CEREBRAL VENOUS THROMBOSIS

Dr. Naveed Ahmed MD, FAHA, FAAN

Medical Director , Primary Stroke Program

Pikeville Medical Center

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In 1825 Ribes described the clinical history of a 45-year-old man who died after a 6-month history of severe headache, epilepsy, and delirium. Postmortem examination showed thrombus of the superior sagittal sinus, the left lateral sinus and cortical vein and parietal region.

Cerebrovascular thrombosis is an unusual cerebrovascular disorder that is of current interest, in part because of the rare cases associated with certain of the COVID-19 vaccines.

Outline

- Incidence
- Pathogenesis
- Clinical findings
- Diagnostic evaluation
- Treatment

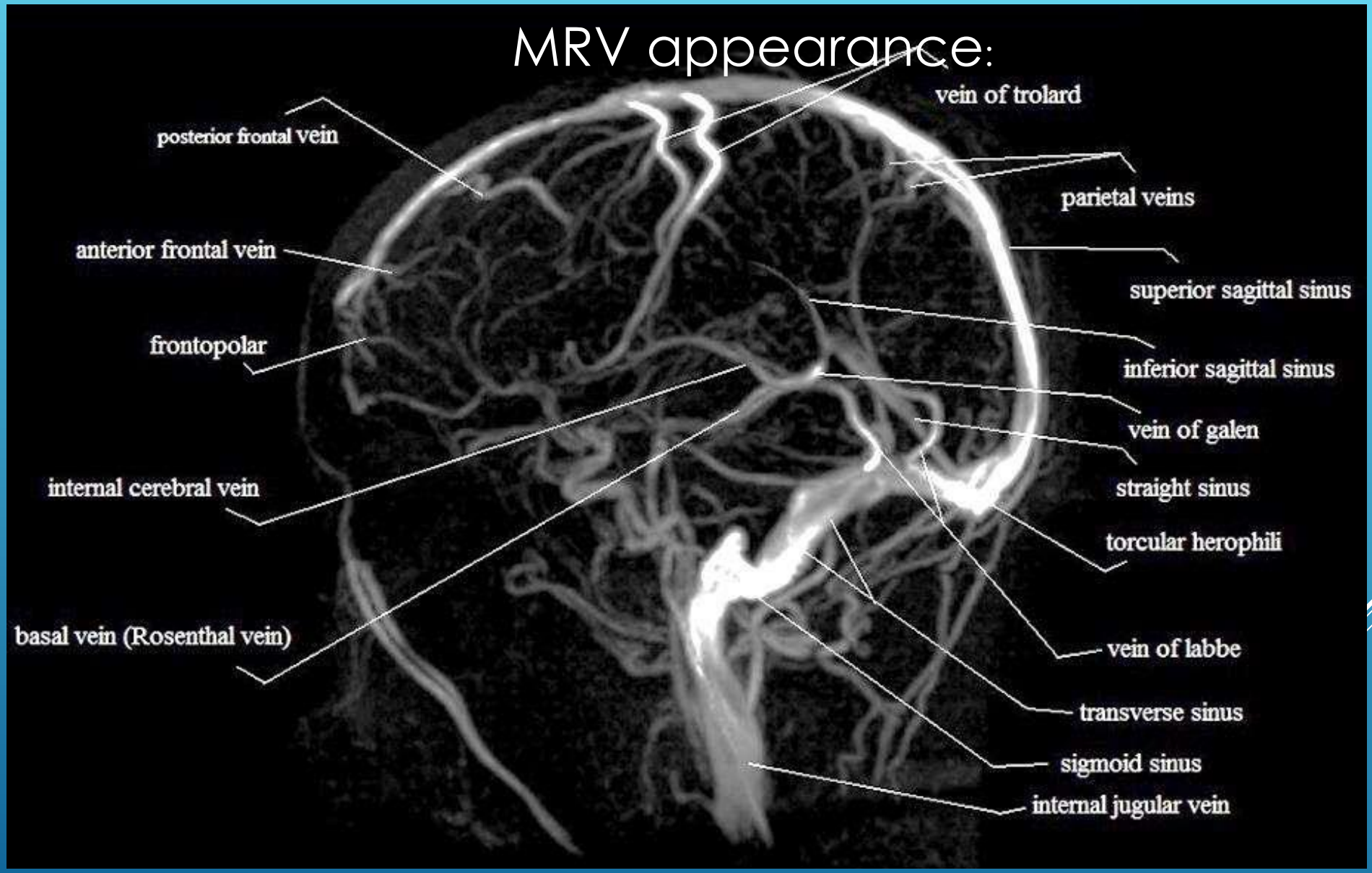
CAN BE CLASSIFIED AS -

- ***Paired***
- Transverse sinus
- Sigmoid sinus
- Superior petrosal sinus
- Inferiror petrosal sinus
- Cavernous sinus
- Sphenoparietal sinus
- Basilar venous plexus

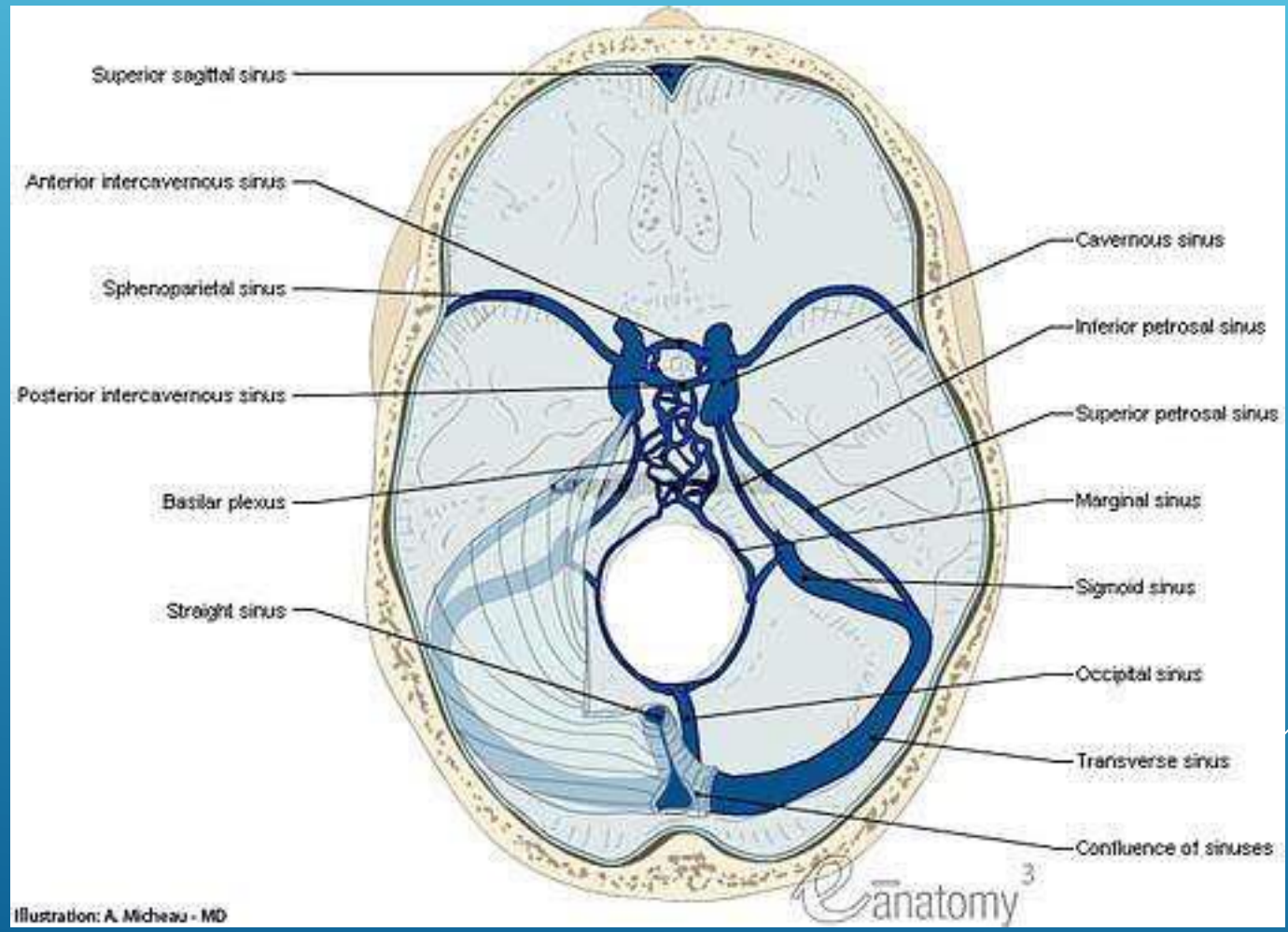
- ***Unpaired***
- Superior sagittal sinus
- inferior sagittal sinus
- Straight sinus
- Occipital sinus
- Intercavernous sinus


Superior sagittal sinus
Trolard
Inferior sagittal sinus
Thalamostriate
Internal cerebral
Straight sinus
Cavernous sinus
V. of Galen
Petrosal sinus
Labbe
Jugular vein
Sigmoid
transverse sinus

MRV appearance:



Anatomy of Venous Sinus system:



Cerebral Venous Thrombosis:

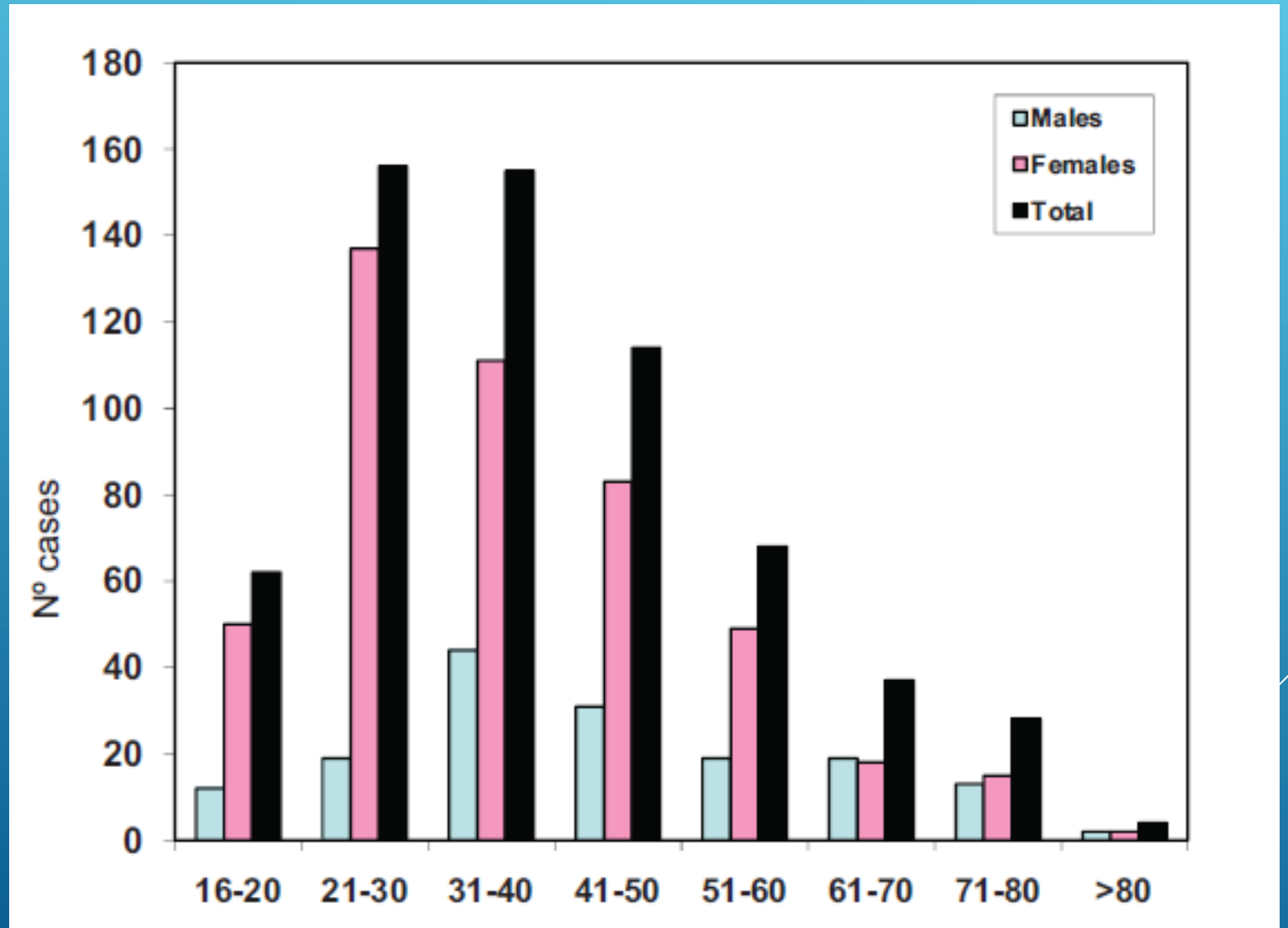
- Thrombosis of the Dural sinus and/or cerebral veins (CVT).
- CVT represents 0.5% to 1% of all strokes.
  – Roughly 5 people per million.
- More commonly seen in young individuals.
- 78% of 624 cases in International Study on Cerebral Venous and Dural Sinuses(ISCVT) Thrombosis occurred in patients < 50 years of age.

Incidence

- Although a rare disease the incidence is much higher than classically thought. This is also illustrated by the multicenter international study on CVT which recruited 630 patients in a 3 year period.
- All age group, 20-40 years old
- F > M 3 : 1,

ISCVT Data:

- Prevalence ranges between 3 to 9%.



Cause and Pathogenesis

- The risk factors for venous thrombosis in general are linked classically to the Virchow triad. – stasis of the blood, changes in the vessel wall, and changes in the composition of the blood.

- Acquired - surgery, trauma, pregnancy, puerperium, antiphospholipid syndrome 6% , cancer, exogenous hormones, Oral contraceptives 10%, More as a risk factor than a cause because it is commonly found with other conditions SLE, Bechet's and congenital Thrombophilia

- Genetic causes- inherited thrombophilias 22% .

Prothrombotic Conditions:

Prothrombin Gene, Factor V Leiden Mutation and Prothrombin G20210A Mutation 10 – 20 %

- Antiphospholipid and Anticardiolipin Antibodies.
- Antithrombin III, Protein C, and Protein S Deficiency.
- Hyperhomocysteinemia.

- Cerebral venous thrombosis can be caused by rare but pathophysiologically related hypercoagulable states:

Heparin-induced thrombocytopenia (HIT)

Autoimmune (A HIT)

Vaccine Induced thrombotic thrombocytopenia (VITT)

Associated with Thrombosis, Low Platelet count & DIC

Mediated by Platelet activating antiboidies to Platelet Factor 4 (PF4)

CVT with two adenoviral vector vaccines against COVID-19 (1 case per 100,000 vaccine recipients for the AstraZeneca and 1 per million for the Johnson & Johnson/Jansen) mainly in women has been characterized by immune thrombotic thrombocytopenia mediated by platelet activating antibodies to PF4

CVT < 1% of patients with severe acute respiratory syndrome coronavirus 2) SARS-CoV-2 infection in one series and in 2 of 22 COVID-19 related strokes
No anti-PF antibodies or thrombocytopenia

Pregnancy and Post partum:

- 2% of pregnancy-associated strokes are attributable to CVT.
- Approximate frequency - 12 cases per 100 000 deliveries.
- During pregnancy (last trimester) and for 6 to 8 weeks after birth, women are at increased risk of venous thromboembolic events.
- Increased prothrombotic factors, infection, instrumentation, dehydration, caesarian, HTN

Oral Contraceptives:

- 22 times more chance of having CVT than those not using OCP's.
- Presence of other thrombophilias increases the risk further.

Cancer: 7.4 % IN ISCVT

- Hematologic malignancies.
- Direct tumor compression.
- Hypercoagulable state associated with cancer chemotherapeutic and hormonal agents

Para meningeal Infections:

- Infections of ear, sinus, mouth, face, and neck.
- 8.2% of all cases (ISCVT series).
- CVT caused by infection is more common in children.

Other identified causes:

- Paroxysmal nocturnal hemoglobinuria, iron deficiency anemia, thrombocythemia, heparin induced thrombocytopenia, thrombotic thrombocytopenic purpura, nephrotic syndrome, inflammatory bowel disease, systemic lupus erythematosus, Bechetts disease, epidural blood patch, spontaneous intracranial hypotension, lumbar puncture.

Clinical finding

- Most common : headache(earliest symptoms) and Seizure
- Nausea, vomiting, visual change, Papilledema from increase intracranial pressure
- Confusion, agitation, mental status change
- Focal neurological deficit from venous hypertension and cerebral infarction
- Aphasia, hemianopia, hemi sensory loss
- Acute mimic acute ischemic stroke, sub acute are more common Fluctuating or progressive

Clinical Diagnosis of CVT:

- Clinical findings fall in to 2 categories.

– Those due to increased ICP– Those due to focal brain infarction/ hemorrhage.

- Headache is the most common symptom – 90%.

– Diffuse and often progresses in severity over days to weeks.
– minority of patients may present with thunderclap headache.
– 25% with CVT can present with headache and papilledema alone.

Venous infarction/ hemorrhage:

– Hemiparesis and aphasia 44 %
– Psychosis and other cortical dysfunction can occur.

Clinical feature to site

- Superior sagittal sinus is most commonly involved.

– Headache, increased intracranial pressure, and papilledema.
– Motor deficit, seizure.
– Scalp edema and dilated scalp veins.
– Cortical involvement of frontal, parietal, occipital areas.

- Lateral sinus thrombosis:

– Features of middle ear infections.
– Increased intracranial pressure and distension of the scalp veins.
– Hemianopia, contralateral weakness, and aphasia.
– Temporal cortical involvement seen.

- 16% of patients with CVT have thrombosis of the deep cerebral venous system.

– Thalamic or basal ganglia infarction.
– Decreased mentation, encephalopathy.

Clinical finding- cont.

- Clinical feature to site

– Cavernous sinus CVT : eyelid edema, chemosis, retro orbital pain and exophthalmos, paralysis of CN III,IV, V1,V2,VI

– Involve deep venous system : akinetic mutism, coma, Decerebration Memory disturbance, minor confusion

– Cerebellar vein thrombosis : extremely rare and often lethal

Features specific to CVT:

- Roughly 40% presents with partial/generalized seizure.
- Relative bilateralism of symptoms/ signs/ imaging.
- Slowly progressive symptoms.

– In ISCVT:
acute (<48 hours) in 37% of patients,
sub acute (>48 hours to 30 days) in 56% of patients, and
chronic (>30 days) in 7% of patients.

Clinical finding Summary

- Clinical feature to the site

– Superior sagittal sinus or transverse sinus : isolated intracranial hypertension

– Extend to cortical vein : focal deficit, seizure

– Bilateral deficit : late sign of superior sagittal sinus

– Transverse sinus CVT may associated with otalgia, otorrhea, cervical tenderness and lymphadenopathy

Work Up:

- A complete blood count.
- Chemistry panel.
- Sedimentation rate.
- Measures of the prothrombin time and activated partial thromboplastin time.
- Screening for potential prothrombotic conditions that may predispose a person to CVT.

Diagnostic evaluation

- Key diagnostic because clinical highly variables
- CT
  - Dense vein
  - Cord sign : hyper dense on NC CT
  - Dense triangle sign(delta sign) : specific to SSS on Contrast CT
  - First 1-2 weeks after thrombosis
  - False positive : neonate, dehydration, elevated hemoglobin
  - False negative is high

Diagnostic evaluation

- MRI

– MRA, MRV : best method

– Thrombus, edema, hemorrhagic infraction

– False positive : sinus congenitally absent or hypoplastic

– False negative : methemoglobin mimic flowing blood, pt. not cooperative, poor technic

- Lumbar Puncture:
  - Elevated opening pressure in > 80%
  - Unless there is clinical suspicion of meningitis, examination of the cerebrospinal fluid (CSF) is typically not helpful.

D-Dimer:

- A product of fibrin degradation.
- Diagnostic role in exclusion of DVT.
- Sensitivity of 97.1%, a specificity of 91.2%, a negative predictive value of 99.6%.
- A normal D-dimer level according to a sensitive immunoassay or rapid enzyme-linked immunosorbent assay (ELISA) may be considered to help identify patients with low probability of CVT (Class IIb; Level of Evidence B). If there is a strong clinical suspicion of CVT, a normal D-dimer level should not preclude further evaluation.

Common Pitfalls in the Diagnosis of CVT:

- Intracranial Hemorrhage:

– 30% to 40% of patients with CVT present with ICH.

– Prodromal headache, bilateral parenchymal abnormalities, and clinical evidence of a hypercoagulable state.

– In patients with lobar ICH of otherwise unclear origin or with cerebral infarction that crosses typical arterial boundaries, imaging of the cerebral venous system should be performed (Class I; Level of Evidence C).

- Isolated Headache/Idiopathic Intracranial Hypertension:

– Headache alone or headache and papilledema and/or 6th nerve palsy (25%).

– A new, atypical headache; headache that progresses steadily over days to weeks despite conservative treatment; and thunderclap headache can help identify CVT.

– In patients with the clinical features of idiopathic intracranial hypertension, imaging of the cerebral venous system is recommended to exclude CVT (Class I; Level of Evidence C).

– In patients with headache associated with atypical features, imaging of the cerebral venous system is reasonable to exclude CVT (Class IIa; Level of Evidence C).

Imaging in the Diagnosis of CVT:

- Non Invasive Imaging:
  – CT, MRI, Ultrasonography.

- Invasive Imaging:
  – Cerebral Angiography and Direct Cerebral Venography.

CT:

- Plain CT being abnormal only in <30% of CVT cases.
- Hyperdensity of a cortical vein or Dural sinus seen.
- Acutely thrombosis : Hyperdensity.
- Thrombosis of the posterior portion of the superior sagittal sinus may appear as a dense triangle – Dense delta sign.
- Ischemic infarction/hemorrhage may be seen.

– Not obeying any vascular territory.

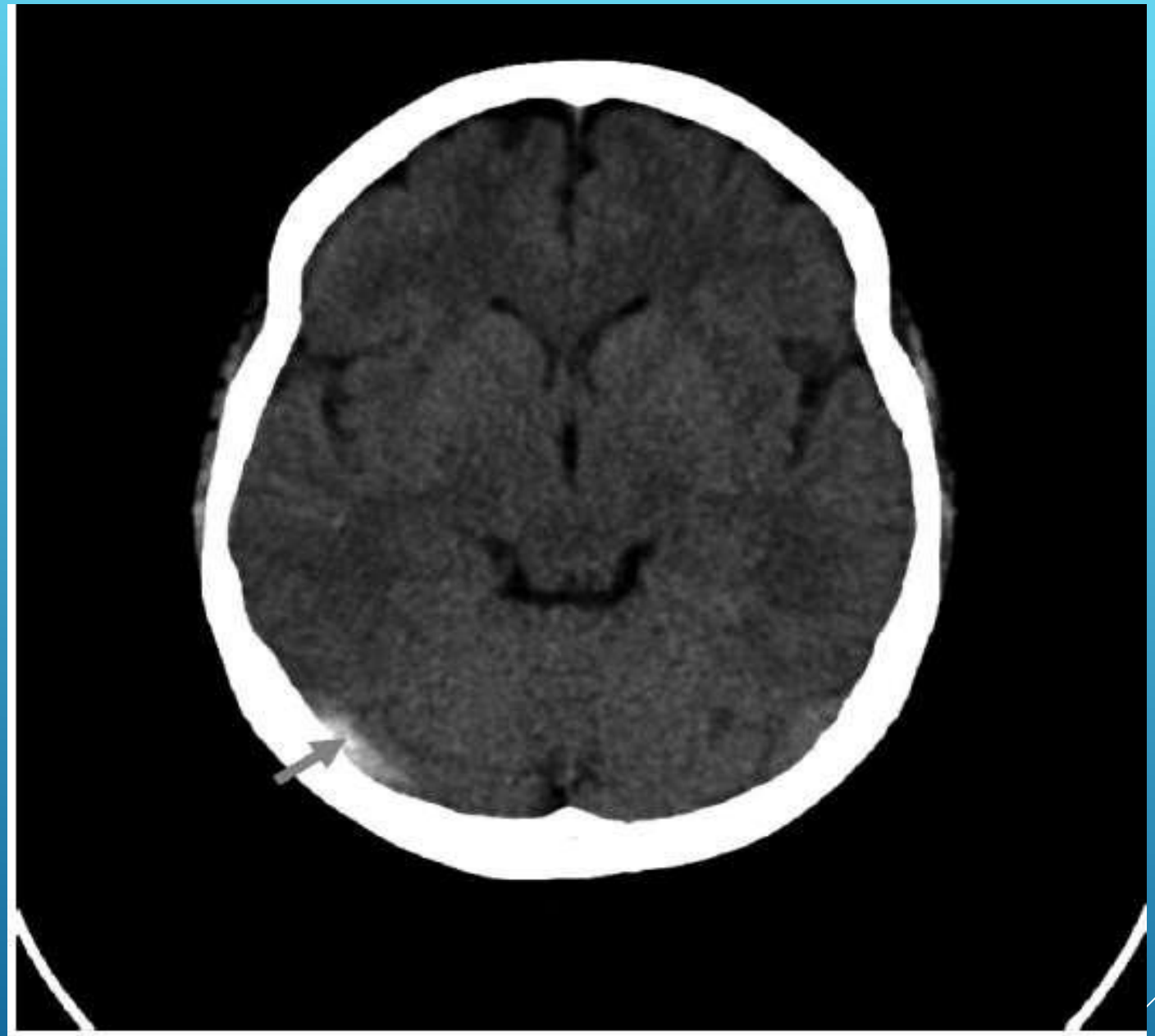


Figure 3. Noncontrast computed tomography head scan showed spontaneous hyperdensity of right transverse sinus.

- Contrast-enhanced CT:
  - Filling defect within the vein or sinus.
  - may show the classic “empty delta” sign, in which a central hypo intensity due to very slow or absent flow within the sinus is surrounded by contrast enhancement in the surrounding triangular shape in the posterior aspect of the superior sagittal sinus.

- CT Venogram.

MRI

- T1WI
  - Acute thrombus – isointense with brain
  - Subacute thrombus – hyperintense
  - Chronic thrombus - isointense
- T2WI
  - Acute thrombus –hypointense (can mimic normal flow void)
  - Subacute thrombus – hyperintense
  - Chronic thrombus – hyperintense
- T2*GRE
  - Hypointense thrombus usually blooms

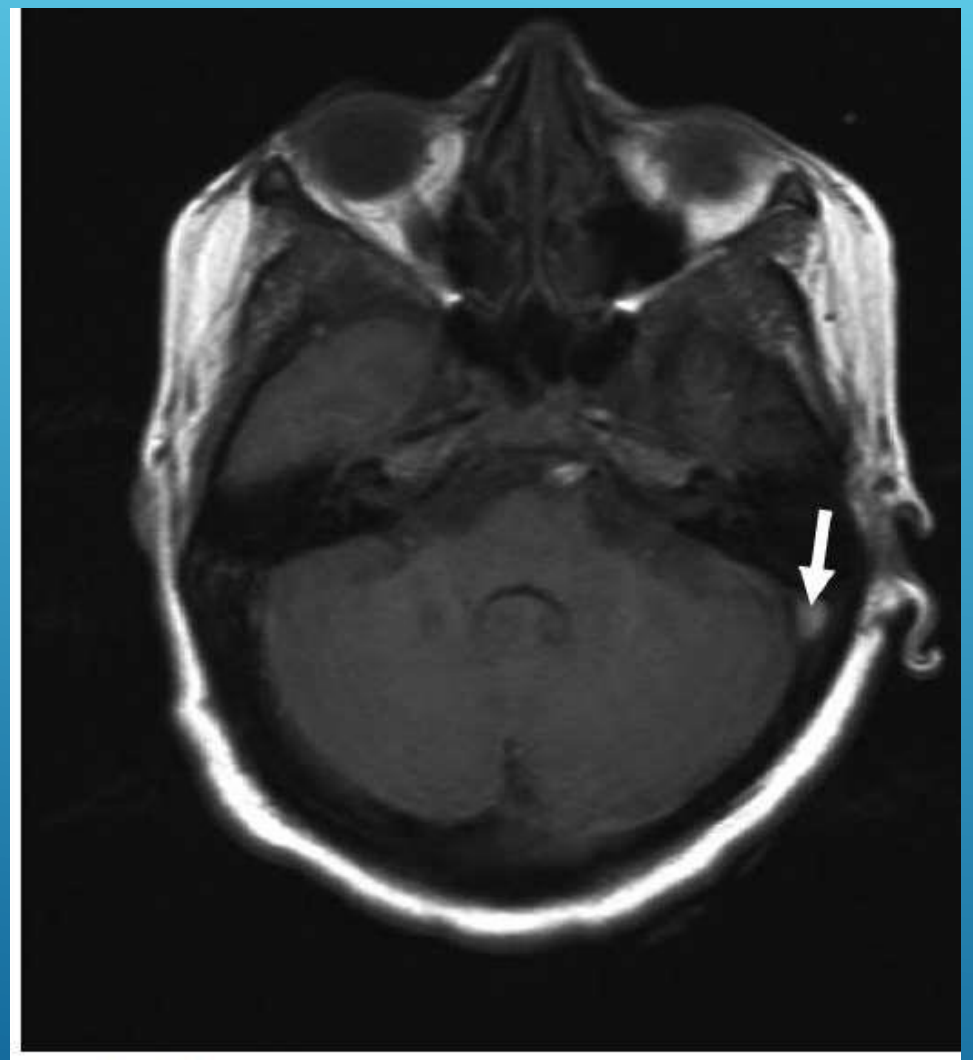


Figure 5. Flair magnetic resonance image showing hypersensitivity signal at left sigmoid sinus (arrow).

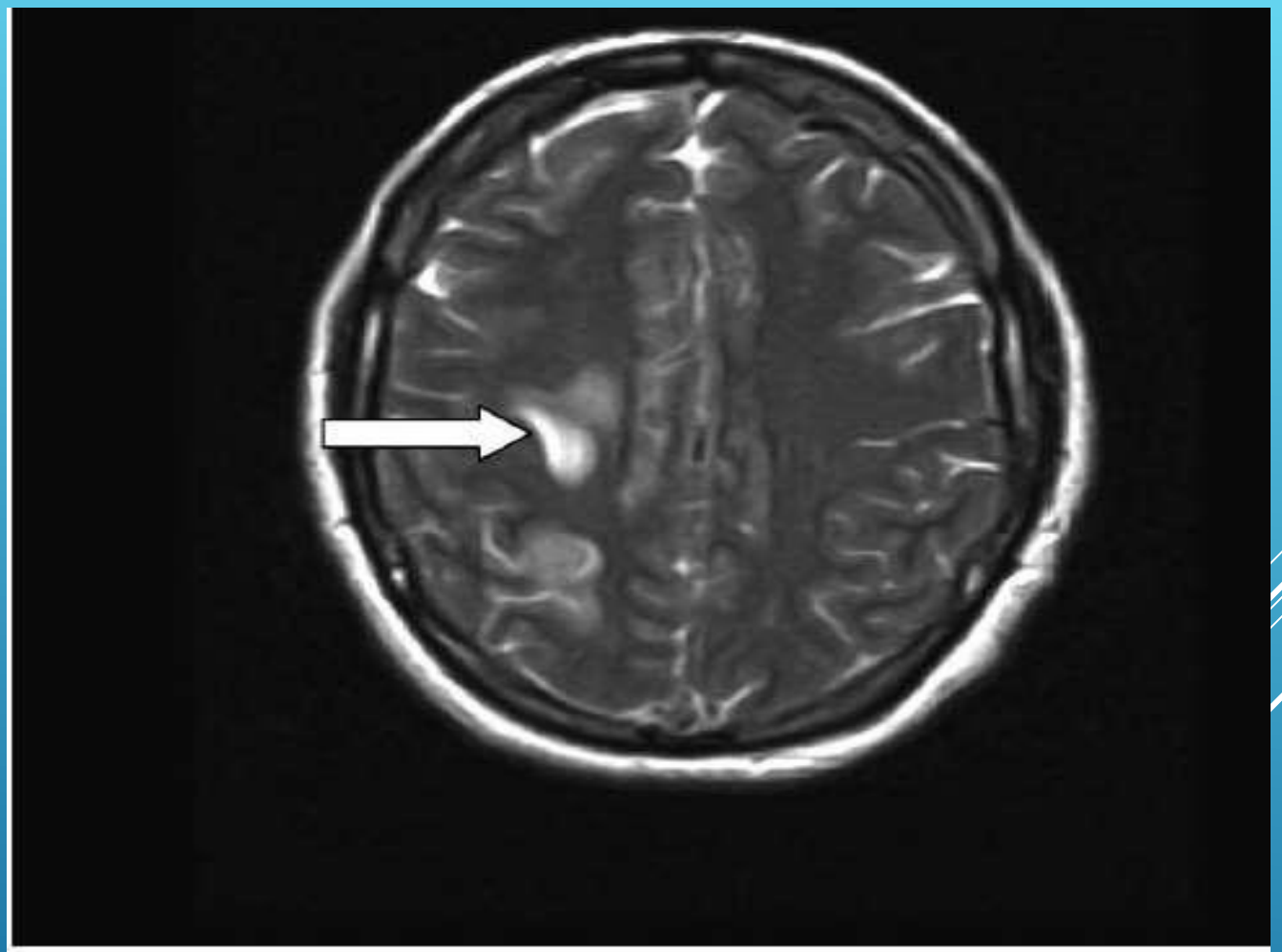


Figure 6. T2-weighted magnetic resonance image showing high-intensity bland venous infarct in frontal lobe.

- Types of parenchymal hemorrhage in CVT:

Superior sagittal sinus thrombosis. usually correspond to Brain parenchymal changes in frontal, parietal, and occipital lobes;

Lateral (transverse) and sigmoid sinus Thrombosis. Usually correspond to Brain parenchymal changes in Temporal lobe

Vein of Galen or straight sinus thrombosis usually correspond to Brain parenchymal changes - Thalamic hemorrhage, edema, or intraventricular hemorrhage.

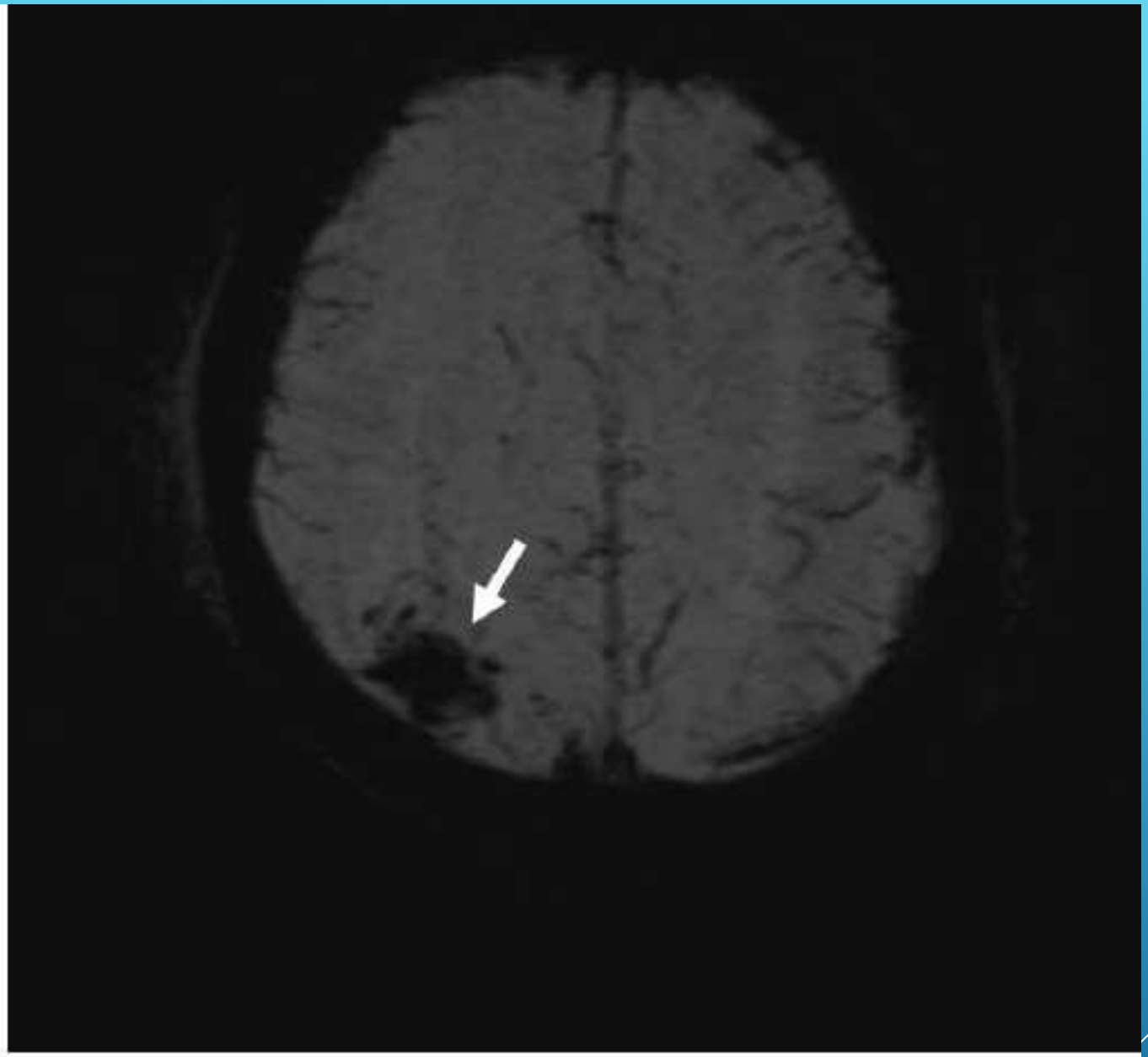
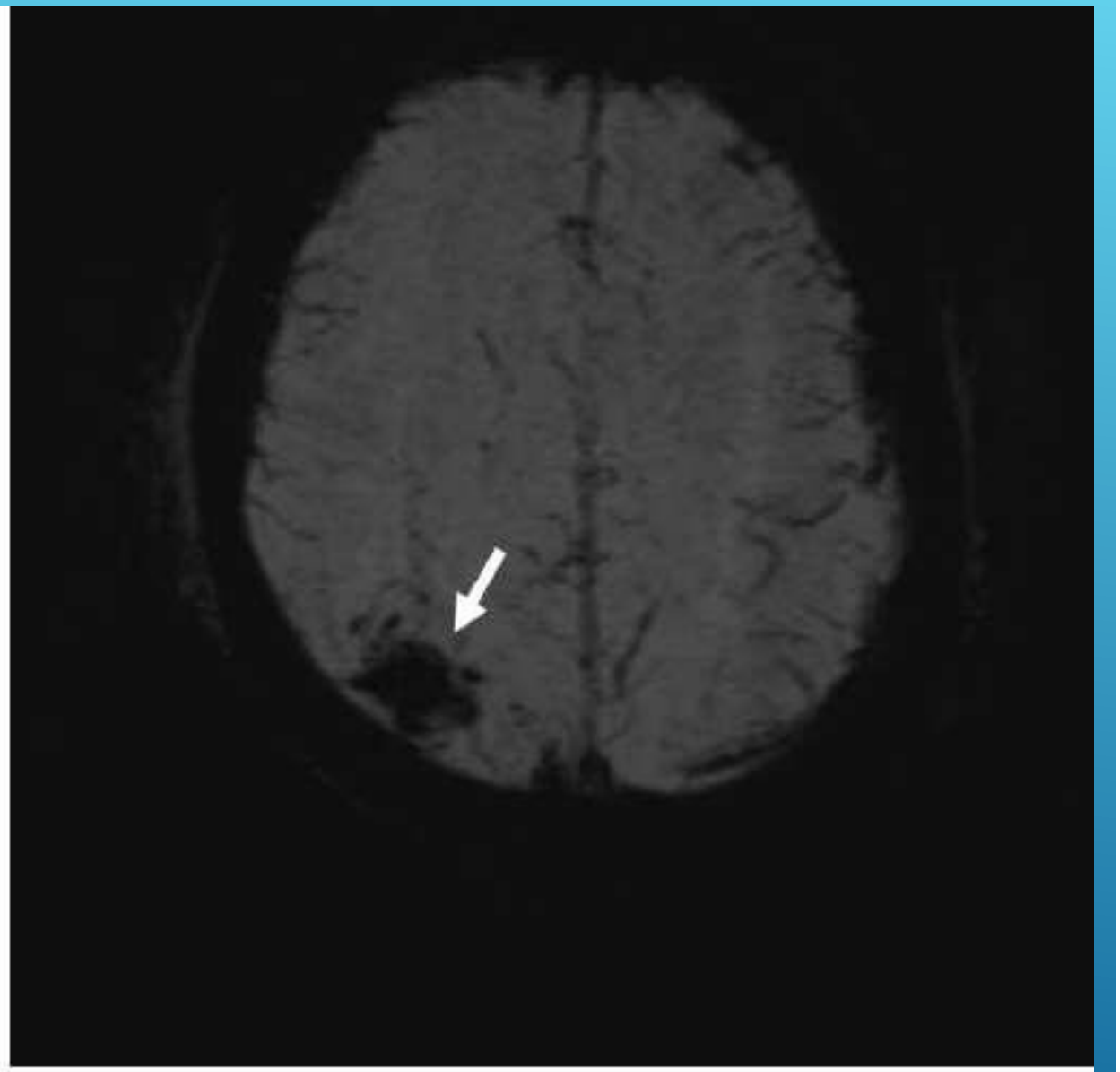


Figure 7. Susceptibility-weighted magnetic resonance image showing hemorrhagic venous infarct in the right parietal lobe.



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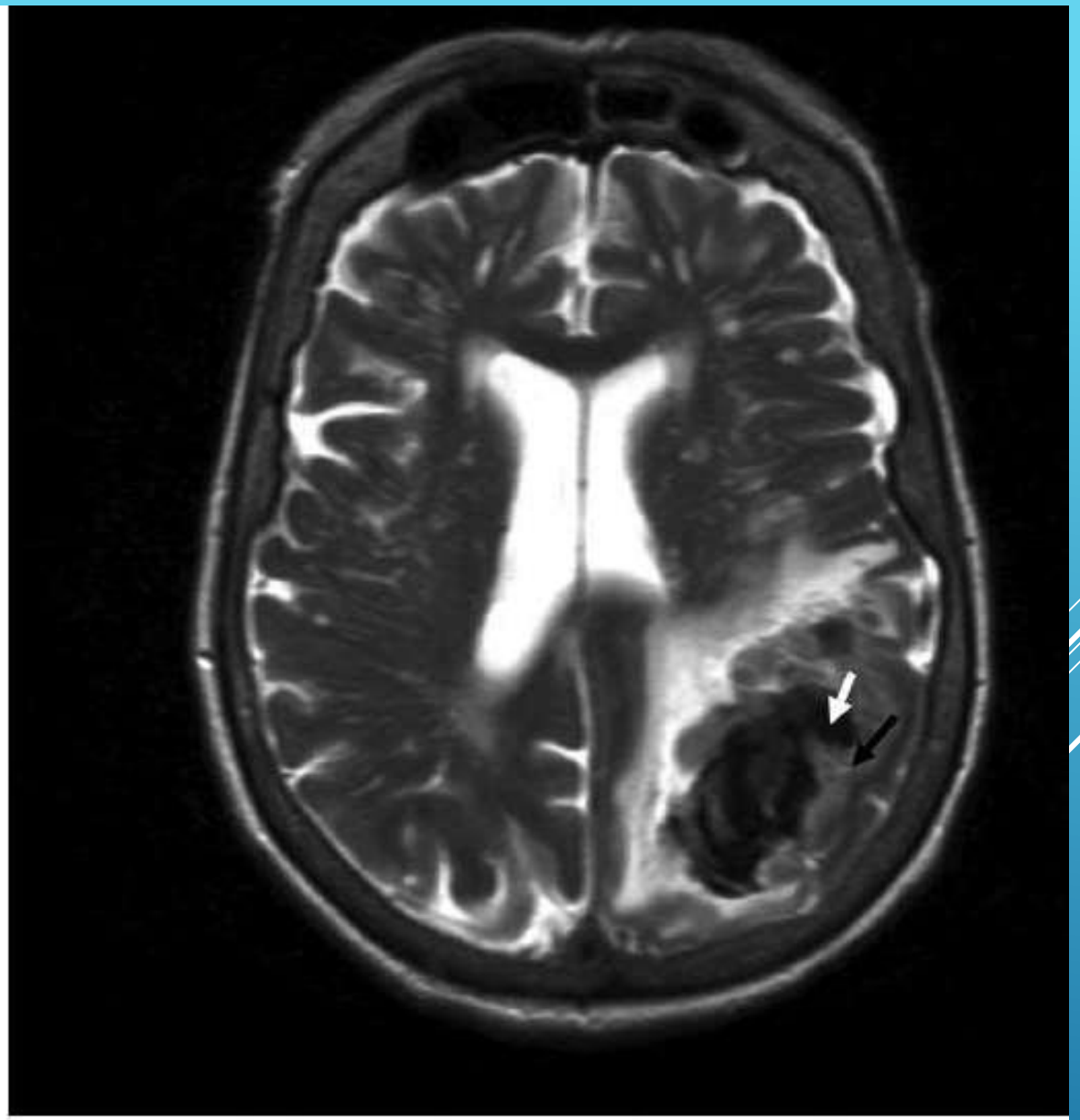

Figure 8. T2-weighted magnetic resonance image showing mixed hypointensity (white arrow) and isointensity (black arrow) signals representing an acute hemorrhage at left parietal lobe.

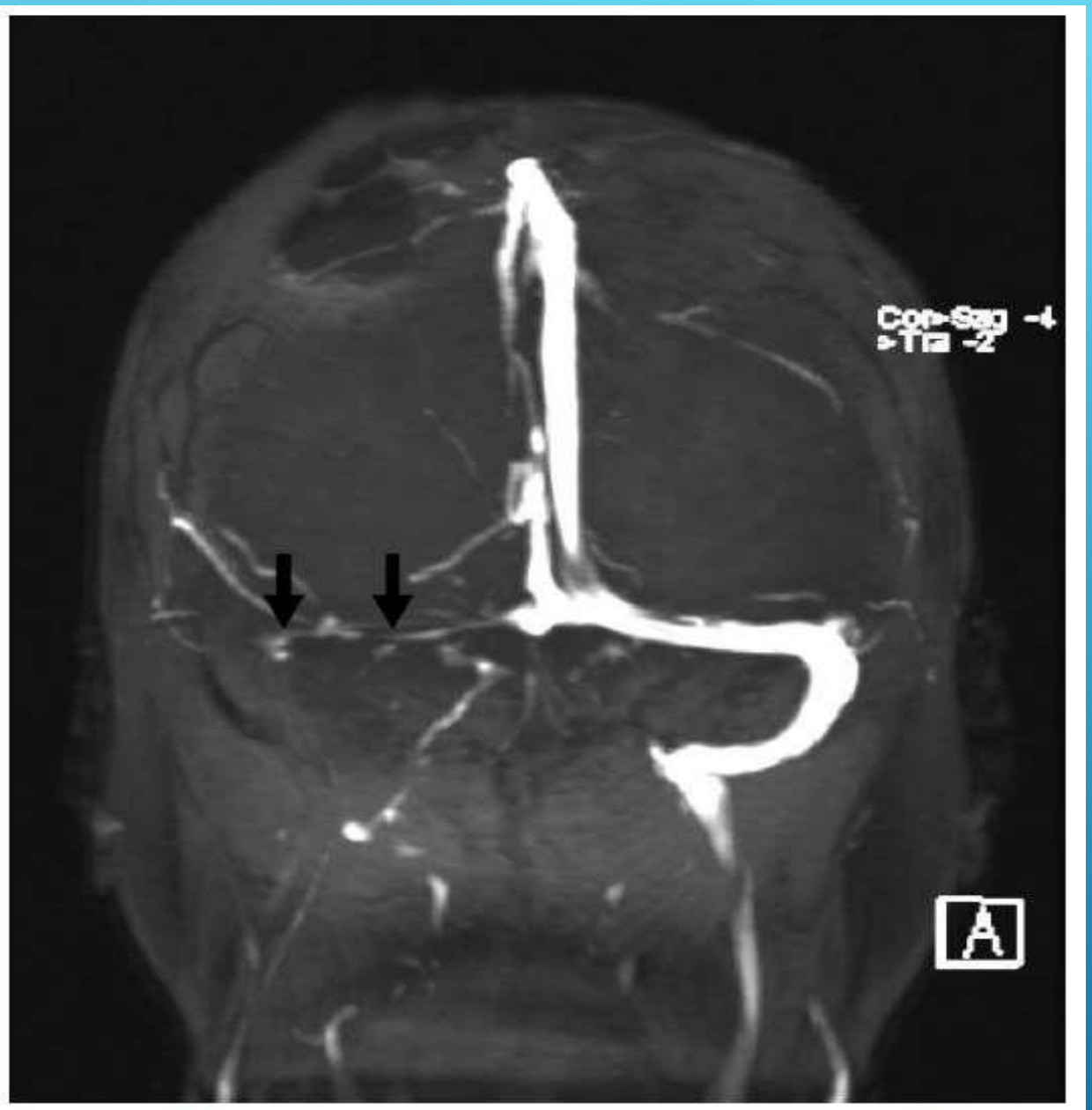

Figure 11. Magnetic resonance venography confirmed thrombosis (black arrows) of right transverse and sigmoid sinuses and

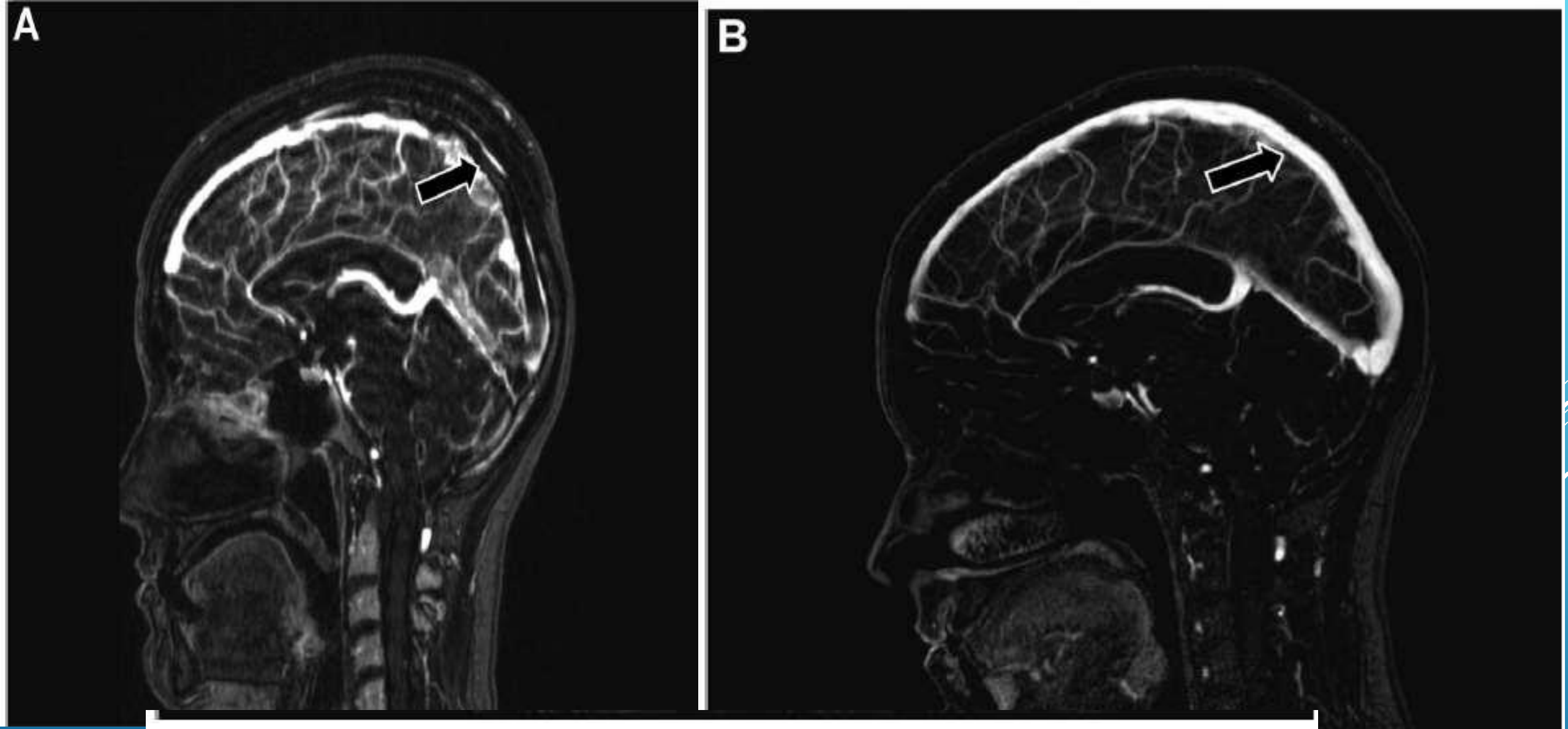

Figure 12. Magnetic resonance venogram showing thrombosis (black arrows) of the superior sagittal sinus and sigmoid sinuses. **A,** 2 days after symptom onset. **B,** 1 year follow-up after oral anticoagulation therapy (OAC).

Invasive Diagnostic Angiographic Procedures:

- Cerebral Angiography and Direct Cerebral Venography:
  – Reserved for situations in which the MRV or CTV results are inconclusive.
  – If an endovascular procedure is being considered.
- Delayed phase of angiography shows sinus.
  – CVT seen as filling defects or delay in visualization of sinus.
  – Normally 7 to 8 second after arterial phase.

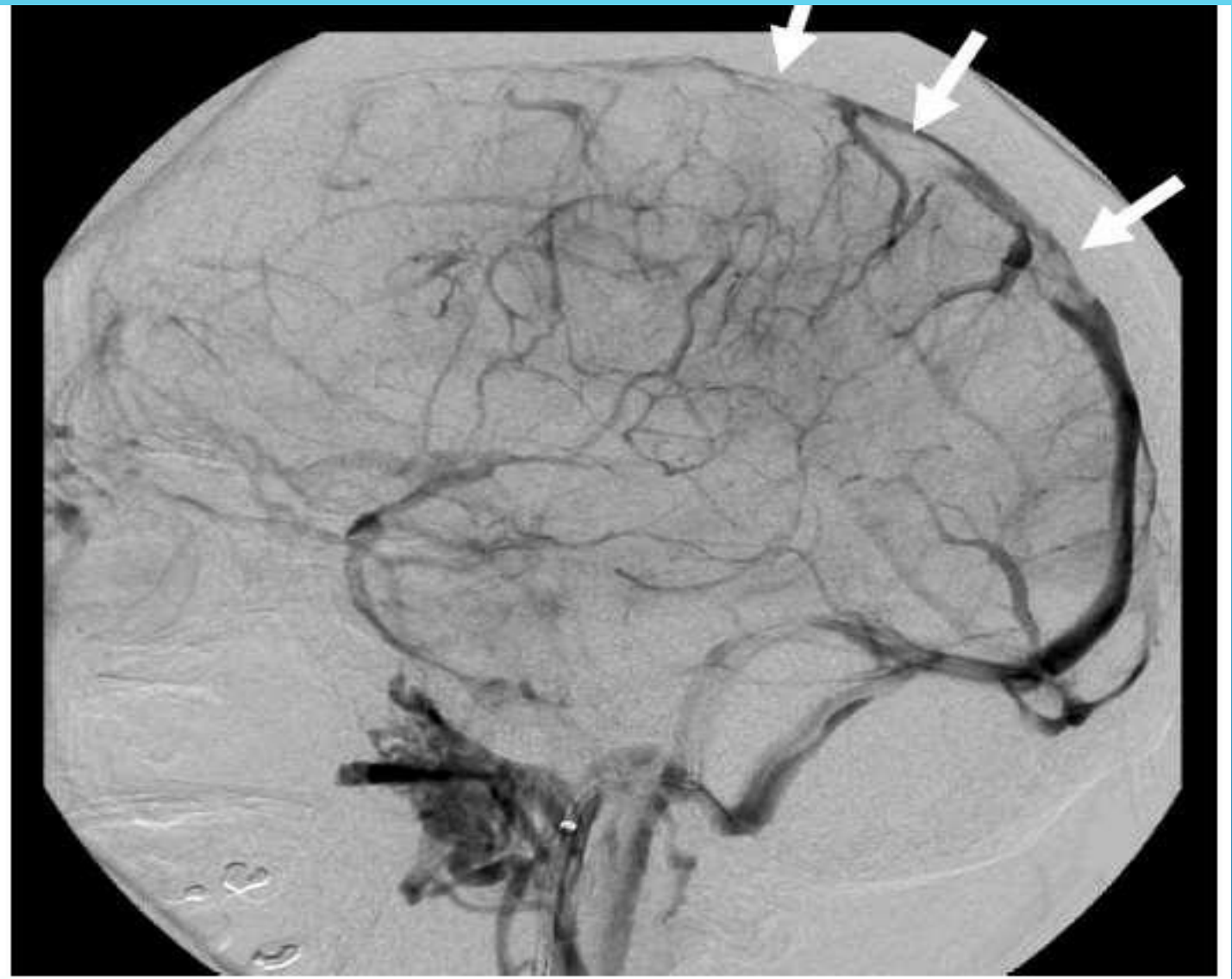

Figure 14. Venous phase of direct carotid angiogram and catheter venogram showed extensive thrombosed superior sagittal sinus (white arrows) and cortical veins. The direct venogram also showed collateral cortical veins.

Management and Treatment:

- Organized care is one of the most effective interventions to reduce mortality and morbidity after acute stroke.

- Management of CVT in a stroke unit is reasonable for the initial management of CVT to optimize care and minimize complications..

Initial Anticoagulation:

- Acute anticoagulation: Heparin is indicated.
- Presence of pre treatment ICH is not a contraindication.
- No definite recommendation regarding dosage.
- LMW heparin is preferred over UFH.
- Anticoagulation appears safe and effective.

Other Treatments:

– 9% to 13% have poor outcomes despite anticoagulation.
– Anticoagulation alone may not dissolve a large and extensive thrombus.
– Partial or complete recanalization rates for CVT ranged from 47% to 100% with anticoagulation alone.

- Thrombolytic therapy is used if clinical deterioration continues despite anticoagulation or if a patient has elevated intracranial pressure that evolves despite other management approaches.
- Direct Catheter Thrombolysis.
- Mechanical Thrombectomy/Thrombolysis
  - Balloon-Assisted Thrombectomy and Thrombolysis.
  - Catheter Thrombectomy.
- Surgical thrombectomy is rarely done.

- Aspirin has no role in the management of CVT.
- Steroids are contraindicated.
  – Associated with high mortality and morbidity.
- Antibiotics – indicated if there is associated infections.

Management and Prevention of Early Complications:

- Seizures:

– Seizures are present in 37% of adults, 48% of children, and 71% of newborns who present with CVT.

– Seizures increase anoxic damage.

– Anticonvulsant treatment after even a single seizure is reasonable.

– Prophylactic use of antiepileptic drugs may be harmful.

- Early seizures indicate brain parenchymal involvement.

– Supra tentorial lesions.

- Hydrocephalus

– Arachnoid granulation function may be impaired and result in communicating hydrocephalus (6.6%).

– obstructive hydrocephalus is less common – due to ventricular hemorrhage.

– Raised ICP should be managed urgently as venous pressure is already high.

Long-Term Management and Recurrence of CVT:

- The overall risk of recurrence of any thrombotic event (CVT or systemic) after a CVT is around 6.5%.
- The risk of other manifestations of VTE after CVT ranges from 3.4% to 4.3%.
- Systemic VTE after CVT is more common than recurrent CVT.

- Thrombophilias have been stratified as mild or severe on the basis of the risk of recurrence.

– Deficiencies of antithrombin, protein C, and protein S, with a 19% recurrence at 2 years, 40% at 5 years, and 55% at 10 years.
– Homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; and antiphospholipid syndrome are categorized as severe.

- Testing to be done 2 to 4 weeks after completion of anticoagulation.

Recommendations:
In patients with provoked CVT (associated with a transient risk factor),vitamin K antagonists may be continued for 3 to 6 months, with a target INR of 2.0 to 3.0 (Class IIb; Level of Evidence C).

- In patients with unprovoked CVT, vitamin K antagonists may be continued for 6 to 12 months, with a target INR of 2.0 to 3.0 (Class IIb; Level of Evidence C).
- For patients with recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia (i.e., homozygous prothrombin G20210A; homozygous factor V Leiden; deficiencies of protein C, protein S, or antithrombin; combined thrombophilia defects; or antiphospholipid syndrome), indefinite anticoagulation may be considered, with a target INR of 2.0 to 3.0 (Class IIb; Level of Evidence C).

- Consultation with A Hematologist to assist in the prothrombotic testing

Management of Late Complications:

- Headache:

– 50%

– In Lille study 29% fulfilled criteria for migraine, and 27% had headache of the tension type.

– In patients with persistent or severe headaches, appropriate investigations should be completed to rule out recurrent CVT.

– Lumbar puncture may be needed to exclude elevated intracranial pressure.

- Seizures:

– Remote seizures affect 5% to 32% of patients.
– Most occur in the 1st yr. of follow up.
– Risk factors for remote seizures- hemorrhagic lesion on admission in MRI/CT, early seizure, paresis.

- Visual Loss:

– More common in Pt with papilledema.
– Severe visual loss due to CVT rarely occurs (2 to 4%).
– Visual acuity and formal visual field testing should be done.

- Dural Arteriovenous Fistula:

– Dural fistulas can be a late complication of persistent Dural sinus occlusion with increased venous pressure.

– The fistula can close and cure if the sinus recanalizes.

– A preexisting fistula can be the underlying cause of CVT.

– A cerebral angiogram may help identify the presence of a Dural arteriovenous fistula.

CVT in Special Populations:

- CVT During Pregnancy:
  - Incidence 1 in 2500 deliveries to 1 in 10 000 deliveries.
  - Greatest risk - third trimester and the first 4 postpartum weeks.
  - Up to 73% of CVT in women occurs during the puerperium.
  - Cesarean delivery appears to be associated with a higher risk of CVT.

- Vitamin K antagonists are associated with fetal embryopathy.
- UHF also causes teratogenicity
- LMW Heparin is the drug of choice.
- No contra indication for future pregnancies.
- LMW Heparin during future pregnancies and post partum period can be beneficial.

Outcome

- Mortality rate 30-80 %

- Poor Prognosis

– Coma
– Extreme age : infant, elderly
– Site of thrombosis : deep venous system, cerebellar system
– Severe intracranial pressure
– Underlying : sepsis, malignancy

Thanks

Time for questions


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