INTRODUCTION

A cerebral venous thrombosis (CVT) is an uncommon type of stroke accounting for 0.5% of all strokes. The pathogenesis is multifactorial, and the disease could occur at any age, including in neonates. However, a prothrombotic condition plays a key role in its occurrence. Because of the thrombogenic effect of estrogen, an increased incidence in women who take oral contraceptives as well as in pregnant women has been highlighted in previous reports, particularly in Europe and America where a high use of oral contraceptives has been reported. This study was conducted on the premise that there have been no clinical reviews of CVT in Korea, and, thus the clinical characteristics of 36 CVT patients in a single center were reviewed and compared with those in previous studies.

MATERIALS AND METHODS

From August 2005 to May 2013, 40 patients diagnosed with CVT were treated in a single center. Three patients who were not evaluated for prothrombotic conditions because of personal reasons were excluded from the study group. One patient, who was transferred to another hospital with an incomplete work-up, was excluded, and 36 patients were included in the study. We retrospectively collected these patients' data regarding age, sex, disease stage, pathogenesis, location, laboratory findings, and treatment modalities were retrospectively collected. The results were compared with those of previous studies in other countries.
RESULTS

Patient data

The patient group included 21 men and 15 women with a mean age of 46.9 years at diagnosis (ranging from 3 months to 77 years). In the age groups by decades, the highest prevalence was seen in the sixth decade (n=9).

Within the patient group, 14 (38.9%) patients were in the acute stage at the time of diagnosis, 11 (30.1%) were in the sub-acute stage, and 11 (30.1%) were in the chronic stage.

Concerning the pathogenesis, 8 (22.2%) cases resulted from a prothrombotic condition, 7 (19.4%) were because of a post-operative change, 5 (13.9%) were from an infection, 2 (5.6%) followed a trauma, 2 (5.6%) resulted from local invasion of a preexisting brain tumor, 1 (2.8%) was cancer-related, 1 (2.8%) was related to systemic diseases (chronic renal disease and gout), 1 (2.8%) occurred after hormonal replacement (estradiol hemihydrate) therapy, 1 (2.8%) resulted from a congenital anomaly, and 1 (2.8%) was caused by iron-deficiency anemia. No definitive cause was found in 7 patients (19.4%).

The specific laboratory findings of the 8 patients with a prothrombotic condition are presented in Table 1.

Among the 7 patients in the post-operative change group, 2 patients had undergone a craniotomy for a parasagittal meningioma, 1 for a right occipital skull plasmacytoma, 1 for a left vestibular schwannoma, 1 for a right vagus schwannoma, 1 for a right cerebellar hematoma following an arteriovenous malformation rupture, and 1 for a left cerebellopontine angle meningioma.

In the infection group, the patients had infections in the following locations: a right superior ophthalmic vein thrombophlebitis, a right periorbital abscess and diffuse pachymeningitis, central nervous system aspergillosis, a right otomastoiditis, and a fungal sinusitis with brain abscess.

The radiological findings showed that 13 patients (36.1%) had a hemorrhagic infarction at diagnosis, whereas 23 (63.9%) were without a hemorrhage. None of the hematomas resulted in a severe mass effect that warranted emergency surgical decompression.

A dural AVF was initially present in 8 patients (22.2%) and was

| Patient | Age | Sex | Laboratory finding | Hemorrhagic infarction |
|---------|-----|-----|---------------------|-----------------------|
| 1       | 17  | M   | Pr C↓, Pr S↓        | Yes                   |
| 2       | 31  | M   | L-AC (+), Pr S↓     | No                    |
| 3       | 42  | M   | TAT↑, Plt↑          | Yes                   |
| 6       | 53  | F   | Plt↑, Pr S↓, AT↓    | No                    |
| 4       | 54  | F   | Pr S↓, Plt↑         | Yes                   |
| 5       | 59  | M   | Pr C↓, Pr S↓, L-AC (+) | Yes              |
| 7       | 70  | M   | Pr C↓, Pr S↓        | Yes                   |
| 8       | 77  | F   | Pr S↓               | Yes                   |

TAT: thrombin-antithrombin complex, Plt: platelet, L-AC: lupus anticoagulant, Pr S: protein S activity, AT: antithrombin II, Pr C: protein C activity, ↓: decreased, ↑: increased
newly diagnosed during the follow-up in 1 patient (2.8%). All the patients underwent endovascular dural AVF embolization.

By location, 22 patients had a thrombosis predominantly in the transverse and/or sigmoid sinus, 6 patients mainly in the superior sagittal sinus, 3 patients in the cavernous sinus, 4 patients within the cortical vein, and 1 patient in the deep venous system.

A brief summary of the clinical characteristics of the patients is provided in Table 2.

Relationship with hemorrhagic infarction

Each pathogenesis group was analyzed for an association with hemorrhagic infarction.

Of the 8 patients in the prothrombotic group, 6 had a hemorrhagic infarction, and 2 had a venous infarction without a hemorrhage. Of the 28 patients in the non-prothrombotic group, 7 patients had a hemorrhagic infarction, whereas 21 had a venous infarction without a hemorrhage. The prothrombotic group had more frequent hemorrhagic infarctions, whereas the non-prothrombotic group had more venous infarctions, which was statistically significant ($p=0.016$) (Table 3).

The identical analysis was conducted for each pathogenesis entity; the remaining differences were insignificant.

Table 2. Clinical characteristics of the 36 CVT Patients

| No. | Sex | Age | Stage | Hemorrhage | Location | Pathogenesis | Dural AVF | Dural AVF embolization |
|-----|-----|-----|-------|------------|----------|--------------|-----------|-----------------------|
| 1   | M   | 59  | Subacute | Yes    | TS/SS    | Prothrombotic condition | None     | -                     |
| 2   | F   | 61  | Chronic   | No     | SSS       | Idiopathic | None     | -                     |
| 3   | F   | 47  | Subacute   | No    | TS/SS    | IDA          | Secondary | Yes                  |
| 4   | M   | 31  | Chronic  | No    | SSS       | Prothrombotic condition | None     | -                     |
| 5   | M   | 1   | Acute  | Yes   | TS/SS    | Trauma       | None     | -                     |
| 6   | F   | 54  | Acute | Yes    | TS/SS    | Prothrombotic condition | None     | -                     |
| 7   | M   | 48  | Subacute | Yes | TS/SS    | Trauma       | None     | -                     |
| 8   | M   | 42  | Acute | Yes    | CV       | Prothrombotic condition | None     | -                     |
| 9   | M   | 70  | Acute | Yes   | TS/SS    | Prothrombotic condition | Initial  | Yes                  |
| 10  | M   | 39  | Subacute | No    | TS/SS    | Idiopathic | Initial   | Yes                  |
| 11  | M   | 46  | Acute | No    | TS/SS    | Post-op change | None     | -                     |
| 12  | M   | 51  | Subacute | No  | CS       | Infection   | None     | -                     |
| 13  | M   | 32  | Subacute | No  | TS/SS    | Idiopathic | None     | -                     |
| 14  | F   | 57  | Acute | No    | TS/SS    | Post-op change | None     | -                     |
| 15  | M   | 13  | Subacute | No    | SSS       | Infection   | None     | -                     |
| 16  | M   | 52  | Chronic | No   | SSS       | Tumor invasion | None     | -                     |
| 17  | M   | 49  | Chronic | No   | CS        | Infection   | None     | -                     |
| 18  | M   | 14  | Acute | No    | TS/SS    | Post-op change | None     | -                     |
| 19  | F   | 53  | Subacute | No  | TS/SS    | Prothrombotic condition | None     | -                     |
| 20  | M   | 35  | Chronic | Yes | TS/SS    | Post-op change | None     | -                     |
| 21  | F   | 69  | Subacute | Yes | TS/SS    | Idiopathic | Initial   | Yes                  |
| 22  | F   | 73  | Acute | Yes   | TS/SS    | Idiopathic | Initial   | Yes                  |
| 23  | M   | 44  | Chronic | No   | TS/SS    | Idiopathic | Initial   | Yes                  |
| 24  | M   | 17  | Acute | Yes   | CV       | Prothrombotic condition | None     | -                     |
| 25  | F   | 73  | Acute | No    | SSS       | Post-op change | None     | -                     |
| 26  | F   | 7   | Acute | No    | TS/SS    | Infection   | None     | -                     |
| 27  | F   | 0   | Acute | No    | TS/SS    | Congenital anomaly | None     | -                     |
| 28  | M   | 63  | Subacute | No  | TS/SS    | Idiopathic | Initial   | Yes                  |
| 29  | F   | 75  | Chronic | No   | CS        | Infection   | None     | -                     |
| 30  | M   | 65  | Chronic | No   | TS/SS    | Systemic disease related | Initial  | Yes                  |
| 31  | F   | 77  | Chronic | Yes | DV       | Prothrombotic condition | Initial  | Yes                  |
| 32  | M   | 36  | Chronic | No   | SSS       | Tumor invasion | None     | -                     |
| 33  | M   | 51  | Chronic | No   | TS/SS    | Cancer-related | None     | -                     |
| 34  | F   | 55  | Subacute | Yes | CV       | Estrogen   | None     | -                     |
| 35  | F   | 72  | Acute | No    | TS/SS    | Post-op change | None     | -                     |
| 36  | F   | 58  | Acute | No    | CV       | Post-op change | None     | -                     |

AVF: arteriovenous fistula, M: male, F: female, SS: sigmoid sinus, TS: transverse sinus, SSS: superior sagittal sinus, CV: cortical vein, DV: deep vein, IDA: iron deficiency anemia, Post-op: post-operative
Pathogenesis

Pregnancy, puerperium and oral contraceptives

Pregnancy and the puerperium are common causes of transient prothrombotic states because pregnancy induces several prothrombotic changes in coagulation. Hypercoagulability is hypothesized to be aggravated after delivery as a result of volume depletion and trauma. A CVT associated with pregnancy and puerperium accounts for 21% of all the causes of CVT, according to the ISCVT study. Approximately 2% of pregnancy-associated strokes are attributable to CVT. The frequency of puerperium CVT is reported to be approximately 12 cases per 10000 deliveries. Estrogen-containing oral contraceptives play an important role in the pathogenesis of CVT in young women. In most CVT studies, the use of oral contraceptives is the most frequent risk factor in women; the rate of usage was 47% in the ISCVT and as high as 96% in an Italian study.

In our study group, 1 CVT event was related to estrogen use; none were related to pregnancy. A potential explanation for this finding is that Korea has considerably low crude birth and fertility rates as well as a markedly low usage of oral contraceptives by Korean women compared to that in the United States and many European countries. The crude birth rate (9.6 births per 1000 population) and fertility rate (1.3 births per woman) in Korea are among the lowest in the world. The use of oral pills as a means of contraception in Korea is as low as 2.0%, whereas that rate is tenfold higher in the United States and up to twentyfold higher in many European countries.

Post-operative change

Iatrogenic injury to the venous sinus during and after surgery near the sinuses might induce CVT, as observed in 7 of our patients. No study has investigated the incidence of iatrogenic CVT following surgery. There have been case reports of CVT after applying topical hemostatic matrix and cautery at the nearby sinus, as well as studies on the incidence at the remote site after lumbar CSF drainage. In our study group, all of the seven cases displayed localized CVT near the surgical lesion, which implies iatrogenic injury to these sinuses. The assumed causative factors are mannitol and CSF drainage during a craniotomy, which induces hyper-osmolality that aggravates CVT. Overexposure of the sinus leads to desiccation of the dura surrounding the sinus, leading to shrinkage and thrombosis. Retraction against the venous structures might limit blood flow and subsequent stasis and thrombosis. Maintaining adequate hydration and minimizing sinus exposure and retraction against venous structures is necessary during surgery near the sinuses. Dominant sinuses should never be sacrificed, and careful decision-making is required when occluding non-dominant sinuses.

Because iatrogenic CVT might be asymptomatic or present with a headache, which is a non-specific symptom after craniotomy, complete pre-operative and post-operative imaging studies including angiography or venography are essential for the diagnosis of iatrogenic CVT.

DISCUSSION

The clinical characteristics of 36 Korean patients diagnosed with CVT in a single center were reviewed in this study, which focused on the relationship of hemorrhagic infarction, disease stage, location of CVT, and pathogenesis. The differences with previous reports from other countries have been emphasized.

| Pathogenesis                  | Hemorrhagic infarction | p-value |
|-------------------------------|------------------------|--------|
| Prothrombotic condition       | Yes: 6                | No: 2  | 0.0157* |
| Non-prothrombotic condition   | Yes: 7                | No: 21 |        |

*Statistically significant
Prothrombotic condition

The prothrombotic condition is the most widely studied risk factor for CVT. The incidence of the prothrombotic condition in CVT was reported to be 34.1% in the 624 cases in the ISCVT\(^\text{16,20}\) and 21% in the 182 cases in a recent multicenter study by de Freitas et al.\(^\text{17}\). A prothrombotic condition is associated with numerous factors. The roles of antiphospholipid antibodies, antカードリシン抗体, natural anticoagulant protein (antithrombin III, proteins C and S) deficiencies, and factor V Leiden gene mutation have been described in past studies.\(^\text{18,19}\) In our patient group, the incidence of a prothrombotic condition was 22%, which is similar to or slightly lesser than in previous studies.

Dural AVF

The relationship between dural AVF incidence and CVT is complex and not completely understood. Thrombosis of the cerebral venous sinus could later induce a dural AVF, as seen in one of our patients, and a pre-existing fistula could be the underlying cause of CVT.\(^\text{40}\) A dural AVF could spontaneously close after the sinus recanalizes. In cases in which a dural AVF is found with the initial diagnosis of CVT, the order of the timing of the two disease entities could not be clearly decided. To clarify the actual incidence of dural AVF and CVT and the relationship between them, larger cohort studies with long-term angiographic evaluation are required.

Infection

Infection is hypothesized to cause CVT by altering the coagulation cascade and inducing a hypercoagulable state in patients with an active infection.\(^\text{10}\) Infection accounted for 8.2% of all the cases in the ISCVT series.\(^\text{4}\) Cavernous and transverse sinus thrombosis cases are most frequently associated with infections such as sinusitis, otitis, and mastoiditis, with Staphylococcus aureus as the most frequently reported pathogen.\(^\text{41}\) In our study, the incidence of infection was 13.9%, and in the 3 patients with a cavernous sinus thrombosis, infection was the cause.

Prothrombotic condition and hemorrhagic infarction

The probability of a hemorrhage might increase with coagulopathy, and patients with hypercoagulability are less likely to experience a bleeding diathesis.\(^\text{13}\) In this study, the incidence of a hemorrhagic infarction was significantly higher in the patients with a prothrombotic condition. In arterial infarctions, a large-volume infarction, a delayed time of reperfusion and collateral flow failure are the factors associated with hemorrhagic transformation.\(^\text{43}\) Similarly, the authors hypothesize that hypercoagulability leads to a more rapid thrombosis formation and venous sinus occlusion, which results in a more abrupt venous stasis and increased intracranial pressure, resulting in an increased probability of hemorrhagic transformation.

This issue has not been investigated previously, and this study has certain limitations. First, the specificity and sensitivity of the hypercoagulability laboratory values might be altered because confounding factors were neglected. Defining 1 or 2 positive findings of numerous hypercoagulability laboratory tests as a prothrombotic condition might be controversial. In addition, the sample size is limited, with 8 of the 36 patients having a prothrombotic condition. More tests and larger randomized trials are needed to sufficiently verify this hypothesis. Finally, this study was conducted retrospectively; the patient data extracted from the medical charts were initially recorded for clinical use rather than for research purposes. In spite of these limitations, however, our study contains unique information on the characteristics of CVT patients in a Korean sample and on the significance of the relationship between hemorrhagic infarction and prothrombotic condition.

CONCLUSION

In this study, CVT was more prevalent in men, and the peak age at diagnosis was in the sixth decade of life. The most common cause was a prothrombotic condition, followed by infection and post-operative change. This finding was comparable with reports from Europe or America, in which CVT was more common in younger women.\(^\text{46}\) The low proportion of Korean women on oral contraceptives and the low birth rate in Korea might have influenced those results. A hemorrhagic infarction was more common in the prothrombotic group than in the non-prothrombotic group (\(p=0.016\)). Further studies with larger cohorts are required to evaluate the clinical characteristics of CVT patients in Korea and to establish appropriate therapeutic strategies.

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