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A retrospective study of risk factors for calf muscle venous thrombosis in patients with cerebral hemorrhage

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Abstract

Objective: To investigate the risk factors for calf venous thrombosis in patients with cerebral hemorrhage, so as to provide a reference for clinical decision.
Method: Three hundred and ninety six intracerebral hemorrhage (ICH) patients were enrolled in this retrospective study from January 2017 to December 2019. Risk factors and predictors of occurrence for calf muscle venous thrombosis (CMVT) were analyzed by Chi-square test and logistic regression analysis. *Results:* One hundred and twenty eight ICH patients with CMVT and 268 without CMVT were included in the study. Demographic features comparison showed that ICH with CMVT patients showed older average age than those without CMVT (p=0.039). Co-morbid diseases analysis showed that patients with CMVT tend to complicate with diabetes mellitus (DM) (p=0.040). The comparison of laboratory examinations showed serum level of glucose (p=0.011), fibrinogen (p=0.046) and D-Dimer (p=0.007) to be significantly different. For clinical manifestations, the GCS score and muscle strength level were related to occurring of CMVT. Multivariate logistic regression identified higher age (OR=1.036, 95%CI =1.009-1.064, P= 0.008), higher D-Dimer level (OR=2.379, 95%CI =1.338-4.231, P= 0.003), low GCS (OR=0.932, 95%CI =0.868-0.998, P= 0.044) and lower affected side muscle strength (0-3 grade) (OR=1.624, 95%CI =1.009-2.614, P= 0.046) to predict higher incidence of CMVT in ICH patients.
Conclusion: Older age, higher D-Dimer level, lower GCS score and lower affected side muscle strength were associated with higher incidence of CMVT in ICH patients. Clinicians should consider prophylactic treatment to prevent CMVT in ICH patients with these risk factors.

Keywords: Calf muscle venous thrombosis, deep venous thrombosis, intracerebral hemorrhage, D-dimer

INTRODUCTION

Calf muscle venous thrombosis (CMVT) refers to deep venous thrombosis (DVT) of the lower extremity, located between gastrocnemius venous plexus and soleus venous plexus. It accounts for 5.6-31.3% of DVT of the lower extremity.[1] Intermuscular venous thrombosis has been reported to be associated with pulmonary embolism. There are few reports of cerebral hemorrhage complicated by intramuscular venous thrombosis. When CMVT occurs in patients with cerebral hemorrhage, there are usually no obvious symptoms, and the use of anticoagulant therapy is controversial, which may underestimate the harm of intramuscular venous thrombosis caused by intracerebral hemorrhage. This study retrospectively analyzed the clinical data of patients with intracerebral hemorrhage combined with intramuscular venous thrombosis to explore its clinical characteristics.

METHODS

From January 2017 to December 2019, 396 hemorrhagic stroke patients were recruited from the Department of Neurology and Neurosurgery of Tianjin Huanhu Hospital. The inclusion criteria were as follows: (1) Patients with spontaneous ICH (<6 hours); (2) increased systolic BP, 150-220 mmHg. The exclusion criteria were: (1) CMVT patients with pulmonary embolism or deep venous thrombosis; (2) Patients with a history of thrombosis or autoimmune diseases and vasculitis were prone to venous thrombosis in the past; (3) Patients with incomplete clinical data; (4) Patients with cerebral hemorrhage need surgery or die; (5) The patients were divided to two groups by

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with or without CMVT according to the results of lower limb Doppler ultrasonography. This prospective study was approved by the Huanhu Hospital ethnics committee.

Experimental design

Color Doppler ultrasound was performed by the same sonographer. Muscle strength was graded by the manual muscle test (MMT) approved by the British Medical Research Council (MRC). Muscle strength of the lower extremities was assessed by physicians who had worked in the ICU of Neurology for more than 10 years. Muscle strength of the lower extremities was divided into 4-5 grades (Affected side limb muscle strength≥4) and 0-3 grades (Affected side limb muscle strength≤3).

Statistical analysis

Continuous data are expressed as mean standard deviation and processed by Student's t-test. Categorical data are reported as numbers (percentages) and processed by Chi-square test. The relationship between two variables is predicted by linear regression. A binary logistic regression model is established by ENTER method. Odds ratio (OR) and its 95% confidence interval (CI) were determined. Cutoff points were calculated using receiver operating characteristic (ROC) curves. P values< 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

Clinical characteristics of CMVT patients

The mean age of all 396 patients with ICH (168 women and 228 men) was 62.46 ± 8.94 years, including ICH in which 128 (32.3%) had intramuscular venous thrombosis. The patients were divided into two groups, with or without intramuscular venous thrombosis. The demographic differences between ICH patients with and without CMVT were calculated, and there was no gender difference. ICH patients with CMVT were older than those without CMVT (Table 1). There were no differences in comorbidities, hyperlipidemia, and coronary artery disease, but for diabetes, CMVT patients tended to complicate DM (p = 0.040, table 1). Both groups had similar daily habits, including smoking and drinking history, and physical examination, including BMI, Systolic and diastolic blood pressures. About one-third of all ICH patients suffer from lower extremity discomfort symptoms. The most typical clinical discomforts are local pain (17.9%) and swelling (12.6%).Other common complaints include local skin temperature abnormalities (4.0%) and local skin color (1.8%).However, when comparing these symptoms in ICH patients with and without CMVT, No specific clinical manifestations of venous thrombosis of the lower extremities were identified (Table 2).

Table 1: Baseline characteristics of patients with ICH

Characteristics	Number of patients (n=396)	Percentage (%)
Demographics		
Female	168	42.4
male	228	57.6
Age	62.46 ± 8.94	NA
CMVT	128	32.3
Clinical manifestations		
No abnormality	276	69.7
Local pain	71	17.9
Lower extremity swelling	50	12.6
Local skin temperature	16	4.0
Local skin color	7	1.8

ICH: intracerebral hemorrhage; CMVT: calf muscle venous thrombosis

Table 2: Comparison between ICH patients with and without CMVT

Characteristics	ICH with thrombosis (n=128)	ICH without thrombosis (n=268)	P value
Age	63.80±9.52	61.82±8.60	0.039*
Gender	56.2%	58.2%	0.712
Co-morbid disease			
Hyperlipidemia	40 (31.2%)	67 (25.0%)	0.190
Diabetes mellitus	24 (18.8%)	30 (11.2%)	0.040*
Smoking	32 (25.0%)	59 (22.0%)	0.509
Alcohol	26 (20.3%)	41 (15.3%)	0.213
Coronary artery disease	12 (9.4%)	22 (8.2%)	0.698
Vital signs at admission			
BMI	25.66±2.18	25.67±1.88	0.988
Systolic pressure (mmHg)	139.20±12.40	140.35±13.87	0.425
Diastolic pressure (mmHg)	84.15±15.04	84.98±15.27	0.612
Clinical manifestations			
No abnormality	67.2%	70.9%	0.453
Local pain	21.1%	16.4%	0.257
Lower extremity swelling	11.7%	13.1%	0.707
Local skin temperature	3.1%	4.5%	0.523
Local skin color	2.3%	1.5%	0.548
Baseline characteristics of patients			
White cell count($x10^9$/L)	7.58±2.38	7.61±2.14	0.907
Glucose level (mmol/L)	6.11±2.52	5.49±1.53	0.011*
Total cholesterol (mmol/L)	4.60±0.98	4.64±1.04	0.712
HDL (mmol/L)	1.47±0.34	1.51±0.34	0.250
LDL (mmol/L)	2.80±1.04	2.70±0.86	0.324
Triglycerides (mmol/L)	2.35±1.90	2.07±1.65	0.137
Fibrinogen(g/L)	3.51±1.10	3.29±0.67	0.046*
D-Dimer(mg/L)	0.79±1.17	0.50±0.35	0.007*
PT(s)	11.42±0.77	11.35±0.75	0.392
APTT(s)	28.21±3.02	28.27±3.63	0.887
Hs-CRP (mg/L)	4.47±7.74	4.85±2.49	0.589
HCY (μmol/L)	9.35±6.92	8.96±6.31	0.578
GCS	7.95±3.20	8.71±3.31	0.031*
Muscle strength (grade 0-3)	46.1%	29.9%	0.002*

ICH: intracerebral hemorrhage; CMVT: calf muscle venous thrombosis; BMI: Body Mass Index; HDL: high density lipoprotein; LDL: low density lipoprotein; PT: Prothrombin time; APTT: activated partial thromboplastin time; Hs-CRP: high-sensitivity C-reactive protein; HCY: homocysteine; GCS: Glasgow Coma Scale.

Risk factors and laboratory tests

To determine the risk factors that may be associated with the occurrence of CMVT in ICH patients, we compared laboratory tests between ICH patients with and without CMVT. The results showed that serum glucose, fibrinogen and D-dimer concentrations were significantly different between the two groups (Table 2). Other laboratory tests such as white blood cell count, lipid levels, clotting time, serum Hs-CRP and HCY were similar between the two groups (Table 2). On the other hand, our results showed that the level of coma and muscle strength were related to the occurrence of CMVT in ICH patients. The GCS score and the occurrence of lower limb low muscle strength (grade 0-3) were significantly different between the two groups (Table 2).

Regression analysis of risk factors for CMVT

To understand whether those significantly different factors were independent risk factors for CMVT in ICH patients, binary logistic regression analysis was performed and age, D-dimer level, GCS score and lower limb muscle strength were identified as independent risk factors (Table 2). Higher age (OR = 1.036, 95%CI =1.009-1.064, P= 0.008), higher D-dimer level (OR = 2.379, 95%CI =1.338-4.231, P =0.003), low GCS (OR = 0.932, 95%CI =0.868-0.998, P= 0.044) and lower limb muscle strength (grade 0-3) (OR = 1.624, 95%CI =1.009-2.614, P= 0.046) would predict a higher incidence of MCVT in ICH patients with patience (Table 3). Therefore, clinicians should pay more attention to ICH patients with these characteristics.

In summary, the incidence of MCVT in patients with cerebral hemorrhage is not low; it is usually silent; age, D-dimer GCS and lower limb muscle strength 0-3 grade are risk factors.

DISCUSSION

Deep venous thrombosis is not easy to detect clinically, especially in comatose patients with ICH who usually have impaired consciousness and sensory deficit, so the misdiagnosis rate of DVT is high and the diagnosis is late.[2] The incidence of DVT in patients with hemorrhagic stroke is almost four times higher than that in patients with ischemic stroke.[3] CMVT is usually clinically silent. Moreover, it is often underdiagnosed. Many investigator have proposed that the formation of intramuscular venous plexus thrombosis is one of the main causes of DVT.[4]There are increasing reports of severe DVT caused by the spread of CMVT thrombus, leading to pulmonary embolism (PE) with CMVT thrombus detachment, leading directly to PE. However, there is still widespread controversy about the epidemiological characteristics and clinical significance of MCVT. Gillet *et al*. followed 128 patients with MCVT and found that 7% of them were PE.[5] Lautz *et al*. reported a 3.9% incidence of PE in 406 patients with MCVT.[6] Marcus *et al*. followed 57 patients with MCVT and found that 5 patients developed PE with an incidence of 8.8%.[7]

Our study shows that the incidence of CMVT is not as low as previously reported when examined with ultrasound. Isolated leg muscle thrombosis is mainly clinically characterized by unilateral leg fullness, dilatation and tightness. There is no swelling or slight swelling in the legs and skin tension is not high. However, the incidence of these symptoms is low and is not clinically easy to detect. All of this leads to the delay in diagnosing CMVT promptly and may lead to the spread of thrombosis to major deep veins and pulmonary embolism. Newly formed or incompletely organized thrombi may shed and enter the pulmonary artery with blood flow,

Table 3: Binary logistic regression to identify risk factors for calf muscle venous thrombosis (CMVT) in intracerebral hemorrhage (ICH) patients

Risk factors	OR (Exp (B))	Significance (P)	95% CI for Exp(B)	
			Lower	Upper
Age	1.036	0.008*	1.009	1.064
D-Dimer	2.379	0.003*	1.338	4.231
GCS	0.931	0.044*	0.868	0.998
Muscle strength (grade 0-3)	1.624	0.046*	1.009	2.614
Diabetes Mellitus	1.127	0.731	0.571	2.221
Fibrinogen	1.244	0.112	0.950	1.630
Glucose	1.095	0.175	0.960	1.250

GCS: Glasgow Coma Scale

leading to pulmonary embolism.[8] In our study, the results showed that age, GCS and muscle strength grade 4-5 were risk factors for CMVT. There were many reasons for the older age as a risk factor, including progressive reduction in exercise and intensity, vascular aging, and decreased muscle pump function.[9] The GCS score is the most commonly used scale for assessing craniocerebral injury. The lower the score, the more severe the coma. Patients with low GCS score may have prolonged bed rest, and stagnant calf blood flow. Retrospective studies have also shown that GC < 8 has a greater impact on DVT. This is similar in our findings.[10] Patients with unilateral limb muscle strength grades 0 to 3 have a higher incidence of DVT. For patients with severe hemiplegia whose muscle strength is lower than grade 3, blood stasis from prolonged bed rest can lead to the accumulation of coagulation factors and exacerbate hypercoagulability. On the other hand, venous valves of calf muscles are fewer, so patients with severe hemiplegia are prone to CMVT.[11]

The common currently used D-dimer detection methods have low specificity, high predictive value and high diagnostic sensitivity for acute lower extremity venous thrombosis. If D-dimer is less than 500 ug/L (enzyme-linked immunosorbent assay), the possibility of acute or active lower extremity venous thrombosis can be excluded.[12-14] Some researchers also reported that D-dimer was <500 g/L in approximately 35% of CMVT patients, suggesting that this test has limited sensitivity to exclude CMVT.[15] Negative results of D-dimer help exclude acute intermuscular venous thrombosis. This study suggests that physicians should pay attention to the occurrence of intermuscular venous thrombosis as D-dimer increases. So we suppose that CMVT is a clinical condition that can develop into deep venous thrombosis and lacks specific clinical manifestations. We should attach great importance to older age, muscle strength grade 0-3, increased D-dimer and lower GCS score. The best way to help early identification of CMVT is to control risk factors and prevent the occurrence of CMVT as early as possible.

There are some limitations in this study. First, the number of patients is small and is from a single-center. Thus, our results needs to be validated in a larger sample size population. Second, the risk factors analyzed in this study is not comprehensive; we did not analyze factors such as past medication history, and hemorrhage imaging results. Increasing the factors included in the analysis may improve the sensitivity of the model. Whilst angiography is the gold standard for the diagnosis of venous thrombosis, we used B-ultrasound examination which is less sensitive.

DISCLOSURE

Conflict of interest: None

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