THE BIGGER PICTURE OF LARGE HEMISPHERIC INFARCTION

Disease and Management
TODAY’S PANELISTS

Panel Chair

Edward C. Jauch, MD, MS, FAHA

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Stephan A. Mayer, MD, FCCM

Jeffrey L. Saver, MD, FAHA, FAAN, FANA

Sean I. Savitz, MD

Expert Panelists
OBJECTIVES

Review complexities associated with the diagnosis, treatment, and management of LHI

Understand key considerations and decision points throughout the journey of a patient with LHI

Discuss forward-looking strategies to optimize patient outcomes

LHI, large hemispheric infarction.
Audience Question: What is your primary specialty?

Please go to Slido.com to participate in the audience response questions

- Event code: BiogenLHI

ICU, intensive care unit.
LHI, large hemispheric infarction.

Audience Question: How many patients with LHI do you typically see per month?

Please go to Slido.com to participate in the audience response questions
- Event code: BiogenLHI
Ms. S, 59 years old, is a mother of 2 children and grandmother of 3 children, with a history of atherosclerosis.

On Monday afternoon, she was at the park with her grandchildren when she noticed she was having trouble seeing clearly.

She also noticed some weakness on her right side but was unconcerned and continued on with her daily activities.

4 hours later, Ms. S’s son came over to pick up his kids and noticed that Ms. S had paralysis in her right arm and on the right side of her face and was having difficulty communicating.

Ms. S’s son immediately dialed 9-1-1.
FUNDAMENTALS OF LHI AND ASSOCIATED LIFE-THREATENING EDEMA

Speaker: Sean I. Savitz, MD
LHI IS ONE OF THE MOST DEVASTATING FORMS OF ACUTE ISCHEMIC STROKE\(^1\)

Constitutes \(~14\%\) of all strokes\(^2\)

- Source is almost exclusively cardioembolic\(^4\)

Has an annual incidence of 10-20 per 100,000 people\(^3\) and a mortality rate of up to 80\%\(^1\)

- Is a malignant infarction caused by an occlusion that can affect the entire territory of the middle cerebral artery\(^5\)
  - At least partially involves the basal ganglia

LHI, large hemispheric infarction.

LHI IS DEFINED BY VARIOUS CLINICAL FEATURES


LHI, large hemispheric infarction.
CEREBRAL EDEMA MAY PROGRESS OVER TIME AS THE PATIENT PROGRESSES TO LHI

Ischemic injury and large-vessel occlusion: Reduced cerebral blood flow

- Cytotoxic edema
  - Failure of Na⁺/K⁺ pumps
  - Calcium influx
  - Cell swelling

- Vasogenic edema
  - BBB deterioration
  - Leakage of serum proteins into brain

Progressive cerebral edema can result in
- Increasing intracranial pressure, worsening ischemia
- Midline shift and brain herniation leading to progressive brainstem dysfunction

BBB, blood-brain barrier; LHI, large hemispheric infarction.

STROKE SOCIETIES PROVIDE GUIDELINES FOR MANAGEMENT OF AIS, LHI, AND CEREBRAL EDEMA

Available guidelines are based largely on expert experience

Management of AIS and cerebral edema

AHA/ASA

Management of LHI

NCS and German Society for Neuro-Intensive Care and Emergency Care

Guidelines emphasize the need for early diagnosis

AHA, American Heart Association; AIS, acute ischemic stroke; ASA, American Stroke Association; LHI, large hemispheric infarction; NCS, Neurocritical Care Society.

INITIAL ASSESSMENT AND DIAGNOSTIC WORKUP

Speaker: Jeffrey L. Saver, MD, FAHA, FAAN, FANA
SEVERAL APPROACHES FACILITATE ASSESSMENT OF PROGRESSION TO LHI

The neurological exam and various neuroimaging methods provide a range of information\textsuperscript{1,2}

LHI, large hemispheric infarction.

EARLY ASSESSMENT OF NEUROLOGICAL FUNCTION GUIDES NEXT STEPS

Standardized scales can be used to assess LHI progression and guide treatment initiation. NIHSS: Most widely used for initial stroke assessments

- Dominant severe hemispheric infarctions
  - NIHSS score >20

- Nondominant severe hemispheric infarctions
  - NIHSS score >15

Visual disturbance, aphasia, and neglect are also important clinical markers

LHI, large hemispheric infarction; NIHSS, National Institutes of Health Stroke Scale.

THE CASE OF MS. S: USING IMAGING TO FACILITATE DIAGNOSIS

• Ms. S was taken to the ER following her aphasia and right-sided paralysis

Next Steps

• Upon initial evaluation of Ms. S, Dr. Smith noticed gaze deviation, global aphasia, and hemiparesis
• Dr. Smith’s notes indicate
  – NIHSS score of 22
  – Global left hemisphere syndrome
  – Time last known well, 4 hours ago

CTA, computed tomography angiography; CTP, computed tomography perfusion; ER, emergency room; MRI, magnetic resonance imaging; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale.

Audience Question: The first imaging procedure you perform is NCCT. What imaging would you perform next?
Imaging is an important aspect of the evaluation of patients with stroke and possible progression to LHI

- Noncontrast computed tomography
- Computed tomography angiography
- Computed tomography perfusion
- Diffusion-weighted MRI
- Magnetic resonance angiography
- Perfusion-weighted MRI
- Cerebral angiography

DW-MRI, diffusion-weighted magnetic resonance imaging; MRI, magnetic resonance imaging.

PREDICTORS OF CEREBRAL EDEMA AND POOR OUTCOME FOLLOWING ISCHEMIC STROKE

Neurological exam and imaging can reveal features associated with increased risk of developing LHI

- High NIHSS score
- Depressed level of consciousness
- Unilateral or bilateral pupillary dilation
- Early nausea and vomiting
- Early ischemic change on CT affecting >50% of MCA territory
- >145 mL lesion volume on DW-MRI
- Infarct volume >220 mL on CT
- ASPECT score ≤7

ASPECT, Alberta Stroke Program Early CT; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; LHI, large hemispheric infarction; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

MANAGEMENT STRATEGIES

Speaker: Tudor G. Jovin, MD
Guidelines recommend therapies for AIS, LHI, and associated edema\textsuperscript{1-3}

Management of AIS\textsuperscript{1} and cerebral edema\textsuperscript{3}  
AHA/ASA

Management of LHI\textsuperscript{2}  
NCS and German Society for Neuro-Intensive Care and Emergency Care

Prompt treatment is important to minimize long-term disability and impairment\textsuperscript{4}

AHA, American Heart Association; AIS, acute ischemic stroke; ASA, American Stroke Association; LHI, large hemispheric infarction; NCS, Neurocritical Care Society.

Biochemical tests can identify parameters associated with unfavorable outcomes after acute ischemic stroke to aid in initial treatment selection.

- Blood glucose
- Oxygen saturation
- Renal function
- Troponin levels
- Complete blood count
- Cardiac markers
- Prothrombin time
- International normalized ratio
- Activated partial thromboplastin time
- Sodium levels

LHI, large hemispheric infarction.
THE GOAL IN SEVERE STROKE IS TO PREVENT PROGRESSION FROM LVO TO LHI

Reperfusion strategies aim to maximize the probability of good functional clinical outcomes\textsuperscript{1,2}

LVO

LHI

\textbf{rt-PA:} Beneficial in patients presenting within \(\leq4.5\) hours of symptom onset\textsuperscript{1}

\textbf{Thrombectomy:} Treatment window may be extended to 24 hours\textsuperscript{3}

LHI, large hemispheric infarction; LVO, large vessel occlusion; rt-PA, recombinant tissue plasminogen activator.

THE CASE OF MS. S: MANAGING PATIENT AFTER ADMISSION TO ICU

- Dr. Smith noted that Ms. S displayed global left hemisphere syndrome and had an NIHSS score of 22

Next Steps
- 8 hours after hospital admission and 12 hours after initial onset of symptoms, Dr. Smith performed thrombectomy on Ms. S
- Dr. Smith noted TICI 2B and BP 192/108 and had Ms. S admitted to the ICU, where her BP was controlled
- Upon re-examination of Ms. S, Dr. Smith noted the following:
  - Stable NIHSS score of 20
  - CT shows large infarct but no bleeding or MLS
  - Ms. S is euvolemic, with Na⁺ levels at 138
  - IVC is noncollapsing, CVP = 7 mm Hg
  - Temperature is 37.7°C
  - Blood glucose is 160 mg/dL

Audience Question: Which of the following orders is your next priority?
Clinicians may use a variety of approaches to reduce systemic complications, including cerebral edema\textsuperscript{1}

<table>
<thead>
<tr>
<th>General Measures Aim to Reduce Systemic Complications\textsuperscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of fever\textsuperscript{1}</td>
</tr>
<tr>
<td>Maintenance of normoglycemia\textsuperscript{1}</td>
</tr>
<tr>
<td>Head elevation\textsuperscript{1}</td>
</tr>
<tr>
<td>Maintenance of normovolemic\textsuperscript{1}</td>
</tr>
<tr>
<td>Blood pressure management\textsuperscript{1}</td>
</tr>
</tbody>
</table>

Supportive clinical evidence is limited\textsuperscript{2}

EARLY MEDICAL MANAGEMENT SHOULD FOCUS ON PREVENTING EDEMA AND INCREASES IN ICP

Methods of reducing ICP differ in their mechanism of action

<table>
<thead>
<tr>
<th>Osmotherapy</th>
<th>Hyperventilation</th>
<th>Barbiturates</th>
<th>Anti-edema Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creates an osmotic gradient across the BBB&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Induces hypocarbia&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Lowers cerebral metabolic activity&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Various mechanisms of action, including some (eg, SUR1 inhibition&lt;sup&gt;3&lt;/sup&gt;) currently under investigation</td>
</tr>
<tr>
<td>Mannitol and hypertonic saline are commonly used&lt;sup&gt;2&lt;/sup&gt;</td>
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</tbody>
</table>

Choice of methods is based on patient symptoms<sup>4</sup>

BBB, blood-brain barrier; ICP, intracranial pressure; SUR1, sulfonylurea receptor 1.

THE CASE OF MS. S: CONSIDERING CRITERIA FOR HEMICRANIECTOMY

• Several general measures were taken to control Ms. S’s BP and fluid levels, and her NIHSS score was stable going into her neurology consultation

Next Steps

• During the consultation, the neurosurgeon noted the following:
  – E3 M6 V4 but aphasic with R neglect and RHH
  – Flaccid R hemiplegia, normal LUE tone, and shows 2 fingers

• Ms. S’s family hears Dr. Smith consulting with the neurosurgeon and wants to understand what “hemicraniectomy” means, including the potential risks and benefits

BP, blood pressure; E, eye opening; LUE, left upper extremity; M, motor response; NIHSS, National Institutes of Health Stroke Scale; R, right side; RHH, right homonymous hemianopia; V, verbal response.

Audience Question: What would be an appropriate trigger for a hemicraniectomy?
DECOMPRESSIVE SURGERY MAY RELIEVE HIGH ICP ASSOCIATED WITH CEREBRAL EDEMA

The decision to perform a hemicraniectomy requires assessment of multiple factors

**Potential benefit¹**
- Increasing the likelihood of survival
- Increases likelihood of favorable functional outcome

**Timing of possible procedure**
- Within 24-48 h of stroke onset but prior to herniation symptoms²

**Potential risks include²**
- Disability and functional dependency
- Pain, infection, bleeding, and fluid collection

**Individual patient characteristics, including²**
- Patient age
- Dominant vs nondominant hemisphere involvement

ICP, intracranial pressure.

MONITORING TOOLS

Speaker: Stephan A. Mayer, MD, FCCM
THE CLINICAL EXAM IS RECOMMENDED TO MONITOR DISEASE PROGRESSION IN PATIENTS WITH LHI¹

Scales allow objective measurement of changing clinical status¹

<table>
<thead>
<tr>
<th>National Institutes of Health Stroke Scale</th>
<th>Glasgow Coma Scale</th>
<th>Oculomotor Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provides a quantitative measure of key components of a standard neurological exam²</td>
<td>Measures best eye, motor, and verbal response to assess levels of consciousness³</td>
<td>Identifies impaired visual function⁴</td>
</tr>
</tbody>
</table>

Important note: Oversedation can cause these types of clinical changes to be missed

LHI, large hemispheric infarction.

THE CASE OF MS. S: NEUROMONITORING CONSULTATION

• Given Ms. S’s current stable condition, the neurosurgeon holds off on performing decompressive surgery

Next Steps

• The neurosurgeon and Dr. Smith discuss neuromonitoring options for Ms. S

Audience Question: Neurosurgery asks whether you want an ICP monitor. In addition to the clinical exam, what is your next neuromonitoring plan?

cEEG, continuous electroencephalography; ICP, intracranial pressure; TCD, transcranial Doppler.
MULTIPLE APPROACHES FOR MONITORING DISEASE PROGRESSION

In addition to clinical measures, physicians may use other strategies to monitor disease progression.

<table>
<thead>
<tr>
<th>TCD Ultrasonography</th>
<th>ICP Monitors</th>
<th>EEG</th>
<th>Pupilometer</th>
<th>Oxygen Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assesses midline shift and offers a minimally invasive alternative to neuroimaging</td>
<td>Measures ICP via ventricular catheters or intraparenchymal/extradural/subdural/subarachnoid probes</td>
<td>Helps predict clinical course and estimate prognosis</td>
<td>Evaluates pupil size and reactivity to light</td>
<td>Measures partial oxygen pressure of brain tissue</td>
</tr>
</tbody>
</table>

Guidelines for these techniques are generally based on observational evidence.

CT, computed tomography; EEG, electroencephalogram; ICP, intracranial pressure; LHI, large hemispheric infarction; MRI, magnetic resonance imaging; TCD, transcranial Doppler.

THE CASE OF MS. S: PREPARING FOR HEMICRANIECTOMY

• Unfortunately, after her original neurosurgery consultation, Ms. S’s condition begins to deteriorate

Next Steps
• Ms. S becomes more lethargic and is barely able to follow commands, and Dr. Smith notes the following:
  – LUE is flexing to midline
  – Left pupil is mid-position but is less reactive than right pupil
• The neurosurgeon is called, and Ms. S is taken to the OR for a hemicraniectomy
• During the post-op examination
  – Post-op CT shows a good surgical result, with restoration of midline structures
  – Ms. S has a stable GCS score of E3 M5 V3 and tolerates CPAP for 8 h

Audience Question: What is the most important next step to minimize postoperative complications and length of stay?
LOOKING TO THE FUTURE

Speaker: Edward C. Jauch, MD, MS, FAHA
THE CASE OF MS. S: HOSPITAL DISCHARGE AND FOLLOW-UP

- Despite her deteriorating condition, the hemicraniectomy was successful

Next Steps
- Ms. S is discharged from the hospital 12 days after her surgery and is sent to long-term acute care after tracheotomy and PEG
- 3 months after her initial symptoms, Ms. S is doing well
  - At her follow-up, Dr. Smith notes an mRS score of 3
- Ms. S is able to walk with the aid of a cane and is once again able to visit the park with her grandchildren

In this fictional case study, the patient was able to return home but was not able to resume all of her normal activities

However, there are numerous strategies that should be considered to optimize patient treatment

mRS, modified Rankin Scale; OR, operating room; PEG, percutaneous endoscopic gastrostomy.
STRATEGIES FOR THE FUTURE

Establish Stroke Protocols for Ground and Air Transport Crews\(^1\) and Implement MSUs\(^2\)

Provide Education and Protocols to Smaller Remote Hospitals and Establish Telestroke\(^1\)

Develop Recommendations for Palliative Care\(^1\)

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MSU, mobile stroke unit.

CLINICAL TRIALS SEEK TO EVALUATE OPTIONS TO IMPROVE TREATMENT OF STROKE AND/OR LHI

<table>
<thead>
<tr>
<th>THROMBECTOMY</th>
<th>DHC</th>
<th>PHARMACOLOGICAL TREATMENTS</th>
</tr>
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<tbody>
<tr>
<td><strong>Trials</strong></td>
<td><strong>Objectives</strong></td>
<td><strong>Trials</strong></td>
</tr>
<tr>
<td>MR CLEAN¹ (Phase 3)</td>
<td>Functional outcomes within different therapeutic windows¹-³</td>
<td>DECIMAL⁶,⁷ (Phase 3)</td>
</tr>
<tr>
<td>DEFUSE 3² (Phase 3)</td>
<td></td>
<td>DESTINY⁶,⁸ (Phase 3)</td>
</tr>
<tr>
<td>DAWN³,⁴ (Phase 2/3)</td>
<td></td>
<td>HAMLET⁶,⁹ (Phase 3)</td>
</tr>
<tr>
<td>TENSION⁵ (Phase 3)</td>
<td>Comparative safety/efficacy vs best medical care alone⁶</td>
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</table>

DHC, decompressive hemicraniectomy; LHI, large hemispheric infarction.

**SUMMARY**

<table>
<thead>
<tr>
<th>Disease Fundamentals</th>
<th>Initial Assessment</th>
<th>Management</th>
<th>Monitoring</th>
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<tbody>
<tr>
<td>A large vessel occlusion may progress into a malignant infarction that affects the entire territory of the middle cerebral artery(^1)</td>
<td>The clinical exam and neuroimaging assess patient progression to LHI(^2,3)</td>
<td>Early medical management focuses on preventing edema and increases in ICP(^4)</td>
<td>The clinical exam is useful in monitoring disease progression(^5)</td>
</tr>
</tbody>
</table>

Expanding access to stroke education and protocols and seeking improved therapy options are additional strategies for patient success\(^6\)

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ICP, intracranial pressure; LHI, large hemispheric infarction.

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Please go to Slido.com to participate in the audience response questions

- Event code: BiogenLHI

Audience Question: Please rank your agreement with the following statement:
“This symposium has improved my understanding of LHI.”

LHI, large hemispheric infarction.
FINAL THOUGHTS

Please remember to fill out your evaluation forms. Thank you.