Stroke and Traumatic Brain Injury Markers

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Learning objectives

• Understand the pathophysiology of ischemic and hemorrhagic stroke, subarachnoid hemorrhage, and Alzheimer’s disease.
• Understand the characteristics of an ideal brain-related biomarker.
• Describe the biomarkers for stroke, SAH, TBI, and AD.
• Discuss current limitations of these biomarkers
• Understand the need of multi-marker analysis
Ideal characteristics for brain injury marker: comparison to cardiac

- One biomarker rapidly increased in blood after injury
  Cardiac troponin.
- Rapid assay
- Immunoassays for Tn widely available
- Highly sensitive and specific for injury vs. mimics
  Troponin not increased in other chest pain etiologies (skeletal muscle, pancreatitis, etc).
- Differentiate between precursor disease, e.g.,
  transient ischemic attack (TIAs).
  Troponin increased in both AMI and UA
Ideal characteristics for brain injury

- Differentiate between ischemic vs. hemorrhagic etiologies.
  - Tn increased in both STEMI & nSTEMI
- Results used for infarct sizing
  - Tn can be used for this.
- Results used to determine therapy.
  - Tn cannot be used to guide therapy
- Risk stratification for adverse outcomes
  - Tn effective
- Obviate the need for imaging techniques.
  - Does not replace ECG or echocardiography
Stroke in America

- No. 3 cause of death when considered separately from other CV diseases (heart disease and cancer).
- 700,000 Americans experience a new or recurrent stroke each year.
- Of all strokes, 88% are ischemic, 9% are intracerebral hemorrhagic, and 3% are subarachnoid hemorrhage.
- Age-adjusted incidence for first stroke are (per 100,000):
  - 167 white males
  - 138 white females
  - 323 black males
  - 260 black females
Diagnostic markers for stroke
Misdiagnosis of stroke
Norris et al. Lancet 1982;1:328-31

• 821 patients consecutively admitted from ER
• Evaluators- interns then neurology
• Initial studies- history and physical, LP, EEG, CT
• Pre-CT misdiagnosis 13%
• Post-CT misdiagnosis 16%
• Corrected diagnoses:
  – Seizures, previous stroke, dementia, intoxication
Conditions that mimic stroke

- Stroke mimic rate 19%
- Four conditions majority of mimics
  - Unrecognized seizures/postictal
  - Systemic infections
  - Brain tumor
  - Toxic metabolic
- 14 other diagnoses…
Current limitations in the diagnosis of acute stroke

• CT-scan useful for hemorrhagic but not ischemic stroke.
• CT abnormalities not observed during the initial few hours.
• Several neurologic diseases produce similar symptoms.
• High-end imaging techniques not readily available in the ED (e.g., transcranial doppler echo).
• Absence of a suitable blood biomarker.

(Allder Lancet, 1999;354:1523)
Blood in brainstem

Hemorrhagic stroke

 Courtesy V. Wu, MD Effingham, IL
NINDS time recommendations

- Door-to-MD: 10 minutes
- Door-to-Stroke Team notification: 15 minutes
- Door-to-CT scan: 25 minutes
  **Window for biomarker testing**
- Door-to-Drug: 60 minutes (80% compliance)
- Door-to-Admission: 3 hours
### Candidate stroke markers


<table>
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<th>Biomarker type</th>
<th>CNS isch vs. ICH early dx late dx TIA dx size severity worsening prognosis</th>
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## Candidate stroke markers

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S100

- S100: Acidic cytoplasmic calcium binding glial protein (21 kDa) containing 2 subunits:
  - $S_{100}^{\alpha\alpha}$: heart.
  - $S_{100}^{\alpha\beta}$: glial cells
  - $S_{100}^{\beta\beta}$: astrocytes and Schwann cells
Release of S100β
Fassbender et al. J Neurol Sci 1007;148:101

No S100β in healthy controls

Sensitivity
(n=24)
4 h: 12%
8 h: 21%
10 h: 37%
24 h: 61%
72 h: 57%
Overall: 71%
S100β and infarct size
Neuron specific enolase

- 78 kDa dimeric (γγ) enzyme
- Catalyzes conversion of 2-phosphoglycerate $\rightarrow$ phosphoenolpyruvate located in the cytoplasms of neurons and neuroendocrine cells.
- Release into blood requires breakdown of blood-brain barrier
Release of NSE
Fassbender et al. J Neurol Sci 1007;148:101
BNP in stroke

EHT: essential hypertension
ICH: intracerebral hemorrhage
CI: cerebral infarction
Af: atrial fibrillation
Subarachnoid hemorrhage

arachnoid membrane
pia matter
Case report

- 45-year old female complains of severe headache, nausea, photophobia, and neck pain.
- She waits 24 hours before coming to the ED.
- Physical examination showed retinal hemorrhages and loss of pupillary light reflex.
- She undergoes a CT scan and lumbar puncture.
Case report

- CT scanning is gold standard but loses sensitivity after 12 h.
Xanthochromia for SAH

- Rupture of intracranial vessel $\rightarrow$ RBC into CSF
- Cleared by microglial cells
- Free hemoglobin is metabolized by heme oxygenase 1 and biliverdin reductase $\rightarrow$ bilirubin
- Unconjugated bilirubin can remain for 2 to 3 weeks before being cleared.
Methods for detecting xanthochromia

- Visual
- Spectrophotometric
  
  Baseline correction
  
  Multi-wavelength

Multiwavelength correction
\[ A_1 = \varepsilon_1 bC_{\text{hem}} + \varepsilon_1 bC_{\text{bili}} + \varepsilon_1 bC_{\text{prot}} \]
\[ A_2 = \varepsilon_2 bC_{\text{hem}} + \varepsilon_2 bC_{\text{bili}} + \varepsilon_2 bC_{\text{prot}} \]
\[ A_3 = \varepsilon_3 bC_{\text{hem}} + \varepsilon_3 bC_{\text{bili}} + \varepsilon_3 bC_{\text{prot}} \]

Case: bilirubin: 0.34 mg/dL
hemoglobin: 7.12 mg/dL
protein: 585 mg/dL

control case

heemoglobin
billirubin
Clinical trial of SAH: LC vs multiwavelength

CSF from 70 confirmed SAH and 70 non-SAH patients
BNP after subarachnoid hemorrhage
Taub, Wu et al. Neurocrit Care 2011;15:13-8

The diagram shows the rate of cerebral infarction (%) at different BNP levels (pg/mL). The BNP levels are divided into four categories:

1. <46 pg/mL: N=10/30
2. 46-105 pg/mL: N=6/30
3. 106-275 pg/mL: N=11/31
4. 285-3504 pg/mL: N=19/28

The rate of cerebral infarction increases significantly with higher BNP levels.
Traumatic brain injury
Prevalence of TBI
CDC data

• 1.4 million Americans sustain a traumatic brain injury/year
• 275,000 hospitalizations, 80,000 disabilities, and 52,000 deaths.
• Iraq/Afghanistan conflicts, approximately 20% of combat personnel suffered TBI.
Case report

- Duane Duerson played safety for the Chicago Bears 1985 Super Bowl Team.
- Complains of headaches, blurred vision and a deteriorating memory.
- Suicide (GSW to chest) in 2011.
- Handwritten note to family: “Please, see that my brain is given to the NFL’s brain bank.”
Case report

Autopsy of brain slices.
FDA-cleared biomarkers for TBI:
The NFL establishes its Mild Traumatic Brain Injuries (MTBI) committee.

Sept. 2002 - Bennet Omalu, M.D., finds structural deformity in the brain of Mike Webster, who suffered multiple concussions, and exhibited dementia plus psychiatric illness in life. He names the condition Chronic Traumatic Encephalopathy (CTE). This is the first evidence linking brain beginning with Dr. Omalu's investigation of Mike Webster's brain in 2002 and continuing to the present, neurosurgeons and neuropathologists Omalu, Julian Bailes, Robert Cantu, and Ann McKee examine the brains of 17 former NFL players who were known.

Mike Webster, d. 2002

Justin Strzelekcyz, d. 2004 auto accident

Terry Long, d. 2005 - suicide

July 2005 - The peer-reviewed journal Neurosurgery publishes an article by Omalu reporting his findings.

Neurosurgery declines to retract Omalu's article and publishes another by him.

NFL MTBI committee doctors Ira Casson, Elliot Pellman and David Viano denounce Omalu's article and demand that it be retracted.

Andre Waters, d. 2006 - suicide

March 2007 - The NFL adopts the “88 Plan” which provides for financial support (up to $88,000/year) to former NFL players suffering from dementia.

March 2007 - The head of NFL's MTBI committee, Dr. Elliot Pellman resigns amid controversy over his qualification as a neuropsychologist to lead the MTBI studies.

Tom McHale, d. 2008 - accidental drug O.D.

March 2008 - The NFL changes return-to-play rules for players who sustain concussions and other head traumas.

Gerald Small, d. 2008

Curtis Whitley, d. 2008

Chris Henry, d. 2009 - auto accident

Oct 2009 - U.S. House Judiciary Committee convenes hearings on the legal issues relating to football head injuries. Dr.'s Omalu, Bailes, Cantu, and McKee give sworn testimony.

Lou Creekmur, d. 2009 - complications of dementia

John Grimsley, d. 2008 - accidental GSW

Dave Duerson, d. 2011 - suicide
S100b, d-dimer, and MMP-9 after TBI
DeFaxio et al. World Neurosurg 2013, epub ahead of print

Poor vs. improved status.

Admission

24-h
Alzheimer’s Disease
Amyloid beta

- 36-43 amino acid peptide processed by the amyloid precursor protein via $\beta$ and $\gamma$-secretase
- Component of amyloid plaques in association with Alzheimer's disease
- A$\beta$ is neurotoxic.
Tau protein

- Stabilizes microtubules that are abundant in the CNS.
- Hyperphosphorylation of the tau protein can result in the self-assembly of tangles of PTFs implicated in Alzheimer’s.
Biomarkers in Alzheimer

**MMSE vs. Predicted MMSE**

MMSE Predicted by 2 Markers: IL-2 and AB Oligomers

**MMSE = Mental acuity score**

Based on Alzheimer’s patients only
Multi-marker testing
Multimarker approach for neurology biomarkers

- Allows simultaneous targeting of different component of ischemic cascade
- Minimizes inaccuracies caused by aberrant value of one analyte
- May allow diagnosis of different stroke subtypes
### NSE, MBP, S-100β, thrombomodulin


<table>
<thead>
<tr>
<th>Marker</th>
<th>Proportion of positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>0.89 (0.72-0.98)</td>
</tr>
<tr>
<td>MBP</td>
<td>0.39 (0.22-0.59)</td>
</tr>
<tr>
<td>S-100 β</td>
<td>0.32 (0.16-0.52)</td>
</tr>
<tr>
<td>Thrombomodulin</td>
<td>0.43 (0.24-0.63)</td>
</tr>
<tr>
<td>≥1 marker on panel</td>
<td>0.93 (0.76-0.99)</td>
</tr>
</tbody>
</table>
NSE/carnosinase ratio
Urinary proteomic peptide profile

Capillary electrophoresis migration time
Molecular weight
Urinary proteomic peptide profile

Mild stroke vs. controls
Other biomarker stroke panel approaches
Case report
Jauch, Univ. Cincinnati

• Scenario:
  – 58 year old man develops sudden onset left sided weakness, loss of balance and slurred speech.
  – Patient calls 911 for ambulance 90 min after symptom onset.
  – Patient arrives to tertiary care center without stroke team.
Case report

• Initial vital signs stable.
• History of hypertension and smoking.
• Neurologic exam confusing to emergency physician:
  – Right facial droop and gaze palsy
  – Left arm and leg weakness
  – Dysarthria
Case report

• CT scan and basic laboratory values unremarkable.
• Physician contacts stroke team via telemedicine to review case.
• MMX result reported to emergency physician.
MMX biomarker results

Patient’s MMX highly suggestive of acute ischemic stroke

Optimal specificity

Optimal sensitivity
High sensitivity mass spectrometry

MALDI-TOF MS (proteins)  LC-MS/MS (small molecules)
Commercial platforms for multimarkers

BioPlex 2200
Interpretative software for multi-marker analysis
Hypothetical neural network for stroke diagnosis

Inputs
Demographic
Neuronal
Inflammation
Hemostatic
Cytokine
Genetic
RNA Expression

Hidden

Outputs
Ischemic stroke
Hemorrhagic stroke
Healthy
Physician Health Study:
92 SNPs from 56 candidate genes related to inflammation, thrombosis and lipid metabolism. 319 incident cases of ischemic stroke and 2090 disease-free controls.
Summary

• Clinical evaluation and neuroimaging will remain paramount

• Biomarker panel complements physical examination and neuroimaging

• Wide variety of practice settings may benefit from biomarker panel

• Early biomarker data can:
  – Facilitate triage
  – Promote faster throughput
  – Complement other diagnostic tools
Quiz

Which single biomarker is used for stroke?

A. S100
B. Neuron specific enolase
C. Myelin basic protein
D. Carnosinase
E. No single marker

Answer: E. A multimarker approach will likely be the most successful.
Which is correct concerning stroke biomarkers?

A. D-dimer is an example of a neuronal marker
B. S100b is an example of an inflammatory marker
C. NSE is an example of a genetic marker
D. Superoxide dismutase is an example of an oxidative stress marker
E. TNF-α is an example of a hemostatic marker

Answer: D. A multi-marker approach will likely require biomarkers from each of these pathophysiologic processes.
Quiz

Which is correct regarding CSF bilirubin measurement?

A. Assays typically used in serum are acceptable
B. Testing should be done within 4 h of symptoms
C. Presence of CSF hemoglobin also indicates an SAH
D. Xanthochromia is characterized by a yellow color
E. Bilirubin can be measured photometrically at 420 nm

Answer: D. A visual inspection of CSF is acceptable in the absence of hemoglobin
Quiz

What is the most common etiology of subarachnoid hemorrhage?

A. Ruptured aneurysm
B. Hemorrhagic stroke
C. Traumatic brain injury
D. Multiple sclerosis
E. Ischemic stroke

Answer: A. A ruptured aneurysm will cause a bleed.