

Clinical Aspects of Cerebral Venous Thrombosis: Experiences in Two Institutions

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Objective : Cerebral venous thrombosis (CVT) is a rare condition for which few clinical reviews have been conducted in Korea. Our aim was to investigate, risk factors, clinical presentations/courses, and outcomes of 22 patients treated for CVT at two centers.

Materials and Methods : A retrospective analysis was conducted, selecting 22 patients diagnosed with and treated for CVT at two patient care centers over a 10-year period (January 1, 2004 to August 31, 2015). Patient data, pathogenetic concerns (laboratory findings), risk factors, locations, symptoms, treatments, and clinical outcomes were reviewed.

Results : Mean patient age at diagnosis was 54.41 ± 16.19 . Patients most often presented with headache (40%), followed by seizure (27%) and altered mental status (18%). Focal motor deficits (5%), visual symptoms (5%), and dysarthria (5%) were less common. Important predisposing factors in CVT included prothrombotic conditions (35%), infections (14%), hyperthyroidism (18%), trauma (14%), and malignancy (4%). By location, 9 patients (40%) experienced thrombosis of superior sagittal sinus predominantly, with involvement of transverse sinus in 20 (90%), sigmoid sinus in 12 (40%), and the deep venous system in 5 (23%). Treatment generally consisted of anticoagulants (63%) or antiplatelet (23%) drugs, but surgical decompression was considered if warranted (14%). Medical therapy in CVT yields good functional outcomes.

Conclusion : Mean age of patients with CVT in our study exceeded that reported in Europe or in America and had difference in risk factors. Functional outcomes are good with use of antithrombotic medication, whether or not hemorrhagic infarction is evident.

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INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare condition that accounts for 0.5-1% of all strokes and usually affects young to middle-aged adults.¹⁾⁴⁾⁶⁾⁹⁾¹⁴⁾²⁸⁾³⁰⁾³³⁾

Findings at presentation are variable but range from simple headache to severe neurologic dysfunction, depending on degree of intracranial pressure increases, resultant venous infarction or hemorrhage, and locations affected.⁶⁾⁹⁾²⁸⁾³⁰⁾ Symptoms may reflect cerebral

sinus or cortical vein thrombosis.

Numerous risk factors for CVT have been cited in the literature. Prothrombotic states in inherited diseases, such as deficiency of antithrombin III or proteins C and S, have been implicated; and a predisposition may develop as a consequence of pregnancy (or puerperium), oral contraceptive use, cancer, or infection. However, the hierarchy of risk factors in CVT varies worldwide.³⁾⁵⁾¹³⁾¹⁶⁾²¹⁾²⁴⁾

The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) lists inherited prothrombotic conditions (34%) as leading causes of CVT¹⁴⁾, whereas in Pakistan and in the Middle East, infections (5%) and postpartum states (17%), respectively are most common.¹⁹⁾ Current guidelines advise either local or

systemic thrombolysis in patients who deteriorate clinically, despite adequate anticoagulation.¹³⁻¹⁵⁾ This is done on a case-by-case basis, with close consultation between neurologists and intensive care providers. However, the optimal treatment is still unclear.

Although research in CVT has been active, assimilating data on clinical characteristics and outcomes, such pursuits seldom pertain to Korea.²⁶⁾ Our aim was to describe clinical aspects of CVT, including presenting signs/symptoms, risk factors, radiologic findings, and outcomes, based on review of records at two patient care centers. Common features were then identified and comparisons made with data gathered in other studies.

Table 1. Clinical characteristics and outcomes of patients with CVT (n = 22)

No.	Sex	Age	PMHx	Clinical symptom	Duration (days)	GCS	Location	Infarction/Hemorrhage	mRS (Discharge)	Recanalization
1	M	43	Mastoiditis,	Headache	90	15	SSS/TS/SS	N	1	No
2	M	36	None	Seizure	1	15	SSS	I	1	Yes
3	M	30	None	Seizure	1	15	TS	H	0	Yes
4	M	45	None	Headache	3	15	TS	H	0	N/A
5	F	74	None	Altered mentality	1	9	TS	H	6	N/A
6	F	77	HTN	Headache	10	15	SSS/TS	N	1	N/A
7	M	43	None	Seizure	1	15	TS	N	1	Yes
8	M	27	DVT	Headache	3	15	SSS/TS	N	1	Yes
9	M	72	Bladder cancer	Seizure	1	14	SS/DCV*	I	1	N/A
10	F	26	HTN	Altered mentality	5	13	TS	H	1	Yes
11	F	71	HTN	Altered mentality	1	12	TS/SS	H	1	Yes
12	F	56	None	Headache	1	15	TS	N	1	N/A
13	F	63	Hyperthyroidism	Headache	1	15	TS/SS	N	0	Yes
14	F	35	HTN	Seizure	30	15	TS	H	0	Yes
15	F	66	Hyperthyroidism	Headache	1	15	TS	N	0	Yes
16	F	62	None	Aphasia	30	15	TS/SS	H	1	No
17	F	64	lymphoma	Motor deficit	1	13	SSS/TS	H	3	Yes
18	M	51	HTN	Seizure	1	7	SSS/TS	H	1	Yes
19	M	64	HTN	Mental change	1	8	SSS/TS	H	6	N/A
20	M	56	URI	Diplopia	3	15	SSS/TS	N	1	No
21	F	51	Hyperthyroidism	Headache	10	15	TS/DCV [†]	I	1	Yes
22	F	85	None	Headache	3	15	SSS/TS	H	6	N/A

n = number; CVT = cerebral venous thrombosis; DCV = deep cerebral vein; DVT = deep vein thrombosis; H = infarction with hemorrhagic transformation; HTN = hypertension; I = infarction; ITP = idiopathic thrombocytopenic purpura; mRS = modified Rankin Score; N = none; N/A = data not available; PMHx = past medical history; SSS = superior sagittal sinus; SS = straight sinus; TS = transverse-sigmoid sinus; URI = upper respiratory infection.

*Vein of Galen; [†]Internal cerebral vein

MATERIALS AND METHODS

Between January, 2006 and August 2015, 2651 patients presenting with strokes were admitted to two care centers. Among them were 22 patients diagnosed with CVT who qualified for clinical and radiologic retrospective review. All patients underwent brain computed tomography (CT). If CT findings or patient symptoms were suspicious of venous thrombosis, magnetic resonance venography (MRV) was performed, using a 1.5-Tesla MR imager (GE Medical Systems Inc., Waukesha, WI, USA). Any diagnosis that could not be made by MRV was established through further testing, such as conventional cerebral angiography.

Routine laboratory screenings of prothrombotic conditions were checked, particularly serum levels of antithrombin III; proteins C and S; anti-phospholipid, anti-cardiolipin, and anti-ds DNA, antibodies; factors V and VIII; homocysteine; lupus anticoagulant; and thyroid hormones. Dates of symptom onset and hospital admission were noted, in addition to signs/symptoms and Glasgow Coma Scale (GCS) scores on admission. Imaging outcomes were recorded and sorted by location and number of thrombi and by complications (eg, venous infarction and hemorrhagic transformation). Clinical outcomes at discharge and 12 months later were scored according to modified Rankin scale (mRS) as good (0-2), disabled (3-5); or fatal (6).

RESULTS

At time of diagnosis, mean age of patients (male, 10; female, 12) was 54.41 ± 16.19 years (range, 27-85 years) (Table 1). In terms of predisposing factors, prothrombotic conditions were identified in eight patients (36%), infections in three (mastoiditis, 2; upper respiratory, 1; 14%), hyperthyroidism in four (18%), trauma in two (9%), and malignancy in one (diffuse large B-cell lymphoma; 5%). Another patient (5%) had a history of deep vein thrombosis. In three patients (14%), causes were indeterminate. The distribution of

Table 2. Predisposing factors in cerebral venous thrombosis

Parameter	Total
Prothrombotic conditions	
CH50	3
Protein S deficiency	1
Coagulation factor VIII	2
LA	1
Homocysteinemia	2
APA	1
Hyperthyroidism	4
Trauma	2
Infection	3
Malignancy	1

APA = anti-phospholipid antibody; LA = Lupus anticoagulant

prothrombotic conditions are summarized in Table 2.

The most common symptom was headache (9/22, 40%), followed by seizure (5/22, 23%), altered mental status (4/22, 18%), focal motor deficits, visual symptoms, and dysarthria (Table 3). Mean duration of illness at presentation was 7 days (range, 0-90 days).

Imaging results indicated that three patients (13%) had cerebral infarcts at diagnosis, whereas 11 (50%) had suffered hemorrhagic transformation of infarcts. Severe intracranial hypertension in two patients prompted emergency surgical decompression. In eight patients (37%), signs of infarction or hemorrhage were lacking. By location, thrombosis of superior sagittal sinus predominated in nine patients (40%). Transverse sinus was involved in 20 patients (90%), sigmoid sinus in 12 (40%), and straight sinus in 5 (23%). Vein of Galen and internal cerebral vein, which are components of deep cerebral vein, were involved in 2 patients (Table 4).

Treatment strategies depended on circumstances,

Table 3. Clinical features of cerebral venous thrombosis

Parameter	n (%)
Headache	9 (40)
Seizure	6 (27)
Mental status change	4 (18)
Focal motor deficits	1 (5)
Visual symptoms	1 (5)
Dysarthria	1 (5)

n = number

Table 4. Sinus involvement in cerebral venous thrombosis

Localization by imaging	n (%)
Superior sagittal sinus	9 (40)
Transverse sinus	20 (90)
Sigmoidal sinus	12 (54)
Straight sinus	5 (19)
Deep cerebral vein	2 (7)

n = number

based on status at presentation, overall condition, and risk of bleeding. Fourteen patients were given anti-coagulants, with or without antiplatelet drugs, and five patients received antiplatelet therapy only. Two patients required emergency decompressive craniectomy, one for trauma-related hemorrhage and the other for hemorrhagic infarction at diagnosis.

Another patient with a poor prognosis after severe hemorrhage was simply observed, receiving no medication (Table 5). None of the patients given systemic anticoagulants developed new hemorrhages during follow-up. However, intracerebral hemorrhage occurred 6 months after onset of CVT in one patient who was left untreated (no anticoagulation or antiplatelet therapy).

In addition to antithrombotic medications, other treatments were prescribed as indicated by clinical presentation and etiology. Antiepileptics were used in patients with seizures, and mannitol was administered in conjunction with decompressive craniectomy to lower intracranial pressure.

At discharge, 19 patients showed symptomatic improvement (mRS scores < 2), and aside from one death (due to spontaneous intracranial and subsequent intraventricular hemorrhage), most remained in good condition 1 year later. Fifteen patients (77%) underwent MRV during follow-up (mean interval, 1.13 years),

Table 5. Treatment distribution in cerebral venous thrombosis

Medication	Total, n (%)
Anticoagulants	14 (63)
Antiplatelet drugs	5 (23)
None	3 (14)

with 12 (80%) showing signs of thrombotic resolution. The other three patients did not, although one has since done so. Three patients were ascribed mRS scores > 2 at discharge, two having expired after emergency surgical decompression and one with disabled status.

Illustrative case summaries

Patient 1

A 36 year-old man with no past medical problems presented to the hospital emergency department with seizure (10-min duration), marked by generalized tonic-clonic convulsive movement, left-sided eye deviation, hypersalivation, and tongue-biting. The episode ended without medication, leaving him disoriented as to time and place. He claimed to have suffered a headache for 14 days prior to arrival. Both general and neurologic examinations were unremarkable, despite a temperature of 38.0° C. Laboratory findings showed elevations of white blood cell count, myoglobin, ammonia, lactate dehydrogenase (LDH), and CH50, but lumbar puncture produced normal, acellular cerebrospinal fluid.



Fig. 1. Contrast enhanced computed tomography of brain showing 'empty delta sign' (arrow), indicative of sinus thrombosis (triangular area of enhancement with relatively low-attenuating center).

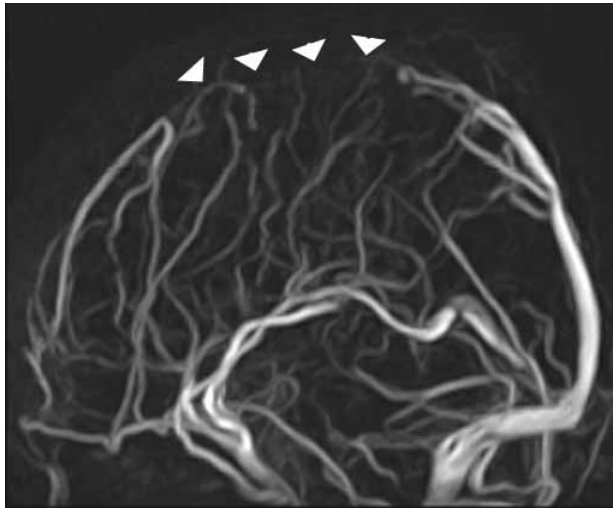


Fig. 2. MRV of brain: signal loss in superior sagittal sinus (arrow heads), reflecting thrombosis with occlusion. MRV = magnetic resonance venogram.

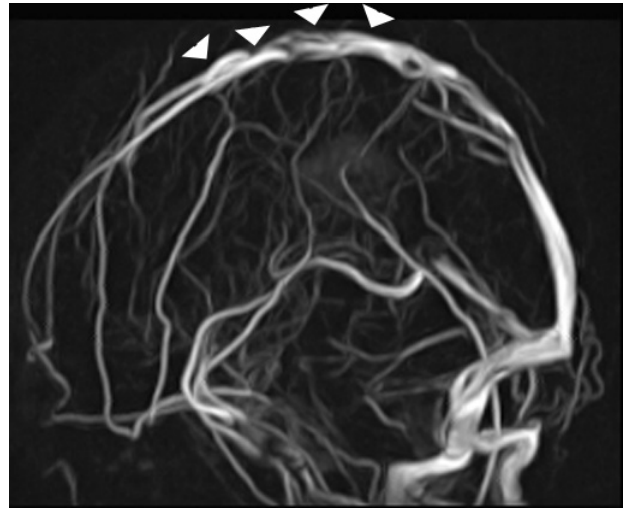


Fig. 3. Follow-up MRV of brain: signal visible in superior sagittal sinus (arrowheads) indicates recanalization (5 months after onset). MRV = magnetic resonance venogram.

A contrast-weighted CT of the brain was then performed. Although lacking definitive signs of infarction or hemorrhage, an 'empty delta sign' (ie, triangular area of enhancement with a relatively low-attenuating center) was identified, signifying sinus thrombosis (Fig. 1). MRI of the brain, with MRV, revealed signal loss in superior sagittal sinus (Fig. 2). The patient was admitted to the neurology intensive care unit, and heparin anticoagulation was initiated. Once adequate, a switch was made to warfarin, which was continued for 6 months. At time of discharge, a mild headache persisted but was much improved from the pre-admission state. Follow-up MRV 5 months after discharge showed evidence of recanalization, with signal detected in superior sagittal sinus (Fig. 3).

Patient 2

A 45 year-old man with no past medical problems presented to our care center with severe headache, which was sudden in onset. Both general and neurologic examinations were unremarkable. Laboratory diagnostics returned a positive serum test for rheumatoid factor as the sole abnormality. A contrast-weighted CT of brain, with angiogram, showed a small intracerebral hematoma of left temporal lobe and left cer-

ebellum, with high density (likely thrombus) at left transverse and sigmoid sinuses (Fig. 4). MRI of the brain disclosed a high-signal lesion at left temporal lobe on T2- and diffusion-weighted imaging, with increased ADC value, and a dark signal-intense lesion at left temporal lobe on susceptibility-weighted imaging, suggesting venous hemorrhagic infarction. Occlusion

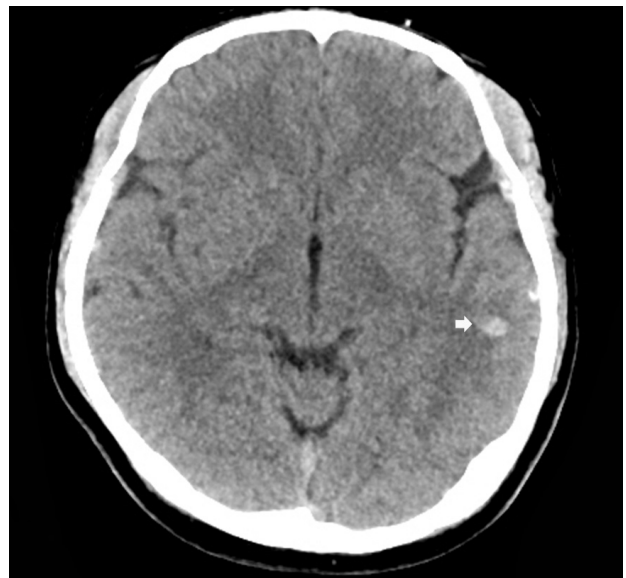


Fig. 4. Contrast enhanced computed tomography of brain: intracerebral hematoma of left temporal lobe (arrow). Venous infarction with hemorrhage was also considered because of sole symptom without prominent factor.

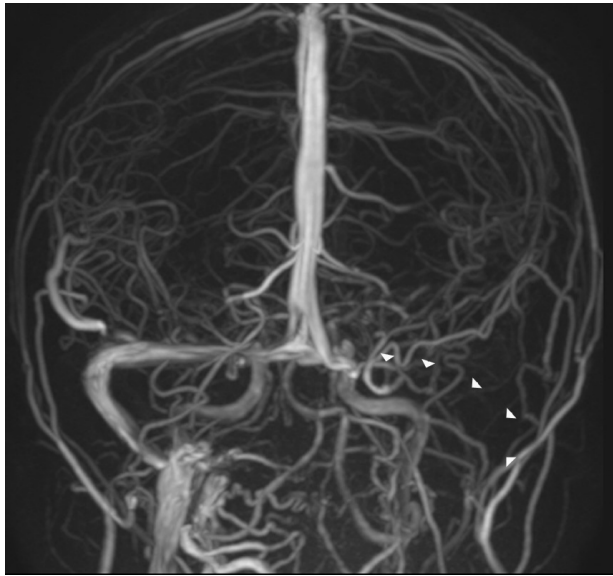


Fig. 5. MRV of brain: occlusion of left transverse/sigmoid sinus and left internal jugular vein (arrowheads). MRV = magnetic resonance venogram.

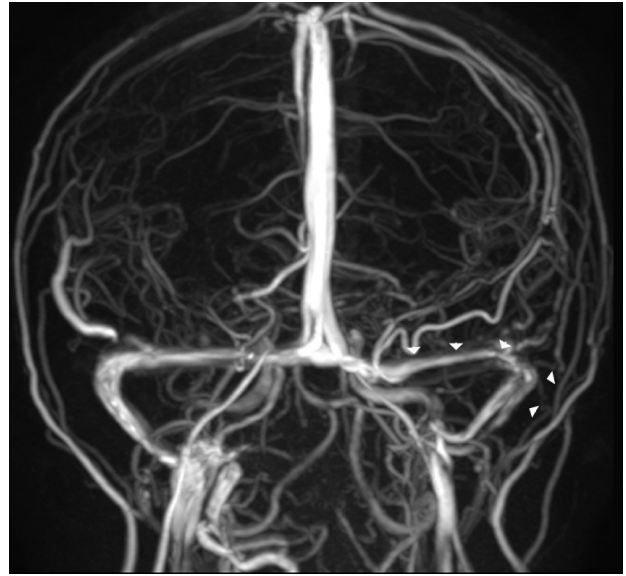


Fig. 6. Follow-up MRV of brain: flow signal in left transverse and sigmoid sinuses (arrowheads) now visible (9 months after onset). MRV = magnetic resonance venogram.

of left transverse/sigmoid sinus and left internal jugular vein was evident on MRV (Fig. 5). The patient was admitted to the neurology intensive care unit and heparin was started for anticoagulation. Once adequate, heparin was switched to warfarin for a 6-month course. At discharge, the patient was free of headache, with good functional status in follow-up. MRV done 9 months after discharge confirmed reappearance of flow signal in left transverse and sigmoid sinuses (Fig. 6).

DISCUSSION

Incidence and risk factors of CVT

CVT is an uncommon type of stroke that affects approximately 5 people per million annually and accounts for 0.5-1% of all strokes in Western nations.¹⁴⁾³⁴⁾³⁵⁾ CVT is also more common in younger adults.¹⁴⁾²⁸⁾²⁹⁾ In the largest cohort study to date (ISCVT), mean age of patients was 39.1 years, with a female predominance (75%). However, our patients (mean age, 54.41 ± 16.19 years) were considerably older by comparison. This finding may be related to an unprecedented upsurge in the aging population of Korea. Many earlier stud-

ies have also reported a significant female predominance (70-80% in women of childbearing age), stemming from prothrombotic conditions during pregnancy and delivery (Table 6).²⁾⁵⁾⁸⁾¹²⁾¹⁶⁾²⁴⁾²⁵⁾ Contrary to recent studies of CVT in other countries, no such gender imbalance was encountered in our analysis (male, 11; female, 12).

General awareness of CVT is improving, but diagnosis and management remain challenging, given the array of symptoms and the lack of consistent treatment. Also, CVT has been linked with a multitude of risk factors, including prior medical conditions (thrombophilias, inflammatory bowel disease), transient influences (pregnancy, dehydration, infection), certain medications (oral contraceptives, substance abuse), and random events (head trauma), just to name a few.¹¹⁾¹³⁾¹⁴⁾¹⁶⁾²¹⁾²⁴⁾³¹⁾³³⁾ In our cohort, pregnancy and estrogen use were immaterial. Relative to Western countries, our study has considerably lower crude birth and fertility rates, as well as markedly lower usage of oral contraceptives. Moreover, in 4 (18%) of our female patients, there was underlying hyperthyroidism, which has not been implicated as yet in CVT. According to one source, hyperthyroidism

Table 6. Comparison of the most frequent clinical aspects, risk factors, treatments, and outcomes of CVT according to different series

Study	Year	No. of cases	Mean age (year)	Location (%)	Risk factor (%)	Treatment (%)	mRS (< 2)*
Breteau et al. ⁷⁾	2003	55	39	TS/SS (69)	OC (43) Prothrombotic condition (18)	Anticoagulation (98)	42
Ferro et al. ¹⁴⁾	2004	624	39	SSS (62)	OC (54) Prothrombotic condition (34)	Anticoagulation (83) Antiplatelet (6)	493
Khealani et al. ¹⁹⁾	2008	109	35	SSS (71)	Infection (18) Peripartum (16)	Anticoagulation (67) Antiplatelet (9)	66
Patil et al. ²⁷⁾	2014	50	39	SSS (46)	Infection (78) Prothrombotic condition (24)	Anticoagulation (78)	42
Park et al. ²⁶⁾	2014	36	46	TS/SS (61)	Prothrombotic condition (22)	Anticoagulation (36) Antiplatelet (8)	N/A
Souirti et al. ³²⁾	2014	30	29	TS/SS (70)	Peripartum (33) Infection (26)	Anticoagulation (90)	20

CVT = cerebral venous thrombosis; mRS = modified Rankin Score; N/A = data not available; OC = oral contraceptive; SSS = superior sagittal sinus; SS = straight sinus; TS = transverse-sigmoid sinus.
*Number of patients with mRS score less than 2

may cause thromboembolic events by inducing vascular endothelial dysfunction, reducing fibrinolytic activity, and increasing factor VIII and homocysteinemia levels.²²⁾

CVT with hemorrhagic infarction

In past investigations, approximately 30-40% of patients with CVT have presented with intracerebral hemorrhage (including hemorrhagic infarction).¹⁴⁾¹⁵⁾²⁹⁾ Half of the 22 patients we studied similarly showed imaging evidence of hemorrhagic infarction. Until recently, however, radiologic criteria for assessing hemorrhagic infarction in CVT were not often discussed. It was presumed that large-sized baseline lesions on MRI and persistent venous occlusion were responsible, but in rats, both rate and size of venous infarcts increase with age, suggesting a greater vulnerability in the aged brain.²³⁾ In this study, MRI images of most patients with hemorrhagic infarction revealed arteriosclerotic deterioration of arteries and non-visible cortical veins, as well as poor collateral circulation. From our perspective, such alterations are likely to increase vulnerability, allowing intraparenchymal leakage of blood at high venous and capillary pressures.

Outcomes of a previous Korean study further indicate that hemorrhagic infarction is more frequent in a prothrombotic setting.²⁶⁾ Although hypercoagulability

clearly may precipitate thrombosis and sinus occlusion, resulting in venous stasis, intracranial hypertension, and abrupt transition to hemorrhage, the incidence of hemorrhagic infarction was not significantly higher in patients of ours with prothrombotic conditions. Only three of such patients suffered hemorrhagic infarctions. We therefore attribute such occurrences to aging arteriosclerotic vessels (as above) rather than hypercoagulability, reflecting the skewed elderly segment of Korean population.

Treatment and outcomes of CVT

Traditionally, the prognosis is poor for a majority of patients with CVT.¹⁾⁴⁾⁶⁾¹⁰⁾¹⁷⁾²⁰⁾ However, the ISCVT cites a mortality rate at discharge of only 4.3%, and a recent systematic review of CVT showed that the mortality of patients with CVT has substantially declined over time, owing to better treatments, a shift in risk factors, and (most importantly) heightened detection of less critical disease through improved diagnostics.⁶⁾¹³⁻¹⁵⁾³⁰⁾³⁴⁾³⁵⁾

The most logical treatment for CVT is heparinization.¹³⁾¹⁴⁾¹⁸⁾³⁰⁾ Overall, 14 of our patients (64%) received anticoagulants, whereas five received antiplatelet drugs only, and two patients requiring decompressive craniectomy were denied both. In other studies, anticoagulants have been used in 80% of subjects. There is controversy in this regard, fearing that venous in-

farcts will become hemorrhagic; and many of the patients with sinus thrombosis (~40%) suffer hemorrhagic infarcts before anticoagulant treatment is instituted.¹⁴⁾¹⁸⁾²⁸⁾³⁴⁾ In these circumstances, some physicians may prefer antiplatelet drugs to reduce the risk of intracranial bleeding.

Two of our patients (8%) were scored as deaths (due to elevated intracranial pressure) at discharge, which is within the mortality range (4.3-15%) reported elsewhere. The other 20 patients, all managed medically, had favorable clinical outcomes at discharge, with only one suffering significant disability (hemiparesis). At 1-year follow-up, 19 patients had no impairments, with one succumbing to spontaneous intracerebral hemorrhage. The recovery rate and clinical outcomes we observed are similar to those appearing in the literature.

The small sample size is the chief limitation of this study. Despite access to data from two separate centers over a 10-year period, only 22 patients diagnosed with and treated for CVT were identified. The generalizability of these demographics may thus be limited. Another limitation is the retrospective design, forcing us to rely on documentation of clinical features and outcomes in medical records. Such data were not originally intended for investigational purposes.

CONCLUSION

In this study, patients suffering CVT were considerably older and had no female predominance than those evaluated in comparable investigations globally. And risk factors for CVT had low relationship with pregnant or oral contraceptives comparing with Western country. Either anticoagulation or antiplatelet therapy showed good prognosis in our study, which needs further analysis.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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