Special Types of Brain Hemorrhage (Part 2 of 3)

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C VT

Continued
Which MRV Is Which Case?
Axial T2 GRE: A tubular aspect suggestive of a thrombosed cortical vein, which is responsible for an ICH.
Case

- 56 yo man presenting w/ blurred vision, new-onset headache, and vague constitutional symptoms (malaise, nausea, fatigue)
- PMHx
  - Prostate CA
- Exam
  - Normal
Case: Summary

- Patient w/ known, diffusely metastatic prostate CA
- Presented w/ new-onset HA
- Evident SSS partial thrombosis
- Patient refused further w/u or Rx
Case

☐ 32 yo man w/ complaints of new-onset headache X 2 weeks, nausea, and visual problems

☐ PMHx
  □ No identifiable issues

☐ Exam
  □ L sup VF loss, L neglect
Case: Summary

- Healthy, young man with new-onset headache
  - Found to have a venous HI and R transverse sinus thrombosis
  - Found to have Protein C deficiency and an abnormal LA profile
  - Placed on HEP then WARF
  - Loss to f/u...
Case

- 13 yo girl w/ > 24-h of lethargy, flu-like symptoms, and vomiting
- PMHx
  - Down’s syndrome, autism
- Meds
  - Included OCAs
Exam
- Afebrile
- Supple neck
- Moves all extremities
- Eyes closed and does not attend to stimuli
- Does not follow commands
- Toes upgoing
Case: Summary

- 13 yo w/ deep CVT
  - RFs include OCAs and recent dehydration
  - I could NOT find a reported relationship between Down’s and CVT
  - Coagulation profiles=normal
Consequences of CVT

- Highly variable
- Depends on availability of pre-existing collateral venous channels and propagation of the thrombus along the veins
SSS, For Example

☐ Classically
  ■ Extensive bilateral cortical/adjacent white matter infarctions
  ■ W/ or w/o petechial hemorrhages

☐ Can present w/ edema and no infarction

☐ Can present w/o any brain changes
<table>
<thead>
<tr>
<th>Site/Veins</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS</td>
<td>59.5 to 98.0%</td>
</tr>
<tr>
<td>Lateral sinus</td>
<td>10.0 to 67.5%</td>
</tr>
<tr>
<td>Straight sinus</td>
<td>00.0 to 25.0%</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>00.0 to 05.0%</td>
</tr>
<tr>
<td>Cortical veins</td>
<td>03.5 to 50.0%</td>
</tr>
<tr>
<td>Deep veins</td>
<td>00.0 to 25.5%</td>
</tr>
<tr>
<td>More than one</td>
<td>05.5 to 74.0%</td>
</tr>
<tr>
<td>Presenting Neuro SSx (n=160) w/ CVT</td>
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<tr>
<td>------------------------------------</td>
<td></td>
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<tr>
<td>HA</td>
<td>82.0%</td>
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<tr>
<td>Papilloedema</td>
<td>50.5%</td>
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<tr>
<td>Seizures</td>
<td>42.0%</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>39.0%</td>
</tr>
<tr>
<td>Disordered LOC</td>
<td>30.5%</td>
</tr>
<tr>
<td>Multiple CN palsies</td>
<td>10.5%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>02.0%</td>
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<tr>
<td>Bilat or alternating cortical signs</td>
<td>01.5%</td>
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<tr>
<td>Clinical Sign</td>
<td>Percentage</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>HA</td>
<td>31.0 to 91.0%</td>
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<tr>
<td>Papilloedema</td>
<td>07.0 to 80.0%</td>
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<tr>
<td>Focal deficit</td>
<td>27.0 to 79.0%</td>
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<tr>
<td>Seizures</td>
<td>10.0 to 60.0%</td>
</tr>
<tr>
<td>Altered LOC</td>
<td>10.0 to 93.0%</td>
</tr>
</tbody>
</table>
HAs on CVT

- Most frequent symptom
- Probably caused by
  - Increased ICP
  - And by distension of sinus wall or local inflammation or leakage of blood
- Can be any grade of severity
- Can be diffuse or localized
- Mostly persist and worse on recumbency
- Can be “thunderclap” and mimic SAH
- Can mimic migraine and be
  - Unilateral
  - Intermittent
  - Or associated with visual phenomena
CVT: Mode of Onset

- Acute mode of onset
  - Presence of focal signs
  - Ranging from 28.0 to 54.0% of non-puerperal cases
  - Higher in OB cases
  - Higher in infectious cases
Subacute or chronic mode of onset

- Presence of HA
- Ranging from 25.0 to 42.0%
- Higher in inflammatory diseases
- Higher in coagulopathic disorders
CVT: Patterns of Presentation

- First and most common pattern in those where mode of onset data available
  - In about 75% of CVT cases
    - Presence of focal signs
    - If in association w/ HA, seizures, or altered MSE should raise suspicion of CVT
- Second most common
  - Isolated intracranial hypertension w/ HA, papilloedema, and eventually CN 6 palsy
- Third and most misleading
  - Subacute, diffuse encephalopathy mainly characterized by decreased LOC, w/o clear localizing signs or recognizable features of increased ICP
Fourth classical pattern (cavernous)

- Acute painful ophthalmoplegia associated with chemosis and ptosis
Some unusual patterns including
- w/ SAH and simulating a ruptured IA
- “Recurrent TIAs”
- Migraine-like
- Hearing loss
- Acute confusional state

Totally asymptomatic
CVT: Outcome

- If the patient survives, prognosis for recovery of function is much better than in arterial stroke.
- Disabling sequelae in about 15% of survivors.
- **Long-term outcome**
  - Very little known
  - Residual epilepsy in 10.0 to 30.0% of those who seizures in the acute phase

- **Recurrence**
  - At 11.7% in one series of 77 patients followed for mean of 78-mos
  - Highest in those w/ thrombophilia
Causes of CVT

- See lists in major texts

- 149 patients studied
- Univariate analysis
  - Factor V, protein C, protein S, and elevated Lp(a) were all found to be significantly associated w/ CVT
Cont-

Multivariate analysis

- Only the combination of a prothrombotic RF (FV Leiden, PC def, PS def, ATII def, ACLAbs) with an underlying condition (trauma/immobilization, steroids, infections, birth asphyxia, DM, metabolic disease, nephrotic syndrome, obesity, and OCAs) (OR=3.9) increased Lp(a) (OR=4.1), and PC def (OR=11.1) had independent associations with CVT.

- Increased risk of CVT
  - Pts using OCAs (OR=5.59)
  - Pts w/ FV Leiden (OR=3.38)
  - Pts w/ prothrombin gene mutation (OR=9.27)
  - Pts w/ hyperhomocysteinemia (OR=4.07)
Management and Treatment

- Organized care
  - The most effective interventions to reduce mortality and morbidity following acute stroke
- CVT is an uncommon but potentially serious and life-threatening cause of stroke
- Based on findings for stroke unit care in general, management of CVT in a stroke unit is reasonable for the initial management of CVT in order to optimize care and minimize complications
Initial Anticoagulation

- There are several rationales for anticoagulation therapy in CVT
  - To prevent thrombus growth
  - To facilitate recanalization
  - To prevent DVT/PE

- Controversy has ensued because cerebral infarction with hemorrhagic transformation or ICH is commonly present at the time of Dx of CVT
Two available randomized controlled trials have compared anticoagulant therapy to placebo or open control in patients with confirmed CVT.

- One trial of 20 patients assessed intravenous UFH using dose adjustment to achieve an aPTT twice the pre-treatment value compared to placebo.
- The primary outcome was a CVT severity scale at 3 months, the secondary outcome was ICH.
- The trial was stopped early after 20 of a planned 60 patients were enrolled because there was a benefit of treatment.
The other trial of 59 patients compared SQ nadroparin to placebo for 3 wks followed by 3 mos of oral anticoagulation (without placebo control) in those randomized to nadroparin.

- The study was blind during the first 3 weeks and open label thereafter.
- Primary outcomes were scores for ADLs, the Oxford Stroke handicap scale, and death.
- Secondary endpoints were symptomatic ICH and other major bleeding.
- At 3 months, 13% in the nadroparin group had a poor outcome compared to 21% with placebo (treatment difference in favor of nadroparin).
Meta-analysis of these two trials revealed a non-statistically significant RRR of death or dependency with anticoagulation

- RR 0.46, with a risk difference in favor of anticoagulation of -13%
- The RR of death was 0.33, risk difference -13%
A third trial randomized 57 women with puerperal CVT confirmed only by CT imaging and excluding those with hemorrhage on CT.

- Treatment was with SQ HEP 5000 IU every 6 hours, dose adjusted to an aPTT 1.5 times baseline for at least 30 d after delivery.
- Outcome assessment was not blinded.
- Three patients in the control group either died or had residual paresis compared to none in the HEP group.
In the special situation of CVT with cerebral hemorrhage on presentation

- Even in the absence of anticoagulation, hemorrhage is associated with adverse outcomes
- In one trial of nadroprarin, all 6 deaths in the trial overall occurred in the group of 29 patients with hemorrhage on their pre-treatment CT scan
- None of the deaths were attributed to new or enlarged hemorrhage
- Cerebral hemorrhage was strongly associated with mortality, but not with cerebral bleeding on Rx
A number of observational studies, both prospective and retrospective, are available, primarily from single centers.

- In a retrospective study of 102 pts with CVT:
  - 43 had an ICH
  - Among 27 (63%) who were treated with dose-adjusted, intravenous heparin after the ICH:
    - 04 died (15%)
      - Often from underlying conditions (eg. cancer) and not necessarily from ICH-related issues
    - 14 (52%) pts completely recovered
The largest study by far was the ISCVT

- 624 patients at 89 centers in 21 countries
- Nearly all patients were treated with anticoagulation initially and mortality was 8.3% over 16 months
- 79% had complete recovery (modified Rankin scale 0-1)
- 10.4% had mild to moderate disability (mRS 2-3)
- 2.2% remained severely disabled (mRS 4-5)
Few studies had sufficient numbers of patients not treated with anticoagulation to adequately address the role of anticoagulation in relation to outcome.

Data from observational studies suggest a range of risks for ICH after anticoagulation for CVT:
- Zero to 5.4%.

In conclusion, limited data from randomized controlled clinical trials in combination with observational data on outcomes and bleeding complications of anticoagulation support a role for anticoagulation in treatment of CVT, regardless of the presence of pre-treatment ICH.
Management and Treatment

Fibrinolytic Therapy

- Although patients with CVT may recover with anticoagulation therapy
  - 9-13% have poor outcomes despite anticoagulation
- Anticoagulation alone may not dissolve a large and extensive thrombus and the clinical condition may worsen even during HEP Rx
  - Incomplete recanalization or persistent thrombosis may explain this phenomenon
Combining four studies including 114 CVT pts

- Partial or complete recanalization at 3-6 mos was observed in 94 (82.5%)

- In general, thrombolytic therapy is used if clinical deterioration continues despite anticoagulation or if a patient has elevated ICP that evolves despite other management approaches.
Direct Catheter Thrombolysis

- A systematic review including 169 patients w/ CVT treated with local thrombolysis showed a possible benefit for those with severe CVT, indicating that fibrinolytics may reduce case fatality in critically ill patients
- ICH occurred in 17% of patients after thrombolysis and was associated with clinical worsening in 5%
Mechanical Thrombectomy/ Thrombolysis

- For patients with extensive thrombus persisting despite local administration of fibrinolytic agent, rheolytic catheter thrombectomy may be considered.
- Surgical thrombectomy is uncommonly needed, but may be considered if severe neurological or visual deterioration occurs despite maximal medical therapy.
The use of these direct intra-sinus thrombolytic techniques and mechanical therapies are only supported by case reports and small case series.

If clinical deterioration occurs despite use of anticoagulation, or the patient develops mass effect from a venous infarction or intracerebral hemorrhage causing intracranial hypertension resistant to standard therapies, then these interventional techniques may be considered.
Management and Treatment

Seizures

- Seizures are present
  - In 37% of adults, 48% of children and 71% of newborns presenting with CVT
- No clinical trials have studied either the optimal timing or medication choice for AEDs in CVT but since seizures increase the risk of anoxic damage, AED Rx after even a single seizure is reasonable
- In the absence of seizures, the prophylactic use of AEDs drugs may be harmful
Hydrocephalus

- The SSS and lateral dural sinuses are the principal sites for CSF absorption by the arachnoid granulations.
  - In CVT, function of the arachnoid granulations may be impaired resulting in failure of CSF absorption and communicating hydrocephalus.

- Obstructive hydrocephalus is a less common complication from CVT and results from hemorrhage into the ventricular system.
Intracranial Hypertension

- Up to 40% of patients with CVT present with isolated intracranial hypertension
- Clinical features include progressive headache, papilledema and third or sixth nerve palsies
- No randomized trials are available to clarify optimal treatment
- Measures to reduce the thrombotic occlusion of venous outflow may resolve intracranial hypertension
Intracranial Hypertension-cont

- Reduction of increased ICP can be immediately accomplished by lumbar puncture
- Acetazolamide may have a limited role in the acute management of intracranial hypertension for pts with CVT
Management and Treatment: Recommendations

- Class I Recommendations

- In patients with CVT and a single seizure with parenchymal lesions, early initiation of AEDs for a defined duration is recommended to prevent further seizures.

- Patients with CVT and a suspected bacterial infection should receive appropriate antibiotics and surgical drainage of purulent collections of infectious sources associated with CVT when appropriate.
Class I Recommendations

- In patients with CVT and increased ICP, monitoring for progressive visual loss is recommended, and when this is observed, increased ICP should be urgently treated.

- In patients with a past history of CVT who complain of new, persisting or severe headache, evaluation for CVT recurrence and intracranial hypertension should be considered.
Class II Recommendations

- For patients with CVT, initial anticoagulation with adjusted-dose UFH or weight-based LMWH in full anticoagulant doses is reasonable, followed by WARF, regardless of the presence of ICH.
- Admission to a stroke unit is reasonable for treatment and for prevention of clinical complications of patients with CVT.
Class II Recommendations

In patients with CVT and a single seizure w/o parenchymal lesions, early initiation of AEDs for a defined duration is probably recommended to prevent further seizures.

In patients with CVT and increased ICP, it is reasonable to initiate Rx with acetazolamide. Other therapies (lumbar puncture, optic nerve decompression or shunts) can be effective if there is progressive visual loss.
Class II Recommendations

- Endovascular intervention may be considered if deterioration occurs despite intensive anticoagulation treatment.
- In patients with neurological deterioration due to severe mass effect or ICH causing intractable intracranial hypertension, decompressive hemicraniectomy may be considered.
Class II Recommendations

- Testing for prothrombotic conditions can be beneficial for the management of patients with CVT. There is a very limited value, however, of testing in the acute setting or in patients on WARF.
Class II Recommendations

- In patients with provoked CVT (associated w/ a transient risk factor), WARF w/ a target INR of 2.0-3.0 may be continued for 3 to 6 mos
- In patients with unprovoked CVT, WARF w/ a target INR of 2.0-3.0 may be continued for 6 to 12 mos
Class II Recommendations

- For patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia indefinite anticoagulation may be considered with a target INR of 2.0-3.0
- Consultation with a physician with expertise in thrombosis may be considered to assist in the prothrombotic testing and care of patients with cerebral venous sinus thrombosis
Class III Recommendations

- For patients with CVT, steroid medications are not recommended, even in the presence of parenchymal brain lesions on CT/MRI, unless needed for another underlying disease.
- In the absence of seizures, the routine use of AEDs in patients with CVT is not recommended.
Incidence estimates for CVT during pregnancy and the puerperium

- Range from 1 in 2500 deliveries to 1 in 10,000 deliveries in Western countries
- ORs range from 1.3 to 13
- The greatest risk periods for CVT include the third trimester and the first 4 post-partum weeks
- Up to 73% of CVT in women occurs during the puerperium
- Caesarian delivery appears to be associated with a higher risk of CVT
Vitamin K antagonists, including WARF, are associated with fetal embryopathy and bleeding in fetus and neonate and thus are generally contraindicated in pregnancy.

Anticoagulation for CVT during pregnancy and early in the puerperium consists of LMWH in the majority of women.

As in non-pregnant women, fibrinolytic therapy is reserved for patients with deterioration despite systemic anticoagulation and has been reported during pregnancy.
Future Pregnancies and Recurrence

- Patients with previous VTE are at increased risk of further venous thrombotic events when compared to healthy individuals.
- Based on the available evidence, CVT is not a contraindication for future pregnancies.
- Considering the additional risk that pregnancy adds to women with previous history of CVT, prophylaxis with LMWH during future pregnancies and the postpartum period can be beneficial.
CVT in Special Populations (Pregnancy): Recommendations

- Class I Recommendation

  For women with CVT during pregnancy, LMWH in full anticoagulant doses should be continued throughout pregnancy, and LMWH or WARF w/ a target INR 2.0-3.0 should be continued for at least 6 wks postpartum (for a total minimum duration of therapy of 6 mos)
Class II Recommendations

- It is reasonable to advise women with a past history of CVT that future pregnancy is not contraindicated. Further investigations regarding the underlying etiology and a formal consult with a hematologist and/or maternal fetal medicine specialist is reasonable.
Class II Recommendations

- It is reasonable to treat acute CVT during pregnancy with full dose LMWH rather than UFH.
- For women with a past history of CVT, prophylaxis with LMWH during future pregnancies and the post-partum period is probably recommended.
The incidence of pediatric CVT

- 0.67 per 100,000 children per year
- Neonates comprise 43% of pediatric patients with CVT
- Prothrombotic disorders ranged from 33-66% of neonatal and pediatric CVT and are frequently present in the presence of other risk factors for CVT
- As in adults, a high index of suspicion for CVT and specific venous imaging is required make a diagnosis
In neonates, 2D time of flight (TOF) MRV has several pitfalls, including a focal area of absent flow where the occipital bone compresses the posterior superior sagittal sinus in the supine position.

- Present in up to 14% of neonates w/o CVT
- Therefore, CT venography is frequently required to confirm the presence of CVT suggested by MRV
CVT is associated with a significant frequency of adverse outcomes in neonates, older infants and children.

- In neonates, long term follow-up is required to ascertain the outcomes, because deficits may only become evident with brain maturation over many years.
- Among neonates with CVT, neurological deficits are observed in 28% to 83%.

- No randomized clinical trials have been conducted in pediatric CVT.
- Therefore, treatment practices have been primarily extrapolated from adult studies.
CVT in Special Populations (Pediatrics): Recommendations

- Class I Recommendations

- Supportive measures for children with CVT should include appropriate hydration, control of epileptic seizures, and treatment of elevated ICP
Class I Recommendations

- Given the potential for visual loss owing to severe or long-standing increased ICP in children with CVT, periodic assessments of the visual fields and visual acuity should be done, and appropriate measures to control elevated intracranial pressure and its complications should be instituted.
Class I Recommendations

- In all pediatric patients, if initial anticoagulation treatment is withheld, repeat neuroimaging including venous imaging in the first week after diagnosis is recommended to monitor for propagation of the initial thrombus or new infarcts or hemorrhage.
Class II Recommendations

- In children with acute CVT diagnosed beyond the first 28 days of life, it is reasonable to treat with full dose LMWH even in the presence of ICH.
- In children with acute CVT diagnosed beyond the first 28 days of life, it is reasonable to continue LMWH or WARF for 3 to 6 mos.
Class II Recommendations

- In all pediatric patients with acute CVT, if initial anticoagulation is started, it is reasonable to perform a head CT or MRI scan in the initial week after treatment to monitor for additional hemorrhage.

- Children with CVT may benefit from thrombophilia testing to identify underlying coagulation defects, some of which could affect the risk of subsequent re-thromboses and influence therapeutic decisions.
Class II Recommendations

- Children with CVT may benefit from investigation for underlying infections with blood cultures and sinus radiographs
- In neonates with acute CVT, treatment with LMWH or UFH may be considered
Class II Recommendations

Given the frequency of epileptic seizures in children with an acute CVT, continuous electroencephalography monitoring may be considered for individuals who are unconscious and/or mechanically ventilated.
Class II Recommendations

- In neonates with acute CVT, continuation of LMWH for 6 wks to 3 mos may be considered.
- The usefulness and safety of endovascular intervention is uncertain in pediatric patients, and its use may only be considered in carefully selected patients with progressive neurological deterioration despite intensive and therapeutic levels of anticoagulant treatment.
Neurological Worsening After Diagnosis

- Neurologic worsening may occur in 23% of the pts, even several days after diagnosis
  - About one-third of pts with neurologic deterioration will have new parenchymal lesions when neuroimaging is repeated
  - Patients with depressed consciousness on admission are more likely to deteriorate
Early Death

- Approximately 3-15% of patients die in the acute phase of the disorder
  - In the ISCVT, 21/624 patients (3.4 percent) died within 30-d from symptom onset
- Risk factors for 30-d mortality were
  - Depressed consciousness, altered mental status, thrombosis of the deep venous system, right hemisphere hemorrhage, and posterior fossa lesions
Early Death

- The main cause of acute death with CVT is transtentorial herniation secondary to a large hemorrhagic lesion followed by herniation due to multiple lesions or to diffuse brain edema.
- Status epilepticus, medical complications, and PE are among other causes of early death.
Late Death

Deaths after the acute phase are predominantly related to the underlying conditions, in particular malignancies.
Long-Term Outcome

- In the ISCVT study
  - Complete recovery at last follow-up (median 16 mos) was observed in 79% of the pts
  - However, there was an 8.3% overall death rate and a 5.1% dependency rate (mRS≥3) at the end of follow-up
- From 7 cohort studies
  - The overall death and dependency rate is 15% (95% CI 13-18)
Neuropsychological and Neuropsychiatric Sequelae

- There is little information on the long term neuropsychological and neuropsychiatric outcome in CVT survivors.
- Despite the apparent general good recovery in most patients with CVT, approximately one-half of the survivors feel depressed or anxious, and minor cognitive or language deficits may preclude them from resuming their previous jobs.
<table>
<thead>
<tr>
<th>Risk Factors for Long-Term Poor Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS infection</td>
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<tr>
<td>Any malignancy</td>
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<tr>
<td>Thrombosis of the deep venous system</td>
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<tr>
<td>ICH on the admission CT/MR</td>
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<tr>
<td>Glasgow coma scale score (GCS) &lt;9</td>
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<tr>
<td>Mental status disturbance</td>
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<tr>
<td>Age &gt;37 years</td>
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<tr>
<td>Male gender</td>
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</tbody>
</table>