Update on Intracerebral Hemorrhage

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Intracerebral Hemorrhage

- Traumatic
- Spontaneous

Primary (80-88%): due to spontaneous rupture of small vessels damaged by HTN or cerebral amyloid angiopathy
Secondary: AVM’s, aneurysms, tumor, coagulopathies (warfarin), hemorrhagic infarction esp. venous sinus thrombosis, vasculitis, vasculopathies, sickle cell disease

Spontaneous ICH

- 40,000-50,000/ year in US
- ~10-15% of all strokes, more at VUH
- High mortality: 40% survive 1st 30 days
  - 12 mo mortality—50%
- Incidence 10-20/100,000
- Increases w/ age, racial predelictions (Japanese, African Americans)
- Risk factors: Advanced age, HTN, kidney disease, EtOH, very low cholesterol, genetics (apo ε2, ε4 in amyloid angiopathy), drug abuse

Deep, 35-70%; lobar, 15% to 30%; cerebellum, 5% to 10%; and brain stem, 5% to 10%.

Most Common Sites and Sources of Spontaneous ICH:

A. Cortical lobes:
   Penetrating cortical branches of ACA, MCA, PCA
B. Basal ganglia:
   Lenticulostriate br.’s MCA
C. Thalamus:
   Thalamogeniculate br.’s PCA
D. Pons:
   Paramedian br.’s Basilar a.
E. Cerebellum:
   Penetrating br.’s PICA, AICA, SCA

Sites of HTN Hemorrhages:

• Putaminal/External capsule: ~ 50-60%
• Thalamic: 15-25%
• Pontine: 5-10%
• Cerebellar: 2-5%
• Subcortical white Matter: 1-2%

Initial Symptoms in ICH:

• Usually during daytime activity, w/ abrupt onset, and then progression of:
  – Altered LOC 50%
  – Nausea/vomiting 40-50%
  – Headache 40%
  – Seizures >10%
  – Focal neurological deficits
• BP tends to be higher than in ischemic stroke

Case

48 yr old woman w/ hx HTN, cocaine abuse found unresponsive @ home, BP 250/130, BIBA, intubated, no brainstem reflexes, ‘failed’ apnea test
Her CT scan:

ICH Prognosis, Hemphill et al.

• Iphone/ipad app: ‘Neuro Toolkit’
Estimate of Volume of Hematoma, cm$^3$

$$A \times B \times C \times 2$$

Where $A$ is maximum hematoma diameter in cm, $B$ is diameter perpendicular to $A$, and $C$ is the number of slices showing hematoma multiplied by the slice thickness (typically 0.5cm)

- Broderick JP, Brott TG et al., Stroke 1993; 24: 987-93

Basal Ganglia ICH

- 49 yr old man w/ hx EtOH, no regular medical care, found down by brother, conscious, w/ left neglect, moderate hemiparesis
- CT: 6x2 cm ICH, 5mm midline shift, IVH

One Week’s VUMC ICH Admissions:

CT Imaging of ICH

- Blood is hyperdense relative to brain, and is evident immediately after onset of symptoms
- Hematomas can appear hypodense in severe anemia
- ‘Spot sign’ on postcontrast CT, small enhancing focus within hematoma, predicts hematoma enlargement
- Fluid-fluid levels in hematomas related to coagulopathy
- Hematomas become isodense between 1-6 weeks, and hypodense >6 weeks

Table 2.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age</th>
<th>Hemodynamics</th>
<th>Ty-SOd</th>
<th>Ty-MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive</td>
<td>&gt;4</td>
<td>Intensive care</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Severe</td>
<td>2-4</td>
<td>Intensive care</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>1-2</td>
<td>Intensive care</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Late (1-6 days)</td>
<td>1-2</td>
<td>Tissue perfusion</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Chronic (&lt;14 days)</td>
<td>&lt;2</td>
<td>Tissue perfusion</td>
<td>Very high</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Abbreviations: H, hours; L, days; FH, hemorrhagic HRI, magnetic resonance imaging

Adapted from Broderick WP.33


23 yr old F, sudden, severe HA after taking ‘energy’ drink

FLAIR MRI sequence

FLAIR MRI: L ICH
Arteriogram

Reversible cerebral vasoconstriction syndrome

- RCVS is a spectrum of disorders characterized by prolonged by reversible vasoconstriction associated with thunderclap headache.
- More common in women, esp post-partum or associated with vasoactive drugs.
- Associated with ischemic or hemorrhagic stroke, also convexity SAH
- Thought to be due to autoregulation failure of cerebral arterial tone with sympathetic overactivity, which may begin distally and progresses to proximal branches of COW.

RCVS: Largest Prospective Series

- 89 pts, France: 46 used vasoactive substances, 9 postpartum
- 34% had intracranial hemorrhage (cortical SAH 27, ICH 11, SDH 2)
- Pts w/ hemorrhage were older, 90% female, more likely migraineurs, more likely to have persistent focal deficits, associated ischemic strokes, PRES in acute stage, worse outcomes
  - Ducros et al, Stroke 2010;41:2505-11

Criteria for Reversible Cerebral Vasoconstriction Syndrome

- Acute and severe headache (often thunderclap) with or without focal deficits or seizures
- Unilophasic course without new symptoms more than 1 month after clinical onset
- Segmental vasoconstriction of cerebral arteries shown by noninvasive angiography (eg, MRA or CTA) or direct catheter angiography
- No evidence of aneurysmal SAH
- Normal or near-normal CSF profile (protein level <100 mg/dL, WBC count <15 cells/μL)
- Complete or substantial normalization of arteries on follow-up angiography within 12 weeks of clinical onset
  - Adapted from the International Headache Society criteria for acute reversible cerebral angiopathy and the criteria proposed in 2007 by Calabrese et al, as proposed by Ducros LancetNeurology 2012;11(10):906-917

ICH Management:

- ABC’s
- ICU generally
- Anti-edema therapy: coag. end products activate inflam. cascade →vasogenic, cytotoxic edema, disruption of BBB
- Reversal of warfarin (Vit K, FFP, PCCs- Factors IX, II, VII, X) *Class 1, level C
- ? Surgery
- Seizure tx *Class 1, A-B
- Recurrent ICH risk associated w/ BP at f/up
ICH Deterioration

- 25% secondary deterioration in LOC in 1st 3 hrs; usually due to expansion of hematoma
- In the first 24-48 hrs: deterioration often 2° edema
- Intraventricular blood assoc. w/ higher mortality, but EVD can get clotted, infected

BP Management

- When BBB disrupted CBF passively dependent on CPP
- To optimize CBF MAP should not be lowered excessively
- However ICH expansion associated w/ elev. BP in 1st few hrs
- BP management: MAP < 130 if hx HTN
  - (CPP=MAP-ICP)
  - CPP > 60-70 mm Hg

BP Management in ICH, 2010

ICH Guidelines

- INTERACT (INTensive BP Reduction in Acute Cerebral Hemorrhage Trial), 2008, and ATACH (Antihypertensive Treatment in Acute Cerebral Hemorrhage) trials
- In patients presenting with a systolic BP of 150-220 mm Hg, acute lowering of systolic BP to 140mm Hg is probably safe *new recommendation (Class IIa, LOE B)

BP Lowering in ICH

- ATACH-I a feasibility and safety trial of IV nicardipine for acute HTN mgmt in ICH found acute lowering of BP to 110-140 mm Hg safe, but study underpowered to detect benefits in clinical outcomes or attenuated ICH growth.
- ATACH-II underway, evaluating nicardipine to treat BP in ICH, endpoints include clinical outcomes and ICH growth.

TABLE 2. Suggested Recommended Guidelines for Treating Elevated Blood Pressure in Spontaneous ICH

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>If SBP is &gt;200 mm Hg or MAP is &gt;150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 3 minutes.</td>
</tr>
<tr>
<td>2.</td>
<td>If SBP is &gt;160 mm Hg or MAP is &gt;120 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure &gt;60 to 80 mm Hg.</td>
</tr>
<tr>
<td>3.</td>
<td>If SBP is &gt;160 mm Hg or MAP is &gt;120 mm Hg and there is not evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (avg. MAP at 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reassess the patient every 15 minutes.</td>
</tr>
</tbody>
</table>

SIP indicates systolic blood pressure; MAP = mean arterial pressure

ICH Guidelines, Broderick, et.al., Stroke, June, 2007, 2010 updates

TABLE 3. Intravenous Medications That May Be Considered for Control of Elevated Blood Pressure in Patients With ICH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intravenous Bolus Dose</th>
<th>Continuous Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>5 to 20 mg every 15 min</td>
<td>2 mg/min (maximum 200 mg/h)</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>NA</td>
<td>5 to 15 mg/h</td>
</tr>
<tr>
<td>Enalapril</td>
<td>250 µg/kg IV/infusion dose</td>
<td>25 to 300 µg/kg⁻¹·min⁻¹</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.25 to 5 mg IV every 6 h</td>
<td>NA</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5 to 20 mg IV every 30 min</td>
<td>1.5 to 5 µg/kg⁻¹·min⁻¹</td>
</tr>
<tr>
<td>Nipride</td>
<td>NA</td>
<td>0.1 to 10 µg/kg⁻¹·min⁻¹</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>NA</td>
<td>20 to 400 µg/min</td>
</tr>
</tbody>
</table>

IVP indicates intravenous push; NA, not applicable. *Because of the risk of precipitous blood pressure lowering, the enalapril initial test dose should be 0.625 mg.

ICH Guidelines, Broderick, et.al., Stroke, June 2007
ICH Management, 2010 Class I Recs, AHA Guidelines:

- Severe coagulopathy should be tx with appropriate factor replacement
- INR elevated, warfarin withheld, replacement of Vit K dependent factors and IV Vit K to correct INR
- ICDs and elastic stockings to prevent DVT
- ICU monitoring, management
- Glucose monitored, goal is normoglycemia
- Treat clinical seizures with AEDs
- AMS, with electrographic seizures on EEG should be tx.
- Cerebellar ICH pts who are deteriorating, have BS compression and/or hydrocephalus should have surgical removal of ICH
- After acute ICH, BP should be ‘well-controlled’

Acute Seizures after ICH

- 109 pts. w/ stroke (46 ischemic, 63 ICH) prospective EEG monitoring x 72 hrs.
- Seizures occurred in 28% w/ICH, vs 6% w/ischemic stroke (usually focal, 2° gen.)
- Sz’s associated w/NIHSS worsening (14.8-18.6) and increase in midline shift
- Trend towards increase in poor outcome

Vespa, et al. NEUROLOGY 2003;60:1441-1446

“Until the present, intracerebral hemorrhage has been the stroke subtype that has defied attempts to find a scientifically proven effective therapy.”


IVH Case

- 67 yo man w/ HTN, CAD, DM, HLD, prior stroke on warfarin
- Acute HA, ataxia, progressive somnolence, nausea, vomiting
- Local ED: CT: extensive L IVH
- INR 3.9, got Vit. K

BEFORE and AFTER Tx:

CLEAR IVH III Trial

- Multicenter randomized trial of patients with relatively small ICH (<30cc) with IVH treated with either 1mg intraventricular tPA every 8 hrs or placebo until significant IVH clearance until safety endpoint (re-hemorrhage) or 5 days.
- Endpoints are clinical functional outcomes
ICH Therapy

• If ICH associated with t-PA or coagulopathy: 10mg Vit K slow IV if warfarin, either FFP or Prothrombin complex concentrates (Factors VII, X, XI, prothrombin, proteins C and S)
• Activated recombinant Factor VII (NovoSeven) used in hemophilia, converts Factor X to Factor Xa, stops bleeding, efficacious in reducing hematoma volume in Phase II, but failed to demonstrate clinical improvement in Phase III trial.

Surgery in ICH

• Meta-analysis of 3 randomized, controlled trials found higher rate of death or dependency at six months (83% vs. 70%) in surgical group
  • Hankey, GJ. Hon C. Stroke 1997:82:2126-32
• STICH pilot study found lower mortality in surgical group (6% vs 24%) at 1 mo, similar results at 6 mos (17 vs 24%)

International Surgical Trial in Intracerebral Hemorrhage

• ISTICH, 1033 pts.
  • “Early Surgical Intervention” or “Initial Conservative Treatment” is the best option in patients with spontaneous supratentorial Intracerebral haemorrhage (ICH)
• >2cm ICH, GCS >=5
• Surgical approach: 77% craniotomy, others: burr hole, endoscopy, stereotaxy
  • 6-month follow-up

ISTICH

• No significant difference in outcome between groups
• Pts w/ ICH close to cortical surface (< 1 cm) benefited from early surgery
• ISTICH II trial ongoing looking at early surgery in superficial hematomas

Cerebellar Hemorrhage
Cerebellar hemorrhage

- Mortality related to size, location, compression of adjacent brainstem structures smaller, more lateral better outcome
- <10% of ICH's are cerebellar
- Abrupt onset HA, N/V, ataxia, vertigo, dysarthria, nuchal pain, LOC
- Tx: conservative if <3 cm, awake, GCS >14; suboccipital craniotomy if AMS, large clot, but intact brainstem reflexes
- Ventriculostomy if hydrocephalus present

Worrisome findings for deterioration in Cbl ICH:

- Systolic BP > 200 mm Hg
- Pinpoint pupils, abnormal corneals, oculocephalics
- Hemorrhage involving vermis
- Hematoma > 3.0 cm
- Brainstem distortion
- Intraventricular hemorrhage
- Upward herniation
- Acute hydrocephalus

Midline Cerebellar hemorrhage

Thrombolytics via indwelling intracranial catheter

Stereotaxy

- Auer et al. randomly assigned 100 patients to undergo stereotactic-guided endoscopic evacuation vs. medical therapy:
- Improved outcome, mortality in surgical group at 6 mos: 40% minimal or no deficits, vs. 25% medical group

What About Less Invasive Surgery

- Thrombolytics into hematoma matrix via indwelling intracranial catheter q 6-8h
- Pilot study demonstrated a 50% reduction in hematoma volume, low recurrent bleeding rates and death
  - MISTIE trial
Minimally Invasive (Stereotactic) Surgery for rt-PA for ICH Extraction (MISTIE)

**INCLUSION CRITERIA:**
- Age 18-75
- GCS < 13 or NIHSS > 6
- Spontaneous supratentorial ICH
- > 20cc
- Stable clot at second CT scan, 6 hrs later
- First dose within 54 hrs of initial CT
- SBP < 200mmHg or MAP < 130 mm over 6 hrs
- Historical Rankin score 0-1

**EXCLUSION CRITERIA:**
- Infratentorial ICH
- Vascular malformation or tumor
- Irreversibly impaired brainstem function
- Unlikely to complete f/up
- Co-morbidity unlikely to survive at 180 days

MISTIE II Results

- Trend towards improved survival at 120 days with surgical tx, 47 vs 44%
- At 6 months, no change in mortality, but increased mRS 1, 2, and 3 in surgical tx, fewer mRS 4 and 5
- More separation of groups, increase in mRS 1, 2, 3 at 12 month follow-up

MISTIE Summary

- MIS + rt-PA is safe
- MIS + rt-PA is effective at removing clot
- Surgical Performance of MIS + rt-PA can be standardized
- Accuracy of MIS is critical to clot size reduction

When to Angiogram?

- Lobar or primary IVH regardless of age and HTN
- Putaminal, thalamic, cerebellar ICH if normotensive and < 45 yrs old
- All patients w/ no clear cut cause of ICH who are surgical candidates, particularly younger stable patients w/ out hypertension
- Consider if SAH associated w/ parenchymal clot, and recurrent ICH
- MRI/A improving but sensitivity has not been established

Case

- 40 year-old healthy man w/ R neck pain, fullness x 3 days, and then HA x 3 days, lost control of car, found having GTC seizure at scene, 2 further seizures en route
- No prior or family history of migraine, stroke, seizures
- CT scan:

CT scan at admission
MRV
- MRV demonstrated absent flow in right transverse, sigmoid sinuses and jugular vein
- Dx: Venous sinus thrombosis→hemorrhagic nfarct→seizures
- + Lupus anticoagulant

Lobar hemorrhage

Amyloid angiopathy
- AKA congophilic angiopathy increases w/ advancing age, probably commonest cause of recurrent ICH in elderly
- Deposition of nonbranching fibrillar proteins w/ crystallographic characteristics of $\beta$-pleated sheet into cortical, leptomeningeal vessel walls, and surrounding brain parenchyma
- Contractile elements of arteries replaced by noncontractile amyloid beta protein
- Arterial walls stain intensely w/ Congo red, and birefringence on polarized light
- Often multiple, spare BG, occur at corticomedullary junction

Summary
- Intracerebral hemorrhage, while still a devastating illness, is finally receiving the attention it deserves in the stroke community, and treatments are being developed that will likely improve outcomes.
- Prevention still must be emphasized, mainly by treating hypertension

ICH Key References
- The ICH score: a simple, reliable grading scale for ICH. Hemphill, JC, et.al. Stroke, 2001;32:891-897
- Spontaneous ICH. Qureshi, AI, et.al. NEJM, Vol.344, No.19, May 10, 2001