Acute Neurologic Syndromes

tPA?

NOT!

Elaine J. Skalabrin MD
Vascular Neurology
 Neurohospitalist-Neurointensivist
PeaceHealth Oregon
Intravenous t-PA Exclusion Criteria

- Time of symptom onset > 180 (or qualified 270) minutes before treatment would begin.
- Evidence of intracranial hemorrhage on pretreatment computer tomography (CT).
- Clinical presentation suggestive of subarachnoid hemorrhage
- Only minor or rapidly resolving stroke symptoms.
- Within 3 months of any intracranial operations, serious head trauma, or previous stroke.
- Major surgery within last 14 days.
- History of gastrointestinal or urinary tract hemorrhage within 21 days.
- Recent arterial puncture at a noncompressible site.
- Recent lumbar puncture.
- On repeated measurements, systolic blood pressure > 185 mm of mercury or diastolic blood pressure > 110 mm of mercury at the time treatment is to begin, or patient requires aggressive blood pressure treatment.
This is the worst headache of my life

Subarachnoid Hemorrhage
65 yo man with headache then collapse with right hemiplegia and initial BP of 240/110

Intracerebral Hemorrhage
CASE #1

• 72 yo old woman with history of atrial fibrillation who present after one hour of progressive aphasia. Exam shows global aphasia but no weakness. Radiologist reports CT negative, all labs negative except INR 2.8

Is she a iv tpa candidate?
Is she an IA tpa candidate?
Subacute Subdural Hematoma
CASE #1
RED FLAGS

72 yo old woman with history of atrial fibrillation who present after one hour of progressive aphasia. Exam shows global aphasia but no weakness. Radiologist reports CT negative, all labs negative except INR 2.8

ALWAYS Look at the scan!!
Acute Ischemic Stroke
Intravenous t-PA Inclusion Criteria

INCLUSION CRITERIA

• Age 18 years or older

• Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
Objectives

1. Classify common acute stroke syndromes
2. Describe acute non-stroke syndromes including PRES, RCVS, CVT and migraine
3. Distinguish non-stroke neurologic conditions, evaluation and treatment

Disclosures: None

Disclaimer: This is a general clinical pearls talk- there are always exceptions to the rule
Goal of Therapy in all Neurologic Emergencies

• ACUTE Setting
  – Identify syndrome
  – Take immediate action to reduce disability
  – Minimize Risk

• SUBACUTE setting
  – Understand etiology
  – Prevent second event
Review of Acute stroke syndromes

• Large artery strokes
  – Right MCA/PCA
  – Right ACA
  – Left MCA/PCA
  – Left ACA
  – Basilar
  – PICA/AICA/SCA (Cerebellar)

• Lacunar syndromes
  – Dysarthria clumsy hand
  – Pure motor
  – Sensorimotor
  – Pure sensory
  – Ataxia hemisensory
Other Acute Non-stroke Syndromes

- High spinal cord lesion (hemorrhage)
- Seizure
- Sudural hematoma (subacute)
- Conversion Disorder
- Unmasking of old deficit (same symptoms, less severe, identified trigger)
- Transient Global anemia
- Hypoglycemia/ Hyperglycemia/Hypocalcemia
- Syncope/presyncope
- Mass lesion
- Radiculopathy/neuropathy
- Multiple sclerosis/ other acute inflammatory disease
Safety of tPA in Stroke Mimics

Of 56 cases
  26.5%  Conversion Disorder
  19.5 % Complicated Migraine
  19.5%  Seizure

Table 3. Prevalence and Outcomes of SM Among Patients Treated With IVT Across Different Stroke Registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>IVT (No.)</th>
<th>SM (No., %)</th>
<th>sICH in SM (No., %)</th>
<th>OE in SM (No., %)</th>
<th>FI in SM (No., %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan</td>
<td>151</td>
<td>6 (4%)</td>
<td>0</td>
<td>NA</td>
<td>1 (17%)†</td>
</tr>
<tr>
<td>Basel</td>
<td>250</td>
<td>7 (3%)</td>
<td>0</td>
<td>0</td>
<td>6 (86%)‡</td>
</tr>
<tr>
<td>Houston</td>
<td>512</td>
<td>69 (13%)</td>
<td>0</td>
<td>0</td>
<td>60 (87%)†</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>254</td>
<td>9 (4%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Phoenix</td>
<td>539</td>
<td>56 (10%)</td>
<td>0</td>
<td>0</td>
<td>54 (96%)†</td>
</tr>
<tr>
<td>Overall</td>
<td>1706</td>
<td>147 (9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>121 (68%)</td>
</tr>
</tbody>
</table>

(95% CI, 7% to 10%)  (95% CI,* 0% to 2.3%) (95% CI,* 0% to 2.4%) (95% CI,* 81% to 93%)

SM indicates stroke mimic; IVT, intravenous thrombolysis; sICH, symptomatic intracranial hemorrhage; OE, orolingual edema; FI, functional independence defined as a modified Rankin Scale score of 0 to 1; NA, not available.

*Calculated by the Adjusted Wald method.
†At hospital discharge.
‡At 3 mo.
Acute Neurologic Syndromes

- Migraine
- Cerebral Venous Thrombosis
- Reversible Cerebral Vasconstriction Syndrome
- Posterior Reversible Encephalopathy Syndrome
- Meningitis with Vasculopathy
Migraine

The process of migraine pain.

When the trigeminal system is activated (1), peptides are released (2) prompting an inflammatory reaction. This increases flow of sensory traffic through the brain stem (3), the thalamus and ultimately the cortex (4).
<table>
<thead>
<tr>
<th>Features of Stroke</th>
<th>Features of Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sudden onset; maximal on onset and persistent</td>
<td>• Marching progression</td>
</tr>
<tr>
<td>– Exceptions: ie stuttering lacunar</td>
<td>• Time course variable</td>
</tr>
<tr>
<td>• Respects vascular territories (identifiable syndrome)</td>
<td>• Numbness and dizziness are prominent features</td>
</tr>
<tr>
<td>• Headache is absent or minor feature (simultaneous)</td>
<td>• May be associated with visual aura, nausea or confusion (does not respect vascular territories)</td>
</tr>
<tr>
<td>• Usually have vascular risk factors (previously recognized or unrecognized)</td>
<td>• Headache often follows neurologic symptoms</td>
</tr>
<tr>
<td></td>
<td>• History of migraine (may be remote)</td>
</tr>
</tbody>
</table>
Case #2

- 28 yo male presents with T 38.1 severe headache, nausea and vomiting and right sided numbness. Thirty minutes after arrival to the ED he develops a nonfluent aphasia.
- CT is negative
- Tpa?
- LP
  - WBC 231 (98% Lymphs) CSF glucose and protein normal, GS negative
HaNDL
Headache and Neurologic Deficit
Lymphocytosis in CSF

- Also known as Pseudomigraine with temporary neurological symptoms and lymphocytotic pleocytosis (PMP)
- Pathophysiology unknown (infectious or inflammatory)
- Recurrence unlikely after 12 weeks
Case #3

• 52 yo woman with acute onset aphasia. According to her family she is has no vascular risk factors and is generally healthy but suffered from severe diarrhea 10 days ago that resolved except persistent headache. Exam shows fluent aphasia and questionable right visual field cut
Tpa or not?
Venous thrombosis
Venous thrombosis misdiagnosed as enhancing tumor
Venous thrombosis
Patient undiagnosed and treated

Decline in LOC but may not develop weakness
Deep Venous thrombosis presents with alteration of consciousness without focal finding.
CVT
Age and Sex Distribution

Figure 1. Age and sex distribution of cerebral venous and sinus thrombosis (CVT) in adults. Bars represent the number of patients with CVT for the specific age/sex category. Data provided by Dr Jose Ferro from the International Study on Cerebral Venous and Dural Sinuses Thrombosis.
Predisposing Conditions for Cerebral Venous Thrombosis

- Hypercoaguability (Factor V Leiden, prothrombin mutation, APS, Protein C/S deficiency, hyperhomocystemia)
- OCP and postpartum
- Severe dehydration
- Medications: androgen, danazol, lithium, Vitamin A, IVIG, ectacy, tamoxifen, L-asparaginase
- Cancer
- Perimeningeal infection (mastoidisitis, otitis media, sinusitis)
- Intracranial hypotension
- PNH, iron deficiency anemia, nephrotic syndrome, polycythemia, thrombocythemia
- SLE, Behcet, Inflammatory bowel disease, thyroid disease, sarcoidosis
Proposed Algorithm for the Management of CVT

Clinical suspicion of CVT
(See section on “Clinical Diagnosis of CVT”)

MRI T2*-weighted imaging + MRV
CT/CTV if MRI not readily available

CVT (confirmed by imaging)

No evidence of CVT
Consider other differential diagnosis
- Arterial Stroke
- Idiopathic intracranial hypertension
- Meningitis
- Idiopathic intracranial hypotension
- Brain abscess
- Brain neoplasm, among others

Initiate anticoagulation (IV heparin or SC LMWH)
if no major contraindications

Neurological improvement or stable
Continue oral anticoagulation
for 3-12 months or lifelong according to the underlying etiology
a) Transient reversible factor
b) Low-risk thrombophilia
c) High-risk/inherited thrombophilia
(See section on “Long-Term Management and Recurrence of CVT”)

Neurological deterioration or coma despite medical treatment
Severe mass effect or ICH on repeated imaging
May consider decompressive hemicraniectomy
(lifesaving procedure)

No or mild mass effect on repeated imaging
May consider endovascular therapy (with or without mechanical disruption)

All patients should receive support for the prevention of complication and symptomatic therapy
(eg, management of seizures, intracranial hypertension)
Case #3
Red Flags and Take home

• 52 yo woman with acute onset aphasia. According to her family she is has no vascular risk factors and is generally healthy but suffered from severe diarrhea 10 days ago that resolved except persistent headache. Exam shows fluent aphasia and questionable right visual field cut

• Imaging appearance (edema and hemorrhage) often looks much worse than clinical picture
Case # 4

- 64 yo man presents to ED with acute onset confusion. He is agitated can speak fluently but confabulates. His BP is 200/120
- Labs show new elevation of creatinine of 3.4
- Head CT read as bilateral subacute occipital lobe strokes
Posterior Reversible Encephalopathy Syndrome
Posterior Reversible Encephalopathy Syndrome

- Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is a syndrome characterised by headache, confusion, seizures and visual loss. It may occur due to a number of causes, predominantly malignant hypertension, eclampsia and some medical treatments. On magnetic resonance imaging (MRI) of the brain, areas of edema (swelling) are seen. The symptoms tend to resolve after a period of time, although visual changes sometimes remain
PRES

- PRES occurs due to the use of drugs like tacrolimus and cyclosporine, hence it may occur in people who have undergone an organ transplant, in which these drugs may be used to suppress transplant rejection. It also occurs due to eclampsia, severe high blood pressure and hypercalcemia. Low magnesium levels can augment PRES.
<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>No. of Patients</th>
<th>Primary PRES Cause</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>58</td>
<td>CSA for transplant</td>
<td>34</td>
</tr>
<tr>
<td>Mental status changes(^a)</td>
<td>10</td>
<td>Hypertension</td>
<td>17</td>
</tr>
<tr>
<td>Visual symptoms or loss</td>
<td>3</td>
<td>Eclampsia</td>
<td>5</td>
</tr>
<tr>
<td>Severe headache</td>
<td>3</td>
<td>Tacrolimus</td>
<td>4</td>
</tr>
<tr>
<td>Aphasia</td>
<td>1</td>
<td>Cocaine, methamphetamine use</td>
<td>3</td>
</tr>
<tr>
<td>Facial numbness</td>
<td>1</td>
<td>TTP/ITP</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Combined chemotherapy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lupus erythematosus</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic renal failure</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PEG L-asparaginase</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemolytic uremic syndrome</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOS, anaphylaxis?</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOS, alcohol withdrawal?</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOS, steroids?</td>
<td>1</td>
</tr>
</tbody>
</table>

Note—CSA = cyclosporine A, TTP/ITP = thrombotic or idiopathic thrombocytopenic purpura, PEG = polyethylene glycol, NOS = not otherwise specified.

\(^a\)Include acute decrease in consciousness or in responsiveness or acute confusion.
Classical MRI Appearance of PRES
PRES imaging variants
Regional Involvement of PRES

Fig. 4—Bar graph shows regional involvement by posterior reversible encephalopathy syndrome (PRES) in 76 patients. Number of patients in each region are listed in or above each bar.
Case # 5

- 49 yo female who presents with a sudden severe headache and progressive visual changes. PMH is negative. She denies drug use but consumes energy drinks daily and smokes marijuana. Exam shows mild word finding difficulties, right visual field cut.
- Head CT is negative.
- Tpa?
Reversible Cerebral Vasoconstriction Syndrome (RCVS)

- **Reversible cerebral vasoconstriction syndrome** (RCVS, sometimes called Call-Fleming syndrome or by a number of other names) is a poorly understood disease in which the arteries of the brain develop vasospasm without a clear cause (such as hemorrhage or trauma).
  - Vasospasm narrows arteries and can trigger severe headaches that wax and wane. When the vasospasms subside the headaches are relieved.
  - Symptoms result from vasospasms that narrow arteries, especially those around the circle of Willis, which can lead to a dramatic headaches that are often of the thunderclap headache (sudden-onset) character.
  - Ischemia damage in these patients which presents 3–4 days after headache onset as focal neurological symptoms.
### Table 1. Conditions Associated with Reversible Cerebral Vasoconstriction Syndromes*

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy and puerperium</td>
<td>Early puerperium, late pregnancy, eclampsia, preeclampsia, and delayed postpartum eclampsia</td>
</tr>
<tr>
<td>Exposure to drugs and blood products</td>
<td>Phenylpropanolamine, pseudoephedrine, ergotamine tartrate, methergine, bromocryptine, lisuride, selective serotonin reuptake inhibitors, sumatriptan, isomethiptine, cocaine, ecstasy, amphetamine derivatives, marijuana, lysergic acid diethylamide, tacrolimus (FK-506), cyclophosphamide, erythropoetin, intravenous immune globulin, and red blood cell transfusions</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Hypercalcemia, porphyria, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma, postcarotid endarterectomy, and neurosurgical procedures</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>No identifiable precipitating factor</td>
</tr>
<tr>
<td></td>
<td>Associated with headache disorders, such as migraine, primary thunderclap headache, benign exertional headache, benign sexual headache, and primary cough headache</td>
</tr>
</tbody>
</table>

### Table 2. Summary of Critical Elements for the Diagnosis of Reversible Cerebral Vasoconstriction Syndromes*

- Transfemoral angiography or indirect CTA or MRA documenting multifocal segmental cerebral artery vasoconstriction
- No evidence for aneurysmal subarachnoid hemorrhage
- Normal or near-normal cerebrospinal fluid analysis (protein level < 80 mg%, leukocytes <10 mm³, normal glucose level)
- Severe, acute headaches, with or without additional neurologic signs or symptoms
- Reversibility of angiographic abnormalities within 12 weeks after onset. If death occurs before the follow-up studies are completed, autopsy rules out such conditions as vasculitis, intracranial atherosclerosis, and aneurysmal subarachnoid hemorrhage, which can also manifest with headache and stroke.

*CTA = computed tomography angiography; MRA = magnetic resonance angiography.
<table>
<thead>
<tr>
<th>Variable</th>
<th>RCVS</th>
<th>PACNS</th>
<th>SAH</th>
<th>Arterial Dissection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female predominate; ratio 2–3:1</td>
<td>No sex predilection</td>
<td>Female predominate, ratio 1.6:1</td>
<td>No sex predilection</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute (seconds to minutes)</td>
<td>Typically subacute to chronic</td>
<td>Acute (seconds)</td>
<td>Acute or subacute</td>
</tr>
<tr>
<td>Headache</td>
<td>Acute and severe, throbbing, often thunderclap</td>
<td>Insidious and progressive, dull aching</td>
<td>Thunderclap</td>
<td>Thunderclap in about 13%</td>
</tr>
<tr>
<td>CSF examination</td>
<td>Normal or near-normal</td>
<td>Abnormal in &gt;95% of PACNS; variably abnormal in non-PACNS variants</td>
<td>Abnormal (elevated erythrocyte count, xanthochromia)</td>
<td>Normal</td>
</tr>
<tr>
<td>CT/MRI of brain parenchyma</td>
<td>Normal in the majority of patients; or shows symmetric arterial “watershed” infarctions or parenchymal brain hemorrhage. In addition, small SAH overlying the cortical surface or reversible brain edema may occur.</td>
<td>Abnormal in 90% of cases of PACNS; No characteristic findings but small infarctions in gray or white matter, varying ages, affects multiple vascular territories with or without diffuse white matter lesions</td>
<td>SAH, which usually correlates with the size and severity of arterial vasospasm. Ischemic stroke and brain edema can develop distal to the site of vasospasm. Rare patients can have “CT-negative” SAH.</td>
<td>Results of brain CT and MRI are normal in the absence of ischemic stroke. Axial MRI or CTA may show crescentic intraluminal hematoma involving the vertebral or internal carotid artery.</td>
</tr>
<tr>
<td>Neurovascular imaging</td>
<td>By definition, shows diffuse areas of multiple stenoses and dilatation involving intracranial cerebral arteries. These abnormalities are present in the acute stage and are reversible within days to weeks.</td>
<td>Variable sensitivity. Frequently normal in PACNS; otherwise, findings range from single or multiple arterial cut-off areas, to luminal irregularities in single or multiple arteries, to diffuse abnormalities that are occasionally indistinguishable from RCVS. These abnormalities are frequently irreversible.</td>
<td>Usually shows saccular aneurysm or alternate cause of the bleeding (e.g., arteriovenous malformation). Vasospasm typically is not multifocal, affects 1–2 medium arteries, and peaks between days 4 and 11. Acute vasospasm on the day of onset is extremely rare.</td>
<td>Long-segment stenosis, double-lumen, intimal flaps, and arterial pseudoaneurysms are characteristic angiographic signs. Stenosis resolves in 90% within 3 months. Unlike RCVS, stenosis is smooth, involves extracranial carotid extracranial and intracranial vertebral arteries, and involves a single vessel (except in rare cases of multivessel dissection).</td>
</tr>
</tbody>
</table>

*CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging; PACNS = primary angiitis of the central nervous system; RCVS = reversible cerebral vasoconstriction syndrome; SAH = subarachnoid hemorrhage.
Case #6

• 18 year old female two weeks postpartum from normal vaginal delivery (epidural anesthetic) who presents with severe headache, fever and aphasia and right sided weakness.

• Non-contrast Head CT negative

• LP
  – WBC 4200 (89% PMNs) glucose low and protein normal, GS + cocci

• Lumbar MRI – epidural abscess
Meningitis—Stroke (KT)
Meningitis—Stroke (KT)
Meningitis—Stroke (KT)
Transcranial Doppler in Bacterial Meningitis

![Graph showing CBFV (cm/s) over different days]
Red Flags

- Headache as a prominent feature
- FEVER
- No vascular risk factors
- Non-anatomic symptoms (mute and left sided weakness but not left handed)
- ANY CT findings
- Disconnect between imaging and clinical findings
Final case

- 32 year old with history of migraine, who has had one week of atypical left sided headache then presents with ED with nausea, vomiting, diplopia, severe dysarthria and first left, than right-sided hemiparesis. Exam shows dysconjugate gaze severe dysarthria but no facial droop, right sided moderate weakness.
- Noncontrast head CT is negative, labs are normal.
- Tpa?
- Diagnosis?
Acute Basilar Thrombosis from Vertebral dissection
Cerebrovascular Dissection

- Disruption of intima with infiltration of blood between mural layers
- Common cause of stroke in young and middle-aged adults
  - 5-20%
- Associated with trauma, neck manipulations, or can be spontaneous.
- More common in patients with collagen vascular diseases.

Schievink, NEJM 2001; 334:898
Cerebrovascular Dissection

- Features
  - Wall thickening
  - Stenosis & occlusion
  - Pseudoaneurysms
  - Intimal flaps
  - Thrombus & emboli

- Common Sites
  - Carotid: 1-2 cm beyond bifurcation to skull base
  - Vertebral: Below C6 (V1) or above C2 level (V3, V4)
MRI/MR Angiography

- MRI
  - Diffusion imaging for acute stroke
- MR Angiography
  - Flame-shaped occlusion
  - Long segment stenosis
  - Luminal irregularity
  - Pseudoaneurysm
- Intramural hematoma
  - T1 fat sat neck
  - Crescent shape or round rim
  - Methemoglobin

34 yo woman, right ICA dissection
Early Recurrent Risk

Beletsky et al., 2003 Stroke

Bioussé et al., 1995 Stroke

High risk period - 1st month
Final case

Take Home

• 32 year old with history of migraine, who has had one week of atypical left sided headache then presents with ED with nausea, vomiting, diplopia, severe dysarthria and first left, than right-sided hemiparesis. Exam shows dysconguate gaze, severe dysarthria but no facial droop, right sided moderate weakness.

• Diagnosis: Migraine vs Conversion disorder-----but only after dissection is ruled out!
Conclusion

• TPA is a safe effective intervention in a select population
• Ischemic stroke is clinical diagnosis
• Explore the history and physical to exclude or include nonstroke or atypical syndromes
• Order the right test
• Look at the imaging!!!
• Limit Disability


Tsivgoulis G, et al. Safety Outcomes of Intravenous Thrombolysis in Stroke Mimics A 6 year, single-Care Center Study and a Pooled Analysis of Reported Studies Stroke (2011) 42:00-00


ENLS
Emergency Neurological Life Support