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Clinical presentation of venous thromboembolism in inflammatory bowel disease ☆

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Abstract

Background and aims: Patients with inflammatory bowel disease (IBD) are at increased risk of venous thromboembolism (VTE), but data on frequency, site of thrombosis and risk factors are limited. We sought to determine prevalence, incidence as well as location and clinical features of first VTE among IBD patients.
Methods: We evaluated a cohort of 2811 IBD patients for a history of symptomatic, objectively confirmed first VTE, recruited from 14 referral centers. Patients with VTE before IBD diagnosis or cancer were excluded. Incidence rates were calculated based on person-years from IBD diagnosis to first VTE or end of follow-up, respectively.
Results: 2784 patients (total observation time 24,778 person-years) were analyzed. Overall, of 157 IBD patients with a history of VTE, 142 (90.4%) had deep vein thrombosis (DVT) and/or pulmonary embolism (PE), whereas 15 (9.6%) had cerebral, portal, mesenteric, splenic or internal jugular vein thrombosis. The prevalence and incidence rate of all VTE was 5.6% and 6.3 per 1000 person years, respectively. Patients with VTE were older at IBD diagnosis than those without VTE (34.4±14.8 years vs 32.1±14.4 years, p=0.045), but did not differ regarding sex, underlying IBD and disease duration. 121 (77.1%) VTE were unprovoked, 122 (77.7%) occurred in outpatients and 78 (60.9%) in patients with active disease. Medication at first VTE included corticosteroids (42.3%), thiopurines (21.2%), and infliximab (0.7%).
Conclusion: VTE is frequent in IBD patients. Most of them are unprovoked and occur in outpatients. DVT and PE are most common and unusual sites of thrombosis are rare.

1. Introduction

Inflammatory bowel disease (IBD) is a risk factor for first as well as recurrent venous thromboembolism (VTE), which are often serious events associated with high mortality.[1–13] VTE is common in Western populations affecting 1-2 per 1000 persons per year among Europeans.[14] Compared to non-IBD subjects, patients with IBD are at a 2- to 4-fold increased risk of VTE, which seems to affect Crohn's disease (CD) and ulcerative colitis (UC) to a similar extent.[2–8] This risk for VTE has been described in several population-based and hospital-based cohort studies as well as in case control studies.[2–8] The mechanism leading to the increased thrombotic risk in IBD is not known. However, acquired risk factors seem to play the most relevant role.[12] On the one hand active disease and associated inflammation are thought to be the main reason.[6,12] Thus, IBD, especially at the time of an acute flare-up, can be regarded as a prothrombotic condition.[7,12] Many haemostatic alterations that confer a hypercoagulable state have been described and appear to be related to disease activity in IBD.[12] Furthermore, fistulas and abscesses complicating the course of CD might also provoke VTE. On the other hand patients with IBD are often exposed to well-established thrombosis risk factors such as surgery, immobilization, dehydration, and central venous catheters, which might additionally contribute to the increased risk of VTE.[3,10,12]

The most common sites of VTE in IBD patients as well as in non-IBD subjects are deep venous thrombosis (DVT) and pulmonary embolism (PE).[12] But also unusual sites have been reported, including the cerebrovascular, portal, mesenteric, or retinal veins.[12,15–21] In almost all publications about VTE in IBD patients only DVT and PE have been regarded without considering other locations.

We performed a nationwide multicenter study to determine the prevalence and incidence of all VTEs, including DVT and PE as well as other sites of thrombosis, in a large cohort of IBD patients and to describe associated clinical features at the time of first VTE.

2. Methods

2.1. Study design and patients

The study was performed as a multicenter cohort study with 14 participating centers in Austria specialized in the treatment of patients with IBD. Between June 1, 2006, and December 31, 2008, data of all patients older than 18 years with an established diagnosis of IBD (based on clinical, endoscopic, histological, and radiological criteria according to European Crohn's and Colitis Organisation (ECCO) guidelines),[22,23] who attended the outpatient clinics of the respective referral center were screened and retrospectively evaluated for a diagnosis of VTE that occurred after the diagnosis of IBD. This study is a subanalysis of a previously published study on the risk of recurrent VTE in IBD patients compared with non-IBD patients.[11] Detailed methods and the results have been described previously.[11] Briefly, IBD- and VTE-related data were collected from a standardized questionnaire provided to the patient by the treating physician or via telephone interview by the study coordinator (AS). The information of the patients was double-checked by reviewing patient charts and missing data were added and further reviewed for accuracy and completeness by two investigators (GN and AS).[11]

Patients with VTE prior to diagnosis of IBD, cancer, or a VTE not confirmed by objective imaging techniques were excluded. The observation period was defined as the time from diagnosis of IBD to first VTE or end of follow-up, respectively. Screening for genetic thrombotic risk factors

Table 1 Baseline characteristics of IBD patients with and without VTE.

Characteristics	Patients with VTE N=157	Patients without VTE N=2627	P
Age at diagnosis of IBD (y), mean±SD	34.4±14.8	32.1±14.4	0.045
Duration of IBD (y), mean±SD	8.8±9.4	8.9±8.1	0.513
Females, n (%)	89 (56.7)	1315 (50.1)	0.118
Crohn's disease, n (%)	109 (69.4)	1676 (63.8)	0.301
Ulcerative colitis, n (%)	46 (29.3)	889 (33.8)	0.278
Inflammatory bowel disease unclassified, n (%)	2 (1.3)	62 (2.4)	0.124

IBD, inflammatory bowel disease; VTE, venous thromboembolism; y, years.

such as factor V Leiden and factor II G20210A were carried out on genomic DNA as described previously.[11] The study was approved by all local Ethics Committees and patients gave informed consent prior to inclusion in the study.

2.2. Diagnosis and classification of VTE

All VTE had to be objectively confirmed by imaging procedures, such as compression ultrasound or venography for DVT, spiral computed tomography or ventilation/perfusion lung scanning for PE, and computed tomography for VTE of other locations. Patients with both DVT and PE were categorized as having PE. VTEs occurring secondary to trauma, surgery, or pregnancy were classified as "provoked VTEs". All other VTEs were classified as "unprovoked VTEs".[11]

2.3. Outcome variables

The primary outcome variable was the frequency and site of the first VTE. Other outcome variables of interest were age at VTE, sex, presence of provoking factors, oral contraceptive use, body mass index (BMI; calculated as body weight in kilograms divided by body height in meters squared) and IBD-related parameters. These included type of IBD, age at diagnosis, disease extent and behavior (according to the Montreal classification),[24] intestinal IBD-related surgery (bowel resection only), medication, smoking habits, and disease activity at the time of the first VTE. Active Crohn's disease was defined by a Harvey-Bradshaw Index of >4 and active ulcerative colitis was defined by a simple clinical colitis activity index of ≥ 2.5.[25,26] A smoker was defined as a patient who smoked at least 7 cigarettes weekly for at least 1 year.[27]

2.4. Statistical analysis

SPSS 15.0.1 software (SPSS Inc., Chicago, IL) was used for statistical analysis. Data are presented as numbers, percentages, and mean values with standard deviation, respectively. Incidence rates were calculated based on person-years of observation (time from diagnosis of IBD to first VTE or end of follow-up, respectively) and are given as events per 1000 patient years. To compare the differences of these rates between CD and UC Cox regression analysis was used. Groups were compared by the Student *t*-test for continuous variables and chi-square test for categorical variables. $P<0.05$ was regarded significant.

3. Results

3.1. Patients

2811 IBD patients were identified and evaluated for a history of VTE. Twenty-seven patients were excluded due to cancer (n=10), VTE prior to the diagnosis of IBD (n=10), or a non-objective diagnosis of VTE (n=7) leaving 2784 IBD patients for further analysis.

One-hundred-fifty-seven patients (5.6%) had a history of objectively confirmed VTE. The characteristics of patients with and without VTE are given in Table 1. Patients with VTE were older at the time of diagnosis of IBD compared to patients without VTE, but did not differ with regard to sex, underlying IBD or duration of disease. The mean observation period for all patients was 8.8 years (SD±9.4 years) resulting

Table 2 Prevalence and incidence rates of VTE.

	All (n=2784)	CD (n=1785)	UC+IBDU (n=999)	P
Observation time (years), mean±SD	8.8±9.4	8.8±8.2	8.9±8.2	0.734
Prevalence all VTEs, %	157 (5.6%)	109 (6.1%)	48 (4.8%)	0.171
Incidence all VTEs/1000 py	6.3	6.95	5.4	0.122
Prevalence DVT±PE, %	142 (5.1%)	102 (5.7%)	40 (4.0%)	0.059
Incidence DVT±PE/1000 py	5.7	6.50	4.50	0.038

VTE, venous thromboembolism, DVT, deep venous thromboembolism, PE, pulmonary embolism, CD, Crohn's disease, UC, ulcerative colitis, IBDU, inflammatory bowel disease unclassified; py, person years.
Patients with IBDU were added to the group of patients with UC.

in 24,778 total person years (Table 2). The incidence rate of all VTE was 6.3/1000 person years.

3.2. Clinical features of VTE

The majority of VTE was DVT and/or PE (n=142; 90.4%) (Table 3). The corresponding results of prevalence and incidence rate for DVT+/PE were 5.1% and 5.7/1000 person years, respectively (Table 2). Other locations of thrombosis were rare (n=15; 9.6%) and included portal, superior mesenteric, splenic, internal jugular, and cerebral veins (Table 3). This group of patients with unusual sites was too small and heterogeneous with regard to location of thrombosis to perform meaningful subgroup analyses. Most of the VTEs were spontaneous without evidence of provoking factors (77.1%) and most of them occurred in outpatients (77.7%). Surgery (28 out of 36; 77.8%), central venous catheters (n=6; 16.7%), and trauma (n=2; 5.5%) were identified provoking factors. Three patients received thromboprophylaxis with low molecular weight heparin at the time of VTE, which occurred secondary to surgery, trauma or immobilization due to pneumonia, respectively. Almost two-thirds of the patients had active disease at the time of first VTE. Medication at first VTE included 5-aminosalicylic acid (54%), corticosteroids (42.3%), thiopurines (21.2%), and infliximab (0.7%) (Table 3). The prevalence of genetic thrombotic risk factors including factor V Leiden and prothrombin mutation are given in Table 3.

Prevalence and incidence rate of DVT and/or PE were higher in CD than in UC (5.7% vs. 4.0%, p=0.059; 6.4 vs. 4.5 per 1000 person-years, p=0.038) (Table 2). No difference was found between CD and UC for the frequency of all VTE. Patients with inflammatory bowel disease unclassified were added to the group of patients with UC.

3.3. Recurrent VTE

Thirty-nine of 157 (24.8%) patients had recurrent VTE. Most of the recurrent VTEs occurred at the same location as the first VTE (n=27; 69.2%). In detail 18/24 (75%) of patients with initial DVT had DVT at recurrence, whereas 9/12 (75%) of those with initial PE had PE at recurrence. Details are given in Fig. 1.

4. Discussion

There is good evidence that patients with IBD are at increased risk of venous thromboembolism (VTE). While the majority of IBD patients with VTE is suffering from DVT and/or PE, data of unusual locations of thrombosis are lacking.[1–13] Here we present the data of a large series of IBD patients with objectively confirmed VTE, which is a subanalysis of a previously published study on the risk of recurrent VTE in IBD patients. Our study includes the first detailed report of unusual VTE sites. Ten percent of all VTEs in IBD were located at other sites such as portal, superior mesenteric, splenic, internal jugular, and sinus veins. Since inflammation is primarily located in the gut one could expect a higher rate of thrombosis in the abdominal veins. However, until now only case reports and case series but no exact data of the frequencies of these unusual locations of thrombosis have been reported,[12,15–21] except in a recently published study which described an increased risk for portal vein thrombosis in IBD patients.[8] Thus, to the best of our knowledge the present results are the first which report the prevalence and incidence rate of all VTE in IBD including also unusual locations.

Table 3 Clinical characteristics and risk factors of 157 inflammatory bowel disease patients with a first venous thromboembolism.

Characteristics	
Age at first VTE (y), mean ± SD	43.2 ± 14.9
Location of VTE, n (%)	
Proximal leg veins	56 (35.7)
Distal leg veins	18 (11.5)
Upper extremity	4 (2.5)
Pulmonary embolism	64 (40.8)
Portal vein	4 (2.5)
Superior mesenteric vein	2 (1.3)
Splenic vein	1 (0.6)
Internal jugular vein	1 (0.6)
Cerebral vein	7 (4.5)
VTE provoked by surgery/trauma, n (%)	36 (22.9)
Hospitalized at the time of VTE, n (%)	35 (22.3)
BMI>25 kg/m^2, n (%)	51 (32.5)
Smoker at the time of VTE, n (%)	51 (32.5)
OC use at the time of VTE, n (%)	27 (30.3)
Factor V Leiden, n (%)	21 (15.9)
Missing, n	25
Factor II G20210A, n(%)	3 (2.6%)
Missing, n	43
Active IBD at first VTE	78 (60.9)
Missing, n	29
Crohn's disease, n (%)	100 (63.7)
Age at diagnosis: A1/A2/A3, n (%)	5 (5)/ 68 (68)/ 27 (27)
Location: L1/L2/L3/ +L4, n (%)	21 (21)/ 14 (14)/ 40 (40)/ 25 (25)
Behavior: B1/ B2/ B3, n (%)	23 (23)/ 43 (43)/ 34 (34)
Perianal disease, n (%)	40 (40)
Previous surgery, n (%)	60 (60)
Ulcerative colitis, n (%)	56 (35.7)
Proctitis/left-sided/extensive, n (%)	4 (7.0)/ 18(31.6)/ 35 (61.4)
Previous surgery, n (%)	1 (1.8)
Inflammatory bowel disease unclassified, n (%)	1 (0.6)
Medication at first VTE, n (%)	
5-Aminosalicylic acid	74 (54.0)
Corticosteroids	58 (42.3)
Azathioprine/6-mercaptopurine	29 (21.2)
Methotrexate	1 (0.7)
Infliximab	1 (0.7)
Missing, n	20

The number of missing data is given if data were not completely available. The calculation of percentages was referred to available data. BMI, body mass index (calculated as kg/m^2); IBD, inflammatory bowel disease; OC, oral contraceptive; SD, standard deviation; VTE, venous thromboembolism.

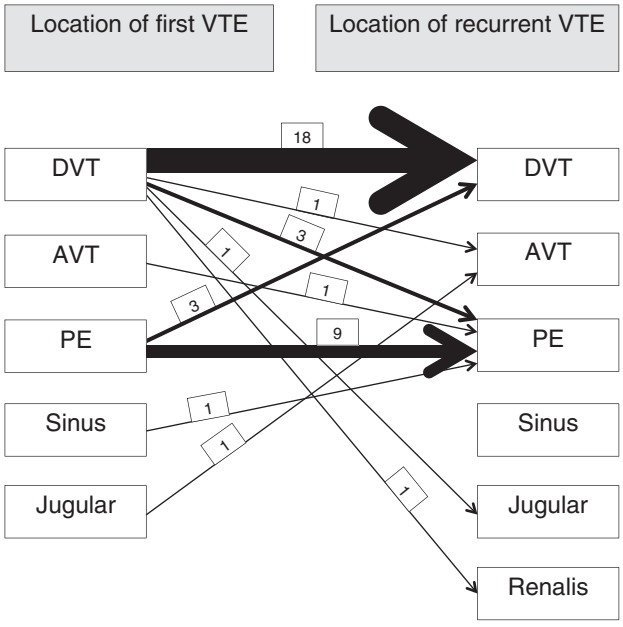

Figure 1 The comparison of the location of the first and the recurrent venous thromboembolism. DVT, deep venous thrombosis; AVT, arm venous thrombosis; PE, pulmonary embolism.

Patients with IBD are also at increased risk of recurrent VTE as reported recently.[11] The location of recurrent VTE tended to be the same as that of the first VTE, which is in line with the literature for non-IBD patients with thromboembolic events. As previously shown in a recent review proximal DVT and particularly PE mostly recur at the same location.[28]

There is good evidence that IBD itself is likely to be an independent risk factor for thrombosis.[1–13] That risk could not be found in patients with rheumatoid arthritis as well as coeliac disease compared to control subjects.[3] The reason for the increased risk of thrombosis in IBD is not completely understood.[12] From the clinical point of view it is particularly associated with an acute flare-up and hospitalization.[6] The underlying pathomechanism of VTE in IBD seems to be multifactorial, but acquired risk factors appear to play the most relevant role.[11,12] The inflammatory state has been related to many alterations of the coagulation and fibrinolytic system as well as to the activated state of platelets.[12,29] The association between inflammation and venous thromboembolic events has been demonstrated in a large cohort study of non-IBD patients, which indicated that increased levels of C-reactive protein and therefore inflammation may be a risk factor for VTE.[30]

The prevalence was 5.6% for all VTEs and 5.1% for DVT and/or PE which is within the range of previous reports.[1,3,12] The incidence rate was 6.3 per 1000 person years for all VTE and 5.7 per 1000 person years for DVT and/or PE in the present study and, thus, somewhat higher than in several population-based investigations which reported incidence rates of 2.4 to 4.6 per 1000 person years.[2,6,7] We found a higher incidence rate of DVT and/or PE in CD compared to UC. This observation is in contrast to the data of Nguyen and colleagues, who reported a higher risk of thrombosis in UC patients.[5] The higher incidence rate in all IBD patients and particularly in CD patients in our study compared with the results of population-based studies can be caused by a selection bias. Our study included patients from referral IBD centers. It is possible that patients treated in such specialized centers suffer from more severe disease with more flare-ups and complications. Thus, our data are more likely to represent the frequency of VTE among IBD patients of referral centers than population-based data. There is good evidence that patients with active IBD are at the highest risk of VTE.[6] This can be supported by our results, since 60.9% of the patients had active disease at the time of VTE. In a British population-based cohort study corticosteroid prescription was used as a surrogate marker for disease activity.[6] Based on very recently presented data we cannot exclude that the medication itself influences the risk of VTE since biologic use was associated with a major reduction in VTE compared with steroid use.[31] In our study nearly half of the patients were under treatment with corticosteroids at the time of the first VTE.

Recommendations regarding thrombosis prophylaxis in IBD patients focus on hospitalized patients due to the highest absolute risk found in these patients, especially in case of an acute flare-up.[13,32,33] For example, the American College of Chest Physicians strongly recommends VTE prophylaxis with low-molecular-weight heparin, unfractionated heparin, and fondaparinux in acutely ill patients with IBD who are admitted to hospital and confined to bed.[32] A recent update of these guidelines defines several risk factors for VTE in hospitalized medical patients such as inflammatory disorders, without specification for IBD.[34]

A statement of the European Crohn's and Colitis Organisation is enunciated more expanded and suggests to consider prophylaxis in all hospitalized IBD patients.[33] But we have to keep in mind that nearly 80% of all VTEs in IBD patients occur in outpatients and will not be covered by these recommendations. However, the absolute risk of VTE during an acute flare-up is much lower in ambulatory than in hospitalized IBD patients (6.4/1000 person years vs. 37.5/1000 person years).[6] Clinical and cost effectiveness of thrombosis prophylaxis during ambulatory IBD flare-ups are completely unclear.[13] Thus, until now there are no consensus statements on VTE prophylaxis during acute flare-ups in ambulatory IBD patients.[13] In the absence of large controlled trials evaluating efficacy and safety of thromboprophylactic regimens in IBD outpatients low molecular weight heparin at prophylactic dose may be considered during acute flare-ups when additional risk factors including history of thrombosis, advanced age or immobilization are present. This decision should be made on an individual basis and in consideration of the patient's bleeding risk.

Our study has several strengths and some limitations. The major strength of our study is the investigation of a large cohort of IBD patients and rigorous inclusion of only patients with objectively confirmed thrombotic events. We also included thromboembolic events other than DVT and/or PE in our analysis. On the other side we have only limited information about CD-specific data on patients without VTE, which, therefore, makes it difficult to establish thrombosis risk factors in IBD patients. Furthermore, as mentioned above the inclusion of patients of tertiary referral centers could lead to a selection bias. Thus, we cannot rule out that a potential selection bias as well as the retrospective design of our study might have influenced our observations.

In conclusion, the present study confirms that venous thromboembolic events are common in IBD patients. About 90% of all VTEs in IBD patients are DVT and/or PE, other sites of thrombosis include sinus, portal, mesenteric, splenic and internal jugular veins. Most of the patients have active disease at the time of VTE. Thus, this clinical feature should be in the focus of thrombosis prophylaxis.

Conflict of interest

Guarantor of the article: Gottfried Novacek, MD. No potential competing interests.

Specific author contributions

PP: analysis and interpretation of data, acquisition of data, drafting of the manuscript

WM: study concept and design, statistical analysis, critical revision of the manuscript, acquisition of data, approval of the final version of the manuscript

HT, WP, AM, TH, AK, TF, HF, PK, RP, WT, BJ, AS, BB, CD: critical revision of the manuscript, acquisition of data, approval of the final version of the manuscript

WR, HV: study concept and design, critical revision of the manuscript, acquisition of data, approval of the final version of the manuscript; no conflicts of interest exist

AS: execution of the study, critical revision of the manuscript, approval of the final version of the manuscript

AW: technical support, acquisition of data, critical revision of the manuscript, approval of the final version of the manuscript

SE: study concept and design, analysis and interpretation of data, acquisition of data, drafting of the manuscript

GN: study concept and design, obtained funding, analysis and interpretation of data, study supervision, acquisition of data, drafting of the manuscript;

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