

Clinical Communications: Adults

CEREBRAL VENOUS THROMBOSIS: A CASE REPORT

Nishant Anand, MD,* Carmie Chan, MD,* and N. Ewen Wang, MD†

*Stanford Kaiser Emergency Medicine Residency Program, Stanford, California and †Division of Emergency Medicine, Stanford University School of Medicine, Palo Alto, California

Reprint Address: Ewen Wang, MD, Division of Emergency Medicine, Stanford University School of Medicine, 701 Welch Road, Building C, Palo Alto, CA 94304

□ Abstract—The incidence of cerebral venous thrombosis (CVT) is three to four cases per one million in adults and seven cases per one million among children. We discuss a case of CVT in a 19-year-old woman with a history of migraine headaches. A CVT most commonly presents acutely, with a wide variety of signs and symptoms in young adults and children. The most common presenting complaint in adults is severe headache. The most frequently thrombosed sinuses are the lateral, cavernous, and superior sagittal sinuses. Risk factors include any genetic or acquired prothrombotic conditions, including pregnancy and the peripartum period. Computed tomography may show the classic “delta sign,” although magnetic resonance imaging with magnetic resonance venography is more sensitive. Treatment is controversial at this time. Options include fibrinolysis, anticoagulation, mechanical thrombectomy, or surgery. Despite the lack of agreement on management of CVT, the prognosis of CVT has improved, due to an increasing frequency of diagnosis. © 2009 Elsevier Inc.

□ Keywords—Cerebral venous thrombosis; sinus thrombosis; stroke

INTRODUCTION

Headaches present a diagnostic and therapeutic challenge for emergency physicians. Headaches are a common Emergency Department (ED) complaint, accounting for 2.6% of ED visits (1). Although most headaches are benign, many serious conditions, including subarachnoid hemorrhage, in-

tracranial tumor, other hemorrhagic stroke, or cerebral venous thrombosis (CVT) may present with headache. The annual incidence of CVT is three to four cases per one million, with 75% of adult patients being women, and up to seven cases per one million among children. The majority of adult patients, up to 80%, will have good neurologic outcome if diagnosed correctly (2). Among childhood cases of CVT, neonates are the most commonly affected age group. In contrast to adults, about half of the children affected suffered neurological impairment or death from CVT (3). We will discuss a case of cerebral venous thrombosis and etiologies, diagnostic tools, and therapeutic options.

CASE REPORT

A 19-year-old right-hand-dominant woman was brought to the ED by her friends for a severe headache that had acutely become unbearable. In addition, the patient had woken up feeling weak. When she tried to get out of bed and walk, she would fall to the left side. She felt that her left arm and leg were not as strong as usual. She took Ibuprofen and metoclopramide without relief.

The patient stated that she had been to the ED 2 days prior with a headache. During that visit, she received Reglan and morphine, with decrease in the severity but without complete resolution of the headache. No diagnostics had been performed.

The patient had experienced headaches since her return from Mexico 3 weeks prior. This headache was not like her previous migraines, but it was not the worst headache of her life. Associated symptoms included photophobia, nausea, occasional non-bloody emesis, and chills for the last 10 days.

The patient had a past medical history of B-12 deficiency anemia. She had been receiving monthly B-12 injections. The patient had been diagnosed by her primary care physicians with migraine headaches 3 years prior. She had never previously been to the ED for headaches, nor had a computed tomography (CT) scan of the head ever been obtained.

The patient's medications included the monthly B-12 shots and oral contraceptives. She had been on the same regimen for the past few years. The patient was not aware of any cancer history, bleeding problems, or hypercoagulability in her family. She was a college student and lived in a dormitory. She had not received a meningococcal vaccination. She denied nicotine, alcohol, and intravenous drug use.

On physical examination, the patient was an age-appropriate woman who appeared uncomfortable. She was lying in the room with the lights off. The temperature was 37°C (98.6°F) oral, pulse 85 beats/min, blood pressure 109/61 mm Hg, and respirations 16 breaths/min. She was alert and oriented times three. The cardiovascular, pulmonary, and abdominal examinations were benign. The pupils were equal and reactive to light bilaterally. The extraocular movements were intact. No diplopia was reported. Visual fields were grossly normal. There was weakness with closing the eyes. Smiling revealed a left facial paralysis sparing the forehead. The tongue was midline. Strength of the left deltoid, bicep, tricep, hand flexors and extensors, hip flexors, quadriceps, hamstrings, tibialis anterior, and gastrocnemius were 2/5 compared to 5/5 on the right. Pain sensation was decreased on the left side of the body. Reflexes were hyperactive on the left with clonus and upgoing toes. Gait was not assessed.

Workup in the ED showed a normal complete blood cell count with a white blood cell count of 5600, hematocrit 28.8, mean corpuscular volume 69.3, platelets 424. Chemistry panel results were as follows: sodium 138, potassium 4, chloride 106, bicarbonate 24, BUN 10, creatinine 0.6, glucose 107, calcium 8.9. Total bilirubin was 0.5, alkaline phosphatase 44, AST 22, ALT 16.

Computed tomography (CT) scan showed low attenuation of the right basal ganglia, thalamus, internal capsule, and head of caudate with adjacent mass effect, and asymmetric enlargement of the right lateral ventricle. There was high attenuation along the straight sinus and posterior interhemispheric fissure (Figure 1). After consulting with neurosurgery, an emergent magnetic reso-

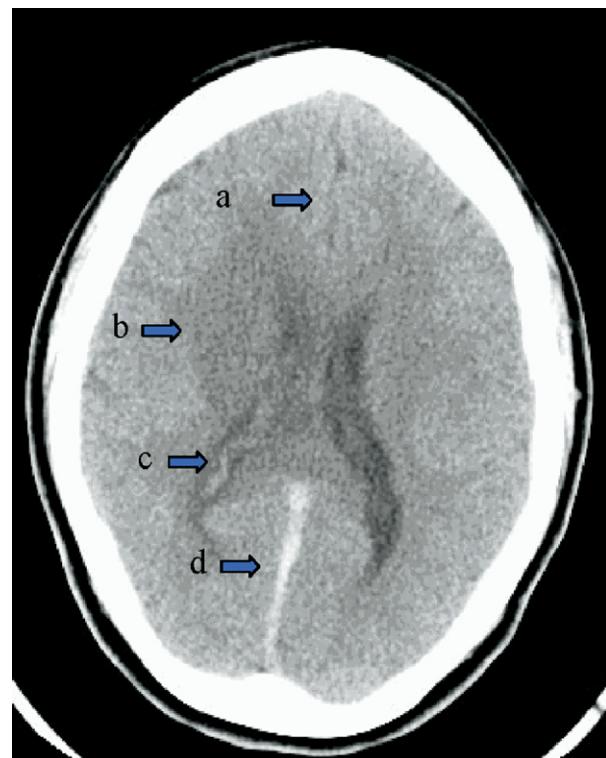


Figure 1. Computed tomography scan showing mild shift (a), infarcted tissue (b), blood in the ventricle (c), and thrombosis in the straight sinus (d).

nance imaging (MRI) scan of the head was obtained. The MRI scan showed thrombosis of the straight sinus, deep internal cerebral veins, left sigmoid and transverse sinuses. There was infarction of the thalamus, caudate and basal ganglionic nuclei, with mild mass effect (Figures 2, 3).

DISCUSSION

Cerebral venous thrombosis (CVT) presents with a wide variety of signs and symptoms. Due to the rarity of the disorder, much of the knowledge about CVT has been obtained through case reports, retrospective studies, and a few small prospective studies. The International Study on Cerebral Vein Thrombosis (ISCVT) is an international, multi-center prospective observational study striving to obtain prospective data on CVT. The ISCVT collaborators have published four abstracts thus far relating to risk factors, management, and prognosis of CVT (4). Research on CVT in children is limited. Age-related differences in hemostatic, vascular, and neurologic systems between children and adults make extrapolation from adult data difficult (3). Despite the paucity of research, the prognosis of CVT has improved, due largely to improvements in diagnosis.

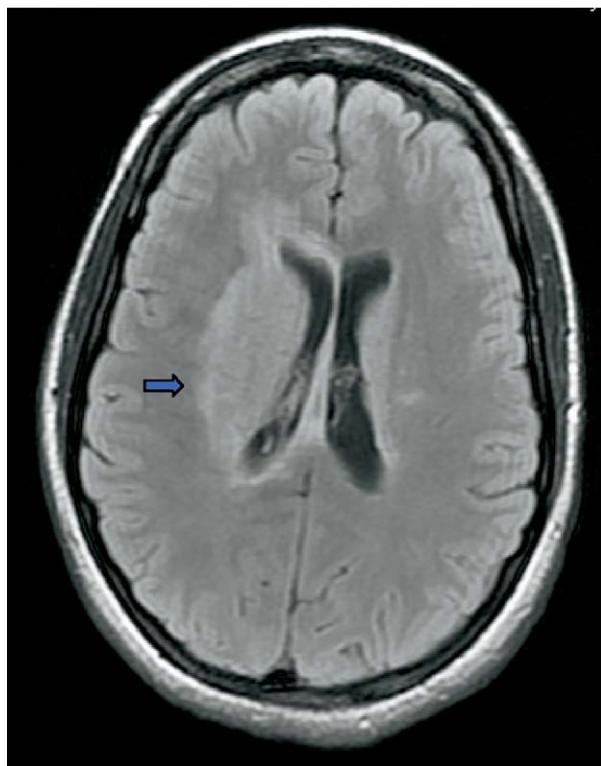


Figure 2. Magnetic resonance image illustrating infarcted tissue (arrow).

A CVT most commonly presents with acute onset of symptoms. The most frequently thrombosed sinuses are the lateral, cavernous, and superior sagittal sinuses; the straight sinus and vein of Galen are less frequently involved. The pathogenesis of this disorder can be explained by the effects of occlusion of both the cerebral veins and the major venous sinuses (2). The cerebral veins drain into the major sinuses, which in turn drain into the internal jugular veins. Blockage in any part of this system will result in higher hydrostatic pressures being transmitted backwards into the veins. Thrombosis of the cerebral veins causes localized edema of the brain and venous infarction, leading to ischemia and cytotoxic edema from damage to the cellular membrane pumps; in addition, disruption of the blood-brain barrier causes vasogenic edema. The developing venous infarcts may also transform into hemorrhagic infarcts. Occlusion of the venous sinuses leads to development of intracranial hypertension by blocking absorption of cerebrospinal fluid (2).

Risk factors for CVT include any genetic or acquired prothrombotic conditions, including pregnancy and puerperium. A predisposing risk factor or direct cause can be identified in the majority of adult and pediatric cases of CVT. The incidence of peripartum CVT is about 12

cases per 100,000 deliveries. Reviews of CVT cases related to pregnancy have found an increased risk late in pregnancy and immediately after delivery, as well as an association with delivery by caesarean section, preeclampsia, and infection (5). The mortality rate of pregnancy-related CVT is 2–10% less than the risk of death from CVT associated with other causes (6). Oral contraceptives also have been associated with an increased risk of CVT, likely related to increased prothrombogenicity. Other prothrombotic risk factors include high homocysteine levels, and low folate and vitamin B12 levels (7). Any history of previous thrombotic disease, such as venous thrombosis, should also be considered a risk factor. In one series of 79 patients with CVT, 11.4% had a history of deep venous thrombosis (DVT) and 16.5% had a positive family history for venous thrombosis (8). Any prothrombotic condition is a risk factor for DVT and CVT; additional risk factors for DVT also include obesity, surgery, and immobilization. Researchers suggest that CVT is due purely to circulating coagulation factors in the blood and vascular wall defects, whereas DVT, which is a more common disorder, is affected by multiple other factors (9).



Figure 3. Thrombosis of the straight sinus, deep internal cerebral veins, left sigmoid and transverse sinuses. (a) Illustrates normal flow. (b) Illustrates absence of flow due to thrombus.

A CVT also may be caused by mechanical factors, including head trauma, neurosurgical procedures, or injury to sinuses or jugular vein, including venous catheterization. Generally, CVT after trauma has a subacute course, usually presenting a few days to weeks after the injury (10). Lumbar punctures may also cause sinus thrombosis; low cerebrospinal fluid pressure after a lumbar puncture causes downward traction on the cortical veins and sinuses, possibly leading to thrombosis (2). Infectious etiologies of CVT include extension from osteomyelitis, sinus thrombophlebitis, or complications of otitis media and mastoiditis. The incidence of infection-related CVT is higher in children than adults (3). Other risk factors include polycythemia, cryofibrinogenemia, sickle-cell anemia, leukemia, disseminated intravascular coagulation, systemic lupus erythematosus, sarcoidosis, inflammatory bowel syndrome, and Behcet syndrome.

The diagnosis of CVT can be challenging. The most common presenting complaint is severe headache (80–90%), which may be acute or subacute, and is more often localized rather than diffuse and often constant (11–13). Such headaches may mimic migraines or subarachnoid hemorrhages. CVT has been reported to present with a subarachnoid hemorrhage (SAH), although unlike other types of SAH, the basal cisterns were spared in CVT cases presenting with SAH (14).

Patients with CVT may also present with focal neurologic deficits. Thrombosis of the superior sagittal sinus may present with a hemiplegia with subsequent involvement of the other hemisphere, due to development of cortical lesions on the other side of the sagittal sinus. If severe, involvement of the superior sagittal sinus may lead to signs of increased intracranial pressure and coma. Thrombosis of the cavernous sinus may classically cause ptosis, proptosis, chemosis, and extraocular dysmotility due to deficits of cranial nerves III, IV, and VI. Hyperesthesia of the ophthalmic and maxillary division of the fifth cranial nerve and a decreased corneal reflex may be detected. There also may be evidence of dilated, tortuous retinal veins and papilledema. With thrombosis of the superior sagittal sinus and transverse sinus, a 6th nerve palsy may be present. Involvement of the deep sinuses, including straight sinus and vein of Galen, may cause thalamic lesions, leading to behavioral changes such as mutism, delirium, and amnesia. About 23% of patients with CVT present with isolated intracranial hypertension, causing headache and diplopia due to involvement of the sixth cranial nerve, and papilledema (15). Left untreated, patients may suffer permanent visual defects or even blindness. About 40% of patients with CVT present with seizures, which are limited and focal in 50% of these patients, but may also secondarily

generalize into grand mal seizures (2). This percentage is even higher in neonates, in whom seizures may be the presenting complaint for CVT.

Children with CVT may present similarly to adults, with altered level of consciousness, headache complaints, or cranial nerve palsies. For unknown reasons, focal neurological deficits are less common in children compared to adults (3). Neonates with CVT often present with seizures and diffuse neurologic signs.

Given the potential serious complications of a missed CVT, one must think of the diagnosis in patients who present with headache and neurologic symptoms, isolated intracranial hypertension, or those with CT evidence of vascular infarcts in non-arterial distributions. This is especially true in younger patients without the usual vascular risk factors (2). In these cases, a search for predisposing risk factors for CVT may be helpful.

A non-contrast head CT scan may be useful for diagnosis, as well as to rule out other cerebral disorders. The classic finding on non-contrast CT scan is the “delta sign,” a dense triangle within the superior sagittal sinus that is created by thrombosis within the sinus. False-positive “delta signs” may appear in trauma patients with adjacent subdural hemorrhages. On contrast-enhanced CT scan, the “empty delta sign” appears in the superior sagittal sinus from enhancement of the surrounding dura around the thrombosed sinus, which is less dense; however, this sign is only seen in up to 30% of cases (Figure 4) (16). If the CT scan is abnormal but still inconclusive regarding pathology, imaging modalities that can further define CVT include MRI and MR venography, which is the most sensitive test for CVT. The thrombosed sinus has a hyperintense signal on MRI, and venography should demonstrate abnormal flow within the sinuses. If isolated cortical vein thrombosis is suspected (without thrombosis of the sinus), cerebral angiography should also be considered. For neonates, transfontanel Doppler ultrasound may be useful for diagnosis. CT venography is a new technique that may also aid in viewing the cerebral venous system. Currently, the false-negative rate for CT diagnosis is estimated to be about 25% (15).

Treatment for CVT is controversial, and may depend on neurology or neurosurgical preferences within individual institutions. Anticoagulation with heparin is currently the first-line treatment to stop the thrombotic process. Limited evidence has suggested that, even with intracerebral hemorrhage overlying venous infarction, heparin does seem to be safe with no evidence of increased intracerebral bleeding. Treatment with heparin (conventional unfractionated or low molecular weight) also has been shown to be associated with a potentially important reduction in mortality and morbidity, although the statistics are not significant in a recent review (17).

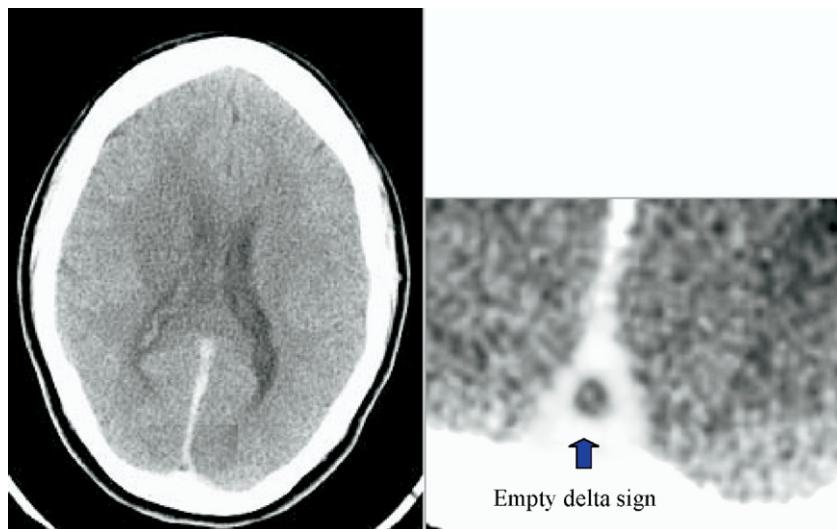


Figure 4. Clot in superior sagittal sinus illustrating the “empty delta sign.”

The duration of oral anticoagulation treatment after the acute CVT has not been systematically studied; most patients are treated with warfarin for 6 months after the initial episode, with target INR 2.5. This recommendation follows established guidelines for treating pulmonary embolism. Recurrence of sinus thrombosis occurs in 2% of patients, with 4% of patients experiencing a recurrent thrombotic event in 1 year (2).

Despite a lack of randomized clinical trials, case reports have also reported success with endovascular thrombolysis, both mechanical and chemical, in patients who deteriorate despite heparin therapy (18,19). Intra-arterial thrombolysis with urokinase and recombinant tissue plasminogen activator (rt-PTA) have been reported with successful recanalization. Most experts agree that thrombolysis should be reserved for patients with a poor prognosis who have not responded to heparin therapy. Platelet glycoprotein IIb/IIIa inhibitors also show promise in rat studies; however, there have been no reports of human treatment (20).

Overall, the prognosis for CVT is quite good, especially compared to arterial stroke. Mortality rates are estimated between 8% and 20%. Poor prognostic factors include male gender, age over 37 years, low Glasgow Coma Scale score, mental status disorders, focal neurologic deficits, hemorrhage or “delta sign” on CT scan, involvement of the deep venous system, central nervous system infection, central nervous system disorder or cancer as a predisposing condition, or presentation with seizures (21,22). Predictors of good outcome include absence of focal deficits, no cancer, and presence of isolated intracranial hypertension. Unlike patients with arterial stroke, most patients with CVT regain indepen-

dence with good neurologic and cognitive long-term outcomes. Most studies estimate that 70–86% of treated patients have no functional disability at 3 years’ follow-up, despite some residual neurologic symptoms (13,21). Long-term complications include seizures (10–16%) and new thrombotic events (4–12%) (8,22,23). It is still unclear whether patients should be placed on long-term anti-seizure medications. There are limited data on long-term outcomes of children with CVT; in a Canadian review, 77% of neonates and 52% of non-neonates were neurologically normal at follow-up (3).

In the case of our patient, neurosurgery was consulted. They initiated a heparin drip, and given the severity of her neurologic findings, decided to administer intravenous tPA, and perform a mechanical thrombectomy on the same day. On day 2, the patient became stuporous and was intubated. She was taken to the operating room by neurosurgery for placement of a frontal external ventricular drain. Deep venous system thromboses with increased intracranial pressure, hydrocephalus, and intraventricular hemorrhage were found. On day 4 she was extubated. A repeat MRI scan showed patent venous sinuses, infarcted right thalamus, basal gangli, and internal capsule. A few days later, the patient had normal alertness, with 3/5 strength on the left that was slightly improved from admission. The sensory deficits were also improved. The intracranial pressure was < 10 and she was transferred out of the Intensive Care Unit. She was discharged on hospital day 42, after being kept in the hospital the last few weeks for rehabilitation. She was seen back in clinic a week later for follow-up and was found to have 4/5 grip strength in the left hand with no functional deficits.

REFERENCES

1. McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 2002 emergency department summary. *Adv Data* 2004;(340):1-34.
2. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005;352:1791-8.
3. deVeber G, Andrew M, Adams C, et al.; Canadian Pediatric Ischemic Stroke Study Group. Cerebral sinovenous thrombosis in children. *N Engl J Med* 2001;345:417-23.
4. International study on cerebral vein thrombosis. Available at: www.iscvt.com. Accessed May 15, 2005. [Abstracts include: Ferro JM, Bousser MG, Barinagarrementeria F, Stam J, Canhão P, ISCVT investigators. Variation in management of acute cerebral vein and dural sinus thrombosis. Ferro JM, Stam J, Bousser MG, Barinagarrementeria F, Canhão P, ISCVT investigators. Prognosis of acute cerebral vein and dural sinus thrombosis; ISCVT results. Canhão P, Ferro JM, Bousser MG, Stam J, Barinagarrementeria F, ISCVT investigators. International study on cerebral vein thrombosis (ISCVT): baseline data. Canhão P, Bousser MG, Barinagarrementeria F, Stam J, Ferro JM, ISCVT investigators. Predisposing conditions for cerebral vein and dural sinus thrombosis.]
5. Cantu C, Barinagarrementeria F. Cerebral venous thrombosis associated with pregnancy and puerperium: Review of 67 cases. *Stroke* 1993;24:1880-4.
6. Lanska D, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. *Stroke* 2000;31:1274-82.
7. Canta C, Alonso E, Jara A, et al. Hyperhomocysteinemia, low folate and vitamin B12 concentrations, and methylene tetrahydrofolate reductase mutation in cerebral venous thrombosis. *Stroke* 2004;35:1790-4.
8. Stoltz E, Rahimi A, Gerriets T, Kraus J, Kaps M. Cerebral venous thrombosis: an all or nothing disease? Prognostic factors and long-term outcome. *Clin Neurol Neurosurg* 2005;107:99-107.
9. Vandenbrouke JP. Cerebral sinus thrombosis and oral contraceptives. *BMJ* 1998;317:483-4.
10. Meena ADK, Jayalaxmi SS, Murthy JM. Cortical sinovenous thrombosis following closed head injury. *Neurol India* 2000;48:195-6.
11. Agostoni E. Headache in cerebral venous thrombosis. *Neurol Sci* 2004;25:S206-10.
12. Terazzi E, Mittino D, Ruda R, et al.; Cerebral Venous Thrombosis Group. Cerebral venous thrombosis: a retrospective multicentre study of 48 patients. *Neurol Sci* 2005;25:3111-5.
13. Iurlaro S, Beghi E, Massetto N, et al. Does headache represent a clinical marker in early diagnosis of cerebral venous thrombosis? A prospective multicentric study. *Neurol Sci* 2004;25:S298-9.
14. Oppenheim C, Domigo V, Gauvrit JY, et al. Subarachnoid hemorrhage as the initial presentation of dural sinus thrombosis. *Am J Neuroradiol* 2005;26:614-7.
15. Grover M. Cerebral venous thrombosis as a cause of acute headache. *J Am Board Fam Pract* 2004;17:295-8.
16. Wasay M. Neuroimaging of cerebral venous thrombosis. *J Neuroimaging* 2005;15:118-28.
17. Stam J, de Brujin SFTM, DeVeber G. Anticoagulation for cerebral sinus thrombosis (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Oxford: Update Software.
18. Canhão P, Falcao F. Thrombolytics for cerebral sinus thrombosis. *Cerebrovasc Dis* 2003;15:159-66.
19. Liebetrau M, Mayer TE, Bruning R, Opherk C, Hamann GF. Intra-arterial thrombolysis of complete deep cerebral venous thrombosis. *Neurology* 2004;63:2444-5.
20. Rottger C, Madlener K, Heil M, et al. Is heparin the optimal management for cerebral venous thrombosis? Effect of abciximab, recombinant tissue plasminogen activator, and enoxaparin in experimentally induced superior sagittal sinus thrombosis. *Stroke* 2005;36:841-6.
21. Breteau G, Mounier-Vehier F, Godefroy O, et al. Cerebral venous thrombosis 3-year clinical outcome in 55 consecutive patients. *J Neurol* 2003;250:29-35.
22. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F, ISCVT investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004;35:664-70.
23. Buccino G, Scoditti U, Patteri I, Bertolini C, Mancia D. Neurological and cognitive long-term outcome in patients with cerebral venous sinus thrombosis. *Acta Neurol Scand* 2003;107:330-5.