Research Square

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

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Abstract

Purpose To investigate the risk factors for calf venous thrombosis in patients with cerebral hemorrhage, so as to provide a reference for customized clinical decision.

Methods 396 intracerebral hemorrhage (ICH) patients were enrolled in this retrospective study from January 2017 to December 2019. Risk factors and predictors of occurrence for Muscle calf venous thrombosis (MCVT) were summarized and analyzed by Chi-square test and logistic regression analysis.

Results: 128 ICH patients with MCVT and 268 without ones were included. Demographic features comparison showed that ICH with MCVT patients showed older average age than those without ones (p=0.039). Co-morbid diseases analysis showed that patients with MCVT 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) was significantly different. For clinical manifestations, the coma degree (GCS score) and muscle strength level were related to occurring of MCVT. 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) will predict higher incidence of MCVT in ICH patients.

Conclusion: According to our study, higher age, higher D-Dimer level, lower GCS score and lower affected side muscle strength were associated with higher incidence of MCVT in ICH patients. Clinical doctors should pay more attention to prevent MCVT in ICH patients which coincide with those risk factors.

Background

Muscle calf venous thrombosis (MCVT) refers to deep venous thrombosis 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 MCVT 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.

Materials And Methods

Patient recruitment: From January 2017 to December 2019, 396 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) (SBP, 150-220 mmHg) increased.
Exclusion criteria included:

(1) MVCT 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.

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

1. **Clinical characteristics of MCVT patients**

The mean age of all 396 patients with intracerebral hemorrhage (168 women and 228 men) was 62.46 ± 8.94 years, including intracerebral hemorrhage 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 MCVT were calculated, and there was no gender difference. ICH patients with MCVT were older than those without MCVT (Table 1). There were no differences in comorbidities, hyperlipidemia, and coronary artery disease, but for diabetes, MCVT patients tended to complicate DM (p = 0.040, talbe1). 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 MCVT, No specific clinical manifestations of venous thrombosis of the lower extremities were identified (Table 2).

2. **Risk factors and laboratory tests:**

To determine the risk factors that may be associated with the occurrence of MCVT in ICH patients, we compared laboratory tests between ICH patients with and without MCVT. 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 MCVT 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).

3. **Regression analysis of risk factors for MCVT**

To understand whether those significantly different factors were independent risk factors for MCVT 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. Therefore, clinicians should pay more attention to ICH patients with these characteristics.

Conclusion

1. The incidence of MCVT in patients with cerebral hemorrhage is not low. 2.Performances are usually silent. 3. 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 intracerebral hemorrhage who are usually conscious and sensory impairment, 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). MCVT usually occurs silently in clinic. Moreover, it is often neglected that many scholars 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 MCVT thrombus, leading to pulmonary embolism (PE) and MCVT thrombus detachment, leading directly to PE. However, there is still widespread controversy about the epidemiological characteristics and clinical significance of MCVT. Gillet followed 128 patients with MCVT and found that 7% of them were PE (5). Lautz reported a 3.9% incidence of PE in 406 patients with MCVT

(6). Marcus 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 MCVT is not as low as previously reported when examined with ultrasound. Isolated leg muscle thrombosis is mainly 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 y low and is not easy to detect. All of this leads to the inability to detect MCVT 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, leading to pulmonary embolism(8).In our study, the results showed that age, GCS and muscle strength grade 4–5 were risk factors for MCVT. There were many reasons for this age distribution. The incidence of ICDVT-related diseases (e.g., hypertension) is increasing. Many other factors may also contribute to age-related ICDVT, 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 condition is. Patients with low preoperative GCS score are more severely ill, Intellectual impairment is severe, often accompanied by limb dyskinesia, so bed rest is long, blood flow is slow, and local blood flow is stagnant. 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 caused by 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 MCVT (11).

At present, commonly 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 MVCT patients, suggesting that this test has limited sensitivity to exclude MCVT (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 MCVT 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 MCVT is to control risk factors and prevent the occurrence of MCVT as early as possible.

There are some limitations in this study. First, this study is a small-scale study and it is a single-center study that still needs to be validated in a larger sample size population. Second, the influencing factors used in this analysis are not included in other results, such as past medication history, and hemorrhage imaging results, etc. Increasing the factors included in the analysis may be important to improve the sensitivity of the model. Angiography is the gold standard for the diagnosis of venous thrombosis on account of B-ultrasound examination has a certain error rate.

Declarations

Ethics approval and consent to participate The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Tianjin Huanhu Hospital.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

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Authors' contributions:

Dr. Xiaogang Gao: contributed to drafting the manuscript and collecting clinical data

Dr. Yi Li: contributed to analysis and interpretation of data and critical revision of the manuscript

Dr. Dongzhe Hou: contributed to searching and screening all relevant references

These authors contributed equally to this work.

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Tables

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
MCVT	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

Table 2, Comparison between ICH patients with and without MCVT.

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(x109/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*

Table 3: Binary logistic regression to identify risk factors for MCVT in 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