Cerebral Venous Sinus Thrombosis in Patients With Inflammatory Bowel Disease: A Retrospective Study

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Research Article

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Abstract

BACKGROUND: Cerebral venous sinus thrombosis (CVST) is a rare and devastating complication of inflammatory bowel disease (IBD). Early diagnose and prompt treatment could improve prognosis.

AIM: The aim of our study was to investigate the clinical data and risk factors of inflammatory bowel disease with diagnosis of CVST.

METHODS: All data of IBD patients were collected from July 2013 and September 2020. Clinical data, risk factors and prognosis were compared between CVST in IBD patients and IBD control group.

RESULTS: The incidence of CVST in our study was 0.48%. The mean age of IBD patients with CVST was 34.9 years. Average disease duration of IBD was 4 years when cerebrovascular events occur. Clinical presentation of CVST included headache (73.1%), vomiting (30.8%), limb dysmetria (26.9%), speech impairment (11.5%), blurred vision (7.7%), Epileptic seizures (7.7%) and drowsiness (3.8%). The most common location for CVST was transverse sinus (61.5%), followed by superior sagittal sinus (30.8%). Anemia, low albumin and elevated D-dimer were independent predictors of CVST in IBD patients. Anticoagulation therapy was effective. Prognosis of IBD patients with CVST was worse than those without CVST.

CONCLUSION: Early identification the risk of and clinical features of CVST in IBD patients is important. Prompt antithrombotic therapy is safe and effective treatment.

1. Introduction

IBD is a chronic inflammatory disease associated with abnormal coagulable state. The risk of thrombosis in IBD is three to fourfold of the general population[1]. Deep venous thrombosis and pulmonary embolism (PE) have been well recognized. Cerebral venous sinus thrombosis (CVST) is a serious complication of IBD with high mortality. The reported incidence of CVST in IBD varied between 0.5–6.7%[2]. Clinical symptoms of CVST could vary from headaches to coma thus making diagnosis difficult. Due to variable clinical manifestations and low incidence, it could be misdiagnosed by physicians.

CVST is suspected to be a consequence of the hypercoagulable state occurring during IBD disease relapse. Several risk factors for vascular thrombosis have been reported for IBD. Smoking, bowel operation history, low hemoglobin, low platelet and low albumin levels might contribute to thrombosis[3]. Since the recognition of inflammation can activate coagulation systems, disease activity contributed to coagulopathy[4]. Episodes of intestinal inflammation elaborated inflammatory cytokines and the development of a prothrombotic state. Treatment of IBD, such as steroid[5], was also reported to be associated with CVST. Precise risk factors for CVST were not clear.

To the best of our knowledge, only a few small sample studies have been published on IBD patients with CVST. Most studies about CVST were case report. CVST often occur during disease flare. Nevertheless,

some case reports did show CVST occurred during disease remission[6]. Better understanding the risk factors and clinical manifestations for CVST may assist with early diagnosis and treatment, thus the prognosis could be improved. This study aimed to investigate risk factors and clinical features of cerebral vascular thrombosis in IBD patients. Furthermore, we aimed to investigated the prevention as well as treatment to CVST in IBD patients.

2. Results

2.1 Prevalence of CVST

A total of 5368 IBD patients were reviewed. Of these IBD patients, 26 patients (n = 20 for UC and n = 6 for CD) were diagnosed with CVST. The incidence proportion of CVST in IBD was 0. 48% (26/5368).

2.2 Characteristics of patients with CVST

Patient demographics and underlying diseases were described in Table 1. The mean age of IBD patients with CVST was 34.9years. The median time interval was 4 years (range: 2 years − 6.9 years). They were 17 males and 9 females. Most CVST events occurred during IBD disease flare (96.2%), only 1 patient (3.8%) during disease remission. Moderate (42.3%) to severe (38.5%) active disease was detected in most patients. Laboratory characteristics and medication was recorded (Table 2 and Table 3). There were no statistical differences in gender, age, disease duration, post operation history, disease Montreal classification, and disease severity between CVST group and IBD controls.

Table 1
Demographic data of IBD patients

Variables	CVST group	Non-CVST group	Total	*p*-value
Age	34.9 ± 15	38.7 ± 10.3	37.9 ± 11.4	0.127
Disease duration	4(2-6.9)	5(2.7–7.3)	4(2–7)	0.304
VTE history	5 (19.2)	2 (1.9)	7 (5.4)	0.004
Diabetes mellitus	3 (11.5)	3 (2.9)	6 (4.6)	0.094
Atrial fibrillation	4 (15.4)	3 (2.9)	7 (5.4)	0.029
operation history	4 (15.4)	35 (33.7)	39 (30)	0.094
Smoking	14 (53.8)	18 (17.3)	32 (24.6)	0.001
Alcohol consumption	8 (30.8)	9 (8.7)	17 (13.1)	0.006
severity				0.45
severe	10 (38.5)	27 (26)	37 (28.5)	
moderate	11 (42.3)	42 (40.4)	53 (40.8)	
mild	4 (15.4)	30 (28.8)	34 (26.2)	
remission	1 (3.8)	5 (4.8)	7 (5.4)	
Values are presented as number (%). VTE, venous thromboembolism				

Table 2
Laboratory characteristics of IBD patients with and without CVST

Variable	CVST group	Non-CVST group	Total	*p*-value
Hemoglobin(g/L)	88 (81.83-93)	104.5 (92–123)	98.60(89–118)	< 0.001
Platelets (x10^9/L)	302.5 ± 138.53	286.42 ± 103.56	289.64 ± 111	0.583
Albumin (g/L)	27.35 ± 4.54	34.00 ± 5.53	32.67 ± 6.0	< 0.001
LDL-C (mmol/L)	2.09 (1.47–2.84)	2.08 (1.71–2.65)	2.08(1.68–2.70)	0.852
hsCRP (mg/L)	23.51(7.75–31.80)	21.4 (7.42–53.2)	21.73(7.74–49.91)	0.673
D-dimer(mg/L)	1.19 (0.26–2.9)	0.2 (0.08–0.42)	0.25 (0.09–0.62)	< 0.001

Table 3
Medication history of IBD cohort and outcome of patients

	CVST group	Non-CVST group	Total	*p*-value
5-ASA	20 (76.9)	70 (67.3)	90	0.342
steroid use	22 (84.6)	54 (51.9)	76	0.002
Azathioprine	12 (46.2)	46 (44.2)	58	0.86
infliximab	6 (23.1)	16 (15.4)	22	0.384
outcome				0.029
deteriorate	4 (15.4)	3 (2.9)	7 (5.4)	
improved	22 (84.6)	101 (97.1)	123 (94.6)	

Neurological symptoms of CVST included persistent headache (73.1%), vomiting (30.8%), limb dysmetria (26.9%), speech impairment (11.5%), blurred vision (7.7%), Epileptic seizures (7.7%) and drowsiness (3.8%). CVST was diagnosed with cranial MRI and MRV in 23 patients, and with CT in 3 patients. The most common location for CVST was transverse sinus (61.5%), followed by superior sagittal sinus (30.8%), sigmoid sinus (23.1%) and straight sinus (7.7%). Infarction was found in 15.4% patients. A total of 104 IBD control patients (80 UC patients and 24 CD patients) were included in the analysis.

2.3 Risk factors of patients with CVST

Multivariate Analysis of risk factors revealed that anemia, low albumin and elevated D-dimer were independent predictors of CVST. Smoking, alcohol consumption, history of thromboembolic disease, atrial fibrillation and steroid usage were not significantly associated with CVST in the multivariate analysis, despite being significant in the univariate analysis (Table 4).

Table 4
Multivariate Analysis of Risk Factors of CVST in IBD patients

	OR	95% C.I.	*p*-value
VTE history	3.24	0.407–25.799	0.267
Atrial fibrillation	1.884	0.12-29.621	0.652
Smoking	2.634	0.51-13.589	0.247
Alcohol consumption	4.681	0.726–30.167	0.104
Hemoglobin	0.951	0.907–0.998	0.042
Albumin	0.793	0.668–0.943	0.008
D-dimer	1.301	1.02–1.661	0.034
Steroid use	0.84	0.171–4.138	0.831

2.4 CVST and treatment response

After the diagnosis of CVST, 23 patients were treated with low-molecular-weight heparin (LMWH) and warfarin. Two patients received novel oral anticoagulants. One patient received aspirin and clopidogrel treatment. No patient suffered massive hemorrhage after antithrombotic treatment. The evolution was favorable in 22 (84.6%) patients and fatal in 4 (15.4%) patients following significant cerebral edema and 2 with infarct progression. Mortality rate of IBD patients with CVST was significantly higher than that of without CVST patients ($p < 0.05$).

3. Discussion

To the best of our knowledge, this is the biggest clinical retrospective sample study to investigate IBD and CVST so far. CVST has been reported as an uncommon and devastating complication of IBD. The incidence of CVST in our study was 0.48%, slightly lower than previous study. The difference might be due to different races and nationalities. CVST is one of disorders of hemostasis. Previous study also showed lower risk of VTE in general East Asian populations and hospitalized IBD patients than Western countries[3]. Besides, owing to the nature of a retrospective study, patients underwent cerebral image examination only when they appear neurological symptoms, so the actual incidence of CVST in IBD might be underestimated.

In our study, CVST often occurs during acute IBD, in rare conditions during remission. Case reports also showed the occasionally events during IBD remission[6]. Male accounted for majority (65.4%). Mean age of CVST with IBD was 34.9 years, lower than reported average age of 40.7 years in CVST patients without IBD[7]. Symptoms of CVST was variable and easily ignored. Headache was the most frequent symptoms. Transverse sinus and superior sagittal sinus were frequently involved. This was in accordance with some previous study[6, 8, 9].

Anemia, low albumin and elevated D-dimer were risk factors for CVST in our study. Previous studies also showed anemia and coagulation abnormalities were frequent risk factors for CVST in most reports[8, 9]. Elevated D-dimer values was an independent risk factor for thromboembolism in IBD. Case report also showed predictive value of D-dimer in CVST[10, 11]. Role of medical treatment for IBD was in controversial. Glucocorticoid was reported to prompt thrombosis by activating coagulation factors and was independent factor for thrombosis in some reports[5, 12]. Scholars also had different opinion[13]. Usage of steroid was more common seen in CVST patients in our study. However, multivariate analysis showed steroid might not be independent risk factor for CVST. Perhaps steroid might be a reason for VET but not for CVST. Further studies are needed to evaluate its role in CVST. Thiopurines and antitumor necrosis factor (TNF), due to their anti-inflammatory properties, might lowered the risk of thrombosis events[14], while some documented high dose of IFX might contribute to CVST[15]. In our study, treatment of IBD did not increase the risk of CVST. The identifying of potential risk factors is important, as specific therapeutic measures and prophylactic anticoagulation to prevent CVST events can reduce mortality and disability.

Treatment of IBD with CVST was the same with patients without IBD. The first-line treatment for CVST is adjusted-dose low-molecular-weight heparin[2]. Novel oral anticoagulants was also recommended for its effectiveness and safety in treating cerebral venous thrombosis [16]. Our study showed anti-thromboembolism therapy was safe. Dose-weighed LMWH did not increase risk of massive bleeding. Besides, 2 patients treated with novel oral anticoagulants also acquire good curative effect.

The prognosis of IBD with CVST was worse than that without CVST. Previous study showed mortality rate of IBD patients with CVST could reach up to 25%[17]. Acutely diagnose and treatment could get better prognosis[9]. For IBD patients with high risk of CVST, prophylactic anticoagulation with heparin or low molecular weight heparin might decrease risk and mortality rates even in IBD patients complicated with CVST[8]. Besides, study also showed prophylaxis of thrombosis for IBD patients was safe and should be recommended[18–20].

Our study had several limitations. First, it is a single-center retrospective study, with limited power to detect significant clinical features. The selection of controls could introduce unintentional bias. Besides, we did not explore mechanism of CVST in IBD patients. Multi-center and further studies are needed to explore preventive and better treatment measures.

In conclusion, CVST was found in 0.48% IBD patients in our series. Patients with IBD were younger and a male predominance compared with those without IBD. Headache was most common symptoms. Anemia, low level of albumin and elevated D-dimer were independent risk factors. CVST could occur during both active and remission phase. Acute antithrombosis therapy might improve prognosis.

4. Materials And Methods

4.1 study population and data collection

This was a retrospective study conducted in the First Affiliated Hospital of Zhengzhou University between July 2013 and September 2020. The diagnosis of IBD was based on clinical, endoscopic, morphological and histological criteria. Diagnosis of CVST were based on clinical symptoms and evidence of thrombosis in cerebral venous sinuses detected by cranial CT, MRI, magnetic resonance venography[9]. Patients with hematological disease, patients taking contraceptives and IBD patients with incomplete clinical data were excluded. In all CVST patients with IBD, we recorded the type of IBD: ulcerative colitis (UC) and Crohn's disease (CD), possible risk factors, clinical manifestations and radiologic features. Controls were randomly selected from diagnosis of IBD without thrombosis for a ratio of 4:1 (controls: cases). All methods were carried out in accordance with relevant guidelines and regulations. This study was approved by Committee of The First Affiliated Hospital of Zhengzhou University, and all patients signed the informed consent.

4.2 Statistical Analysis

Statistical analysis was performed using SPSS 21.0. Results were provided as mean ± standard deviation (SD) and percentages. Univariate analysis, chi-squared test and Fisher's exact test were used to compare categorical variables and unpaired t-test for continuous variables. Variables that showed a *P*-value < 0.05 in the univariate analysis were performed into a logistic regression analysis to identify risk factors associated with the development of CVST.

Abbreviations

CVST, Cerebral venous sinus thrombosis

IBD, inflammatory bowel disease

PE, pulmonary embolism

UC, ulcerative colitis

CD, Crohn's disease

SD, standard deviation

LMWH, low-molecular-weight heparin

VTE, venous thromboembolism

LDL-C, low-density lipoprotein cholesterol

hsCRP, hypersensitive C-reactive protein

5-ASA, 5-aminosalicylate

Declarations

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Author Contributions

Wang Shujun – study design, data extraction and statistical analysis, drafting of the manuscript, approval of the final manuscript. Zhang Huijie, Bai Xia – approval of the final manuscript. Wang Hongjian - study design and supervision, statistical analysis, drafting of the manuscript, approval of the final manuscript.

Conflict of Interest

The authors declare no conflict of interest

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