Cerebral Venous Thrombosis

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Case Presentation: A 20-year-old woman presented with 24 hours of severe left-sided headache associated with nausea, photophobia, and phonophobia. She was previously healthy and was taking only an oral contraceptive pill. On physical examination, she was tachycardic to 110 bpm, normotensive with a blood pressure of 108/64 mm Hg, and appeared uncomfortable. Neurological examination in the emergency department was unremarkable. Migraine headache was considered the most likely cause of her symptoms. After analgesia had improved her symptoms, the patient was discharged with instructions to return if her headache recurred or worsened. She returned 12 hours later with recurrent severe headache. Head computed tomogram (CT) without contrast demonstrated hyperdensities along the left tentorium and involving the left sigmoid sinus that were concerning for cerebral venous thrombosis (Figure 1A and B). A magnetic resonance (MR) venogram was recommended and showed thrombosis of the left transverse and sigmoid sinus and proximal internal jugular vein (Figure 1C and D). The clinical presentation and imaging findings established the diagnosis of cerebral venous thrombosis.

Overview

Cerebral venous thrombosis, including thrombosis of cerebral veins and major dural sinuses, is an uncommon disorder in the general population. However, it has a higher frequency among patients younger than 40 years of age, patients with thrombophilia, and women who are pregnant or receiving hormonal contraceptive therapy. Annual incidence is estimated to be 3 to 4 cases per million.[1] The incidence of cerebral venous thrombosis increases to 12 cases per 100 000 deliveries in pregnant women.[2] Cerebral venous thrombosis occurs 3 times as frequently in women,[3] likely because of increased risk during pregnancy and with hormonal contraceptive use.

Risk Factors

At least 1 risk factor can be identified in >85% of patients with cerebral venous thrombosis (Table 1).[4] In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) cohort, a thrombophilia was noted in 34%, and an inherited thrombophilia was detected in 22%.[4] Inherited thrombophilias associated with cerebral venous thrombosis include deficiencies of antithrombin, protein C, protein S, factor V Leiden mutation, and the prothrombin gene mutation 20210. Antiphospholipid antibodies and hyperhomocysteinemia are acquired prothrombotic states associated with cerebral venous thrombosis.

An additional precipitating factor is often present in patients with thrombophilia who develop cerebral venous thrombosis. Pregnancy, postpartum state, and hormonal contraceptive therapy are the most frequent risk factors in women with cerebral venous thrombosis. Localized infections, such as otitis, mastoiditis, sinusitis, and meningitis and systemic infectious disorders, are also associated with cerebral venous thrombosis. Additional risk factors include chronic inflammatory diseases, such as vasculitides and inflammatory bowel disease, nephrotic syndrome, and malignancy and hematologic disorders, such as polycythemia, essential thrombocytosis, and paroxysmal nocturnal hemoglobinuria. Cerebral venous thrombosis may result from head trauma, local injury to cerebral sinuses or veins, jugular venous cannulation, neurosurgical procedures, and, rarely, lumbar puncture.[1]

Pathophysiology

Two major pathophysiological mechanisms contribute to the clinical presen-

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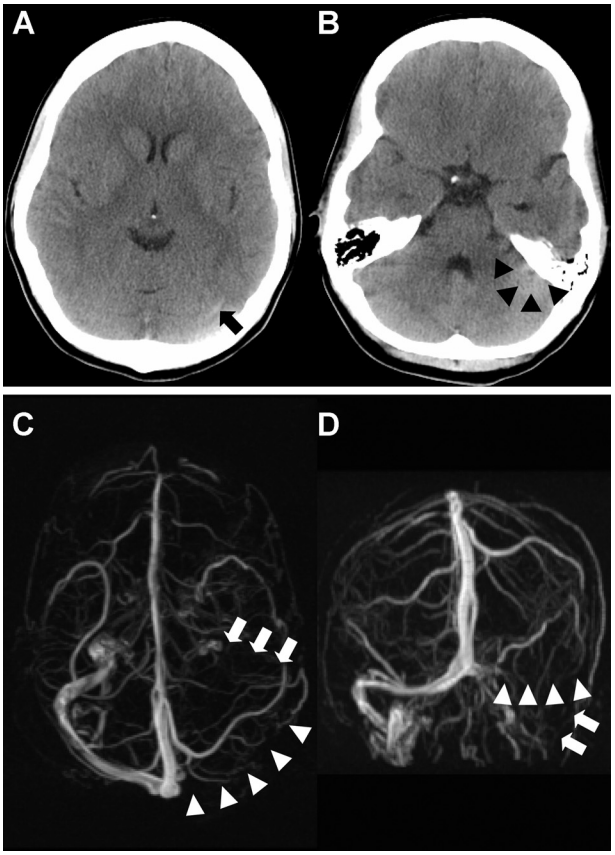

Figure 1. Computed tomogram (CT) of the head without intravenous contrast demonstrating hyperdensities along the left tentorium (arrows, **A**) and involving the left sigmoid sinus (arrowheads, **B**) that were concerning for cerebral venous thrombosis. Magnetic resonance (MR) venography demonstrating thrombosis of the left transverse (arrowheads) and sigmoid sinus and proximal jugular vein (arrows) in the axial (**C**) and coronal (**D**) planes.

Table 1. Risk Factors for Cerebral Venous Thrombosis

Thrombophilia
Deficiencies of antithrombin, protein C, and protein S
Factor V Leiden mutation
Prothrombin gene mutation 20210
Antiphospholipid antibodies
Hyperhomocysteinemia
Women's health concerns
Pregnancy
Postpartum state
Hormonal contraceptive or replacement therapy
Infection
Localized infections such as otitis, mastoiditis, sinusitis
Meningitis
Systemic infectious disorders
Chronic inflammatory diseases
Vasculitides
Inflammatory bowel disease
Cancer
Hematologic disorders
Polycythemia
Essential thrombocytosis
Paroxysmal nocturnal hemoglobinuria
Trauma
Head trauma
Local injury to cerebral sinuses or veins
Jugular venous cannulation
Neurosurgical procedures
Lumbar puncture
Nephrotic syndrome

tation of cerebral venous thrombosis (Figure 2).[1] First, thrombosis of cerebral veins or sinuses can result in increased venular and capillary pressure. As local venous pressure continues to rise, decreased cerebral perfusion results in ischemic injury and cytotoxic edema, disruption of the blood-brain barrier leads to vasogenic edema, and venous and capillary rupture culminates in parenchymal hemorrhage.

Obstruction of cerebral sinuses may also result in decreased cerebrospinal fluid absorption. Cerebrospinal fluid is normally absorbed through arachnoid granulations into the superior sagittal sinus. Thrombosis of cerebral sinuses increases venous pressure, impairs cerebrospinal fluid absorption, and ultimately leads to increased intracranial pressure. Consequently, increased intracranial pressure worsens venular and capillary hypertension and contributes to parenchymal hemorrhage and vasogenic and cytotoxic edema.

Clinical Presentation

The clinical presentation of cerebral venous thrombosis can be highly variable. Onset of symptoms and signs may be acute, subacute, or chronic. Four major syndromes have been described: isolated intracranial hypertension, focal neurological abnormalities, seizures, and encephalopathy. These syndromes may present in combination or isolation depending on the extent and location of cerebral venous thrombosis (Figure 3).

Intracranial hypertension resulting from cerebral venous thrombosis most frequently presents as headache. Headache is the presenting complaint in up to 90% of patients with cerebral venous thrombosis, and is described as subacute in onset 64% of the time.[4,5] However, some patients report acute onset of severe headache mimicking subarachnoid hemorrhage. Headache can be localized or generalized and may worsen with Valsalva maneuvers or position change.[6] Other findings of intracranial hypertension include papilledema and visual complaints. Headache caused by cerebral venous thrombosis is often initially diagnosed as a migraine.

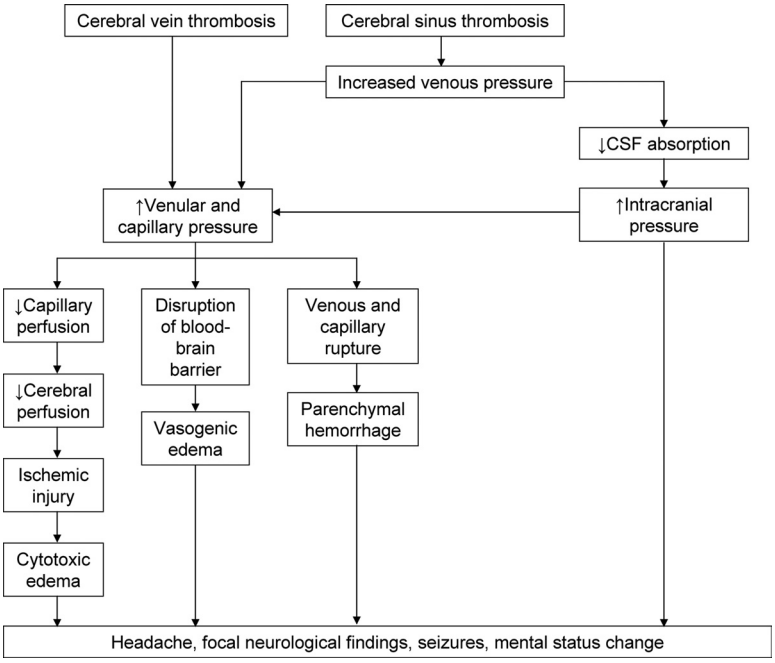

Figure 2. Pathophysiology of cerebral venous thrombosis. CSF indicates cerebrospinal fluid.

Focal neurological deficits are noted in 44% of patients with cerebral venous thrombosis.[5] Motor weakness including hemiparesis is the most common focal finding, and may be present in up to 40% of patients.[4] Fluent aphasia may result from left transverse sinus thrombosis. Sensory deficits are less frequent.

Focal or generalized seizures, including status epilepticus, are observed in 30% to 40% of patients with cerebral venous thrombosis.[5,7] Because seizures occur less often in other types of stroke, cerebral venous thrombosis should be considered in patients with seizures and other focal findings consistent with stroke. Seizures are encountered more frequently with thrombosis of the sagittal sinuses and cortical veins.[7]

Encephalopathy can result from thrombosis of the straight sinus and its branches or from severe cases of cerebral venous thrombosis with extensive cerebral edema, large venous infarcts, or parenchymal hemorrhages that lead to herniation.[1] Elderly patients with cerebral venous thrombosis are more likely to present with mental status changes than younger patients.[8]

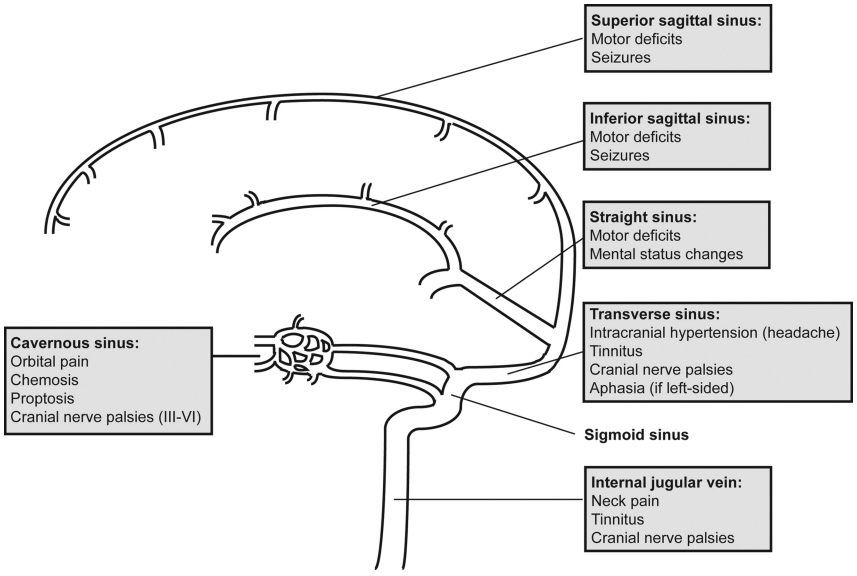

Figure 3. Major clinical syndromes according to location of cerebral venous thrombosis.

Diagnosis

Cerebral venous thrombosis should be considered in patients 50 years of age who present with acute, subacute, or chronic headache with unusual features, signs of intracranial hypertension, focal neurological abnormalities in the absence of vascular risk factors, new seizure disorder, or hemorrhagic infarcts especially if multiple or in nonarterial vascular territories. Because of variability in clinical presentation, delays in diagnosis are common.

Laboratory Testing

Although an elevated D-dimer supports the diagnosis of cerebral venous thrombosis, a normal D-dimer level is not sufficient to exclude the diagnosis in patients with a compatible clinical presentation.[5,9,10] In a study of 239 patients with suspected cerebral venous thrombosis, D-dimer testing was performed in 98 patients.[5] D-dimer testing was associated with a 9% false-positive rate and a 24% false-negative rate.[5]

Imaging

The American Heart Association (AHA)/American Stroke Association (ASA) 2011 Scientific Statement on diagnosis and management of cerebral venous thrombosis recommends imaging of the cerebral venous system in patients with suspected cerebral venous thrombosis (Table 2).[11] Head CT is the most frequently performed imaging study for evaluation of patients with new headache, focal neurological abnormalities, seizure, or change in mental status. Although noncontrast head CT may detect alternative diagnoses or demonstrate venous infarcts or hemorrhages, it has poor sensitivity and shows direct signs of cerebral venous thrombosis in only one third of

Table 2. Clinical Pearls for Diagnosis and Management of Cerebral Venous Thrombosis

Imaging with MR venography or CT should be performed in patients with suspected cerebral venous thrombosis.
Because of the high frequency of thrombophilias among patients who develop cerebral venous thrombosis, screening for hypercoagulable conditions should be performed.
On the basis of data from randomized controlled trials and observational studies, anticoagulation is recommended as safe and effective for treatment of cerebral venous thrombosis.
Anticoagulation with an oral vitamin K antagonist and a target international normalized ratio of 2.0–3.0 is recommended for 3–6 mo in patients with provoked cerebral venous thrombosis and 6–12 mo in those with unprovoked cerebral venous thrombosis.
Patients with recurrent cerebral venous thrombosis, deep vein thrombosis, or pulmonary embolism complicating cerebral venous thrombosis or initial cerebral venous thrombosis in the setting of severe thrombophilia should be considered for indefinite-duration anticoagulation.
Women who have suffered cerebral venous thrombosis in the setting of hormonal contraceptive therapy should seek alternative non–estrogen-based methods for contraception.
Follow-up imaging to assess for recanalization 3–6 mo after diagnosis is recommended.

patients.[11] Signs of cerebral venous thrombosis on CT include hyperdensity in the area of a sinus or cortical vein (cord sign) and filling defects, especially in the superior sagittal sinus (empty Δ sign), in contrast-enhanced studies.[1,11]

Computed tomographic venography provides a rapid and reliable method for detection of cerebral venous thrombosis, especially in patients with contraindications to MR imaging.[11] Computed tomographic venography allows for the diagnosis of subacute or chronic cerebral venous thrombosis because it can detect thrombus of heterogeneous density. Computed tomographic venography is comparable to MR venography for the diagnosis of cerebral venous thrombosis.[12,13] Concerns for radiation exposure, contrast allergy, and contrast nephropathy limit the use of CT venography in certain patients.

Magnetic resonance imaging of the head combined with MR venography is the most sensitive study for detection of cerebral venous thrombosis in the acute, subacute, and chronic phases.[14] Acutely, cerebral venous thrombosis appears isointense to brain tissue on T1-weighted images and hypointense on T2-weighted images.[11] In the subacute phase, thrombus appears hyperintense in both T1- and T2-weight images. In chronic stages, the thrombus can be heterogeneous with variable intensity relative to surrounding brain tissue. On T2-weighted images, thrombus may be directly visualized in cerebral veins and dural sinuses and appears as a hypointense area. Parenchymal lesions associated with cerebral venous thrombosis such as infarction and hemorrhage are often better visualized by MR. The addition of contrast-enhanced MR venography assists in distinguishing anatomic variants such as a hypoplastic sinus from cerebral venous thrombosis. The AHA/ASA 2011 Scientific Statement recommends MR with T2-weighted imaging and MR venography as the imaging test of choice for evaluation of suspected cerebral venous thrombosis.[11] Magnetic resonance imaging with MR venography is more time intensive than CT venography and has limited utility in patients with renal impairment because of the requirement of gadolinium contrast and the associated risk of nephrogenic systemic fibrosis.

Cerebral intraarterial angiography with venous phase imaging and direct cerebral venography are invasive diagnostic techniques that are reserved for rare instances when the clinical suspicion of cerebral venous thrombosis is high but MR or CT venography is inconclusive or if an endovascular procedure is being considered.[11]

Thrombophilia Testing

Because of the high frequency of thrombophilias among patients who develop cerebral venous thrombosis, screening for hypercoagulable conditions should be performed.[11] Thrombophilia testing should include evaluation for the factor V Leiden mutation, prothrombin gene mutation 20210, lupus anticoagulant, anticardiolipin antibodies, hyperhomocysteinemia, and deficiencies of protein C, S, and antithrombin. Protein C, S, and antithrombin levels may be abnormal in the setting of acute thrombosis, anticoagulation, oral contraceptives, or pregnancy.

Prognosis

In a meta-analysis of 1180 patients with cerebral venous thrombosis, the mean 30-day mortality rate was 5.6%.[15] The primary cause of death during the acute phase of cerebral venous thrombosis is transtentorial herniation, most frequently from large venous hemorrhage.[15,16] Although the majority of patients have a complete or partial recovery, 10% are found to have permanent neurological deficits by 12 months of follow-up.[15] Recanalization occurs within the first few months after cerebral venous thrombosis (84% of patients by 3 months) and is limited thereafter.[15] Recurrence of cerebral venous thrombosis is rare (2.8%).[15] However, patients with cerebral venous thrombosis have an increased incidence of venous thromboembolism, including deep vein thrombosis and pulmonary embolism, the majority of which occur within the first year.[17]

Management

Acute phase therapy for cerebral venous thrombosis focuses on anticoagulation, management of sequelae such as seizures, increased intracranial pressure, and venous infarction, and prevention of cerebral herniation.[1] Management of seizures and increased intracranial pressure in patients with cerebral venous thrombosis requires a team approach that includes consultation with neurology and neurosurgery.

Anticoagulation

The rationale for anticoagulation is to prevent thrombus propagation, recanalize occluded sinuses and cerebral

veins, and prevent complications of deep vein thrombosis and pulmonary embolism.[11] Anticoagulation has been controversial for treatment of cerebral venous thrombosis because of the tendency for venous infarcts to become hemorrhagic even before anticoagulants have been administered.[1]

The results of 2 randomized, controlled trials comparing immediate anticoagulation with placebo support the administration of anticoagulant therapy for treatment of cerebral venous thrombosis.[18,19] One trial comparing intravenous unfractionated heparin, titrated to an activated partial thromboplastin time of twice the upper limit of normal, with placebo was terminated after 20 of the planned 60 patients with cerebral venous thrombosis were enrolled because of an early treatment benefit.[19] Among the 10 patients in the placebo group, 1 completely recovered, 6 suffered minor neurological deficits, and 3 died by 3 months. Among the 10 patients in the heparin group, 8 completely recovered and 2 had mild deficits at 3 months. Two patients in the placebo group and none in the heparin group suffered intracranial hemorrhage.

In another randomized trial of 59 patients with cerebral venous thrombosis, the low–molecular weight heparin nadroparin was compared with placebo for 3 weeks followed by 3 months of oral anticoagulation in those assigned to the treatment arm.[18] At 3 months, 13% of patients in the nadroparin arm and 21% in the placebo arm had poor outcomes. No symptomatic intracranial hemorrhages were observed in either group. Meta-analysis of these 2 trials revealed a risk difference for death and disability that appeared to favor anticoagulation (−13%; 95% confidence interval −30% to 3%).[20]

Anticoagulation has posed a particular concern in cerebral venous thrombosis patients presenting with hemorrhagic infarction. In the 2 aforementioned randomized, controlled trials, no new cerebral hemorrhages or extension of hemorrhages present before therapy were observed.[18,19] This observation supports the hypothesis that improvement in venous outflow obstruction with anticoagulation decreases venular and capillary pressure and reduces the risk of further hemorrhage.

On the basis of data from randomized, controlled trials and observational studies, anticoagulation is recommended as safe and effective for treatment of cerebral venous thrombosis with or without intracranial hemorrhage on presentation (Table 2).[11,21] Immediate anticoagulation is administered with either intravenous unfractionated heparin or with subcutaneously administered low–molecular weight heparin as a bridge to oral anticoagulation with a vitamin K antagonist.

Fibrinolysis

Although the majority of patients recover with anticoagulant therapy, a subset of patients with cerebral venous thrombosis have poor outcomes despite anticoagulation. Catheter-directed fibrinolytic therapy, with or without mechanical thrombus disruption, has been considered for patients who have large and extensive cerebral venous thrombosis or who clinically worsen despite anticoagulation. A systematic review of 169 patients with cerebral venous thrombosis suggested a possible clinical benefit with fibrinolysis for those with a severe presentation.[22] However, intracranial hemorrhage occurred in 17% of patients after fibrinolysis and was associated with clinical deterioration in 5%.[22] Another systematic review of 156 patients with cerebral venous thrombosis noted 12 deaths after fibrinolysis and 15 major bleeding complications, including 12 intracranial hemorrhages.[23] On the basis of the limited data available, catheter-directed fibrinolysis may be considered at experienced centers for patients who deteriorate despite intensive anticoagulation.[11]

Surgical Interventions

Surgical thrombectomy is reserved for the rare circumstance in which severe clinical deterioration occurs despite maximal medical therapy.[11] In patients with cerebral venous thrombosis and large parenchymal lesions causing herniation, decompressive surgery, such as craniectomy or hematoma evacuation, has been associated with improved clinical outcomes.[24]

Long-Term Management

Because there are no randomized, controlled trials assessing the optimal duration of anticoagulation for cerebral venous thrombosis, guidelines rely on the evidence and recommendations for deep vein thrombosis and pulmonary embolism. The AHA/ASA 2011 Scientific Statement recommends anticoagulation with an oral vitamin K antagonist and a target international normalized ratio of 2.0 to 3.0 for 3 to 6 months in patients with provoked cerebral venous thrombosis and 6 to 12 months in those with unprovoked cerebral venous thrombosis.[11] Patients with recurrent cerebral venous thrombosis, deep vein thrombosis, or pulmonary embolism complicating cerebral venous thrombosis or initial cerebral venous thrombosis in the setting of severe thrombophilia (homozygosity for prothrombin gene mutation 20210 or factor V Leiden; combined thrombophilias; deficiencies of antithrombin, protein C, or protein S; or antiphospholipid antibodies) should be considered for indefinite duration anticoagulation with a target international normalized ratio of 2.0 to 3.0.

Women who have suffered cerebral venous thrombosis in the setting of hormonal contraceptive therapy should seek alternative non–estrogen-based methods for contraception. The progestin-only pill, levonorgestrel intrauterine device, and copper intrauterine device are reasonable alternatives. Women with a history of cerebral venous thrombosis while receiving hormonal contraceptive therapy, during pregnancy, or during the postpartum period have an increased risk of recurrence during subsequent pregnancies. Prophylactic anticoagulation with low–molecular weight heparin during

future pregnancies and the postpartum period is often recommended.[11]

In addition to clinical follow-up, the AHA/ASA 2011 Scientific Statement recommends follow-up imaging to assess for recanalization 3 to 6 months after diagnosis.[11]

Case Presentation

The patient was immediately started on anticoagulation with therapeutic-dose low–molecular weight heparin and then transitioned to warfarin with an international normalized ratio target range of 2.0 to 3.0. Thrombophilia testing demonstrated heterozygosity for the factor V Leiden mutation. Because her cerebral venous thrombosis was believed to be provoked by the use of a third-generation oral contraceptive pill superimposed on a thrombophilia with factor V Leiden mutation, the patient was instructed to avoid hormonal contraceptive techniques and elected to have an intrauterine device placed. She was treated with therapeutic anticoagulation for 6 months. Repeat MR venography after completion of anticoagulation demonstrated complete recanalization of her left transverse and sigmoid sinus and proximal jugular vein. Her headache completely resolved, and she has not suffered a recurrence of cerebral venous thrombosis.

Disclosures

None.

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