Hiroyuki Nakase, M.D., Toshikazu Takeshima, M.D.,
Toshisuke Sakaki, M.D., Axel Heimann, D.V.M.,
and Oliver Kempski, M.D., Ph.D.

Superior Sagittal Sinus Thrombosis: A Clinical and Experimental Study

ABSTRACT—Sinus-vein thrombosis is increasingly recognized as a much more frequent neurological disorder than was anticipated before. We examined the pathophysiology of superior sagittal sinus thrombosis (SSST) from 19 patients and a rat SSST model. We treated 19 cases with SSST who were diagnosed by angiography. The symptoms of nine patients, who suffered multiple intracerebral hemorrhage, were abrupt. In another ten patients who recovered satisfactorily, the condition progressed slowly and they were treated with heparin and urokinase. Multivariate analysis demonstrated that female, sudden onset (<24 hours) and posterior 1/3 occlusion are related to bad outcome. Experimentally, SSST was induced by ligation and slow injection of kaolin-cephalin suspension into SSS in rats. Regional cerebral blood flow (rCBF) and tissue hemoglobin oxygen saturation (Hb Sao_2) using a "scanning" technique were measured at 48 locations, and fluorescence angiography was performed before and until 90 min after SSST induction. After 48 hours the animals were sacrificed for histological studies. Decrease of rCBF and tissue Hb SO_2 and brain damage were seen in group B (n = 10) with an extension of thrombosis from SSS into cortical veins. Brain injury was not observed in group A (n = 8) with SSS thrombus alone and sham-operated animals (n = 5). In conclusion, a brain with acute extension of thrombus from SSS into cortical veins becomes critical for cerebral blood supply and metabolism. CBF, tissue $HbSO_2$ and repeated angiography can be helpful monitors for the early detection of critical conditions after SSST. As to the therapy, restraint on the ongoing thrombus is essential to protect the brain with SSST, and we encourage the use of combination therapy of heparin and urokinase as early as possible in cases without intracerebral hemorrhage.

Diagnosis of cerebral sinus vein thrombosis (SVT) has always been difficult. It was frequently observed only at autopsy, thus raising the suspicion that SVT often is a lethal disorder. With the understanding of the importance of SVT and the advent of imaging technology, SVT is increasingly recognized as a much more frequent neurological disorder than was anticipated before. Recent experience indicates that SVT has a wide spectrum of clinical manifestations: namely the clinical symptoms and prognosis of SVT observed in patients and animal experiments are quite variable, ranging from no symptom at all to severe venous infarction.[1–4] Due to the elusive nature and diagnostical problems of this disease, the understanding of the underlying mechanism as well as the therapeutical concept remains controversial.

Superior sagittal sinus thrombosis (SSST) is the most common in SVT. Although there are various animal models for the pathological condition,[1–8] the rat

Skull Base Surgery, Volume 8, Number 4, 1998 Department of Neurosurgery, Nara Medical University, Nara, Japan (H.N., T.T., and T.S.) and Institute for Neurosurgical Pathophysiology, Johannes-Gutenberg University Mainz, Mainz, Germany (A.H. and O.K.) Reprint requests: Dr. Hiroyuki Nakase, Department of Neurosurgery, Nara Medical University, 840-Shijo-cho, Kashihara, Nara 634, Japan.

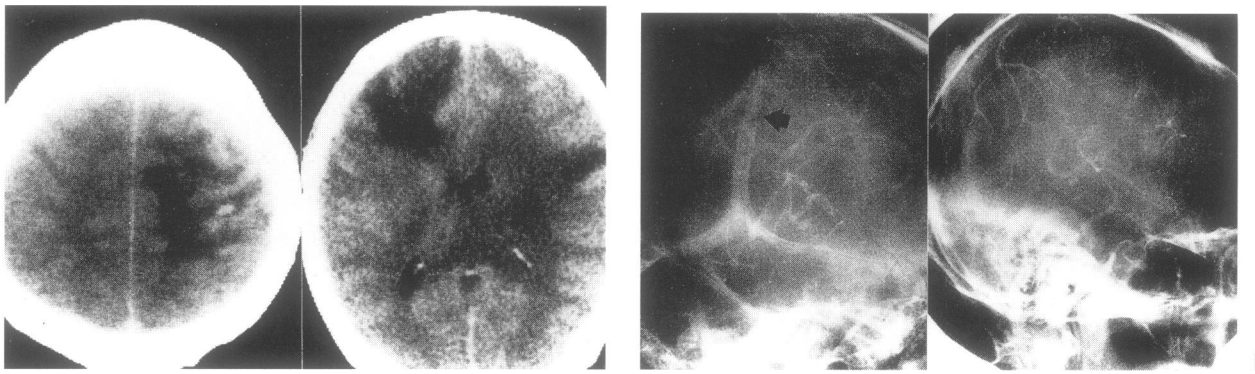

Figure 1. (**A**) Emergent CT revealed low density areas in the right frontocentral and left frontal regions. (**B**) Angiography revealed the occlusion of middle 1/3 in SSS.

model with a combination of SSS ligation and the injection of a thrombogenic material, kaolin-cephalin suspension (a reagent available for the partial thromboplastin time reaction), is currently the most established experimental model, which permits the observation of a true thrombotic process, not mechanical. Recent literature on experimental SSST well documented that (1) SSST causes brian damage when draining cortical veins are involved, not the SSS alone,[1,2,4–6] that (2) increase of cerebral blood volume (CBV) and cerebral edema by venous flow obstruction results in intracranial hypertension and decreases regional cerebral blood flow (rCBF),[2,4,6] and that (3) CBF monitoring could be useful for predicting brain damage subsequent to SVT and cortical vein occlusion.[4,7,8]

We examined the pathophysiology of SSST from a clinical and experimental point of view. To do so, we investigated the prognostic factors from 19 patients with SSST and the mechanism responsible for brain damage following SSST using the rat SSST model. In addition, we had hoped to determine helpful monitors for early detection of critical conditions after SSST.

CLINICAL STUDY

Over the last 7 years, we treated 19 cases with SSST who were diagnosed by computed tomography (CT) scan, magnetic resonance image (MRI), and angiography.

The patients ranged in age from fifteen to sixty-four years (mean 39.4 years old). There were nine male and ten female. The location included six anterior, five middle, eight posterior third of SSS. The onset was sudden in nine and gradual in ten cases. The symptoms were headache in 14, convulsion in 12, motor weakness in 16, coma in seven, and focal deficit in five cases, respectively. The etiology included oral contraceptives in two, pregnancy in one, head injury in one, and unknown in 14. Eleven patients had good prognosis, 3 fair, and 1 bad.

Our treatment regimen includes urokinase therapy (480,000 units/day for 7 days) and administration of heparin (initial intravenous administration of 2,000 units and 20,000 units/days for 2 days) for cases without cerebral hemorrhage. Moreover, treatment for cerebral edema was performed with steroid and hypertonic diuretics.

Illustrative Cases

A 28-year-old woman (Case 1) had a headache and fever, and was brought to our hospital due to generalized convulsion. In the hospital emergency room, the consulting neurosurgeon found the left hemiparesis. Emergent CT showed low density areas in the right frontocentral and left frontal regions (Fig. 1A), and angiography revealed the occlusion of middle 1/3 in SSS (Fig. 1B). Under the diagnosis of SSST, we treated the patients with heparin and urokinase. Also, steroid therapy was applied. The patient improved dramatically the next day. She had no deficit, and had since returned to her job.

A 53-year-old woman (Case 18) was brought to our hospital due to unconsciousness. She was in a coma stage, and had the right hemiparesis. CT showed diffuse brain edema and engorgement of cerebral veins (Fig. 2A), and angiography revealed the occlusion of all SSS (Fig. 2B). Barbiturate therapy was started under the diagnosis of severe SSST; however, the patient died 5 days after admission.

Multivariate Analysis

We examined the factors related to the outcome. Five clinical and radiological factors were analyzed: sex, age, onset, location, and symptoms. The Chi-square test was used to identify correlations between clinical factors and groups. Statistical significance was set at the

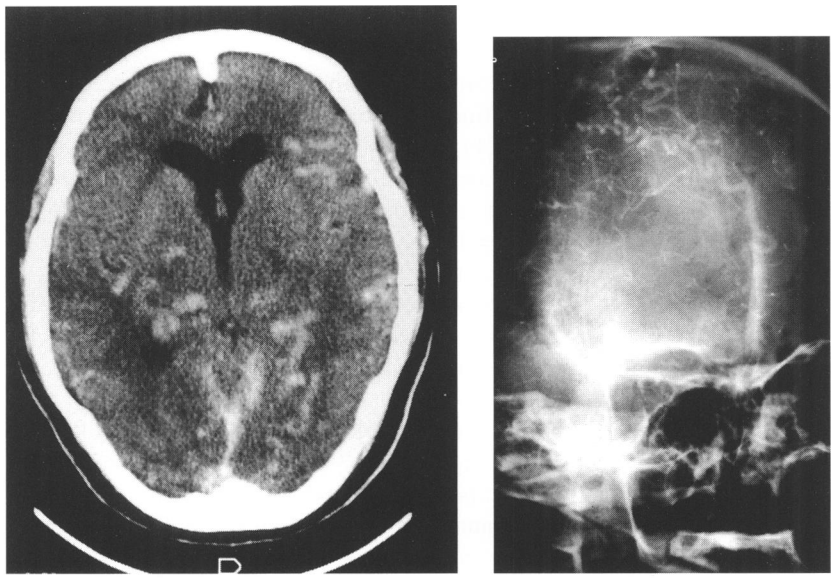

Figure 2. (**A**) Emergent CT showed diffuse brain edema and engorgement of cerebral veins. (**B**) Angiography revealed the occlusion of all SSS.

5% level (P <0.05). Multivariate analysis showed female, sudden onset (<24 hours) and posterior 1/3 occlusion were significantly correlated with bad outcome (Table 1).

EXPERIMENTAL STUDY[8]

Materials and Methods

In twenty-three male Wistar rats (b.w. 320 ± 20.6gm), anesthesia was done by intraperitoneal injection of chloral hydrate (36mg/100g b.w.). Spontaneous ventilation was maintained, and rectal temperature was controlled at 37°C. Polyethylene catheters were inserted into the tail artery and the right femoral vein under an operating microscope (OP-microscope; Zeiss, Wetzlar, Germany). The arterial line served for continuous registration of arterial blood pressure and gas (PaO_2, $PaCO_2$, and arterial pH). After a 2.0 cm midline skin incision, a cranial window (9 mm × 6 mm) was made. The dura was left intact, and the SSS and bilateral parasagittal cortex (the right side dominant) were exposed. Then, fluorescence angiography was was carried out before, 30 minutes after, and 90 minutes after induction of SVT.

Table 1. Factors Related to the Outcome

Factors	*Good–fair (n = 14)*	*Bad–dead (n = 5)*	*Significance (Fisher's exact test)*
Sex			
Male	9	0	*p = 0.033
Female	5	5	
Age (y)			
0–20	2	1	NS
21–60	11	3	
60–	1	1	
Onset			
Sudden (<24 h)	4	5	*p = 0.023
Gradual	10	0	
Location			
Anterior 1/3	6	0	*p = 0.018
Middle 1/3	5	0	
Posterior 1/3	3	5	
Symptoms			
Headache	13	1	NS
Convulsion	9	3	
Motor weakness	13	3	
Coma	3	4	
Focal deficit	5	0	

NS, not significant.

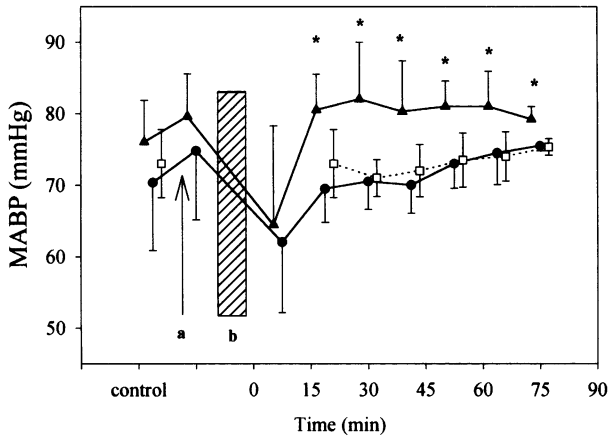

Figure 3. Sequential changes of mean arterial blood pressure (MABP), expressed in mmHg (mean ± SD) in all groups.[8] MABP in group A (▲) (without brain damage) is higher than that in both groups B (with brain damage) and sham-operated animals (Mann-Whitney rank sum test, *:P<0.05). ▲: Group A, ●: Group B, □: sham-operated group.

Local cerebral blood flow (LCBF) was measured using a TSI laser flow blood perfusion monitors (model BPM 403a; TSI, St. Paul, MN, U.S.A.). The tissue hemoglobin oxygen saturation (Hb SO_2) (%) was measured using a monitor (EMPHO II SSK-BB, BGT (Bodenseewerk Geratetechnik GmbH), Germany). LCBF and Hb Sao_2 were measured at 48 (8 × 6) identical locations in a scanning procedure by means of a computer-controlled micromanipulator every 15 minutes for 90 minutes.

The SSS was ligated rostrally and then caudally close to the confluens sinuum using 9-0 proline. A kaolin–cephalin suspension (100 μL, a partial thromboplastin time reagent; Boehringer Mannheim, Germany) was injected into the sinus through a microsyringe over 5 min in fractionated 10μL portions at 30-second intervals.

After the skin wounds were closed, the rats were returned to individual cages and allowed free access to water and food. After 48 hours they were sacrificed for histological studies. In addition, five rats served as sham-operated controls.

Data are expressed as mean values ± SD of the median LCBF and tissue Hb Sao_2. Analysis of variance (ANOVA) for multiple comparison or Mann-Whitney rank sum test was used for comparison of the data among groups. Differences of sequential data were evaluated by ANOVA (Dunnet's test) for repeated measures as well. Statistical significance was accepted at values of $p < 0.05$.

Results

According to the pattern of the fluorescence angiographic findings, animals could be divided into three groups: (1) group A, in which the SSS was thrombosed without cortical vein thrombosis (n = 8); (2) group B, in which the thrombus extends to cortical veins from the SSS. (n = 10); and (3) group C, which is a sham-operated group (n = 5).

Physiological variables showed no significant changes of blood gases (eg, Pao_2, $Paco_2$, and pH) between before and after SSST induction and between groups.

Mean arterial blood pressure in group A kept a statistically significant ~15% higher level during the following experiment than that in groups B and C (from 15 to 90 minutes, A vs B and C, $p < 0.05$, Fig. 3).

The calculation of median rCBF values from the 48 locations in each animal demonstrated no change in group A and sham-operated animals and decrease in group B after the injection of kaolin–cephalin suspension (Mann-Whitney rank sum test, $p < 0.01$) compared with that in group A (Table 2).

The calculation of median tissue Hb Sao_2 values from the 48 locations in each animal revealed no change of tissue Hb Sao_2 in group A and sham-operated animal and significantly decrease just after the ligation of SSS and from 45 minutes after SSST induction until the end of experiment compared with group A ($p < 0.05$) as evaluated by Mann-Whitney rank sum test (Table 3).

Histologically the sham-operated rats showed no histological change at all. The rats from group A revealed no or mild histological change such as slight brain edema. Bilateral parasagittal infarction was characteristic in group B. Petechial hemorrhage around the dilated capillaries was also observed in some animals, but massive hemorrhage and extravasation of Evans blue were not apparent.

DISCUSSION

SVT is a serious, potentially lethal disorder that may present a confusing and nonspecific clinical picture. The prognosis of cerebral venous thrombosis accompanied by severe hemorrhagic infarction in patients is still rather poor, and its suitable treatment and prevention are controversial.[9,10] Recently Einhäupl et al.[9] recommended high-dose heparin treatment as the therapy

Table 2. Sequential Changes of Regional Cerebral Blood Flow in all Groups[8]

Group	*Control*	*Litigation*	*Injection*	*15 min*	*45 min*	*60 min*	*90 min*
A	47.0 ± 11.2	50.8 ± 12.1	44.8 ± 14.8	36.4 ± 12.3	49.4 ± 13.2	50.1 ± 14.2	51.9 ± 9.0
B	44.2 ± 13.1	41.1 ± 9.5	23.2 ± 12.8**	21.5 ± 7.5**	22.9 ± 7.9**	25.0 ± 8.9**	29.9 ± 11.7
Sham	48.6 ± 19.2	52.2 ± 19.2	53.3 ± 21.5	49.1 ± 12.7	49.7 ± 13.0	52.0 ± 10.6	51.6 ± 8.8

Values are means ± SD.** $p < 0.01$.

Table 3. Sequential Changes of Tissue Hemoglobin Oxygen Saturation in all Groups[8]

Group	Control	Litigation	Injection	15 min	45 min	60 min	90 min
A	56.2 ± 9.1	55.8 ± 7.8	50.6 ± 11.0	55.5 ± 9.9	51.3 ± 5.3	51.8 ± 7.0	52.5 ± 5.1
B	51.7 ± 7.0	45.2 ± 9.5*	46.2 ± 11.9	45.2 ± 14.0	45.2 ± 5.2*	40.3 ± 10.7*	35.9 ± 11.2*
Sham	53.4 ± 8.2	57.9 ± 1.4	55.4 ± 9.6	55.4 ± 9.6	54.7 ± 13.0	56.5 ± 12.0	57.1 ± 12.3

Values are means ± SD.* $p < 0.05$.

of first choice for SVT, even in patients with intracranial bleedings, based on their experience of 115 treated patients with SVT for 15 years. Our clinical study suggested that the therapeutic regimen including heparin and urokinase was effective for patients with SSST when diagnosed early. Therefore, we can recommend this combination therapy of heparin and urokinase in cases without intracerebral hemorrhage. However, a delayed start of treatment and the abrupt development of the disease still lead to a poor outcome.

Thus, we examined the pathological process of critical SSST using the experimental model.[8] We found that only the cases with the extension of thrombus from the SSS to the cortical veins after induction of SVT, which is confirmed by repeated fluorescence angiographies, had brain damage, and the trigger of these pathological processes was surely the extension of the thrombus. In these cases, tissue Hb Sao_2 as well as rCBF decreased after the induction of SVT. Moreover, the reduction of tissue Hb Sao_2 preceded the flow decrease due to the detection of desaturated blood from collateral pathway. Our data suggested the early influence on oxygen transport by SSST, resulting in the ischemia rapidly or almost simultaneously. With time after SSST, reduction of CBF together with tissue Hb Sao_2 developed into below the ischemic threshold. Therefore, we concluded that CBF, tissue Hb Sao_2, and repeated angiography can be helpful monitors for the early detection of critical conditions after SSST, and restraint on the ongoing thrombus is essential to protect the brain with SSST. Taken together, blood pressure of animals without brain damage was approximately 15% higher than that of sham-operated and animals with brain damage. This phenomenon attributes to maintaining cerebral perfusion pressure (CPP). The brain just at a critical level is considered to be sensitive to small change of CPP. This information must be important for the patient care with SSST. Therefore, CPP should be monitored carefully, and any reduction should be treated in patients. However, the mechanism of this phenomenon still remains uncertain, and must to evaluate it for future treatment alternatives. Finally, the thrombus in this experimental model extends progressively, not occluded at once, to the cortical veins, which is similar to the human SSST. Therefore, this model is suitable for the study of the treatment for SVT.

As to the radiological diagnosis for SVT, some authors suggested that MRI can replace angiography.[11,12] With the advancement of the diagnostic tool, SVT could be diagnosed earlier than before. On the other side, other author mentioned the difficulties of MRI-based diagnosis of dural sinus thrombosis. The use of MRI and magnetic resonance angiography in the diagnosis of SVT demands knowledge of the different stages and pitfalls, and intraarterial angiography is still required for certain diagnoses.[13] The patients should be evaluated by angiography as early as possible under the suspicion of SVT.

Recent studies on activated protein C resistance (APC-R) associated with venous thromboembolism rekindled the interest in cerebral venous thrombosis. APC-R is a common inhererited risk factor for venous thrombosis, which is due to a mutation in coagulation factor V (factor V Leiden mutation). According to these reports, this point mutation was found in 20% of patients with cerebral venous thrombosis compared with 2.7% control subjects.[14–17]

In conclusion, a brain with acute extension of thrombus from SSS to cortical veins becomes critical after SSST. The monitors of CBF, tissue Hb Sao_2, and repeated angiography can detect early change after SSST. Also, the current study showed that the maintenance of CPP is quite important in this pathological condition. Regarding the therapy, the combination therapy of heparin and urokinase is effective in cases without intracerebral hemorrhage.

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REFERENCES

1. Frerichs KU, Deckert M, Kempski O, Schurer L, Einhaupl K, Baethmann A. Cerebral sinus and venous thrombosis in rats induces long-term deficits in brain function and morphology - evidence for a cytotoxic genesis. J Cereb Blood Flow Metab 1994;14:289–300
2. Fries G, Wallenfang T, Hennen J, Velthaus M, Heimann A, Schild H, Perneczky A, Kempski O. Occlusion of the pig superior sagittal sinus, bridging and cortical veins; multistep evolution of sinus-vein thrombosis. J Neurosurg 1992;77: 127–133
3. Takeshima T, Miyamoto K, Okumura Y, Tominaga M, Tsujimoto S, Sakaki T. Experimental study of local cerebral blood flow

in cerebral venous occlusion, in Tomita M, Mchedlishvili G, Rosenblum, Heiss W-D, Fukuuchi Y: Microcirculatory Stasis in the Brain, Amsterdam, Elsevier Science, pp 441–444, 1993
4. Ungersböck K, Heimann A, Kempski O. Cerebral blood flow alterations in a rat model of cerebral sinus thrombosis. Stroke 1993;24:563–570
5. Cervos-Navarro J, Kannuki S, Matsumoto K. Neuropathological changes following occlusion of the superior sagital sinus and cerebral veins in the cat. Neuropathol Appl Neurobiol 1994; 29:122–129
6. Gotoh M, Ohmoto T, Kuyama H. Experimental study of venous circulatory disturbance by dural sinus occlusion. Acta Neurochir (Wien) 1993;124:120–126
7. Nakase H, Kakizaki T, Miyamoto K, Hiramatsu K, Sakaki T. Use of local cerebral blood flow monitoring to predict the brain damage after disturbance to the venous circulation: Cortical vein occlusion model by photochemical dye. Neurosurgery 1995;37:280–286
8. Nakase H, Heimann A, Kempski O. Alterations of regional cerebral blood flow and tissue oxygen saturation in a rat sinus-vein thrombosis model. Stroke 1996;27:720–728
9. Einhäupl KM, Villringer A, Meister W, Mehrain S, Garner C, Pellkofer M, Haberl R, Pfister HW, Schmiedek P: Heparin treatment in sinus venous thrombosis. Lancet 1991;338:597–600
10. Sakaki T, Tsunoda S, Morimoto T, Kawata K, Tsujimoto S, Utsumi S. Treatment of aseptic superior sagittal sinus thrombosis. Jpn J Phlebol 1(1):113–124, 1990 (in Japanese)
11. Isensee Ch, Reul J, Thron A. Thrombose des Sinus transversus als Ursache temporaler Blutungen. Stellenwert von MRT und Angiographie. Akt Neurol 1992;19:78–81
12. Padayachee TS, Bingham JB, Graves MJ, Colchester AC, Cox TC. Dural sinus thrombosis; diagnosis and follow-up by magnetic resonance angiography and imaging. Neuroradiology 1991;33:165–167
13. Isensee Ch, Reul J, Thron A. Magnetic resonance imaging of thrombosed dural sinuses. Stroke 1994;25:29–34
14. Brey RL, Coull BM. Cerebral venous thrombosis - role of activated protein C resistance and factor V gene mutation. Stroke 1996;27:1719–1720
15. Zuber M, Toulon PT, Marnet L, Mas JL. Factor V leiden mutation in cerebral venous thrombosis. Stroke 1996;27:1721–1723
16. Deschiens MA, Conard J, Horellou MH, Ameri A, Preter M, Chedru F, Samama MM, Bousser MG. Coagulation studies, factor V leiden, a nd anticardiolipin antibodies in 40 cases of cerebral venous thrombosis. Stroke 1996;27:1724–1730
17. Dulli DA, Luzzio CC, Williams EC, Schutta HS: Cerebral venous thrombosis and activated protein C resistance. Stroke 1996;27:1731–1733

REVIEWERS' COMMENTS

This paper by Nakase and colleagues is a very interesting evaluation of 19 patients with superior sagittal sinus thrombosis (SSST), showing even in this relatively small group the importance of gender, rapid onset and posterior location of thrombus, but surprisingly not finding that age and clinical presentation were not important prognostic factors. The authors extended these interesting observations by developing an experimental model of gradual thrombosis of the SSST in rats. In this model, occlusion is gradual over several days, and in some of the animals goes on to involve cortical veins as well as the SSST. In fact, the animals remained relatively asymptomatic unless the cortical veins were involved. Why some animals developed cortical vein involvement and others did not is not clear. Whether or not activated protein kinase plays a role in the rat models as it may do in human disease is not specifically addressed by the authors.

Lawrence H. Pitts, M.D.

The authors provide an interesting study on the treatment of superior sagittal sinus thrombosis. They made a clinical study with 19 cases and created an experimental model. They conclude that the use of heparin and urokinase in the treatment of sagittal sinus thrombosis is strongly recommended in the management of these patients. The treatment of sagittal sinus thrombosis is controversial and until now there are no large series that support the therapy with heparin and urokinase. We think that a multicentric study should be necessary to demonstrate the benefits of such a therapy. In the mean time the medical treatment will mostly be limited to the use of corticosteroids, mannitol and anticonvulsivants.

Mauro Loyho, M.D.
Tenoch Herrada, M.D.