1] In the United States, TBI is a major cause of death and disability[2] with about 52,000 annual deaths and 3.3 million Americans impaired by its effects. TBI is a contributing factor to over 30% of all injury-related deaths in the United States and it has been referred to as the silent epidemic of our time. [3, 4] European TBI prevalence data is not consistently reported by each country but it has been estimated that 1.6 million head-injured patients are hospitalized annually in Europe with an incidence rate of about 235 per 100,000. There is an average mortality rate of about 15 per 100,000 and a case fatality rate of about 11 per 100. The TBI severity ratio of hospitalized patients is about 22:1.5:1 for mild vs. moderate vs. severe cases, respectively.[5] According to the World Health Organization, TBI will surpass many diseases as the major cause of death and disability by the year 2020.[1]
Brain injuries can be focal, diffuse or a combination of focal and diffuse. The degree of brain injury depends on the primary mechanism/magnitude of injury, secondary insults and the patient's genetic and molecular response. Following the initial injury, cellular responses and neurochemical and metabolic cascades contribute to secondary injury.[6, 7] Focal brain injuries include contusions, brain lacerations, and hemorrhage leading to the formation of hematoma in the extradural, subarachnoid, subdural, or intracerebral compartments within the head. Traumatic brain injury represents a spectrum of injury severity. The number, types, and location of lesions as well as the magnitude of overlapping injuries across this spectrum of injury severity are still not clearly described and are challenging to classify.
There are two aspects to injury caused by TBI - the damage caused by the initial impact or insult, and that which may subsequently evolve over the ensuing hours and days referred to as secondary insults. Secondary insults can be mediated through physiologic events which decrease supply of oxygen and energy to the brain tissue or through a cascade of cytotoxic events. These events are mediated by many molecular and cellular processes.

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- Improving patient stratification by injury severity
- Detecting microinjuries to the brain that cannot be seen by CT
- Advancing assessment of intoxicated, unconscious, sedated, or polytrauma patients
- Identifying patients at risk of developing long-term sequelae

* The *i-STAT TBI Plasma* test is not indicated for all the claims listed here

Reference: 1. Papa L. Exploring the role of biomarkers for the diagnosis and management of traumatic brain injury patients. INTECH Open Access Publisher. 2012. Available at: https://www.intechopen.com/books/proteomics-human-diseases-and-protein-functions/exploring-the-role-of-biomarkers-for-the-diagnosis-and-management-of-traumatic-brain-injury-patients. [Accessed Sep 28, 2020].

Improving care for patients with mild injuries

Recovery After Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers
A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study

- 2019, JAMA NEUROLOGY
- "Most patients with mTBI presenting to level I trauma centers report persistent, injury-related life difficulties at 1-year postinjury, suggesting the need for more systematic follow-up of patients with mTBI to provide treatments and reduce the risk of chronic problems after mTBI."[1]

- **85-90%** of head injuries are managed in the ED/acute care setting [2,3]
- **More than half of patients** with mTBI who present to the ED do not receive any TBI diagnosis[4]

- **58%** of mTBI patients receive no educational materials at discharge from the ED[5]
- **56%** of mTBI patients receive no follow-up care from a physician even when they experience post-concussive symptoms[5]

References: **1**. Nelson LD, Temkin NR, Dikmen S, et al. Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers. *JAMA Neurol*.2019;76(9):1049. **2**. GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:56-87. **3**. Coronado VG, Haileyesus T, Cheng TA, et al. Trends in sports-and recreation-related traumatic brain injuries treated in US emergency departments: the national electronic injury surveillance system-all injury program (NEISS-AIP) 2001-2012. *J Head Trauma Rehabil*. 2015;30(3):185-197. **4**. Powell JM, Ferraro JV, Dikmen SS, et al. Accuracy of mild traumatic brain injury diagnosis. *Arch Phys Med Rehabil*. 2008;89:1550-1555. **5**. Seabury SA, Gaudette E, Goldman DP, et al. Assessment of follow-up care after emergency department presentation for mild traumatic brain injury and concussion: results from the TRACK-TBI study. *JAMA Netw Open*. 2018;1(1):e180210.

The effort to reduce CT utilization

CT offers limited capability beyond identification of brain hemorrhage, and is incapable of identifying parenchymal injury associated with mTBI [1,2]

20X

The radiation dose of head CT (2 mSv) is equivalent to 20 times the radiation dose of a chest X-ray[3]

9%

of CT scans for patients with suspected TBI indicate intracranial bleeding and/or skull fracture[4]

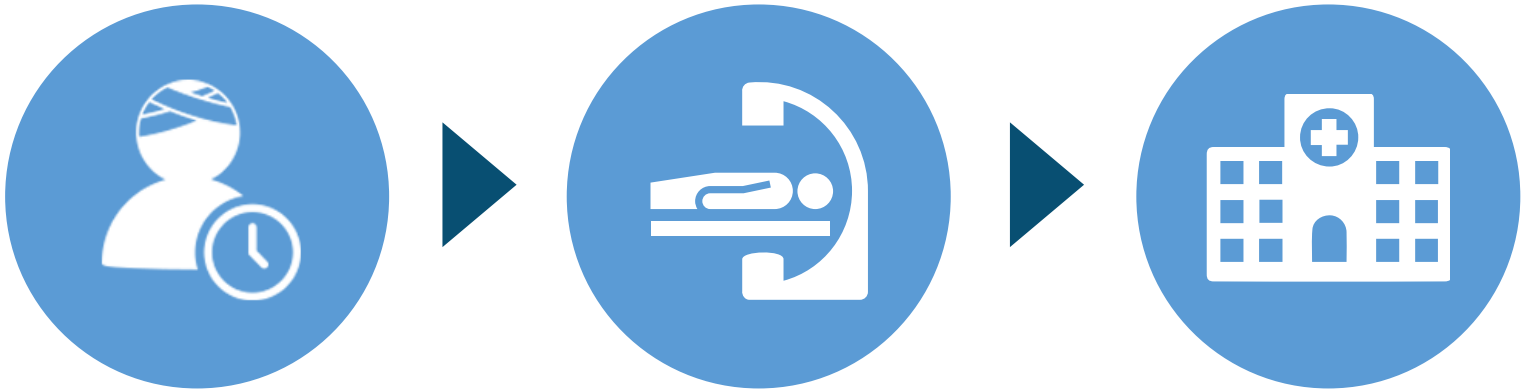
70%

of mTBI patients with normal head CT scans had trauma-related abnormalities on magnetic resonance images.[1]

> *"The number of negative head CT scans represents high-volume, high-cost, but low-value testing—not to mention increasingly recognized radiation risk."*[5] – Korley et al.

References: 1. Yuh EL, Mukherjee P, Lingsma HF, et al. MRI improves 3-month outcome prediction in mild traumatic brain injury. *Ann Neurol*. 2013;73(2):224-235. doi:10.1002/ana.23783. **2**. Yue JK, Cnossen MC, Winkler EA, et al. Pre-injury comorbidities are associated with functional impairment and postconcussive symptoms at 3-and 6-months after mild traumatic brain injury: a TRACK-TBI study. *Front Neurol.* 2019;10:343. **3**. Radiological Society of North America (RSNA) and American College of Radiology (ACR). "Radiation Dose in X-Ray and CT Exams." *Patient Safety*, Mar. 2019, www.radiologyinfo.org/en/info.cfm?pg=safety-xray. [Accessed Oct 5, 2020]. **4.** Korley FK, Kelen GD, Jones CM, et al. Emergency department evaluation of traumatic brain injury in the united states, 2009–2010. *J Head Trauma Rehabil.* 2015;31(6):379-387.

The potential value of brain biomarkers



Provide **objective** data to aid in the evaluation of mTBI[1]

Reduce head CT scans by up to 40%[2]

Potentially improve overall ED **throughput** and opportunity to **reduce length of stay**[3]

References: 1. Korley FK, Kelen GD, Jones CM, et al. Emergency department evaluation of traumatic brain injury in the united states, 2009–2010. *J Head Trauma Rehabil.* 2015;31(6):379-387. **2**. Data on File. **3**. Michelson EA, Huff JS, Loparo M, et al. Emergency department time course for mild traumatic brain injury workup. *West J Emerg Med*. 2018;19(4):635-640.

The i-STAT TBI Plasma test, a biomarker-based assay designed to objectively assess the need for CT

The i-STAT TBI Plasma test combines 2 brain-specific and complementary biomarkers, GFAP and UCH-L1, in a single, multiplex test designed to optimize sensitivity and negative predictive value to help determine the need for CT.[1]

INTENDED USE[1]

The i-STAT TBI Plasma test is a panel of in vitro diagnostic immunoassays for the quantitative measurements of glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) in plasma and a semi-quantitative interpretation of test results derived from these measurements, using the i-STAT Alinity Instrument. The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (Glasgow Coma Scale score 13-15) within 12 hours of injury, to assist in determining the need for a CT (computed tomography) scan of the head. A 'Not Elevated' test interpretation is associated with the absence of acute traumatic intracranial lesions visualized on a head CT scan.

REFERENCE: 1. i-STAT TBI Plasma Cartridge. Instructions for use. Abbott Point of Care Inc. Abbott Park, IL; 2021.

The *i-STAT TBI Plasma* test is to be used with plasma prepared from ethylenediaminetetraacetic acid (EDTA)–anticoagulated specimens in clinical laboratory settings by a healthcare professional. It is not intended for point-of-care use.

Intended Use Statement

The *i-STAT TBI Plasma* test is a panel of *in vitro* diagnostic immunoassays for the quantitative measurements of glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) in plasma and a semi-quantitative interpretation of test results derived from these measurements, using the i-STAT Alinity Instrument. The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (Glasgow Coma Scale score 13-15) within 12 hours of injury, to assist in determining the need for a CT (computed tomography) scan of the head. A 'Not Elevated' test interpretation is associated with the absence of acute traumatic intracranial lesions visualized on a head CT scan.

The test is to be used with plasma prepared from EDTA anticoagulated specimens in clinical laboratory settings by a healthcare professional. The *i-STAT TBI Plasma* test is not intended to be used in point of care settings.

Reference: i-STAT TBI Plasma Cartridge. Instructions for use. Abbott Point of Care Inc. Abbott Park, IL; 2021.

Thank you for attending today's webinar

For additional information, please contact:

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