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Clinical Reasoning: A 24-year-old woman with progressive headache and somnolence

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SECTION 1

A 24-year-old woman presented with progressive somnolence and headache following 2 days of nausea and vomiting. She had a history of developmental delay, attention-deficit disorder, and remote seizures. Medications included combined estrogen-progestin oral contraceptives. On presentation, she was afebrile, somnolent but arousable, groaning incoherently, and unable to follow commands. Optic disc margins were blurred bilaterally. Gaze was midline and deviated downward with restricted spontaneous upward gaze but full lateral gaze. She moved the right side less briskly than the left.

Question for consideration:

1. What is the localization and differential diagnosis of the examination findings?

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SECTION 2

Progressive somnolence, blurred optic disc margins, and forced downgaze indicate elevated intracranial pressure (ICP) with dorsal midbrain compression. Decreased spontaneous movement of the right side could point to a left-sided lesion, although localization can be challenging in the setting of herniation. The progression of symptoms over 2 days indicates a subacute process; the differential diagnosis includes vascular (expanding hematoma, venous sinus thrombosis), neoplastic (intraparenchymal or leptomeningeal disease), infectious (meningitis, encephalitis), and inflammatory (acute disseminated encephalomyelitis) conditions, any of which may lead to CSF flow obstruction. There was no history of trauma suggestive of intracranial injury, progressive localizing neurologic deficits indicating an expanding mass lesion, fever implicating intracranial infection, or prior infection suggestive of postinfectious demyelinating syndrome.

Question for consideration:

1. How would you evaluate and manage the patient?

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SECTION 3

In a patient with signs of elevated ICP, diagnostic evaluation and immediate therapy must proceed in parallel. Our patient received mannitol en route to head CT. Her head CT showed a "cord sign" in the left transverse sinus consistent with cerebral venous sinus thrombosis (CVST) (figure). CT venogram revealed contrast filling defects in the superior sagittal, straight, and left transverse and sigmoid sinuses with significant dilation of cortical veins. MRI demonstrated sulcal susceptibility signal and T2 hyperintensity in fluid-attenuated inversion recovery sequence representing diffuse cortical venous dilation. There was no evidence of infarct, hemorrhage, vascular malformation, or structural abnormality.

Question for consideration:

1. How should the venous sinus thrombosis be managed?

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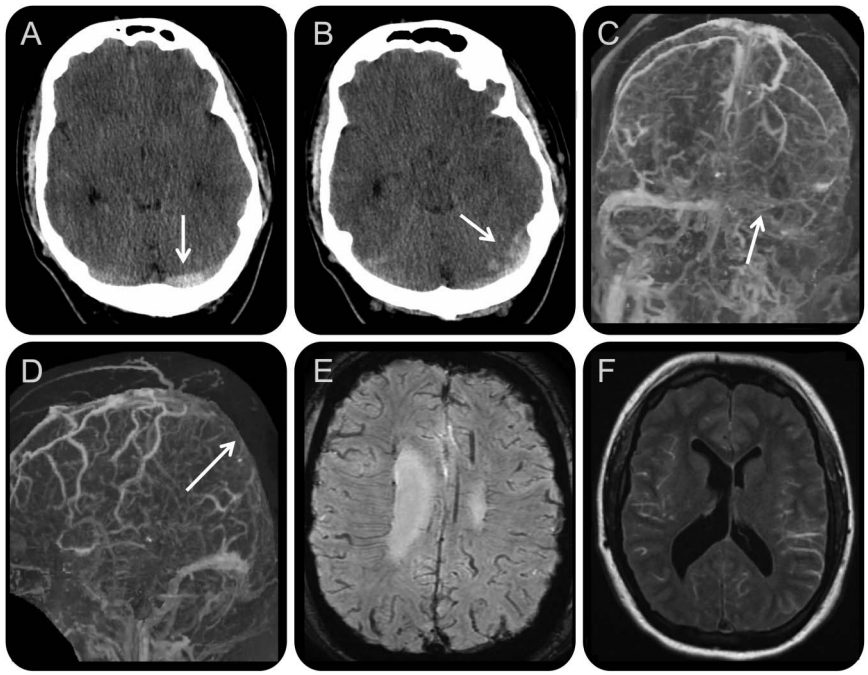
Figure Radiographic findings



Noncontrast head CT shows diffuse sulcal effacement indicating cerebral edema and hyperdensity in left transverse sinus (A; white arrow) extending into sigmoid sinus (B; white arrow) representing acute thrombus. CT venography shows lack of contrast opacification in left transverse sinus (C; white arrow) and posterior segment of the superior sagittal sinus (D; white arrow). MRI shows sulcal susceptibility signal (E) and sulcal fluid-attenuated inversion recovery sequence hyperintensity (F) representing diffuse cortical venous dilation.

SECTION 4

The acute management of CVST involves systemic anticoagulation along with monitoring and management of ICP. The data for systemic anticoagulation come from 2 controlled trials of patients with angiographically confirmed CVST. The initial trial included 20 patients randomized to saline infusion or IV heparin with goal partial thromboplastin time (PTT) of 80–100 seconds for 8 days.[1] Outcome scores using a custom nonvalidated "sinus venous thrombosis severity scale" (headache severity, focal signs, presence of seizures, and degree of consciousness) demonstrated improved outcome in the heparin group starting from day 3 of therapy to 3-month follow-up (8/10 in heparin group recovered completely compared to 1/10 in control group). Three new hemorrhages occurred in the control group, while none occurred in the heparin group. Recanalization rates were not assessed.

A larger randomized controlled trial compared placebo with anticoagulation with nadoparin (a low-molecular-weight heparin [LMWH]) followed by 10 weeks of oral anticoagluation.[2] At 3 weeks, there was no difference in primary outcome (death or Barthel Index <15 points). Secondary analyses showed trends toward decreased death and improved outcome in the treatment group at 3 and 12 weeks. No new symptomatic intracerebral hemorrhages (ICHs) occurred in either group.

These trials demonstrated that heparin and LMWH are safe in patients with CVST even in the presence of ICH and suggested a possible benefit from anticoagulation. No trials have compared heparin and LMWH, but prospective studies suggest that LMWH is associated with increased independence at 6 months with decreased incidence of ICH.[3] Observational studies estimate the risk of ICH from anticoagulation for CVST at 0%–5.4%.[4]

Our patient was treated with IV heparin (continuous infusion without bolus; goal PTT 60–80 seconds) after review of her neuroimaging. She was monitored closely in the neurology intensive care unit given her decreased level of consciousness and increased ICP. After 6 days of treatment, the patient was interactive and able to follow commands, but she was blind and had decreased strength on the right side. Repeat neuroimaging showed new left temporoparietal hemorrhagic infarction and unchanged extensive venous sinus thrombosis.

Question for consideration:

1. What is the role for catheter-directed local therapy, ICP monitoring, or other surgical procedures?

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SECTION 5

Interventional procedures for CVST include catheter-guided thrombolysis, mechanical thrombectomy, and decompressive hemicraniectomy. These procedures are typically reserved for patients with refractory seizures, ongoing ischemic or hemorrhagic strokes, or coma due to persistently elevated ICP despite anticoagulation.[4] There are no controlled trials comparing these interventional procedures with each other, with or in conjunction with anticoagulation, or with no therapy in this severely ill patient subgroup. Similarly, there are no guidelines regarding the use of ICP monitoring devices to direct therapeutic options.

In catheter-directed thrombolysis, a catheter is guided to the occluded sinus for direct infusion of thrombolytics. A meta-analysis including 169 patients concluded that thrombolysis (most frequently with urokinase) is associated with ICH in 17% of cases.[5] Catheter-directed thrombectomy has more recently been used to treat CVST using rheolytic thrombectomy, clot retraction, balloon venoplasty, or a combination of techniques as initial therapy or rescue therapy for refractory symptoms despite anticoagulation.[4,6] A meta-analysis of published case series of 64 patients with CVST treated with mechanical thrombectomy concluded that about 14% died following thrombectomy and 11% had major disability.[6] To address the question of additional efficacy of interventional treatment compared to anticoagulation alone in a critically ill subpopulation of patients with CVST, the Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial is an ongoing randomized trial comparing systemic anticoagulation and endovascular thrombolysis with or without thrombectomy.[7]

For patients with extensive hemorrhage or cerebral edema from venous infarction, decompressive hemicraniectomy has been used to relieve elevated ICP. In a review of 69 patients who had decompressive hemicraniectomy for impending herniation in the setting of CVST, 26 patients (37.7%) had complete recovery (modified Rankin Scale score 0–1) while 15 patients (21.7%) were dead or severely disabled (modified Rankin Scale score 4–6) after 12 months median follow-up.[8] In our patient, since her level of arousal improved with anticoagulation alone, endovascular therapy was not pursued.

DISCUSSION

The estimated incidence of CVST is 5 cases per million annually, accounting for 0.5%–1% of all strokes.[4] A total of 78% of cases of CVST occur in individuals younger than age 50.[4] Clinical symptoms result from elevated ICP, venous infarction, or ICH. Headache is present in 89% of patients, accompanied by a wide spectrum of signs including paresis (37%), seizures (39%), and depressed level of consciousness (14%).[9] In the International Study on Cerebral Vein and Dural Sinus Thrombosis, the largest observational study of CVST (624 patients), congenital and acquired thrombophilia were the most frequent risk factors (34% of cases), followed by pregnancy and puerperium (20%), intracranial infection (10%), medications such as oral contraceptives (7.5%), intracranial or systemic malignancy (7.4%), mechanical compression of the venous sinuses (e.g., traumatic or postsurgical) (4.5%), inflammatory diseases such as systemic lupus erythematosus (5%), and dehydration (1.9%).[9] A total of 44% of patients with CVST had more than one risk factor identified, while no identifiable risk factor was found in 12.5%.[9] Therefore, even in patients with an identified risk factor (such as use of oral contraceptives or recent intracranial infection), we recommend laboratory evaluation for hypercoagulability (including assessment for antithrombin III deficiency, protein C or S deficiency, resistance to activated protein C, factor V Leiden, factor II G20210A mutation, antiphospholipid/anticardiolipin antibodies, hyperhomocysteinemia, and systemic lupus erythematosus) as some patients have an underlying predisposition that increases their susceptibility to thrombotic events when a second hit is introduced. Our patient had no family history or laboratory evidence of hypercoagulabilty; use of oral contraceptives appeared to be her only risk factor.

Definitive diagnosis of CVST requires neuroimaging. Noncontrast head CT has low sensitivity, estimated between 25% and 56%.[10] While digital subtraction angiography is the traditional gold standard, CT and magnetic resonance venography (CTV and MRV) are more readily available in the acute setting. No large comparative trials exist, but CTV and MRV appear to have comparable sensitivity, estimated at 90% or higher depending on the location and caliber of the affected veins.[4] Isolated cortical vein thrombosis can be difficult to image by either technique. The primary advantage of CTV is rapid acquisition time, though MRI/MRV is more sensitive for acute infarction and avoids nephrotoxic contrast.[10] There are no laboratory indicators sensitive or specific enough to confirm or exclude CVST. The fibrin degradation product D-dimer has reported sensitivity greater than 90% though the test is nonspecific.[4] Opening pressure in lumbar puncture is elevated in 83% of patients,[9] but lumbar puncture may be contraindicated in patients like ours with elevated ICP because of the risk of precipitating herniation.

While anticoagulation is the currently recommended treatment for CVST, 14% of patients are dead or dependent 6 months after diagnosis despite modern therapy.[9] Our patient's arousal level improved significantly, but she was left with severely diminished vision potentially from prolonged elevated ICP. Would she have benefited from catheter

thrombolysis/thrombectomy or from invasive ICP monitoring and management? When and for how long should ICP-lowering agents be used? Data from controlled trials do not yet exist to guide interventional therapies or ICP management in patients with CVST. Pending the results of ongoing controlled trials such as TO-ACT, such decisions must be made on an individual basis, balancing principally the hemorrhagic risks of intervention and the deficits accrued from prolonged elevation of ICP.

AUTHOR CONTRIBUTIONS

Drs. Bhattacharyya, Berkowitz, and Jha all participated in conception of this article and drafting/revising the manuscript for content.

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