

Cerebral Venous Sinus Thrombosis: Incidence and Hyperhomocysteinemia as a Risk Factor in Japanese Patients

Makoto Takemaru¹, Masaru Kuriyama^{1*}, Takahiro Himeno¹, Yuji Shiga¹, Yuhei Kanaya¹, Shinichi Takeshima¹, Takeshi Yoshimoto¹, Kazuhiro Takamatsu¹, Yutaka Shimoe¹, Shinzo Ohta² and Akio Tanaka³

Abstract

Background: Cerebral venous sinus thrombosis (CVT) occurs commonly in young female adults and is caused by various risk factors. Our aim was to determine the incidence, clinical characteristics, and risk factors of Japanese CVT patients.

Patients and methods: We performed a retrospective study of CVT patients from January 2010 to June 2015. In the patients who had hyperhomocysteinemia, vitamin levels were measured. To define the clinical characteristics in patients with hyperhomocysteinemia, we statistically compared them to those patients with normal levels of homocysteine.

Results: Sixteen patients (aged 54.6 ± 17.7 years; 13 men and 3 women) were included. The incidence of CVT was 0.23% among all types of strokes or 0.30% of acute ischemic strokes, which was lower than previously reported. The patients were characterized by advanced age, low frequency of headaches, and few female patients, especially female patients using oral contraceptives. The predisposing conditions included a notably high incidence of hyperhomocysteinemia (56.3%). They also included deficiencies of folate, vitamin B12, vitamin B6, or combined deficiencies. Marked hyperhomocysteinemia over 100 nmol/ml was noted in combined deficiencies.

Conclusions: CVT in Japan commonly occurred in older males. The prevalence of hyperhomocysteinemia as a risk factor of CVT was high, and the main underlying disorders were folate and vitamin B12 or B6 deficiencies. This is clinically important, because these acquired risks can be corrected by supplementation therapy to prevent the recurrence of CVT.

Keywords: Cerebral venous sinus thrombosis; Incidence; Risk factors; Hyperhomocysteinemia; Folate; Vitamin B12; Vitamin B6

- 1 Department of Neurology, Brain Attack Center Ota Memorial Hospital, 3-6-28 Okinogami, Fukuyama, Hiroshima, Japan
- 2 Department of Neurosurgery, Brain Attack Center Ota Memorial Hospital, 3-6-28 Okinogami, Fukuyama, Hiroshima, Japan
- 3 Department of Radiology, Brain Attack Center Ota Memorial Hospital, 3-6-28 Okinogami, Fukuyama, Hiroshima, Japan

*Corresponding author: Masaru Kuriyama

✉ kuriyama@shouwa.or.jp

Department of Neurology, Brain Attack Center Ota Memorial Hospital, 3-6-28 Okinogami, Fukuyama, Hiroshima 720-0825, Japan.

Tel: +81 84-931-8650

Fax: +81-926-6798

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Abbreviations

CVT: Cerebral Venous Sinus Thrombosis; Hiper-Hcy: Hyperhomocysteinemia; ISCVT: International Study on Cerebral Vein and Dural Sinus Thrombosis; Hcy: Homocysteine; AED: Anti-epileptic Drugs; DM: Diabetes Mellitus

Introduction

Cerebral venous sinus thrombosis (CVT) is less common than most other types of stroke but is recognized with increasing frequency due to the widespread use of magnetic resonance

imaging (MRI) and rising clinical awareness. As CVT is caused by various underlying diseases, it is important to analyze the causative disorders [1-3], as well as the immediate treatment for thrombosis. CVT occurs commonly in young adults under 40 years old and is about 3-times more common in females than in

males. Its incidence is about 0.5% to 1.0% among all types of stroke [1-3]. There are many risk factors of CVT [1-3]; genetic or acquired thrombophilia and oral contraceptive use are the most common risk factors, and hyper-homocysteinemia (Hcy) is an additional risk factor [4-8]. A meta-analysis of 17 clinical studies showed that oral contraceptive use, Leiden mutation of Factor V, and hyper-Hcy were recognized as statistically significant risk factors (8). A multinational (21 countries), multicenter (89 centers) prospective observational study entitled the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) [9-13] examined 624 cases of CVT and reported that the prevalence of hyper-Hcy is 4.5%. However, Boncoraglio et al. reported from Italy that 10 of 26 patients (38.5%) with CVT had hyper-Hcy (7). The prevalence of hyper-Hcy in CVT may exhibit racial differences. This is the first report about the prevalence and clinical characteristics of CVT with hyper-Hcy from Japan.

Patients and Methods

We retrospectively studied the clinical characteristics, laboratory findings, radiological image findings, causative disorders, and risk factors of hospitalized patients with CVT from January 2010 to June 2015. The diagnosis of CVT was confirmed by CT and MRI combined with MR venography, as well as conventional angiography in some cases. There was no selection bias. In 5 patients hospitalized after 2013 of 9 patients with hyper-Hcy, the folate, vitamin B12, or vitamin B6 levels were measured in their blood. Case 9 has been already reported as a Japanese case report [14]. The differences were statistically estimated by the χ^2 test or the Mann-Whitney U test.

Results

Incidence

There were 16 patients with CVT (aged 54.6 ± 17.7 years), including 13 males (81.3% of the subjects, aged 53.9 ± 17.5 , 25-81 years old) and 3 females (18.7% of the subjects, aged 57.3 ± 22.3 , 43-83 years old). During the period mentioned above, a total of 7073 patients with stroke-including 5281 acute ischemic strokes (74.7%), 1363 intracerebral hemorrhages (19.3%), and 429 subarachnoid hemorrhages (6.1%)- were admitted to our center. Thus, the incidence of CVT was 0.23% of all types of strokes or 0.30% of acute ischemic strokes.

Baseline characteristics

The clinical symptoms were headache (10 cases, 62.5%), nausea and vomiting (6 cases, 37.5%), generalized seizure (6 cases, 37.5%), stupor or coma (6 cases, 37.5%), motor hemiparesis (6 cases, 37.5%), speech disturbance (1 case, 6.3%), and visual disturbance (2 cases, 12.5%). The patients had risk factors and disorders related to CVT, which included oral contraceptive use (1 patient); nephrotic syndrome (2 patients); and colon cancer, multiple sclerosis, multiple myeloma in remission, and epilepsy treated with anti-epileptic drugs (AEDs) (1 patient each). The occluded sinus or cerebral vein was the superior sagittal sinus (SSS) in 12 cases (75.0%), the lateral sinus (LS) in 11 cases (68.8%), both sinuses in 7 cases (43.8%), the straight sinus in 4 cases (25.0%), and the internal jugular vein in 1 cases (6.3%). Additionally, cortical vein thromboses with edema were observed in 12 cases (75.0%), and hemorrhagic lesions accompanied this finding in 5 cases (31.3%).

D-dimer was increased in all patients (5.61 ± 4.39 ug/ml); PT-INR and APTT were slightly decreased in 1 patient and in 5 patients, respectively. Protein S and antithrombin III activity were decreased in 3 patients and in 2 patients, respectively. Activity of protein C was normal in all patients. All patients showed negative or normal levels of anti-nuclear antibody and the antibodies related to antiphospholipid antibody syndrome. Three patients had iron deficiency anemia. CRP (2.67 ± 3.15 mg/dl) and fibrinogen (370 ± 72 mg/dl) levels were increased in 16 patients and 14 patients, respectively (Tables 1 and 2).

Table 1 The clinical characteristics in patients with cerebral venous sinus thrombosis.

Patients n=16		
Sex		13 (81.3)
Age	male	53.9 ± 17.5
	female	57.3 ± 22.3
65 years old \leq		4 (25.0)
Clinical symptoms		
Headache		10 (62.5)
N/Vomiting		6 (37.5)
Seizure		6 (37.5)
Unconscious		6 (37.5)
Hemiparesis		6 (37.5)
Speech disturbance		1 (6.3)
Visual disturbance		2 (12.5)
Location of thrombosis		
Superior sagittal sinus (SSS)		12 (75.0)
Lateral sinus (LS)		11 (68.8)
SSS+LS		7 (43.8)
Straight sinus		4 (25.0)
Internal jugular vein		1 (6.3)
Cerebral lesions		
Cortical vein thromboses		12 (75.0)
Hemorrhagic lesions		5 (31.3)

Table 2 The laboratory findings and risk factors in patients with cerebral venous sinus thrombosis.

Laboratory findings and risk factors		
d-dimer		16 (100)
protein C deficiency		0
protein S deficiency		3 (18.8)
antithrombin deficiency		2 (12.5)
ANA		0
Anti-phospholipid syndrome		0
CRP at admission		16 (100)
fibrinogen at admission		14 (87.5)
anemia (iron deficiency)		3 (18.8)
hyperhomocysteinemia		9 (56.3)
oral contraceptives (female n=3)		1 (33.3)
nephrotic syndrome		2 (12.5)
malignancy		1 (6.3)
Others (associated)		
multiple myeloma		1
multiple sclerosis		1
epilepsy		1

Hyperhomocysteinemia (hyper-Hcy)

Hyper-Hcy was identified in 9 (56.3%) of the 16 patients (**Table 3**). Seven patients (Case 1~7) had slightly to moderately high levels (13.6-21.6 nmol/ml; normal: 3.7-13.5 nmol/ml), and 2 patients (Case 8 and 9) had very high levels (170 and 93.5 nmol/ml). Furthermore, in 9 patients with hyper-Hcy, 1 (Case 6) had folate deficiency, and 1 (Case 7) had vitamin B6 deficiency. And 2 patients (Case 8 and 9) with very high levels of Hcy showed combined deficiencies of folate and vitamin B12. The disorders and habits related to Hcy levels were also shown in **Table 3**. There was 1 patient (Case 4) with multiple sclerosis and low activity of antithrombin III, and 1 patient (Case 7) with multiple myeloma in remission. One patient had total resection of the stomach, 2 had chronic alcoholism, 2 were heavy smokers, 1 had Alzheimer's disease, 2 had diabetes mellitus (DM), and 1 was taking an AED. Two patients (Case 8 and 9) with marked hyper-Hcy were T/T

homozygous for methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism. They received a supplement therapy of folate and vitamin B12, and Hcy levels decreased to normal levels after 4 months.

To define the clinical characteristics in the cases of hyper-Hcy (H group, n=9, 42.5 ± 54.2 nmol/ml), we statistically compared these cases to cases of normal serum Hcy (C group, n=7, 9.6 ± 3.0 nmol/ml). The following baseline characteristics were compared between the 2 groups: age; percentage of older patients (greater than 65 years); sex; clinical symptoms including headache, nausea and vomiting, seizure, unconsciousness, and hemiparesis; laboratory data including levels of D-dimer, CRP, and fibrinogen; and radiological findings including occluded sinuses, cortical venous thrombosis, and hemorrhagic lesions. No differences were found between the 2 groups (**Table 4**).

Table 3 The clinical and laboratory factors related to hyperhomocysteinemia.

Case			Hcy	MTHFR	FA	B12	B6			others
No.	Age	Sex					PAM	PAL	PIN	
1	78	M	14.6	/	/	/	/	/	/	DM, dementia
2	81	M	13.6	/	/	/	/	/	/	DM, gastrectomy
3	72	M	17.8	/	/	/	/	/	/	-
4	25	M	21.6	/	/	/	/	/	/	MS, AT III deficiency
5	55	M	14.6	C/C	17.7	383	0.2>	8.9	3.0>	alcoholism, smoking
6	83	F	18.6	C/C	2.9	673	/	/	/	-
7	54	M	18.1	C/C	6.1	304	0.2>	2.3	3.0>	multiple myeloma
8	36	M	170	T/T	1.1	178	0.2>	7.5	3.0>	AED (epilepsy)
9	63	M	93.5	T/T	2.4	152	/	/	/	alcoholism, smoking

Hcy: Homocysteine (normal values: 3.7-13.5 nmol/mL); DM: Diabetes Mellitus; AED: Antiepileptic Drug; FA: Folate (normal values: 3.6-12.9 ng/mL); B12: Vitamin B12 (normal values: 180-914 pg/mL); PAM: Pyridoxamine (normal values: <0.6 ng/mL); PAL: Pyridoxal (normal values: 6.0-40.0 ng/mL); PIN: Pyridoxine (normal values: <3.0 ng/mL); MS: Multiple Sclerosis; AT: Antithrombin

Table 4 The comparison of baseline characteristics between 2 groups with and without hyperhomocysteinemia.

Variables	Group H	Group C	P
	n=9	n=7	
Age	60.8 ± 20.3	44.5 ± 9.3	0.099
65 years old ☑	4 (44.4)	0 (0.0)	0.103
Sex/male	8 (88.9)	4 (66.7)	0.525
Headache	4 (44.4)	5 (83.3)	0.287
N/Vomiting	4 (44.4)	2 (33.3)	1
Seizure	5 (55.6)	1 (16.7)	0.287
Unconscious	4 (44.4)	2 (33.3)	1
Hemiparesis	5 (55.6)	1 (16.7)	0.287
D-dimer	7.0 ± 5.2	4.2 ± 2.2	0.375
CRP	3.8 ± 3.7	1.3 ± 1.5	0.126
Fibrinogen	352.8 ± 33.8	408.2 ± 107.8	0.242
SSS	6 (66.7)	5 (83.3)	0.604
Cortical VT	9 (100.0)	4 (66.7)	0.525
Hemorrhage	6 (66.7)	1 (16.7)	0.119

Group H: Patients with hyperhomocysteinemia; Group C: Patients with normal level of homocysteine; N: Nausea; SSS: Superior Sagittal Sinus; VT: Venous Thrombosis

Discussion

In general, CVT occurs more commonly in young adults and in females than in males. However, there were some obvious differences in the baseline characteristics between ISCVT 9-13) and our study, such as the average age of the patients (37 years old vs. 54.6 ± 17.7 years old), the percentage of patients over 65 years old (8.2% vs. 25.0%), and the percentage of female patients (74.5% vs. 18.7%). Recently, Ohara et al. [15] and Shindo et al. [16] reported that in Japanese patients with CVT, the average age of the patients was 49 years old and 50 years old respectively, and the percentage of female patients was 50% and 59%, respectively. Our results and their results show that the CVT patients in Japan may be older and comprise less females compared to the CVT patients in Western countries. The most common risk factor in women has been reported to be oral contraceptive use [1-3,17-19]. The oral contraceptive use in Japan has been reported to be less than its use in Western countries [20]. The incidence of CVT in our study was 0.23% of all kinds of strokes or 0.30% of ischemic infarctions, which may be lower than previously reported. This may be due to few young female CVT patients using oral contraceptives in Japan.

The incidence of clinical symptoms was variable and depended on the particular reports; there was an 81% to 98% incidence of headache, a 27-76% incidence of seizure, a 10-64% incidence of unconsciousness, and a 27% to 76% incidence of focal neurological deficits [1-3,9]. Headache is the most common symptom in CVT, but patients without headache are sometimes reported. In ISCVT, CVT patients without headache were frequently older male patients [9,10,13]. Our study showed a low incidence of headache, 62.5%, which we suspected was due to the high percentage of older men in our study.

In the past, CVT was attributed to infections of the face and otomastoid areas, but after the introduction of antibiotics, it is more often related to pregnancy, puerperium, neoplasms, dehydration, genetic or acquired thrombophilia, and oral contraceptives [1-3,21]. Especially in Western countries, CVT is increased by the hypercoagulability induced by oral contraceptive use [17-19]. The odds ratios for CVT caused by oral contraceptive use and the mutation in the prothrombin gene (G20210A) were 10 and 22, respectively. The presence of both the prothrombin mutation and oral contraceptive use dramatically raises the odds ratio to 150 [19]. The patients with CVT in our study had as risk factors oral contraceptive use (1 patient), deficiencies of protein S (3 patients) and antithrombin III (2 patients), nephrotic syndrome (2 cases), iron deficiency anemia (3 patients), colon cancer (1 patient), and multiple myeloma in remission (1 patient). Furthermore, hyper-Hcy was identified in 9 (56.3%) of 16 patients (Table 2).

The metabolism of Hcy is regulated by 2 major pathways—remethylation and transsulfuration. Folate, vitamin B12 and Vitamin B6 play roles through the conversion or catalytic process

in these pathways. Thus, the deficiencies of these vitamins induce hyper-Hcy. Furthermore, environmental factors also have an important influence on the level of serum Hcy. Raised levels are found in some chronic diseases such as DM, and malignancy; after the administration of certain drugs such as oral contraceptives, AEDs, and methotrexate; and in patients of older age, male sex, postmenopausal status, heavy smoking history, etc. Folate and vitamin deficiencies can also occur because of chronic alcoholism, or low intake and disturbed digestive absorption of green or yellow vegetables and other foods containing these vitamins [22-24]. There were 9 cases of hyper-Hcy in our study. There was 1 case of folate deficiency, 1 case of B6 deficiency, and 2 cases of combined deficiencies of B12 and folate. One patient had total resection of the stomach, 2 had chronic alcoholism, 2 were heavy smokers, 2 had DM, and 1 was taking an AED. These disorders and habits may increase the level of Hcy. Additionally, we should recognize that even acquired conditions such as vitamin deficiencies, especially the deficiencies of both folate and vitamin B12, increased the level of Hcy to more than 100 nmol/ml.

Thrombotic diseases are frequently observed in patients with hyper-Hcy. Arterial and venous thromboses are potential complications [25]. Hyper-Hcy is confirmed as a risk factor for CVT [7,8], and its risk ratio is 4-fold compared to controls [26]. The prevalence of hyper-Hcy in CVT might exhibit racial differences [7-9]. Since we identified hyper-Hcy in 56.3% of our CVT patients, the prevalence of hyper-Hcy as a risk factor for CVT could be high in Japan. We report in this study the clinical characteristics in CVT cases, but no statistical differences of clinical characteristics could be found between the 2 CVT groups (with and without hyper-Hcy).

Our study has several limitations. First, this was a retrospective analysis, even though the patients were included without selection bias. Second, our hospital is not a general hospital, so there are fewer consultation requests from the Department of Obstetrics and Gynecology, except for severe emergency cases. Third, despite the fact that this is a hospital-based study, our hospital is the only neurological center in the local area, and hence this is almost a population-based study. In addition, even though CVT is a rare disease, 0.23% of all types of strokes, the number of samples examined in this study is small. Hyper-Hcy is a treatable risk factor in CVT and can be corrected by the supplementation of deficient vitamins and changes in lifestyle. We should pay attention to hyper-Hcy as a risk factor for CVT.

Conclusion

CVT in Japan commonly occurred in older males. The prevalence of hyper-Hcy as a risk factor of CVT was high, and the main underlying disorders were folate and vitamin B12 or B6 deficiencies. This is clinically important, because these acquired risks can be corrected by supplementation therapy to prevent the recurrence of CVT.

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