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# Review

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# Cerebral sinus venous thrombosis in inflammatory bowel diseases

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## Summary

**Background:** It has been estimated that 1.3–6.4% of patients with inflammatory bowel diseases (IBD) are complicated by cerebral venous thrombosis (CVT) at some point of time during the course of their disease.

**Methods:** We retrospectively reviewed and subsequently analyzed data from 65 case reports of IBD patients with CVT. Our sources included MEDLINE and EMBASE, and the references of retrieved articles were also screened.

**Results:** Patients with CVT and IBD were significantly younger than CVT patients without IBD. Female patients were complicated more frequently but at an older age when compared with males. The incidence of ulcerative colitis was almost double compared with Crohn's disease. Active disease was detected in 78.4% of the cases and the proportions of patients with active ulcerative colitis or active Crohn's disease were almost equal. The predominant neurological symptom in these patients was persistent headache (80%) and the most common site of CVT was the superior sagittal sinus (50.7%). Severe iron deficiency anemia was highlighted as a significant risk factor for thrombosis in nearly half of the patients. Transient coagulation abnormalities and hereditary thrombogenic mutations were identified in 23 and 20% of the case reports, respectively.

**Conclusion:** The overall outcome was very good, especially in those patients who were treated acutely with heparin or low molecular weight heparin, suggesting that heparin administration is related with improved neurological outcome and decreased mortality rates even in IBD patients complicated with CVT.

## Introduction

Neurologic manifestations in inflammatory bowel diseases (IBD) seem to be more common than previously estimated. There is evidence of an increased incidence of thrombotic complications in patients with ulcerative colitis (UC) and Crohn's disease (CD); however, cerebral vascular involvement is rare and only 1.6% of total cerebral venous thrombotic events are associated with IBD.[1–4] It is estimated that 1.3–6.4% of adults with IBD and 3.3% of children with IBD develop cerebrovascular complications at some point of time during the course of their disease.[5]

We retrospectively reviewed case reports from IBD patients complicated with cerebral venous thrombosis (CVT). Sources included MEDLINE and EMBASE (last search update performed on 14

November 2012). The search strategy was based on the combination of terms: cerebral venous thrombosis, cerebral sinus thrombosis, inflammatory bowel disease, ulcerative colitis and Crohn's disease. References of retrieved articles were also screened. Only papers written in English were included.

## Demographic data

The literature research highlighted overall 65 IBD patients who were complicated by CVT. A brief overview of the extracted data is presented in Table 1. Harrison and Truelove in 1967 were the first to report an association between CVT and UC in two of their patients.[6] The youngest patients reported were a 7-year-old girl and a 7-year-old boy with UC and CD, respectively.[7,8] Moreover, 15 juvenile patients (23%) younger than 17 years old were respectively reviewed.[5,7–17] A slight female predominance is noticed in this series of case reports, with 37 women and 28 men, respectively. However, the average age that the thrombotic event occurred in men (mean 26 years) is lesser than in women (mean 31 years).[5–48]

UC was more frequently detected in case reports than CD, with 42 and 21 patients, respectively. Active disease has been discovered in 51 (78.4%) of them, whereas in the other 14 patients (21.6%) the disease has been quiescent. Active UC was confirmed in 33 patients (78.5%) and active CD in 15 (71%). Half of the patients (50.7%) were on oral, anal or intravenous corticosteroid treatment[6,8–18,20–24,27–29,31,33,37,39,41,43,45,46] and only one on anti-TNFa treatment[18] at the onset of the cerebrovascular event (Table 1).

## Neurological symptoms

In most of the patients, the predominant neurological symptom on admission was persistent, and mostly global, headache (80%). Unspecified headache was the one and only presenting symptom in seven (10.7%) of these patients.[7,12,14,17–19] Increased intracranial pressure was also accountable for vomiting (29.2%) and papilledema (7.1%). One out of three patients (35.5%) developed tonic–clonic seizures before admission. Altered conscious, aphasic disorders and confusion were present in 21.5% of the total reports. Also frequent accompanying symptoms were hemiplegia or tetraplegia (29.2%) and vision deficits (12.3%), which included blur vision, diplopia, quadrantanopia, hemianopia and one case of cortical blindness. Hemiparesthesia, facial paresthesia, photophobia, vertigo and cerebral ataxia have also been reported (Figure 1a).[5–48]

## Sites of cerebral venous sinus thrombosis

The most common site of cerebral thrombosis in the patients reviewed was the superior sagittal sinus (50.7%) followed by transverse sinuses (33.8%), sagittal sinus (32.3%), lateral sinuses (20%) and cortical veins (16.9%). Multiple cerebral thrombosis in more than one cerebral sinus or cortical vein has been reported in half (50.7%) of them (Figure 1b). In four patients (6.1%) the exact location of intracerebral thrombosis could not be determined due to insufficient data.[9,11,13,21]

## Potential risk factors for venous thrombosis

The two more frequent risk factors for venous thrombosis observed in most of the specific reports were anemia (49.2%) and thrombocytosis (26.1%). Anemia was the only identifiable risk factor for venous thrombosis in 10 patients (15.4%).[13,18,22–27]

Transient coagulation abnormalities, including increased fibrinogen, elevated factor VII, elevated factor VIII, antithrombin III deficiency, protein C deficiency and protein S deficiency coexist with IBD (23%) in many case reports.[10–12,15,19–21,28–32] Hereditary thrombogenic mutations are detected in 13 patients (20%). Five of them were heterozygous for the factor V Leiden gene mutation, two were homozygous for the methylene-tetra-hydro-folate-reductase (MTHFR) gene mutation, one was heterozygous for the MTHFR gene mutation and five were heterozygous for the G20210A prothrombin gene mutation.[5,7,8,17–19,33–35] Only one patient (1.5%) was reported with measured elevated homocystine levels in the laboratory work out,[7] while anticardiolipin and antiphospholipid antibodies were present in three (4.6%) and two (3.07%) patients, respectively.[7,11,14,29]

A positive history for deep venous arm or leg thrombosis and/or pulmonary embolism was reported in seven patients (10.7%).[6,21,36–40] In five of these patients, no other risk factor for venous thrombosis was mentioned and in the other two only anemia and thrombocytosis were detected. Therefore, a positive history of deep venous thrombosis (DVT) should be considered as a risk factor for future thrombotic events and consequently CVT. The use of oral contraceptives has been reported in five female patients (7.6%).[15,18,37] Otitis media, sinusitis and laparotomy could be cumulative if not possible causes of CVT, other than IBD, in four patients.[7,12,16,39] Soong *et al.*[42] suggest that severe dehydration secondary to UC flare was the cause of the CVT in their patient and similarly Targosz-Gajniak *et al.*[43] present protracted immobilization as an additional risk factor for thrombosis in IBD.

**Table 1** Case reports from patients with inflammatory bowel disease complicated by cerebral venous thrombosis

| Author | Age | Sex | IBD | Active | IBD treatment | Neurological symptoms | CVST | Risk factors | Anticoagulation | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Al-Malik and Green[9] | 14 | M | CD | Yes | Steroids, 5-ASA, AZA | Headache, seizure | U (multiple) | Anemia, thrombocytosis, laparotomy | No | Complete recovery |
| Al Tahan *et al.*[10] | 14 | F | UC | Yes | Steroids, 5-ASA | Headache, seizure | SSS | Anemia, pro-S deficiency | Heparin/warfarin | Complete recovery |
| Ansari *et al.*[44] | 48 | F | CD | Yes | – | Headache, vomiting, vertigo, altered conscious, hemiparesis | SSS | No | – | – |
| Bansal and Goel[45] | 30 | M | UC | Yes | Steroids, 5-ASA | Headache, vomiting, diplopia papilledema | SSS | No | LMWH | Complete recovery |
| Benjilali *et al.*[21] | 35 | M | CD | Yes | Steroids, 5-ASA, 6-MP | Headache, confusion | LS | Anemia, thrombocytosis, pro-S deficiency | Heparin/OA | Complete recovery |
| Benjilali *et al.*[21] | 38 | F | CD | Yes | 5-ASA | Altered conscious, tetraplegia | U | Anemia, thrombocytosis, history of DVT | Anticoagulant therapy (U) | Death |
| Ben Sassi *et al.*[11] | 50 | F | UC | No | 5-ASA | Headache vomiting, cerebellar ataxia, cortical blindness | SS | Thrombocytosis, history of DVT | Heparin/warfarin | Complete recovery |
| Ben Sassi *et al.*[11] | 30 | F | UC | Yes | Steroids, 5-ASA, AZA | Headache, seizures, mixed aphasia, hemiplegia | LS | Thrombocytosis, increased fVIII activity, antiphospholipid antibodies | Heparin (iv) | Complete recovery |
| Ben Sassi *et al.*[11] | 74 | F | CD | No | Steroids, 5-ASA | Headache, vomiting, seizures, hemiplegia | U | Anemia, decreased AT III activity | Heparin/warfarin | Complete recovery |
| Ben Sassi *et al.*[11] | 15 | F | UC | Yes | 5-ASA | Headache, vomiting, seizures | LS | Thrombocytosis | Heparin/warfarin | Complete recovery |
| Chauhan *et al.*[22] | 40 | F | UC | Yes | Steroids, 5-ASA | Hemiplegia | SSS, TS, SS | Anemia | Heparin (sc) | Unsuccessful outcome |
| Cognat *et al.*[18] | 29 | F | CD | No | 5-ASA | ICH | SSS, LS | Anemia, OC, otitis media | LMWH or heparin (iv) | Complete recovery |
| Cognat *et al.*[18] | 36 | F | CD | No | No | Headache | LS, SS | Anemia, thrombocytosis, OC | LMWH or heparin (iv) | Complete recovery |
| Cognat *et al.*[18] | 28 | M | CD | Yes | Steroids | Headache, seizures | LS, CV | Anemia | LMWH or heparin (iv) | Complete recovery |
| Cognat *et al.*[18] | 45 | F | CD | Yes | No | Headache, seizures, dysphasia | SSS, LS | Anemia | LMWH or heparin (iv) | Complete recovery |
| Cognat *et al.*[18] | 23 | F | CD | No | Steroids, AZA | Headache | LS | Anemia, FVLm, OC | LMWH or heparin (iv) | Complete recovery |
| Cognat *et al.*[18] | 25 | F | UC | Yes | 5-ASA | Headache, hemiparesis | SSS,CV | Anemia, G20210A prothrombin mutation | LMWH/danaparoid/ fondaparinux | HIT II/complete recovery |
| Cognat *et al.*[18] | 18 | M | UC | No | Steroids, 5-ASA | Headache, hemianopia | LS | Anemia | LMWH or heparin (iv) | Complete recovery |
| Cognat *et al.*[18] | 43 | F | CD | No | Steroids, AZA, cyclosporine, anti-TNFa | Headache, hemiparesis | LS | Anemia, anti-TNFa therapy | LMWH or heparin (iv) | Partial recovery |
| Das *et al.*[46] | 31 | M | UC | Yes | Steroids, 5-ASA, tidicol | Vomiting, seizures, altered conscious | SSS | No | No | Death |
| Das *et al.*[46] | 20 | M | UC | Yes | Various (U) | Seizures | SS, CV | No | No | Death |
| De Cruz *et al.*[37] | 29 | F | UC | Yes | Steroids, 5-ASA, AZA | Headache, vertigo | SSS | OC | Intravascular thrombolysis/OA | Complete recovery |

(continued)

**Table 1** Continued

| Author | Age | Sex | IBD | Active | IBD treatment | Neurological symptoms | CVST | Risk factors | Anticoagulation | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| De Cruz *et al.*[37] | 26 | F | UC | No | Steroids, 5-ASA, AZA | Headache, seizures | TS, SS | History of DVT and PE | Heparin (iv)/warfarin | Complete recovery |
| De Cruz *et al.*[37] | 32 | F | UC | Yes | Steroids, 5-ASA | Altered conscious, hemiparesis, hemianopia, fluent aphasia | TS | No | LMWH (enoxaparin)/aspirin | Complete recovery |
| Derdeyn and Powers[38] | 26 | F | UC | No | 5-ASA, 6-MP | Seizure | CV | Two episodes of DVT | Warfarin | Partial recovery |
| Diakou *et al.*[12] | 17 | M | UC | Yes | Steroids, AZA | Headache | TS, SS | Pro-S deficiency | Heparin (iv)/warfarin | Complete recovery |
| Fischer *et al.*[47] | 26 | F | UC | Yes | 5-ASA | Headache, vomiting | SSS, TS, SS | No | Heparin (iv) | Death |
| Harrison and Truelove[6] | 54 | F | UC | Yes | Steroids | Headache, dysphasia, hemiparesis, quadrantanopia | CV | History of DVT | No | Parietal lobe dysfunction |
| Harrison and Truelove [6] | 34 | M | UC | Yes | Steroids | Headache, seizures, hemiparesis, hemianopia | SS | No | No | Death |
| Hasegawa *et al.*[48] | 32 | M | UC | No | 5-ASA | Headache, hemiparesis | SSS | No | Warfarin (maintenance) | Complete recovery |
| Houissa *et al.*[13] | 56 | F | IC | Yes | Steroids | Seizures | SSS | Anemia | LMWH | Complete recovery |
| Houissa *et al.*[13] | 16 | F | UC | Yes | 5-ASA | Headache, confusion | U | Thrombocytosis | LMWH | Complete recovery |
| Jain *et al.*[28] | 22 | F | UC | Yes | Steroids, 5-ASA | Headache, vomiting, seizures | TS | Increased fibrinogen | LMWH (enoxaparin)/ warfarin | Complete recovery |
| Jain and Nijhawan[23] | 55 | F | UC | Yes | Steroids, 5-ASA | Headache, photophobia, papilledema | SSS | Anemia | LMWH/warfarin | Complete recovery |
| Kao *et al.*[7] | 14 | F | UC | Yes | – | Hemiparesis | SS, CV | No | Heparin (iv), local urokinase thrombolysis/warfarin | Left hemiparesis |
| Kao *et al.*[7] | 7 | F | UC | Yes | – | Headache, aphasia | TS, SS | Anticardiolipin antibodies | No | Mild right pronator drift |
| Kao *et al.*[7] | 20 | F | UC | Yes | – | Headache | SSS, TS | Anticardiolipin antibodies | LMWH | Complete recovery |
| Kao *et al.*[7] | 13 | F | UC | Yes | – | Seizures | SSS, TS, SS | Elevated homocystine levels, prothrombin gene mutation heterozygous | LMWH (1 U/kg) | Complete recovery |
| Kawanishi *et al.*[29] | 30 | M | UC | Yes | Steroids, 5-ASA | Seizures | SSS | Anemia, pro-S deficiency, antiphospholipid antibodies | Heparin (9000 U/d) | Complete recovery |
| Kupfer and Rubin[14] | 23 | F | UC | Yes | 5-ASA, AZA, cyclosporine | Headache, nausea, vomiting | TS, SS | Anemia, sinusitis, otitis media, history of DVT | Heparin (iv)/warfarin | Complete recovery |
| Kupfer and Rubin[14] | 16 | M | CD | Yes | Steroids, 5-ASA, AZA | Headache | SSS, TS | Anemia, anticardiolipin antibodies | Heparin/warfarin | Complete recovery |
| Maag and Prayson[19] | 30 | M | CD | Yes | No | Headache | SSS | Anemia, pro-S and pro-C deficiency, FVLm | No | Death |
| Macri *et al.*[15] | 17 | F | UC | Yes | Steroids, 5-ASA | Headache, seizures, mixed aphasia, hemiparesis, | SSS, CV | Anemia, AT III deficiency, OC | Heparin (nadroparine 0.9 ml/d) | Complete recovery |

(continued)

**Table 1** Continued

| Author | Age | Sex | IBD | Active | IBD treatment | Neurological symptoms | CVST | Risk factors | Anticoagulation | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Markowitz *et al.*[16] | 14 | M | UC | Yes | Steroids, 5-ASA | Headache, hemiparesis | LS, SS | Anemia, thrombocytosis | Aspirin | Complete recovery |
| Moriyama *et al.*[30] | 27 | M | UC | No | 5-ASA | Headache, vomiting | TS, SS | Anemia, AT III deficiency | No | Partial recovery |
| Murata *et al.*[20] | 19 | M | UC | Yes | Steroids, LCAP | Headache | SSS, TS | Anemia, elevated fibrinogen, elevated fVII | Heparin (15 000 U/d) | Complete recovery |
| Nudelman *et al.*[24] | 23 | M | UC | Yes | Steroids, 5-ASA | Headache, hemiparesis, hemiparesthesia | SSS, CV | Anemia | No | Death |
| Ranta and Mokanahalli [31] | 37 | M | AE | Yes | Steroids | Headache, nausea, hemiparesis | SSS | ATIII deficiency | Heparin (iv) | Complete recovery |
| Robison *et al.*[17] | 10 | M | UC | Yes | Steroids | Headache, vomiting | TS, SS | FVLm, homozygous for MTHFR mutation | LMWH (enoxaparin 1 mg/kg) | Complete recovery |
| Rosen *et al.*[8] | 7 | M | CD | Yes | Steroids | Headache, vomiting, blur vision | SSS, TS, SS | Anemia, Thrombocytosis, MTHFR mutation homozygous, prothrombin mutation heterozygous | LMWH (enoxaparin) | Complete recovery |
| Samal *et al.*[25] | 20 | M | CD | Yes | No | Headache, vomiting, seizure, papilledema | SSS, TS | Anemia | Warfarin | Complete recovery |
| Schneidermann *et al.*[32] | 56 | F | CD | Yes | – | Headache, aphasia | CV | Thrombocytosis, elevated fVIII | No | – |
| Sigsbee and Rottenberg [39] | 30 | F | CD | Yes | Steroids | Headache, hemiparesis | SSS, CV | History of PE & DVT | Warfarin | Partial recovery |
| Soong and Carroll [42] | 45 | M | UC | Yes | No | Headache, seizures, papilledema | SSS, LS | Severe dehydration | Heparin/warfarin | – |
| Srivastava *et al.*[26] | 29 | M | UC | No | Steroids, 5-ASA | Headache, vomiting, diplopia, papilledema | SSS, LS, SS | Anemia | LMWH/aspirin | Complete recovery |
| Standridge and de los Reyes[5] | 16 | F | CD | Yes | – | Headache, vomiting, syncope | SSS, TS, SS | Thrombocytosis, G20210A prothrombin gene mutation | Heparin/warfarin | Complete recovery |
| Standridge and de los Reyes[5] | 12 | F | CD | Yes | – | Headache, vomiting, seizure, hemiparesthesia | CV | Thrombocytosis | Aspirin | Complete recovery |
| Standridge and de los Reyes[5] | 18 | F | CD | Yes | – | Headache, facial paresthesia | TS, SS | Thrombocytosis | LMWH (enoxaparin) | Complete recovery |
| Targosz-Gajniak *et al.*[43] | 31 | M | CD | Yes | Steroids | Seizures, sensory aphasia | TS, SS | Thrombocytosis, immobilized (5d) | No | Complete recovery |
| Thorsteinsson *et al.*[41] | 18 | M | UC | Yes | Steroids, 5-ASA, AZA | Headache, vomiting | TS | Anemia, peritonsilitis-incision | Heparin (iv)/fondaparinux | HIT II/complete recovery |
| Tsujikawa *et al.*[27] | 29 | M | UC | Yes | Steroids, 5-ASA | Headache, vomiting, seizure, hemianopsia | SSS | Anemia | Heparin (15 000 U/d) and urokinase (60 000 U/d)/warfarin (2 mg) | Complete recovery |
| Umit *et al.*[33] | 53 | M | UC | Yes | Steroids, 5-ASA | Hemiparesis | SSS, TS | Anemia, thrombocytosis, FVLm | LMWH | Death (sepsis) |
| Xia *et al.*[34] | 42 | F | UC | No | 5-ASA | Headache, nausea, blur vision | SSS | MTHFR mutation heterozygous | Fondaparinux (refractory to enoxaparin and warfarin) | Improved |

(continued)

**Table 1** Continued

| Author | Age | Sex | IBD | Active | IBD treatment | Neurological symptoms | CVST | Risk factors | Anticoagulation | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Yakeryilmaz *et al.*[35] | 23 | F | UC | Yes | 5-ASA | Headache, nausea, hemiparesis | SSS, TS, SS | Anemia, thrombocytosis, FVLm, G20210A prothrombin gene mutation | Heparin (iv, 15 000/d)/warfarin | Improved |
| Yerby and Bailey[40] | 28 | M | UC | No | No | Headache, vomiting, seizures | SSS | Two episodes of DVT | No | Complete recovery |

CVST, cerebral venous sinus thrombosis; M, male; F, female; IC, indermediate colitis; AE, autoimmune enteropathy; U, undetermined; AZA, azathioprine; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; LCAP, leucocytoaphairesis; ICH, intracranial hypertension; SSS, superior sagittal sinus; LS, lateral sinus; TS, transverse sinus; SS, sigmoid sinus; CV, cortical veins; Pro-S, protein S; Pro-C, protein C; fVIII, factor VIII; AT III, antithrombin III; FVLm, heterozygous for factor V Leiden mutation; OC, oral contraceptives; G20210A, prothrombin gene G20210A mutation; DVT, deep venous thrombosis; PE, pulmonary embolism; /, followed by; LMWH, low molecular weight heparin; HIT II, heparin induced thrombocytopenia type II; OA, oral anticoagulants.

A potential risk factor could not be identified in nine patients (13.8%) (Table 2).[6,7,37,44–48]

The percentages above, although indicative, should be cautiously interpreted as in many cases some of the essential screening tests for coagulation abnormalities were not performed.

## The impact of anticoagulation therapy on outcome

From the 25 case report patients (39%) who were treated with heparin or low molecular weight heparin (LMWH) 19 recovered completely, 1 recovered partially and 2 died. However, one of the two patients who died had a nosocomial infection and probably his death was a consequence of sepsis.[33] During the therapy two patients were complicated with heparin induced thrombocytopenia type II (HIT II) but recovered completely after exchanging the anticoagulant to fondaparinux.[18,41] Similarly, 12 out of 15 case report patients treated with heparin or LMWH followed by long-term warfarin administration recovered completely. Even though in a single patient fondaparinux was administrated, because he was refractory to the initial treatment with enoxaparin and warfarin.[34]

The two patients who were reported to be treated with LMWH followed by aspirin recovered completely.[26,37] Warfarin monotherapy in four of the totally reviewed patients resulted in complete recovery in half of them and in partial recovery in the other half.[25,38,39,48] Complete recovery has been reported in another two patients who were exclusively treated with aspirin.[5,16]

Thrombolysis combined with intravenous heparin and followed by oral anticoagulation has been reported only in three IBD patients who were complicated with CVT. In one of them left hemiparesis was still evident at the time of the follow-up evaluation, while the two others recovered completely.[27,37]

Out of the 12 patients in this review who did not receive any form of anticoagulation treatment, only 3 recovered completely, 3 recovered partially and 5 died (Table 3). The decision for not administering anticoagulant therapy in seven of these patients was—according to authors—based on the presence of hemorrhagic infarctions or cerebral hemorrhages on brain CT/MRI scan and the potential risk of intestinal bleeding.[5–7,24,30,37,43]

## Discussion

The mean age of IBD patients at the time of the cerebral thrombotic event in the reviewed case

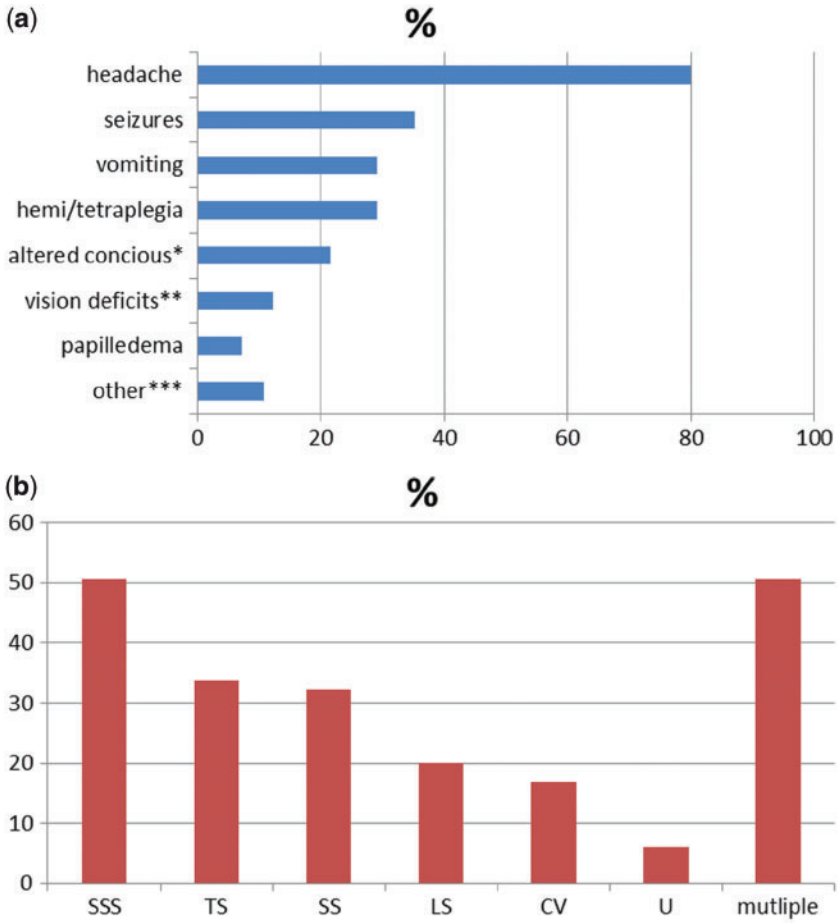


**Figure 1.** (**a**) Sites of CVT in patients with inflammatory bowel disease (SSS, superior sagittal sinus; TS, transverse sinus; SS, sigmoid sinus; LS, lateral sinus; CV, cortical veins; U, undetermined). (**b**) Neurological manifestations of CVT in patients with inflammatory bowel diseases (*confusion, aphasia, dysphasia; **blur vision, diplopia, quadrantanopia, hemianopia, cortical blindness; ***hemiparesthesia, facial paresthesia, photophobia, vertigo, cerebral ataxia).

reports was ~29 years with more than one out of five <17 years old. Our finding that patients with CVT and IBD comorbidity are significantly younger when compared with CVT patients without IBD is consistent with another recent literature review.[18] In this review, female IBD patients were more frequently complicated by CVT but the thrombosis occurred at an older age compared with male.

Jackson *et al.*[49] reported that thromboembolic phenomena were related with the activity of IBD only in patients with CD and not in those with UC. This was not confirmed in our review as the proportions of patients with active UC or active CD were almost equal (78.5 and 71%, respectively). These percentages consist with a retrospective analysis of IBD patients with DVT, in which active UC and active CD were confirmed in 79 and 80%, respectively.[50]

The coagulation activity in IBD is considered to be related to the activity and the colonic extension of the disease; however, Yerby and Bailey[40] reported a case of superior sagittal sinus thrombosis 10 years after panproctocolectomy for UC.[51] This case report is evidence against the theory that mucosal inflammation is responsible for the increased coagulant activity in some patients with IBD.[22] Corticosteroids, even though initially accused for thrombogenic properties, exhibit anti-inflammatory effects, decrease hypercoagulability, promote mucosal degeneration and enhance the action of heparin.[4] Moreover, evidence from controlled trials suggest that steroid treatment do not augment the risk for thromboembolism in both IBD and non-IBD patients.[16]

In many case reports, coagulation abnormalities like thrombocytosis and protein S deficiency were transient and returned to normal values after control of the intestinal inflammation.[10,28,32] Apart from chronic inflammation, acute hemorrhage and steroid treatment are potential causes of thrombocytosis in IBD patients. Either way there is not sufficient evidence to support that solitary thrombocytosis

**Table 2** Referring risk factors for venous thrombosis in patients with inflammatory bowel disease

| Risk factors for thrombosis | Patients (%) |
|---|---|
| Anemia | 32 (49.2) |
| Thrombocytosis | 17 (26.1) |
| Increased fibrinogen | 2 (3.07) |
| Elevated homocystine | 1 (1.5) |
| Elevated fVII | 1 (1.5) |
| Elevated fVIII | 2 (3.07) |
| Protein C deficiency | 1 (1.5) |
| Protein S deficiency | 5 (7.6) |
| AT III deficiency | 4 (6.1) |
| Anticardiolipin ab | 3 (4.6) |
| Antiphospholipid ab | 2 (3.07) |
| FVL mutation | 5 (7.6) |
| MTHFR mutation | 3 (4.6) |
| G20210A gene Prothrombin mutation | 5 (7.6) |
| History of DVT | 7 (10.7) |
| Oral contraceptives | 5 (7.6) |
| Otitis | 2 (3.07) |
| Sinusitis | 1 (1.5) |
| Laparotomy | 2 (3.07) |
| None | 9 (13.8) |

fVII, factor VII; fVIII, factor VIII; AT III, antithrombin III; ab, antibodies; FVL, factor V Leiden; MTHFR, methylene-tetra-hydro-folate-reductase; DVT, deep venous thrombosis.

can cause thromboembolic phenomena.[32] In contrast, severe iron deficiency anemia is highlighted as a significant and independent risk factor for CVT by several case reports and a recent case-control study of 121 patients.[53] This is a very significant finding as almost half of the reviewed patients had anemia, with a mean hemoglobin value of 9.08 g/dl and anemia was the only risk factor in 31% of them.

Even though anemia has a great impact in the quality of IBD patient's life, no official guidelines for both its diagnosis and treatment exist to date. Gasche *et al*.[54] first published a consensus on the diagnosis and management of iron deficiency anemia in patients with IBD, suggesting that iron supplementation should be directly initiated when iron deficiency anemia is detected. Intravenous iron administration was more rapid, more effective and better tolerated, with fewer adverse events compared with oral administration in a recent metanalysis,[55] and thus, could be the preferred route of administration in all cases.[54] Especially, newer low molecular iron dextran is much lower immunogenic and is associated with fewer size effects and anaphylactic reactions, compared with older intravenous iron supplements.[56] Oral iron supplements could be used if intravenous administration is contraindicated, as they are well tolerated by most IBD patients.[57,58]

**Table 3** The outcome of referred therapeutic methods

| Treatment | No patients (%) | Complete recovery (%) | Partial recovery (%) | Death (%) | Unsuccessful outcome (%) | Resistant to treatment (%) | HIT II (%) | Not mentioned (%) |
|---|---|---|---|---|---|---|---|---|
| Heparin or LMWH | 25 (39) | 19 (76) | 1 (4) | 2 (8) | 1 (4) | – | 2 (8) | – |
| Heparin or LMWH/warfarin | 15 (23.4) | 12 (80) | 1 (6.7) | – | – | 1 (6.7) | – | 1 (6.7) |
| LMWH/aspirin | 2 (3.1) | 2 (100) | – | – | – | – | – | – |
| Warfarin | 4 (6.2) | 2 (50) | 2 (50) | – | – | – | – | – |
| Aspirin | 2 (3.1) | 2 (100) | – | – | – | – | – | – |
| Thrombolysis | 3 (4.7) | 2 (66.7) | 1 (33.3) | – | – | – | – | – |
| Anticoagulation (U) | 1 (1.5) | – | – | 1 (100) | – | – | – | – |
| No treatment | 12 (19) | 3 (25) | 3 (25) | 5 (42) | – | – | – | 1 (8) |
| Not mentioned | 1 (1.5) | – | – | – | – | – | – | 1 (100) |
| Total | 65 | 42 (64.6) | 8 (12.3) | 8 (12.3) | 1 (1.5) | 1 (1.5) | 2 (3) | 3 (4.6) |

HIT II, heparin induced thrombocytopenia type II; LMWH, low molecular weight heparin; /, followed by; U, undetermined.

The protein C deficiency is related to an increased incidence of thrombosis in patients with IBD. Factor V Leiden mutation was observed in 7.6% of the patients in this review and this percentage is quite similar to the 5% incidence of this mutation in a previous study of 52 patients with IBD and venous thromboembolism.[49] However, more IBD patients with thrombotic complications are heterozygous for FVLm compared with IBD patients without thrombotic complications,[59] as factor V Leiden heterozygosity augments 5- to 8-fold the risk of thrombosis.[60] Similarly the prothrombin G20210A gene mutation, although not observed more commonly in IBD patients compared with the general population, increases 5-fold the risk of venous thromboembolism.[5] There are conflicting data in the literature about the association of MTHFR mutations and the risk for venous thrombosis, probably because different selection criteria for the patient group have been established in each study.[61–63] Finally, antiphospholipid antibodies are a known risk factor for both venous and arterial thrombosis, but their occurrence in a group of patients with IBD has not been explained yet.[29]

Administration of anticoagulants in CVT prevents new venous infarcts, pulmonary embolism and improves neurological outcome; however, there is a great concern about the hemorrhagic complications.[64] Two recent randomized, controlled trials converge that LMWH is safe and well tolerated for patients with UC but with no additional benefit over standard therapy.[65,66] A meta-analysis confirmed this conclusion and also highlighted that heparin administration was not related with an increased incidence of adverse events in patients with active UC.[67] As for the risk for intracranial bleeding European Federation of Neurological Societies (EFNS) guidelines suggest that patients with cerebral venous sinus thrombosis (CVST) without contraindications for anticoagulation should be treated subcutaneously with body-weight adjusted LMWH or intravenously with dose adjusted heparin, even in the presence of intracranial hemorrhage.[52]

As anticoagulation with heparin seems to be safe and well tolerated in patients with IBD—also in active colitis—and these patients seem to have an overall 3-fold higher risk for thromboembolic complications, which further increases in 15-fold during disease exacerbations; both guidelines from the European Crohn's and Colitis Organization[68] and the American College of Gastroenterologists[69] converge that all hospitalized adult IBD patients, especially those with active disease or prolonged immobilization, should be considered for antithrombotic prophylaxis with either LMWH, unfractioned heparin or fondaparinux.[70] In contrast to adults, anticoagulation prophylaxis in children with IBD has not been routinely recommended, as similar studies in children have not been performed yet.[71]

According to EFNS guidelines oral anticoagulation should be continued for 3 months if CVST was due to a transient risk factor, for 6–12 months in patients with idiopathic CVST or mild thrombophilia (heterozygous factor V Leiden mutation, heterozygous prothrombin G20210A gene mutation and elevated levels of factor VIII) and infinitively in patients with recurrent episodes of CVST or severe thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden mutation, homozygous prothrombin G20210A mutation, presence of antiphospholipid antibodies and combined abnormalities).[52] Therefore, screening for coagulopathies has a great impact on the long-term therapeutic management of cerebral thrombosis in patients with IBD. Particular attention requires the anticoagulation dosage in these patients, as some of the medications used for IBD treatment may directly inhibit platelet activation (5-aminosalycilic acid, azathioprine, 6-mercaptopurine and infliximab) or diminish the effect of warfarin (sulfasalazine and azathioprine).[28,41,43]

Interestingly, results have been published about the effectiveness and safety of local thrombolysis with urokinase or recombinant tissue plasminogen activator (rtPA) in patients with CVST and likewise in IBD patients complicated with thromboembolism.[72–74] However, these results derive from small, uncontrolled studies and thrombolysis is always performed with concomitant intravenous heparin infusion. Thus thrombolysis could probably become an alternative therapeutic option for patients without intracranial hemorrhage on neuroimaging studies and rapid neurological deterioration despite conventional anticoagulant therapy. Even though, no firm recommendation can be made due to lack of steady evidence.[52]

The overall outcome in most of the patients in this review was very good, especially in those treated acutely with heparin/LMWH. Most of the case reports declare complete recovery (64.6%) and only few (26.1%) report poor outcome (partial recovery of death) (Table 3). The outcome rates, although similar with those reported by Cognat *et al.*,[18] are in contrary to a another review that reported death or residual neurological deterioration in half of the patients with IBD and CVST.[29] Alternative therapeutic treatment (LMWH followed by aspirin, monotherapy with warfarin or aspirin and thrombolysis) cannot be evaluated due to the limited number of patients in these categories (Table 3). However, our review of case reports from IBD

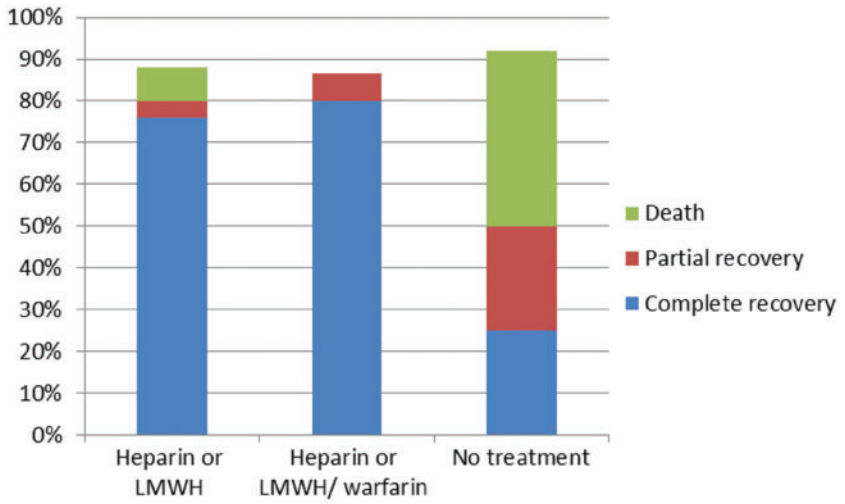


**Figure 2.** The result of anticoagulation therapy on recovery and mortality rates (/, followed by).

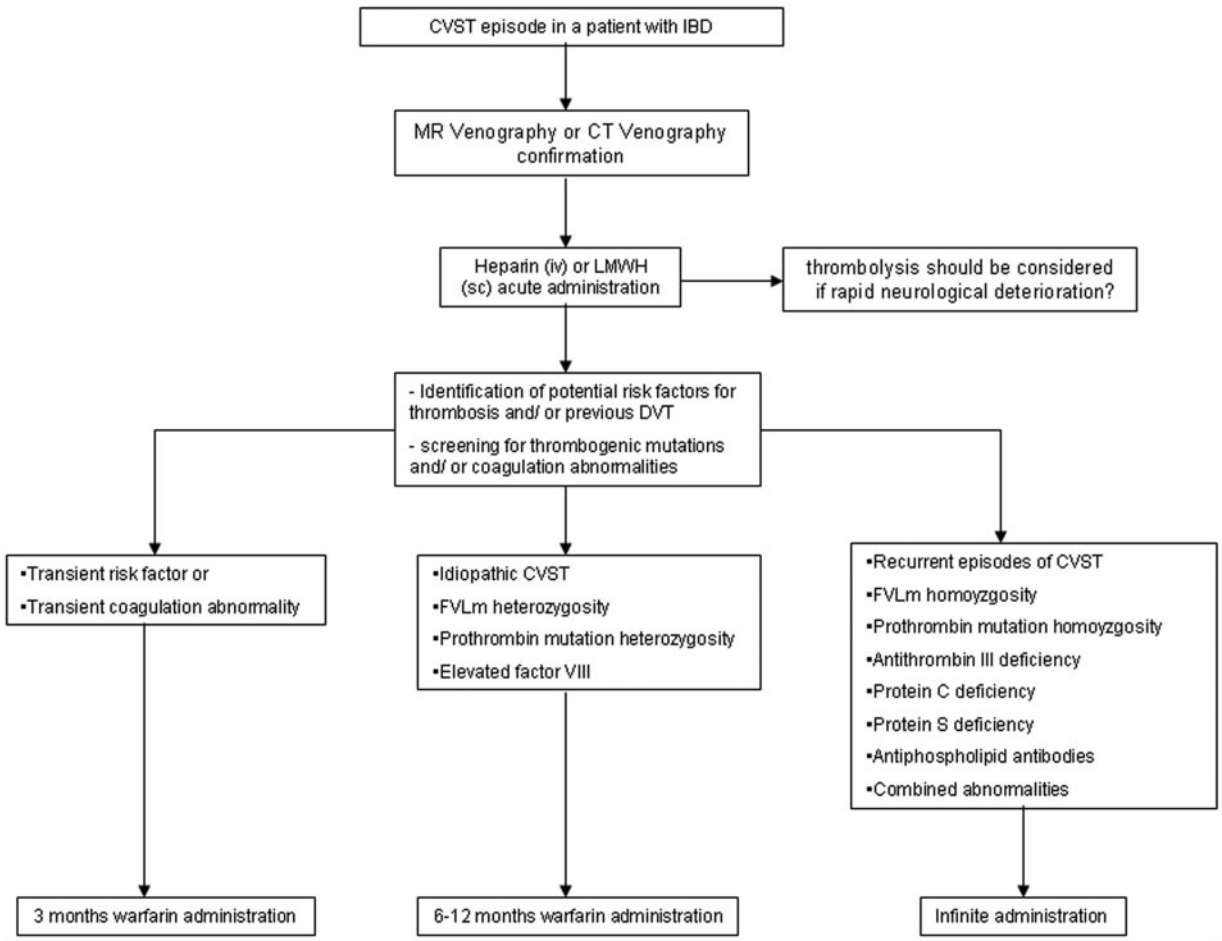


**Figure 3.** Algorithm of CVST management in patients with IBD (FVLm, factor V Leiden mutation).

patients complicated by CVT confirms that heparin administration, especially when followed by oral anticoagulation, is related with better neurological outcome and decreased mortality rates (Figure 2). Finally, an algorithm based on the EFNS guidelines for the management of CVST in patients with IBD is proposed (Figure 3).

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