DIAGNOSIS AND MANAGEMENT OF CEREBRAL VENOUS THROMBOSIS

A Scientific Statement from the American Heart Association

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BACKGROUND ON CEREBRAL VENOUS THROMBOSIS
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• Defined as the presence of a blood clot in the dural venous sinuses, cerebral veins, or both
• Represents 0.5% to 3% of strokes
• Predominantly affects
  • Individuals younger than 55
  • 2:1 female-to-male predominance
• Most survive without physical disability but chronic symptoms (headaches, cognitive concerns, etc.) not uncommon
• Most common factors associated with poor prognosis
  • Advanced age
  • Active cancer
  • Decreased level of consciousness
  • Intracerebral hemorrhage
MOST FREQUENT LOCATIONS OF CEREBRAL VENOUS THROMBOSIS

Legend: Prevalence of sinus involvement in CVT. Percentages may be higher than 100% as many patients may have more than one sinus involved. Please note that internal jugular vein thrombosis represents its concomitant prevalence with CVT (not in isolation).
CLINICAL PRESENTATION OF CEREBRAL VENOUS THROMBOSIS
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• Headache is the most common symptom, occurring in almost 90% of cases
• Focal neurologic deficits (20-50%)
• Seizure (20-40%)
• Encephalopathy and coma (up to 20%)
• Symptoms related to increased intracranial pressure
  • Nausea
  • Transient visual obscurations or vision loss (13-27%)
  • Papilledema
  • Diplopia (6-14%)
  • Other cranial neuropathies (6-11%)
• Most symptoms tend to occur more insidiously than other stroke types with majority peaking more than 48 hours after onset
• Minority with acute onset of thunderclap headache or subarachnoid hemorrhage (<5%), or acute onset focal neurologic deficits (5-40%)
PREDISPOSING FACTORS FOR CEREBRAL VENOUS THROMBOSIS
PREDISPOSING FACTORS FOR CEREBRAL VENOUS THROMBOSIS

- Predisposing factor(s) for cerebral venous thrombosis are identified in the majority of patients
- Oral contraception/hormonal therapies (~8-fold risk)
- Pregnancy/puerperium
- Acquired thrombophilias
- Genetic thrombophilias
- Infections (COVID-19, head/neck)
- Dehydration
- Medications
- Vaccine-induced thrombotic thrombocytopenia

| Table 1: Predisposing factors or medical conditions associated with CVT |
|-------------------------------------------------|---------------------|------------------------|
| Sex—specific and Transgender hormonal treatment | Oral contraceptive (54-71%) Pregnancy/Post-partum (11-59%) Hormone replacement therapy (4%) | Hormone replacement therapy Hormone therapy for transfeminine or transmasculine individuals |
| Other morbidity | Head and neck infections (8-11%) Dehydration (2-19%) Anemia Sepsis Respiratory infections Covid-19 (7.6%) | Obesity (23%) Anemia (9-27%) Other systemic diseases (thyroid disease, nephrotic syndrome, inflammatory bowel disease) 1-2% |
| Other medications | Corticosteroids L-asparaginase Thalidomide Tamoxifen | Myeloproliferative disorders (2-3%) Other malignancy (7%) |
| Malignancy | | |
| Auto-immune | | Antiphospholipid antibody syndrome (6-17%) Connective tissue disease (Systemic lupus erythematosus, Bechet’s, Sarcoidosis) (1%) |
| Other genetic thrombophilia (31-41%) | | Prothrombin 20210A mutation Factor V Leiden mutation MTHFR (C677T) polymorphism Antithrombin deficiency, IAK2 Protein C or Protein S deficiency (can be genetic or acquired) |
| Mechanical | Head trauma (1-3%) Neurosurgical procedures Jugular vein catheterizations (1-2% iatrogenic) | Compressive lesions of venous sinus (meningioma) Dural arteriovenous fistula |
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LONG-TERM SYMPTOMS OF CEREBRAL VENOUS THROMBOSIS AND RECURRENCE RATE
LONG-TERM SYMPTOMS OF CEREBRAL VENOUS THROMBOSIS

• 80-90% Achieve functional independence (modified Rankin Score 0-2)
• Despite high rates of functional independence, high prevalence of residual symptoms
  • Headaches
  • Cognitive concerns
  • Mood
  • Fatigue
• Epilepsy can affect over 10% and is more likely in those with seizures at onset, decreased level of consciousness or focal deficits, hemorrhagic lesions at baseline, or superior sagittal sinus involvement
• Dural arteriovenous fistula can be a complication or precipitant of cerebral venous thrombosis
RECURRENCE RATES AFTER CEREBRAL VENOUS THROMBOSIS

- Recurrent venous thromboembolism risk after CVT ranges between 1-4%/year
- Recurrent CVT risk reported to be <1-2%/year
  - Higher risk for those with severe thrombophilia, history of VTE, those without identified precipitants
- Compared to age- and sex-matched controls those with CVT have higher risk of:
  - Recurrent venous thromboembolism
  - Ischemic stroke
  - Major bleeding
  - Mortality
BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CEREBRAL VENOUS THROMBOSIS
BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CVT

CONVENTIONAL NON-CONTRAST CT HEAD

- Hyperattenuation caused by thrombus (dense vessel sign)
  - Can be present up to 14 days after symptom onset
- Hypodensities not conforming to arterial territories or present bilaterally
- Hemorrhage present in up to 40%
- Cashew-nut sign: juxtacortical C-shaped hyperdensity has high specificity for CVT
- CT Head test characteristics
  - Sensitivity of 0.79
  - Specificity of 0.90
BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CVT

MRI BRAIN

• Evolution of thrombus on MRI is dynamic and signal intensity of the thrombus over time is similar to that of hematoma

• Helpful to corroborate T1/T2 sequences with gradient-recalled echo (GRE), susceptibility-weighted imaging (SWI) sequences or contrast enhanced-MRV
  • Thrombosed blood creates blooming artifact on GRE/SWI which leads to specificity and specificity approaching 100%

• MRI more sensitive than CT in detection of parenchymal brain lesions, such as venous infarctions

• MRI Brain test characteristics
  • Sensitivity 0.82
  • Specificity 0.92
BRAIN AND VASCULAR IMAGING FOR THE DIAGNOSIS OF CVT

- CT venography or MR venography are optimal tests to confirm diagnosis of CVT.
- CT venography allows for clear depiction of superficial and deep cerebral venous system with thrombi present as filling defects.
- CT venography has lower sensitivity than MRI for cortical vein thrombosis.
- MR venography can be performed with or without contrast.
  - Use of gadolinium contrast allows for direct assessment of luminal filling and increases sensitivity of detection of thrombus within smaller veins.
- Time-of-flight and phase-contrast MR venography techniques prone to artifact secondary to complex flow.
- Contrast-enhanced MR venography has comparable sensitivity and specificity to CT venography but provides better characterization between low flow state and hypoplastic signus.
- Contrast-enhanced MR venography and GRE or SWI are recommended for diagnosing cortical vein thrombosis.
THERAPEUTIC ADVANCES IN THE MANAGEMENT OF CEREBRAL VENOUS THROMBOSIS
Objectives of anticoagulation for CVT are:
- Prevent thrombus growth
- Facilitate recanalization
- Prevent recurrent venous thromboembolism (VTE)

Previous guidelines suggest initial use of low molecular weight heparin (over unfractionated heparin) followed by:
- 3-12 months of oral vitamin K antagonists for 3-12 months in context of transient risk factors
- Indefinite oral vitamin K antagonist therapy in context of chronic major risk factors for thrombosis or recurrent VTE

Emerging evidence suggest that direct oral anticoagulants (DOACs) may be a reasonable alternative to oral vitamin K antagonists:
- No significant differences in recurrent VTE
- Potentially lower risk of major hemorrhage with DOACs
- Similar rates of complete recanalization

Persistent areas of equipoise:
- Need for lead-in heparinization and duration of lead-in heparinization
- Need for acute VTE dosing of DOACs
- Who are best candidates for DOACs
- Use of repeated imaging to guide duration of anticoagulation
THERAPEUTIC ADVANCES IN THE MANAGEMENT OF CVT – REPERFUSION & DECOMPRESSION CRANIECTOMY

• Endovascular treatment of CVT offers theoretically faster recanalization and could include
  • Mechanical thrombectomy
  • Intrasinus thrombolysis
  • Combination of mechanical thrombectomy and intrasinus thrombolysis
  • Intrasinus stenting

• Trials have yet to demonstrate that endovascular treatment confers benefit over receiving standard anticoagulation and may be associated with higher mortality

• Endovascular therapy is more typically used as a “rescue treatment” for patients experiencing clinical deterioration or failed or have contraindications to standard therapy

• Decompressive craniectomy should be offered to patients with acute severe CVT and parenchymal lesions with impending herniation as a life-saving therapeutic approach
  • May decrease mortality and improve functional outcomes
Initiate parenteral anticoagulation
Subcutaneous low-molecular-weight heparin (preferred) or unfractionated intravenous heparin
[NB: Intracranial hemorrhage as a consequence of CVT is not a contraindication for anticoagulation]

Clinical/Imaging Shows Stable CVT
Transition to oral anticoagulation (OAC) with direct oral anticoagulant or warfarin. Duration of OAC depends on the etiology: 3-12 months for transient predisposing factors; high-risk thrombophilia/recurrent VTE: indefinite OAC.
[N.B.: LMWH preferred during pregnancy]

Clinical/Imaging with Progression
(i.e.: thrombus propagation)
Consider endovascular therapy (intrasinus thrombolysis or endovascular thrombectomy)
CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS
CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS - PEDIATRIC

• CVT is more common in neonates (6.4/100,000) than in children or adolescents
• CVT needs to be considered early in acute presentations of headache, seizures, focal neurologic deficits, coma, head trauma, hypoxia and/or dehydration
• Management of acute DVT typically involves low molecular weight or unfractionated heparin followed by oral therapy
  • Optimal duration of anticoagulation and preferred oral agent are unclear
• Long-term studies suggest that one in four children despite treatment may develop
  • Late epilepsy
  • Infantile spasms post-neonatal CVT
  • Cognitive impairment
  • Intracranial hypertension
CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS – PREGNANCY AND PUERPERIUM

• CVT incident estimates during pregnancy and puerperium range from 1 in 2,500 deliveries to 1 in 10,000 deliveries in Western countries with ORs ranging from 1.3 to 13.0

• Period of greatest risk is third trimester and the first 6 weeks postpartum with 80% occurring after delivery

• Cesarean delivery associated with higher risk (OR 3.1)

• Prognosis of pregnancy-related CVT similar and maybe better than CVT patients in general

• Low molecular weight heparin is agent of choice during pregnancy and early in the puerperium
  • Vitamin K antagonists associated with fetal embryopathy and bleeding in the fetus and neonate and are contraindicated
  • DOACs are contraindicated during pregnancy and while breastfeeding
  • Future pregnancy is not contraindicated though prophylaxis with low molecular weight heparin is usually recommended
CEREBRAL VENOUS THROMBOSIS IN SPECIAL POPULATIONS – VACCINE INDUCTED THROMBOTIC THROMBOCYTOPENIA

• CVT and thrombocytopenia reported following vaccination for COVID infection
  • Headache the most common presenting feature
  • All patients had thrombocytopenia
  • Some patients found to have antibodies to platelet factor 4 (PF4)
  • Risk lower after mRNA SARS-CoV-2 vaccines compared to adenovirus-based SARS-CoV-2 vaccines (1-5/10,000 vs 13/10,000)

• CVT is rare but carries poor prognosis with mortality rates ranging from 39-61%

• In cases of suspected vaccine induced thrombotic thrombocytopenia recommendations include:
  • Testing for PF4
  • Avoidance of heparin products (consider argatroban, fondaparinux, etc.)
  • Administration of intravenous immunoglobulin 1g/kg body weight daily for 2 days
  • Administration of steroids
  • Transition to oral anticoagulant once there is full platelet count recovery
CEREBRAL VENOUS THROMBOSIS - OVERVIEW

Clinical Suspicion for CVT (see clinical presentation section)

Brain and Cerebral Venous Sinus Imaging
MRI with T2* and MRV
Head CT with CTV

CVT Confirmed

Etiological Evaluation (see table 1)

Clinical: examine for illness, mass effect, facial infection, dehydration, head trauma; stigmata of Faber's syndrome, sarcoid, ulcerative colitis, malignancy, rheumatological conditions, etc.

Exposures: oral contraceptive pills, chemotherapeutic agents, COVID-19 vaccination, etc.

Laboratory tests: hematocrit, complete blood count, renal function, urinalysis, pregnancy test, prothrombin time, activated partial thromboplastin time; additional tests as indicated (erythrocyte sedimentation rate, d-dimer level, liver studies, hypercoagulability panel, antiphospholipid panel, COVID-19 infection, MTHFR gene mutation, homocysteine level, serum protein electrophoresis, etc.)

No evidence for CVT
Consider other diagnosis
- Arterial stroke
- Dopaheptic intracranial hypertension
- Meningitis, brain abscess
- Brain neoplasm, intracranial disorder

Mass Effect with Midline Shift or Signs of Hemiation:
- Consider decompressive hemiepocraniectomy

Initiate parenteral anticoagulation
Subcutaneous low-molecular-weight heparin (preferred) or unfractionated intravenous heparin
[ND: Intravenous heparin as a consequence of CVT is not anticoagulant for anticoagulation]

Clinical/Imaging Shows Stable CVT
Transition to oral anticoagulation (OAC) with direct oral anticoagulant or warfarin. Duration of OAC depends on the etiology: 3-12 months for transient predisposing factors, high-risk thrombophilia, recurrent VTE, indwelling IVC.
[ND: LMWH preferred during pregnancy]

Clinical/Imaging with Progression (i.e., thrombus propagation)
Consider endovascular therapy (intracranial thrombolysis or endovascular thrombectomy)

Legend: This figure summarizes the suggested approach for the diagnosis and management of CVT.