Cerebral Venous Thrombosis
A Descriptive Multicenter Study of Patients in Pakistan and Middle East
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Background and Purpose — The natural history, causative factors, and outcomes of patients with cerebral venous thrombosis from Asia and Middle East have not been well described. This descriptive multicenter study describes the results for cerebral venous thrombosis patients in South Asia and the Middle East.

Methods — The retrospective and prospective data of patients with radiologically confirmed cerebral venous thrombosis were collected from 4 centers located in Pakistan and United Arab Emirates. The demographic, clinical, radiological, and outcome data were recorded and analyzed. Primary outcome was death or dependency (modified Rankin score >2) at the time of hospital discharge.

Results — This study included 109 patients with cerebral venous thrombosis; the presenting features most commonly being observed were headache (81%), focal motor deficits (45%), seizures (39%), and mental status changes (37%). Important predisposing factors included systemic and central nervous system infection (18%), postpartum state (17%), hyperhomocystinemia (9%), genetic thrombophilia (5%), and oral contraceptive pill use (3%). Ninety-six (67%) patients received therapeutic anticoagulation. Seven patients died and 43 had poor outcome at discharge. Focal motor deficits (OR, 2.93; 95% CI, 1.2–7.5; P = 0.018) and hemorrhagic infarctions (OR, 2.81; 95% CI, 1.04–7.85; P = 0.041) were independent predictors of unfavorable outcome at discharge. Hemorrhagic infarction was the most significant factor of long-term unfavorable outcome (OR, 5.87; 95% CI, 1.49–23.02; P = 0.011).

Conclusions — Infections and postpartum state were the most common predisposing factors for cerebral venous thrombosis in this cohort. Most patients (67%) were treated with anticoagulation therapy. Almost 50% of patients were dead or disabled at discharge. (Stroke. 2008;39:2707-2711.)

Key Word: cerebral venous thrombosis

Cerebral venous thrombosis (CVT) is an uncommon cause of stroke with extremely diverse clinical features, predisposing factors, brain imaging findings, and outcome. Its prevalence rate is 5 per 1 million and often affects younger age groups. It accounts for 0.5% of all strokes. This disease may be more common in the South Asian region.

Banerjee et al. in their autopsy series during late 1980s, found that CVT accounts for 10% of all strokes. Recently, Panagariya et al reported that CVT accounts for 17% (64/375) of all strokes. They also noted that CVT accounts for half of all strokes in young people. However, they did not mention the cut-off age for young stroke. Another interesting finding they noted was that 38% of all women who experienced stroke had venous stroke.4 There may be substantial differences in predisposing factors, presentations, therapeutic options, and outcome between developed and developing countries. Though comparison of hospital-based studies may be difficult, these provide important and essential information, especially for relatively uncommon diseases. Despite the fact that community- or population-based studies provide more accurate data regarding disease burden, risk factor prevalence, and long-term outcomes, the hospital-based studies provide useful and reliable information about characteristics of the disease, because these patients are well-investigated and more closely followed-up, especially during acute course of illness.

International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) reported obstetric CVT in only 20% of cases as compared to reports from Mexico and India, which report a much higher frequency. In addition, there is variability among different developing countries. Daif et al from Saudi Arabia report 25% of the patients in their series as having Bechet disease and only 1 out of 40 patients being in postpartum period. The published literature related to CVT from Pakistan is limited to only a few case reports or small case series. Data for this study were collected from 4

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centers, located in 2 different countries of Asia. Our aim was to characterize clinical presentations, risk factors, clinical course, and outcome of the disease in 2 countries that, though geographically separated, share a common feature of having a predominantly South Asian population.

Materials and Methods
Patients (age 10 years or older) admitted consecutively to 4 tertiary care centers (The Aga Khan University Hospital and Liaquat National Hospital, Karachi, Pakistan; Shifa International Hospital, Islamabad, Pakistan; and Rashid Hospital, Dubai, United Arab Emirates) with diagnosis of CVT were identified through ICD-9 coding system of the hospital medical records over a period of ~16 years (1991–2007) and had their medical records reviewed. Data from 1990 to 1996 were reviewed retrospectively, whereas data after 1996 were collected prospectively.

All patients underwent brain imaging (CT scan or MRI) and were reviewed by trained neuroradiologists. Diagnosis was based on established radiological criteria.14–20 Demographic, clinical, laboratory, and radiological data were recorded. Functional status was recorded on modified Rankin scale21 at admission, discharge, and latest follow-up, and was dichotomized as good (score of 0–2) or poor (score >2). Outcome was dichotomized based on modified Rankin scale with score of 0 to 2 considered as favorable; a score >2 was unfavorable. The outcome was recorded at discharge from hospital and at last available follow-up. In addition, in-hospital mortality was recorded separately. Statistical analysis used descriptive, univariate (χ² and t test), and multivariate methods. Factors with P<0.2 on univariate analysis, influencing the outcome, were incorporated in a multiple logistic regression model (purposeful selection method) to detect independent predictors of outcome. Data were analyzed on SPSS version 14.0 (SPSS Inc).

Results
There were 109 patients enrolled from 4 centers (Aga Khan University Hospital, Karachi, Pakistan: 59; Liaquat National Hospital, Karachi, Pakistan: 20; Shifa International Hospital, Islamabad, Pakistan: 11; and Rashid Hospital, Dubai, United Arab Emirates: 19). Median age was 35 (mean, 35.76±13.15; range, 10–76) years, with 91 (83%) being younger than age 46 years. There were 58 (53%) females and 51 (47%) males; the females were 5 years younger than the males (mean age of women, 33.2±10.44; mean age of men, 38.66±15.27 years). The most common presenting features were headache, followed by focal motor deficits, seizures, and mental status changes (Table 1). All but 7 patients were independent before onset of symptoms of the index CVT, but only a 25% of patients were independent at the time of admission (modified Rankin score <3). The reason why large numbers of patients were dependent at the time of admission is most likely attributable to the tertiary care nature of these hospitals, which tend to have sicker patients.

Median duration of presenting illness was 7 (1–200) days. Median diagnostic delay from onset of illness was 10 (0–200) days, and that after hospital admission was 1 (0–15) day.

Eighteen of 58 (31%) females were in postpartum period, and 12 of these 18 (66%) presented within 2 weeks of their delivery. Three of these 18 women underwent Cesarean section (postoperative). Seven (12%) women were using oral contraceptive pills (data were available for only 46 women). Twenty (18%) had an infectious process (tuberculous meningitis, 4; rhino-orbital fungal infection, 3; bacterial meningitis, 2; mastoiditis, 2; malignant otitis externa, 1; nasal pustule, 1; periorbital cellulites, 1; gastroenteritis with dehydration, 2; respiratory tract infection, 1; and urinary tract infection, 1). Six patients had history of recent surgery, including the 3 women who underwent Cesarean section. Three patients had underlying acute lymphocytic leukemia (2 of these received L-asparaginase), 3 had ulcerative colitis, and 1 each had non-Hodgkin lymphoma, myelodysplastic syndrome, glomus jugulare tumor, and Bechet disease. Thirteen patients had hypercoagulopathy, and 1 had systemic lupus erythromatosis (Table 2).

All patients underwent brain imaging. The most common modality used was MRI of the brain (71%), followed by MRV brain (66%), CT head (42%), 4-vessel cerebral digital subtraction angiogram (5%), and CT angiography of the brain.

### Table 1. Clinical and Imaging Features

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>88 (81)</td>
</tr>
<tr>
<td>Focal motor deficits</td>
<td>49 (45)</td>
</tr>
<tr>
<td>Seizures</td>
<td>42 (39)*</td>
</tr>
<tr>
<td>Mental status changes</td>
<td>40 (37)†</td>
</tr>
<tr>
<td>Papilledema</td>
<td>38 (35)</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Fever</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>15 (14)</td>
</tr>
</tbody>
</table>

### Table 2. Autoimmune and Hypercoagulopathy Work-Up

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Patients†</th>
<th>Frequency of Positive Results (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum homocysteine</td>
<td>35</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Protein C</td>
<td>32</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Protein S</td>
<td>36</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Antithrombin-III</td>
<td>27</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>23</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>39</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Antidouble-stranded deoxyribonucleic acid antibodies</td>
<td>31</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>34</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Positive results mean either decreased protein C, protein S, antithrombin-III, or elevated serum homocysteine level or elevated autoantibodies (antinuclear antibodies, antidouble-stranded deoxyribonucleic acid antibodies, lupus anticoagulant, and anticardiolipin antibodies).
†Tests performed in these many patients.

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(2%). Seventy-two (66%) had infarctions and out of these 37 (34%) had hemorrhagic. Three patients had focal subarachnoid hemorrhage. In 54 (50%) patients, only 1 sinus was involved. Superior sagittal sinus was most commonly involved sinus, followed by transverse and sigmoid sinuses (Table 1).

Seventy-three of 109 (67%) received acute anticoagulation, and their average median activated partial thromboplastin time was 54.3 (mean, 55.14±11.28) seconds. In addition, 10 (9%) received low-dose subcutaneous heparin for deep venous thrombosis prophylaxis and 10 (9%) received antiplatelet agents. None of the patients underwent thrombolyses. Antibiotics were administered to 28 (26%) of the patients.

Seven of 13 patients (54%) with either brain or ear, nose, throat region infections received anticoagulation. None of these patients died during hospital stay. Two patients with the infections died during follow-up, and 1 of them received anticoagulants. However, this death was not related to anticoagulation; the patient died of renal failure.

Sixteen of 18 (89%) of patients with postpartum CVT underwent anticoagulation. Nine of the patients who underwent anticoagulation had significant functional disability at discharge. Follow-up was available for 14 patients, and 12 were independent in activities of daily living; 2 remained significantly disabled. Two untreated postpartum CVT patients were independent at follow-up. No patient with postpartum CVT died.

Thirty-seven patients had either acquired or hereditary thrombophilia, and 27 (73%) of these received anticoagulation. Sixteen (59%) of the patients who underwent anticoagulation had poor outcome at discharge as compared to 4 of 10 (40%) who did not receive anticoagulation; however, this difference was not statistically significant (P=0.46). Follow-up was available for 21 patients who underwent anticoagulation. Sixteen of these (76%) were independent compared to 8 of 9 (89%) untreated patients (P=0.63). Two of patients who underwent anticoagulation died during follow-up, but their deaths were not related to anticoagulation. Patients with thrombophilia had more extensive sinus involvement as compared with patients without thrombophilia, i.e., 25 of 37 (68%) patients with thrombophilia had involvement of >1 sinus as compared with 30 of 72 (42%) patients without thrombophilia (P=0.01).

Ten patients had hyperhomocystinemia and 6 (60%) received anticoagulation. One (17%) had poor outcome at discharge as compared with 3 of 4 (75%) who did not receive anticoagulation (P=0.19). All 5 treated patients for whom follow-up was available were independent at their last visit, whereas 3 of 4 (75%) untreated patients were independent. None of the patients with hyperhomocystinemia died.

Twenty-three (21%) patients’ conditions deteriorated during hospital stay, and 4 of these underwent neurosurgical intervention (frontal lobectomy in 2, hematoma evacuation in 1, and ventriculoperitoneal shunt in 1). Thirteen patients received steroids, 7 received mannitol, and 3 received acetazolamide. Median hospital stay was 9 (1–59) days.

Fifty patients were either dead (n=7; 4 males and 3 females) or disabled (modified Rankin score ≥2; n=43) at the time of discharge. None of patients with postpartum CVT died. One of 4 patients with malignancy died during hospital stay. Univariate analysis revealed that coma and focal motor deficit at presentation, infarctions on imaging, and hemorrhagic conversion of infarction were associated with unfavorable outcome. There was also a trend that involvement of deep cerebral venous system and fever at presentation were associated with unfavorable outcome. However, on multivariate analysis, only focal motor deficits (OR, 2.93; 95% CI, 1.2–7.5; P=0.018) and hemorrhagic infarctions (OR, 2.81; 95% CI, 1.04–7.85; P=0.041) were found to be independent predictors of unfavorable outcome. There was also a trend toward unfavorable outcome in patients with deep CVT (OR, 8.32; 95% CI, 0.9–76.38; P=0.061) and coma (OR, 6.93; 95% CI, 0.76–62.76; P=0.085).

Seven (6%) patients died during hospital stay. Coma was found to be independent predictor of in-hospital mortality (OR, 12.9; 95% CI, 2.05–80.83; P=0.006). There was trend that older age (age older than 45) was associated with in-hospital mortality (OR, 4.5; 95% CI, 0.76–26.34; P=0.095).

A median follow-up of 6 months (3 days to 5 years) was available in 72 (66%) patients. Sixty-one of the 72 patients (85%) were independent at their latest follow-up. Three (4%) died and 8 (11%) remain dependent, with modified Rankin score of ≥3. Coma at admission, functional status at discharge from hospital, and hemorrhagic infarctions were found to be significant factors associated with long-term outcome on univariate analysis; however, only hemorrhagic infarction turned out to be a significant factor of long-term unfavorable outcome on multivariate analysis (OR, 5.87; 95% CI, 1.49–23.02; P=0.011).

Discussion
Clinical presentation of CVT is extremely variable, ranging from isolated headache to focal deficits to encephalopathy to psychiatric manifestations to coma.2–22 Clinical presentation of our cohort is almost identical to what has been reported from the west, with exception of mental status changes and coma, which were more common in our cohort.3 Thirty-seven percent of our patients had mental status changes including drowsiness, confusion, and agitation, as compared to 22% reported in ISCVT.9 The ISCVT reports ≈14% of their patients having either coma or stupor, but separate figures for each were not mentioned. In our cohort, we noted that 13% patients were comatose at presentation. The reason for this difference is unclear, but a delayed presentation may be a factor. We noted that ≈25% of patients were independent at the time of admission. These patients were independent because of milder disease, because only 2 had subtle focal motor deficits and 1 had seizures. Three of these had small hemorrhagic infarctions. The reason why large numbers of patients were dependent at the time of admission is most likely related to the tertiary care nature of these hospitals, which tend to get sicker patients. We noted a median duration from symptom onset to hospital presentation as 7 days, as compared to 4 days in ISCVT study.5

Douglas et al23,24 reported that frequency of peripartum intracranial venous thrombosis is 8.9 to 11.6 cases per 100 000 deliveries. In our cohort 31% of the females were in
the postpartum state as opposed to <15% reported from the west.\textsuperscript{5,25} Possible explanations for this difference include home deliveries in unhygienic environments and certain rituals, ie, water deprivation during immediate postpartum period. In addition, because birth rates in our countries are higher than in the west, we might see more postpartum women.

Oral contraceptives have long been attributed to development of CVT and have been reported in 54% to 71% of CVT patients.\textsuperscript{5,25} In our study only 14% of women were using oral contraceptives. This may simply reflect lack of use of oral contraceptives in our region of the world.

Another small but significant difference was central nervous system infections, which were noted in 5% of our patients, as compared to 2% in ISCVT.\textsuperscript{5} However, overall proportions of infections, including that of the ear/nose/throat region and face, were similar to that reported in ISCVT.

Thrombophilia (genetic) is an important cause of CVT and has been reported in 15% to 22% of patients with CVT.\textsuperscript{5,25} We noted genetic thrombophilia in only 5% of our patients. This figure is not only lower than that reported from the west but also lower than that reported by Asian countries like Saudi Arabia. Daif et al.\textsuperscript{8} from Saudi Arabia, reported genetic thrombophilia in 5 of 40 (12.5%) patients.

Hyperhomocysteinemia is an important cause of hypercoagulopathy, which increases the risk of CVT by 4-fold.\textsuperscript{26} Plasma homocysteine was elevated in 10 (9%) of the total patients, which is 2-times higher than that reported in ISCVT.\textsuperscript{5} However, the test was performed in only 35 (32%) of the patients in our study. The reason for this difference is unclear. However, the hyperhomocysteinemia may be more prevalent in our countries, and this warrants an epidemiological survey to confirm or refute this notion.

Only 67% of our patients received anticoagulation. This is much lower than that reported in ISCVT, which reported 85% as having received anticoagulation. This lower rate may reflect physicians’ awareness and reluctance. We noted a much higher death or dependency rate at discharge as compared to that reported recently from the west, ie, 51% vs 19%. This is probably a reflection of severe disease at presentation. The predictors of unfavorable outcome were hemorrhagic infarctions and focal motor deficits. There was also a trend that coma at presentation and involvement of deep cerebral venous system was associated with poor outcome. Similar trends have been reported in the literature.\textsuperscript{5,27}

We noted a death rate of 8% at discharge, which is within the range reported in literature, ie, 4.3% to 15%.\textsuperscript{5,26–28} We found coma to be an independent predictor of death at discharge, and there was also trend that older patients (older than 45 years) were more likely to die during the hospital stay.

Follow-up was available for 72 patients. Sixty-one (85%) had no disability on follow-up. Proportion of complete or near-complete recovery is similar to that reported earlier.\textsuperscript{5,27,28}

Our study is limited by its partly retrospective nature and lack of uniform evaluation in terms of work-up for hypercoagulopathy and autoimmune disorders. This is, however, the limitation of an observational study with different investigational styles of the local neurologists.

To our knowledge, this is the largest published series of CVT from our countries. We have noted some significant differences in risk factor profile for this disease from that of the west, ie, postpartum state, hyperhomocysteinemia, and central nervous system infections were more common in our population. Oral contraceptive use is not a major risk factor in our settings. For unclear reasons, use of anticoagulation is lower as compared to that in the west. This could be partly because of infections related to CVT in patients in our series. The overall outcome of those patients was poorer than any reported series from western countries. This could be attributable to selection bias, because these cases are reported from tertiary care centers. We suggest suspecting this disease in every postpartum woman with neurological symptoms, and we recommend evaluation for hyperhomocysteinemia in cases of CVT. We also recommend a careful search for central nervous system, ear/nose/throat, face, and sinus infections in the setting of CVT. In addition, identifying patients at high risk for unfavorable outcomes may provide opportunity for development of novel therapeutic paradigms including thrombolysis (systemic versus endovascular) and early neurosurgical interventions. Because there are important clinical, etiologic, and therapeutic differences in Asian countries as compared to countries in the west, there is a dire need for well-conducted, large, multicenter, multinational, cohort studies among Asian countries. Large, multicenter, online registries are feasible because of advances in information technology and international collaboration. These may be helpful in identifying regional differences in CVT, as well as for enrolling patients for future randomized trials.\textsuperscript{29}

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Disclosures

None.

References

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