Stroke of the Eye
Central Retinal Artery Occlusion

“To Give or Not to Give” IV tPA
Difficult stroke presentations: Case Based Discussion

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Financial Disclosure

•  (Sadly) None
Learning Objectives

• Learn the possible causes of acute monocular blindness
• Learn the causes of retinal artery occlusion
• Learn the studies on Intravenous (IV) tPA therapy on central retinal artery occlusion
• Learn the studies on Intra-arterial (IA) tPA therapy on central retinal artery occlusion
• Think about what you would do for patients presented with acute monocular blindness
Stroke Alert Case:  
Sudden onset of monocular Blindness

- 80 yo RH woman with PMHx of HTN and HLD presented with sudden onset of blindness in the right eye. She could make out of shadows but couldn’t count fingers.
- Last seen normal: 16:30
- Stroke alert activated: 17:01
- NIHSS 2? (but not hemianopsia)
- Eye exam: limited fundus exam, normal pupillary reflex, no RAPD (relative afferent pupillary defects)
- CT brain – unremarkable
- CTA head and neck – mild atherosclerosis, no flow limiting stenosis, patent right ophthalmic artery
Is this a stroke for sure?
Am I supposed to give IV tPA?
Causes of Acute Monocular Vision Loss without Eye Pain

- Amaurosis fugax
- Retinal artery occlusion ("Stroke of the eye")
- Retinal vein occlusion
- Retinal detachment
- Arteritic ischemic optic neuropathy (AION)/Giant cell arteritis
- Nonarteritic ischemic optic neuropathy (NION)
- Macular hemorrhage
- Vitreous hemorrhage
- Ocular migraine
- Psychogenic/Conversion disorder
Causes of Acute Vision Loss WITH Eye Pain\(^1\):

- Acute angle-closure glaucoma
- Corneal ulcer
- Optic neuritis (usually with pain)
- Endophthalmitis
### Causes of Acute Monocular Vision Loss without Eye Pain

<table>
<thead>
<tr>
<th>Causes</th>
<th>Suggestive Findings</th>
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</thead>
<tbody>
<tr>
<td>Amaurosis fugax</td>
<td>Monocular blindness lasting minutes to hours (typically &lt; 5 min when due to CVA) – DDx: ischemia, retinal vein occlusion, optic nerve compression, papilledema, other ocular causes.</td>
</tr>
<tr>
<td>Retinal Artery Occlusion</td>
<td>Nearly instantaneous onset, pale retina, cherry-red fovea, risk factors for vascular disease</td>
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<tr>
<td>Arteritic AION (anterior ischemic optic neuropathy) /Giant cell arteritis</td>
<td>Headache, jaw or tongue claudication, temporal artery tenderness or swelling, pale and swollen disk with surrounding hemorrhages, occlusion of retinal artery or its branches, proximal myalgia with stiffness (polymyalgia rheumatica)</td>
</tr>
<tr>
<td>Nonarteritic AION</td>
<td>Optic disk edema and hemorrhages, sometimes loss of inferior and central visual fields, Risk factors: DM, HTN, hypotensive episode</td>
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<tr>
<td>Macular hemorrhage</td>
<td>Blood within or deep to retina in and around the macula</td>
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</table>
Causes of Acute Monocular Vision Loss without Eye Pain

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<th>Causes</th>
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</thead>
<tbody>
<tr>
<td>Retinal Detachment</td>
<td>Recent increase in floaters, photopsias (flashing lights), or both visual field defect, retinal folds</td>
</tr>
</tbody>
</table>
| Retinal Vein Occlusion         | Frequent, multiple, widely distributed retinal hemorrhages  
Risk factors (eg, diabetes, hypertension, hyperviscosity syndrome, sickle cell anemia) |
| Vitreous hemorrhage            | Previous floaters or spider web in vision  
Risk factors (eg, diabetes, retinal tear, sickle cell anemia, trauma)                                                                    |
| Ocular Migraine                | Scintillating scotomata, mosaic patterns, or complete loss of vision lasting usually 10–60 min and often followed by headache. Often in young patients. |

Can any of these be a contraindication for IV tPA? Can you differentiate these based on your exam??
Retinal Artery Occlusion

Central Retinal Artery Occlusion (CRAO)
Branch Retinal Artery Occlusion (BRAO)

- CRAO Incidence: 1 in 100,000
- Present with acute, painless loss of monocular vision
- Central retinal artery supplies the inner retina and the surface of optic nerve
- 15-30% of people have cilioretinal artery also supplying the inner retina
  - May spare central vision
- 80% of patients will have visual acuity < 20/400
Causes of Retinal Artery Occlusion

- Carotid artery atherosclerosis (10-30%) – most common
- Cardiogenic embolism – second most common
- Small artery disease – older patients, DM, HTN
- Vascular disease (carotid artery dissection, fibromuscular dysplasia, radiation injury, Moyamoya, Fabry’s)
- Hematologic (sickle cell, hypercoagulable state)
- Inflammatory (Giant cell arteritis – 5%, Susac syndrome, SLE, polyarthritis nodosa, Wegener’s granulomatosis)
Conservative Treatments of CRAO

- Ocular massage
- Anterior chamber paracentesis (sudden drop in ocular pressure may dislodge the embolus)
- IV acetazolamide, IV mannitol (reduction of ocular pressure)
- Vasodilator medications (Penoxifilline, nitroglycerin, isosorbide mononitrate)
- Hyperbaric oxygen therapy

***None of these therapies are proven to be effective\(^9, ^{14}\)***
Acute Treatments of CRAO

Currently no proven treatment/guidelines exists
So What would you do???
Funduscopic exam by ophthalmologist on my patient:

- It confirmed the diagnosis of retinal artery occlusion (and more importantly, it ruled out other eye pathology).
Now What???
Would you give IV tPA?
I DID
Stroke Timeline

- **LSN:** 16:30
- Stroke alert activated: 17:01
- CT head read: 17:15
- CTA head and neck read: 17:22
- Ophthalmology consult requested: 17:25
  - Was instructed to dilate the pupils
  - Total time for ophthalmology consult: ~30 mins
- IV tPA ordered: 18:08
- IV tPA administered: 18:20 (110 minutes from LSN)
That feeling when you gave tPA and you are not sure if you did the right thing...
Did it work???
NOPE.
MRI brain next day

Right cerebellar infarction
What do we know about acute treatment for CRAO “Stroke of the eye”? 

All the major studies have been done by ophthalmologists.
Retinal survival time: Animal studies

2 studies with rhesus monkeys:

• CRAO was produced in 63 eyes of rhesus monkeys. Monkey retina can recovered well after ischemia of 97 minutes. After 105 minutes, the retinal damage was irreversible (1980)\(^1\).

• CRAO was produced in 38 rhesus monkeys. Eyes with CRAO for 97 minutes showed practically no damage. The degree of permanent damage was associated with the duration of CRAO. CRAO lasting for 240 minutes resulted in massive irreversible damage (2004)\(^2\).

CRAO and IV tPA #1 (2002, US)

Intravenous Recombinant Tissue-Type Plasminogen Activator Thrombolysis in Treatment of Central Retinal Artery Occlusion

- **Method**: Prospective study
  - IV tPA (0.9mg/kg, max 90mg) + Anticoagulation with Coumadin and heparin drip bridge + anterior-chamber paracentesis if intraocular pressure > 12 mmHg.

- **Inclusion**:
  - onset < 24 hours
  - confirmed CRAO diagnosis by ophthalmologist

- **Results**:
  - 12 patients enrolled
  - Mean time to receive tPA 5.75 h (range 2 h to 18 h). 10 patients within < 6 h.
  - 9 patients received anterior-chamber paracentesis
  - 4 (33%) had >8 Snellen VA lines of improvement
  - 6 (50%) had 2-4 Snellen VA lines of improvement

- **Complications**:
  - 4 developed neovascular glaucoma within 3 to 4 weeks

- **Conclusion**: IV tPA is beneficial. Paracentesis may be beneficial if it’s done in conjunction with IV tPA.

CRAO and IV tPA #2 (2008, Germany)

*Intravenous Thrombolysis With Low-dose Recombinant Tissue Plasminogen Activator in Central Retinal Artery Occlusion*\(^6\)

- **Method**: Prospective study
  - low dose (50mg) IV tPA + IV heparin x 5 days, ASA 100mg QD
- **Inclusion**:
  - onset < 12 hours, VA < 20/100
  - confirmed CRAO diagnosis by funduscopic exam
- **Exclusion**:
  - Retinal/vitreous hemorrhage
  - Other ocular disease (diabetic retinopathy, macular degeneration)
- **Results**:
  - 28 patients enrolled
  - 32% improved vision (> 3 lines in Snellen visual acuity test)
  - *When tPA was given within < 6.5 h, 41% of patients achieved VA 20/50 or better, and 53% achieved > 3 lines VA improvement.*
- **Conclusion**: Negative study, **BUT** IV t-PA can improve vision for patients with CRAO if given < 6.5 hours after the onset of symptoms.

CRAO and IV tPA #3 (2011, Australia)

Efficacy of intravenous tissue-type plasminogen activator in central retinal artery occlusion: Report from a randomized, controlled trial

**METHODS:** A placebo-controlled, double-blinded, randomized trial

**Inclusion:**
- CRAO confirmed with funduscopic exam by ophthalmologist
- < 24 h within onset of symptoms

**Exclusion:**
- Temporal arteritis by clinical assessment of ESR

**Demographics:**

<table>
<thead>
<tr>
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<th>tPA (n=8)</th>
<th>Placebo (n=8)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Mean age</td>
<td>73±8</td>
<td>67±9</td>
<td>0.18</td>
</tr>
<tr>
<td>Time to presentation (h)</td>
<td>9.1±6.1</td>
<td>3.9±2.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Time to treatment (h)</td>
<td>14.4±6.5</td>
<td>7.3±3.0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Chen CS et al. The efficacy of intravenous tissue plasminogen activator in central retinal artery occlusion: Report from a randomized, controlled trial. Stroke. 2011;42:2229-2234
Efficacy of intravenous tissue-type plasminogen activator in central retinal artery occlusion: Report from a randomized, controlled trial

- **Results:**
  - 16 patients enrolled
  - 2 out of 8 (25%) of the tPA group had transient improvement in VA at 1 wk. These patients received IV tPA at 4.5 h and 6 h from the onset.
  - The improvement was not sustained at 6 months
  - Adverse reaction of tPA: 1 patient had ICH, 1 patient developed retinal rev visualization and vitreous hemorrhage
  - **Early termination** of the study due to 1 patient with significant ICH s/p tPA.

- **Conclusion:**
  - Time window for intervention is likely < 6h.
  - Reocclusion is a potential problem and it may require adjuvant anticoagulation.

CRAO and IV tPA #4 (2016, China)

Observation on therapeutic efficacy of rt-PA intravenous thrombolysis combined with compound anisodine injection on central retinal artery occlusion

- Method: Randomized trial
  - 4 treatment groups and 3 “control” groups with different combinations of IV tPA, sublingual nitroglycerin, retrobulbar atropine injection, IV vitamin, ocular massage, methazolamide, mecobalamine, ozagrel, etc.. It’s a mess.
  - 48 CRAO patients, onset < 72 h.
  - Results: VF defect 74±13% in the control group, 35±16% in the treatment group (p<0.01)

What about IA tPA? Is that effective??
CRAO and IA Finbrinolysis #1
(2002, Germany)

Prognosis of Central Retinal Artery Occlusion: Local Intraarterial Fibrinolysis vs. Conservative Treatment

- **Method**:
  - Retrospective study
  - Conservative treatment (n=116)
  - IA urokinase/rtPA + heparin gtt x 2 d + ocular massage (n=62)
  - Primary outcome: VA improvement with > 1 line on the Snellen chart

- **Inclusion**:
  - Confirmed CRAO by ophthalmologists
  - < 13 days from the onset of symptoms

- **Time to Treatment**:
  - Conservative – median 9 h (mean 24.2±40.4 h)
  - IA tPA – median 9 h (mean 10.8±9.5 h)

- **Results**:
  - Conservative group – 29% patients improved. No differences based on the onset to treatment time.
  - IA tPA group – 52% patients improved, Better results if treated <6h (76% patient improved).
  - 2 thrombotic stroke complications due to catheter manipulation.

CRAO and IA tPA #2 (EAGLE, 2009)

Multicenter study of the European Assessment Group for Lysis in the Eye (EAGLE) for the treatment of central retinal artery occlusion

- **Method**: Randomized, controlled, prospective, multi-center study
  - Control group – conservative treatments, heparin BID x 5d
  - Treatment – IA rtPA + heparin BID 5 days
- **Inclusion**: CRAO with < 20 h from onset, VA < 0.32
- **Exclusion**: BRAO, cilioretinal arteries supplying retina, proliferative diabetic retinopathy, intraocular pressure > 30mmHg, ESR > 30, etc.
- **Results**:
  - 84 patients enrolled (conservative n=40, IA tPA n=44)
  - Time to treatment: conservative 10.99±5.49 h, IA tPA 12.78±5.77 h
  - No significant difference between IA tPA vs. conservative therapy (60% vs. 57.1%).
  - Higher adverse effects in the IA tPA vs. conservative therapy (37% vs. 4.3%).
  - Severe complications in the treatment group: 2 symptomatic ICH cases.
  - **Early termination** of the study due to similar efficacy and higher adverse effects in the IA tPA group.

CRAO and IA tPA #3 (2008, Johns Hopkins)

Local intraarterial fibrinolysis administered in Aliquots for the treatment of central retinal artery occlusion: The Johns Hopkins Hospital

- **Methods**: nonrandomized interventional study, IA tPA vs. conservative tx
  - IA tPA stopped when patency of the central retinal artery is clinically established, or max tPA 20mg
- **Inclusion**:
  - CRAO confirmed by ophthalmologist using ophthalmoscopy
  - < 15 h from the onset
- **Results**: 42 patients enrolled
  - **Time to IA tPA**: 9.3±2.9 h
  - Conservative: n=21, 33% had improvement in VA > 1 line
  - IA tPA: n=31, 76% had **improvement in VA > 1 line**
  - Multivariate logistic regression analysis: The IA tPA group was 36 times more likely to have improvement in VA (p=0.0001).
  - Post hoc analysis showed the IA tPA group was 13 times more likely to have improvement in VA of > 3 lines, and 4.9 times more likely to have final VA of 20/200 or better.
- **Complications**: 2 groin hematomas
- **Conclusions**: Local intraarterial fibrinolysis is associated with an improvement in visual acuity and has few side effects.

Efficacy and Safety of Intra-Arterial Thrombolysis in Central Retinal Artery Occlusion

**Methods**: retrospective study

**Inclusion**: symptom duration \( \leq 24\text{h} \) (or \( \leq 7\text{d} \) for incomplete CRAO)

**Results**:
- 101 enrolled, conservative group (n=44), IA tPA group (n=57)
- Time to treatment: conservative 35.9\( \pm \)27.6h, IA tPA 22.7\( \pm \)30.6h
- For incomplete CRAO, the IA tPA group had greater VA improvement after 1 month
- No significant difference in total or subtotal CRAO.
- Complications: 8% insignificant cerebral infarcts

In Summary

- There is no consensus treatment guidelines for acute CRAO exists currently.
- Conservative treatments have not shown to be effective.
- Observational studies suggest efficacy of early intervention with both IV and IA tPA for acute treatment of CRAO.
- Randomized studies for IV tPA (Australian study) and IA tPA (EAGLE, European study) failed to demonstrate a significant improvement in visual acuity and terminated early due to adverse effects.
  - But they also had some study design flaws.
  - ie; the inclusion criteria (time of onset < 24h and < 20h).
“BE FAST” -- stroke alerts on CRAO/BRAO patients

What do we need to rule out before we give IV tPA? – Challenges of funduscopic exam in ED by neurologists

Is STAT ophthalmology consult worth the time?
- All the studies have been done by ophthalmologists and thorough funduscopic exam was done prior to intervention.

Would you give IV tPA to a patient with CRAO? BRAO?
References:

References:


References:


THANKS FOR LISTENING

ANY QUESTIONS?