

## Review Article



# Cerebrovascular Events in Pediatric Inflammatory Bowel Disease: A Review of Published Cases

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## ABSTRACT

Pediatric inflammatory bowel disease (PIBD) is a multisystem disorder characterized by intestinal and extraintestinal manifestations and complications. Cerebrovascular events (CVE) are rare extraintestinal complications in patients with PIBD. Statistics show that 3.3% patients with PIBD and 1.3–6.4% adult patients with inflammatory bowel disease (IBD) experience CVE during the course of the disease. Therefore, this study aimed to review the records of children with IBD who developed CVE during the course of the disease. We retrospectively reviewed 62 cases of PIBD complicated by CVE. The mean patient age at the time of thrombotic events was 12.48±4.13 years. The incidence of ulcerative colitis was significantly higher than that of Crohn's disease (43 [70.5%] vs. 13 [21.3%] patients). Most patients (87.93%) were in the active phase of IBD at the time of CVE. The mean time interval between the onset of IBD and CVE was 20.84 weeks. Overall, 11 (26.83%) patients showed neurological symptoms of CVE at disease onset. The most frequent symptom on admission was persistent and severe headaches (67.85%). The most common site of cerebral venous thrombosis was the transverse sinuses (n=23, 53.48%). The right middle cerebral artery (n=3, 33.34%) was the predominant site of cerebral arterial infarction. Overall, 41 (69.49%) patients who were mostly administered unfractionated heparin or low-molecular-weight heparin (56.09%) recovered completely. Patients with IBD are at a risk of thromboembolism. CVE may be the most common type of thromboembolism. Based on these findings, the most common risk factor for CVE is IBD flares. In patients with CVE, anticoagulant therapy with heparin, followed by warfarin, is necessary.

**Keywords:** Pediatrics; Inflammatory bowel diseases; Cerebrovascular disorders; Cerebral arterial diseases; Brain infarction

## BACKGROUND

Pediatric inflammatory bowel disease (PIBD) is a multisystem disorder characterized by various intestinal and extraintestinal manifestations and complications. With the increasing prevalence of PIBD worldwide, new, rare manifestations and complications have been

#### Conflict of Interest

The authors have no financial conflicts of interest.

reported. Cerebrovascular events (CVE) are rare extraintestinal complications associated with PIBD. These events include cerebral venous thrombosis (CVT) as an occlusion of the intracranial venous structure (superior sagittal sinus, cortical veins, internal cerebral veins, straight sinus, and some parts of jugular veins) by a clot and cerebral arterial infarction (CAI) as a thromboembolic occlusion of a cerebral artery.

Statistics show that 3.3% patients with PIBD and 1.3–6.4% adult patients experience CVE during the course of the disease [1,2]. However, the precise mechanism of thrombotic events in patients with IBD is unknown. Generally, the risk of CVE is correlated with relapse or disease activity [1,3]. Therefore, in this study, we aimed to review the demographic data, clinical manifestations, risk factors, and sites of CVE in patients with PIBD and investigate the effects of anticoagulant agents on the outcomes of children with IBD who developed CVE during the course of the disease.

## MATERIALS AND METHODS

Articles on PIBD complicated by CVE were reviewed retrospectively. A search was conducted in the PubMed, Medline, and Google Scholar using a combination of the following keywords: “cerebral venous thrombosis,” “cerebral arterial infarction,” “cerebral vascular event,” “pediatric inflammatory bowel disease,” “ulcerative colitis” (UC), and “Crohn’s disease” (CD). Additionally, the references of the extracted articles were screened. Only articles published in English were included in this review. Information related to the case reports on patients with PIBD complicated by CVE is summarized in **Tables 1** [4-41] and **2** [2,4,19,29,42-49].

## RESULTS

### Demographic data

The mean patient age at the time of the thrombotic event was  $12.48 \pm 4.13$  years. The youngest patient was a 1-year-old female patient with UC. Overall, 32 (50.61%) patients were female. Among patients with PIBD, UC was much more common than CD (43 [70.5%] vs. 13 [21.3%] patients). Most patients (87.93%) were in the active phase of IBD at the time of CVE. The proportions of patients with active UC and CD were almost equal (86.04% and 76.92%, respectively). The mean time interval between the onset of IBD and CVE was 20.84 weeks. Overall, 11 (26.83%) patients showed neurological symptoms of CVE at disease onset. The demographics of patients are presented in **Table 3**.

### Clinical manifestations

The clinical manifestations of 56 (UC=43 and CD=13) of 62 patients were documented. The most frequent symptom on admission was persistent and severe headaches (67.85%). The incidence of headaches was similar in female and male patients, and 25 of 38 patients with headaches had UC (65.78%). Further, 41.07% children developed seizures before admission; among them, 56.52% children were female and 73.91% had UC. In addition, vomiting was reported in 14.28% patients. Moreover, sensory and motor neuropathies were detected in 50% patients. Compared to male patients and patients with CD, the rate of sensory and motor neuropathies in both women and UC patients is 61.53%. Altered levels of consciousness in different forms, such as somnolence, confusion, stupor, or coma, were

**Table 1.** Case reports of patients with pediatric inflammatory bowel disease complicated by cerebral venous thrombosis (CVT)

Case report	Age (y)/ Sex	IBD subtype	Time interval between IBD and CVT	Anticoagulant therapy/Outcome	Symptoms	Risk factor	Location of CVT (vessels or brain region)
Al-Malik and Green [5]	14/M	CD	2 y	No <sup>a</sup> /No sequel	Headache, seizure	Disease flare, thrombocytosis, surgery, dehydration	Multiple areas of infarction in the occipital lobes, both frontal lobes, and both parietal lobes
Al Tahan et al. [6]	14/F	UC	6 mo	Heparin, warfarin/ No sequel	Headache, seizure	Disease flare, pro-S deficiency	Hemorrhagic infarctions in the left frontal and parietal lobes, widespread thrombosis in the superior sagittal sinus
Mahmoud Reza et al. [7]	11/M	UC	3 mo	Heparin, warfarin/ No sequel	Headache, orbital pain, photophobia, somnolence, transient blurred vision, vomiting	Disease flare	Superior sagittal sinus
Barclay et al. [4]	13/M	UC	2 wk	Aspirin/Mild hemiplegia	Headache, ataxia, right-sided hemiplegia	Thrombocytosis, history DVT in family	Thalamic and lesion in the left hemisphere involving the motor cortex or radiating fibers
Barclay et al. [4]	11/F	IBD/U	9 mo	No/Mild hemiplegia	Headache, stupor, right-sided hemiplegia	None	Thalamic/Basal ganglia
Barclay et al. [4]	14/M	CD	1 y	LMWH/No sequel	Headache	Thrombocytosis, disease flare	Transverse venous thrombosis
Rabeh et al. [8]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Undetermined
Ben Sassi et al. [9]	15/F	UC	Unknown	Heparin, warfarin/ No sequel	Headache, vomiting, seizure	Thrombocytosis	Lateral sinus
Bridger et al. [10]	14/F	UC	1 y	Death	Unknown	Disease flare	Widespread venous thrombosis
Cognat et al. [11]	18/M	UC	5 y	LMWH, heparin/No sequel	Headache	None	Lateral sinus
Connors et al. [12]	17/F	UC	Unknown	LMWH/No sequel	Headache, confusion, seizure	Disease flare	Superior sagittal sinus, transverse sinus, sigmoid sinus
Calderon et al. [13]	10/F	UC	Unknown	No/Death	Drowsiness, dizziness, right facial droop, right-sided headache	Disease flare	Caudate nucleus, left putamen, left thalamic nucleus
DeFilippis et al. [14]	15/F	CD	5 y	IV heparin/No sequel	Headache	None	Superior sagittal sinus, transverse sinus, cortical vein
DeFilippis et al. [14]	11/F	UC	3 y	IV heparin/No sequel	Headache	None	Superior sagittal sinus, transverse sinus, cortical vein
DeFilippis et al. [14]	10/M	UC	3 y	IV heparin/Coma, death	Headache	None	Superior sagittal sinus, transverse sinus, cortical vein
DeFilippis et al. [14]	12/M	UC	4 y	Heparin/No sequel	Headache	None	Superior sagittal sinus, transverse sinus, cortical vein
Diakou et al. [15]	17/M	UC	1.5 y	IV heparin/No sequel	Headache	Protein S deficiency, disease flare	Transverse sinus, sigmoid sinus
Houissa et al. [16]	16/F	UC	4 y	Heparin/No sequel	Headache, confusion	Disease flare	Undetermined
Jibaly and Kaddourah [17]	11/F	UC	At disease onset	Heparin/No sequel	Headache	Disease flare	Transverse, sigmoid sinuses, jugular vein
Kao et al. [18]	7/F	UC	Unknown	No/Mild motor deficit	Headache, aphasia	Positive anticardiolipin antibody	Transverse sinus, sigmoid sinus
Kao et al. [18]	13/F	UC	Unknown	Heparin/No sequel	Seizure	Elevated homocystein	Superior sagittal sinus, transverse sinus, sigmoid sinus
Kao et al. [18]	14/F	UC	Unknown	Heparin/No sequel	Hemiparesis	None	Sigmoid sinus, cortical veins
Kalbag et al. [19]	8/M	UC	Unknown	None	Unknown	Unknown	Undetermined
Keene et al. [20]	5/M	UC	At disease onset	LMWH/Hemiparesis, dysarthria	Seizure, confusion, hemiparesis, dysarthria	Disease flare, thrombocytosis	Basal ganglia/thalamus and parietal white matter
Keene et al. [20]	12/M	UC	At disease onset	None/No sequel	Bilateral retro-orbital pain	Disease flare, thrombocytosis	Superior sagittal sinus
Kim et al. [21]	17/M	CD	1 y	Heparin/Mild hemiparesis	Right-side weakness, hypesthesia	None	Superior sagittal sinus, cortical vein
Kupfer and Rubin [22]	16/M	CD	4 y	IV heparin/No sequel	Headache	Anticardiolipin antibodies	Superior sagittal sinus, transverse sinus
Kutluk et al. [23]	9/M	UC	At disease onset	Heparin/No sequel	Headache, left ptosis, bilateral papilledema	Disease flare, thrombocytosis	Transverse sinus, sigmoid sinus
Liu et al. [24]	12/F	UC	At disease onset	LMWH/None	Headache, left-sided hemiparesis and numbness, accompanied by intermittent convulsion	None	Superior sagittal sinus, transverse sinus, sigmoid sinus
Macri et al. [25]	17/F	UC	Unknown	Heparin/No sequel	Headache, mixed aphasia, hemiparesis, seizure	Antithrombin III deficiency, OCP	Superior sagittal sinus, cortical vein

(continued to the next page)

**Table 1.** (Continued) Case reports of patients with pediatric inflammatory bowel disease complicated by cerebral venous thrombosis (CVT)

Case report	Age (y)/ Sex	IBD subtype	Time interval between IBD and CVT	Anticoagulant therapy/Outcome	Symptoms	Risk factor	Location of CVT (vessels or brain region)
Markowitz et al. [26]	14/M	UC	9 mo	Aspirin/No sequel	Headaches, hemiparesis	Disease flare, thrombocytosis	Lateral sinus, sigmoid sinus
Martín-Masot et al. [27]	5/-	UC	2 y	IV heparin/No sequel	Headache, seizure, monoparesis	Indwelling catheters, MTHFR mutations, disease flare	Transverse sinus
Marušić et al. [28]	13/M	UC	2 y	Heparin/No sequel	Headache	Disease flare	Superior sagittal sinus, transverse sinus, sigmoid sinus
Mayeux and Fahn [29]	12/F	UC	Unknown	No/Slow recovery	Left focal motor seizure, left hemiparesis, left central facial weakness	Disease flare	Undetermined
Patterson et al. [30]	11/M	UC	Unknown	No/Mild sequel	Unknown	Disease flare	Undetermined
Philips et al. [31]	14/F	IBD/U	Unknown	Local urokinase/No sequel	Neurological deficit	None	Superior sagittal sinus
Prasad et al. [32]	5/F	CD	Unknown	Venous sinus angioplasty and local tPA/No sequel	Headache, expressive aphasia and anomia right homonymous hemiplegia, seizure	Disease flare	Transverse sinus, sigmoid sinus
Rivera-Suazo et al. [33]	3/M	IBD/U	At disease onset	LMWH/No sequel	Seizure	Disease flare	Superior sagittal sinus
Robison et al. [34]	10/M	UC	3 y	Heparin/No sequel	Headache, vomiting	Factor V Leiden	Transverse sinus, sigmoid sinus
Rohani et al. [35]	12/M	UC	1 y	Heparin/No sequel	Headache, confusion, aphasia, seizure, right hemiparesis	Disease flare	Left lateral sinus
Rosen et al. [36]	7/M	CD	Unknown	Heparin/No sequel	Headache, vomiting, blur vision	Thrombocytosis, MTHFR mutation homozygous, prothrombin mutation heterozygous	Superior sagittal sinus, transverse sinus, sigmoid sinus
Rousseau et al. [37]	18/M	UC	Unknown	Anticonvulsant	Unknown	Unknown	Superior sagittal sinus
Selvitop et al. [38]	10/F	CD	5 y	Antibiotic/No sequel	Headache, vomiting, neck pain, stiffness, photophobia, phonophobia, blur vision	Infection	Transverse, sigmoid, cavernous sinuses, internal jugular vein
Shahid [39]	15/M	UC	3 y	LMWH/No sequel	Headache	Disease flare	Superior sagittal, transverse sinuses, internal jugular vein
Standridge and de los Reyes [2]	16/F	CD	5 mo	Heparin/No sequel	Headache, vomiting, syncope	Prothrombin G20210A mutation, disease flare	Superior sagittal, transverse, sigmoid sinuses
Standridge and de los Reyes [2]	18/F	CD	6 y	LMWH/No sequel	Headache, facial paresthesia	Disease flare, thrombocytosis	Transverse sinus, sigmoid sinus
Standridge and de los Reyes [2]	12/F	CD	At disease onset	Aspirin/No sequel	Nausea, vomiting, headache, difficulty walking, left hemiparesis, complex partial seizure with generalization	Thrombocytosis	Cortical vein
Thorsteinsson et al. [40]	18/M	UC	5.5 y	Heparin/No sequel	Headache, vomiting	Infection	Transverse sinus
Zitomersky et al. [41]	8/F	UC	Unknown	LMWH/No sequel	Unknown	Disease flare, PT20210A	Undetermined
Zitomersky et al. [41]	15/F	UC	Unknown	LMWH/No sequel	Unknown	Disease flare	Undetermined

IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis, IBD/U: inflammatory bowel disease unclassified, LMWH: low-molecular-weight heparin, MTHFR: methylenetetrahydrofolate reductase, DVT: deep vein thrombosis, IV: intravenous, OCP: oral contraceptive pill, tPA: tissue plasminogen activator. \*No refers to no administration of anticoagulants.

observed in 16% patients. Ophthalmological manifestations were noted in 21% patients, and blurred vision was the most common manifestation. The clinical manifestations are summarized in **Table 4**.

**Table 2.** Case reports of patients with pediatric inflammatory bowel disease complicated by cerebral arterial infarction (CAI)

Case report	Age (y)/ Sex	IBD subtype	Time interval between IBD and CAI	Anticoagulant therapy/Outcome	Symptoms	Risk factor	Location of CAI (vessels or brain region)
Barclay et al. [4]	7/F	CD	1 mo	Aspirin/Partial recovery	Left hemiparesis, paresthesia	Thrombocytosis, heterozygous for factor V Leiden mutation, family history of TIA, disease flare	Right MCA
Fukuhara et al. [42]	18/M	UC	5 y	None/No sequel	Left hemiparesis	None	Right pons
Gormally et al. [43]	14/M	CD	At disease onset	None/Partial recovery	Left hemiplegia, headache, seizure	Thrombocytosis	Right MCA
Keene et al. [20]	13/F	UC	At disease onset	None/No sequel	Seizure	Disease flare	Right cerebellar hemisphere
Lloyd-Still and Tomasi [44]	5/M	UC	At disease onset	None/Partial recovery, epilepsy developed 10 years later	Right hemiparesis, seizure	Disease flare	Left MCA
Mayeux and Fahn [29]	17/M	UC	Unknown	No <sup>a</sup> /Slow recovery	Sudden left loss of vision with signs of central retinal artery occlusion, seizure	Disease flare	Undetermined
Nelson et al. [45]	18/M	UC	Unknown	No/No sequel	Seizures, coma	Disease flare	Undetermined
Salloum et al. [46]	15/F	UC	8 mo	Aspirin/No sequel	Left hemiparesis, right mouth angle deviation	None	Right MCA
Schneiderman et al. [47]	12/F	UC	1 y	None/Death	Headache, seizure, hemianopia	Disease flare	Distal basilar artery
Standridge and de los Reyes [2]	17/F	IBD/U	At disease onset	Aspirin/No sequel	Severe headache, left-sided hemiparesis and hemiparesthesia, and right facial paresthesia	Disease flare, factor V Leiden heterozygote mutation, thrombocytosis	Left posterior parietal and right pontine/midbrain regions
Tomomasa et al. [48]	1/F	UC	Unknown	None/No improvement	Right hemiplegia, altered consciousness, seizures	Thrombocytosis, disease flare	Left MCA
Yassinger et al. [49]	15/F	IBD/U	Unknown	None/No sequel	Seizure, left hemiparesis	Disease flare	Undetermined

IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis, IBD/U: inflammatory bowel disease unclassified, MCA: middle cerebral artery, TIA: transient ischemic attack.

<sup>a</sup>No refers to no administration of anticoagulants.

**Table 3.** Demographics of patients pediatric inflammatory bowel disease complicated by cerebral venous thrombosis (CVE)

Demographic data	Frequency
Age (y)	12.48±4.13
Sex	
Female	32 (50.61)
Male	30 (49.39)
IBD type	
UC	43 (70.49)
CD	13 (21.31)
Phase of IBD	
Active	54 (87.93)
Passive	8 (12.07)
Active disease	
Active UC	37 (86.04)
Active CD	10 (76.92)
Time interval between onset of IBD and CVE (mean, wk)	20.84
Presence of neurological symptoms of CVE at disease onset	
Yes	11 (26.83)
No	30 (73.17)

Values are presented as mean±standard deviation or number (%).

IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis.

**Table 4.** Clinical manifestations of cerebrovascular event in patients with pediatric inflammatory bowel disease

Clinical manifestations	Frequency		
	Total	UC	CD
Headache	38 (67.85)	25 (65.78)	11 (28.94)
Vomiting	8 (14.28)	4 (50.00)	4 (50.00)
Seizure	23 (41.07)	17 (73.91)	6 (26.09)
Sensory or motor neuropathy	28 (49.84)	17 (61.53)	11 (38.47)
Hemiparesis	13 (23.21)	11 (84.61)	2 (15.39)
Hemiplegia	5 (8.92)	2 (40.00)	2 (40.00)
Paresthesia	5 (8.92)	0	4 (80.00)
Facial neurologic deficit	5 (8.92)	3 (60.00)	1 (20.00)
Dysarthria	1 (1.78)	1 (100.00)	0
Aphasia	4 (7.14)	3 (75.00)	1 (25.00)
Altered level of consciousness	9 (16.02)	7 (77.78)	2 (22.22)
Somnolence	2 (3.57)	2 (100.00)	0
Stupor	1 (1.78)	0	0
Confusion	5 (8.92)	4 (80.00)	1 (20.00)
Coma	1 (1.78)	1 (100.00)	0
Syncope	1 (1.78)	0	1 (100.00)
Ophthalmological findings	12 (21.36)	9 (75.00)	3 (25.00)
Orbital pain	2 (3.57)	2 (100.00)	0
Photophobia	2 (3.57)	1 (50.00)	1 (50.00)
Blurred vision	3 (5.35)	1 (33.34)	2 (66.66)
Hemianopia	2 (3.57)	2 (100.00)	0
Ptosis	1 (1.78)	1 (100.00)	0
Papilledema	1 (1.78)	1 (100.00)	0
Loss of vision	1 (1.78)	1 (100.00)	0

Values are presented as number (%).  
CD: Crohn's disease, UC: ulcerative colitis.

### Thrombosis and infarction sites

In total, 43 of 50 patients with CVT and nine of 12 patients with CAI had documented information on the sites of thrombosis and infarction, respectively. A review of these case reports revealed that the common sites of CVT were the transverse (n=23, 53.48%), superior sagittal (n=20, 46.51%), and sigmoid (n=16, 37.20%) sinuses. The right middle cerebral artery (MCA) (n=3, 33.34%) and left MCA (n=2, 22.23%) were the predominant sites of CAI. The frequencies of CVT and CAI sites are presented in **Tables 5** and **6**.

### Risk factors for venous and arterial thrombosis

Risk factors for venous or arterial thrombosis were identified in 59 of 62 patients. The predominant risk factor for CVE in most reports was IBD flares (59.32%). Thrombocytosis

**Table 5.** Sites of cerebral venous thrombosis (CVT) in patients with pediatric inflammatory bowel disease

Location of CVT (vessels or brain region)	Value (n=43)
Transverse sinus	23 (53.48)
Superior sagittal sinus	20 (46.51)
Sigmoid sinus	16 (37.20)
Lateral sinus	4 (9.30)
Cavernous sinus	1 (2.32)
Cortical vein	8 (18.60)
Jugular vein	3 (6.97)
Occipital lobe	1 (2.32)
Frontal lobe	2 (4.65)
Parietal lobe	3 (6.97)
Thalamus	4 (9.30)
Caudate nucleus	1 (2.32)
Putamen nucleus	1 (2.32)

Values are presented as number (%).

**Table 6.** Sites of cerebral arterial infarction (CAI) in patients with pediatric inflammatory bowel disease

Location of CAI (vessels or brain region)	Value (n=9)
Right MCA	3 (33.34)
Left MCA	2 (22.23)
Right pons	2 (22.23)
Right cerebellar hemisphere	1 (11.12)
Distal basilar artery	1 (11.12)
Left posterior parietal region	1 (11.12)
Midbrain	1 (11.12)

Values are presented as number (%).  
MCA: middle cerebral artery.

and anemia were the main risk factors in 27.11% and 16.94% patients, respectively. Different coagulation defects, including elevated factor VIII levels (n=2), antithrombin III deficiency (n=1), and protein S deficiency (n=3), were reported in 10.16% patients. Hereditary thrombogenic mutations, such as factor V Leiden gene mutation (n=3), methylenetetrahydrofolate reductase (MTHFR) gene mutation (n=3), and prothrombin gene mutation (n=3), were also detected in 13.55% patients.

Laboratory examinations results showed elevated levels of lipoprotein (a) in one patient, elevated homocysteine levels in one (1.69%) patient, and presence of anticardiolipin antibodies in two (3.39%) patients. A positive family history of thromboembolism (e.g., deep vein thrombosis or transient ischemic attack) was reported in two (3.39%) patients. Overall, 16.95% patients showed no potential risk factors for CVE. Moreover, 43.94% patients had more than one risk factor, whereas 38.98% patients had only one risk factor. The probable risk factors for CVE are summarized in **Tables 7 and 8**.

**Table 7.** Risk factors of thromboembolism in patients with pediatric inflammatory bowel disease

Risk factors	Value (n=59)
Disease flare	35 (59.32)
Thrombocytosis	16 (27.11)
Anemia	10 (16.94)
Family history of DVT	2 (3.39)
Protein S deficiency	3 (5.08)
Factor V Leiden mutation	3 (5.08)
MTHFR mutation	3 (5.08)
Prothrombin gene mutation	3 (5.08)
Anticardiolipin ab	2 (3.39)
Elevated fVIII	2 (3.39)
Elevated lipoprotein (a)	1 (1.69)
Elevated homocystein	1 (1.69)
Anti-thrombin III deficiency	1 (1.69)
None	10 (16.95)

Values are presented as number (%).  
MTHFR: methylenetetrahydrofolate reductase, DVT: deep vein thrombosis, fVIII: factor VIII.

**Table 8.** Frequency of risk factors of thromboembolism in patients with pediatric inflammatory bowel disease

Number of risk factors in each patient	Frequency
No risk factor	10 (16.95)
One risk factor	23 (38.98)
More than one risk factor	26 (43.94)

Values are presented as number (%).

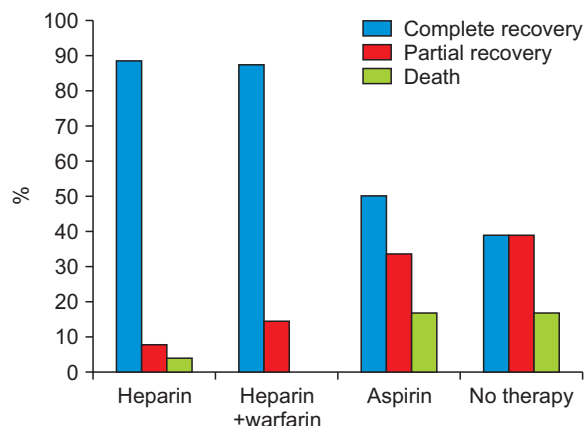


Fig. 1. Outcomes of anticoagulant therapy.

### Effects of therapy on the outcomes

Data on therapy and patient outcomes were available for 59 of 62 patients. They were divided into four groups. The first group included 26 (44.06%) patients who received monotherapy with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Among them, 23 patients recovered completely, two partially recovered, and one died despite anticoagulant therapy due to progression of infarcts into the left hippocampus, right internal capsule, right thalamus, and right medial temporal lobe, with increasing edema, mass effect, and midline shift. During therapy, an 18-year-old boy presented with heparin-induced thrombocytopenia type II, but recovered completely after switching to another anticoagulant (fondaparinux).

The second group included seven (11.86%) patients who received warfarin therapy after heparin administration. Six of seven children treated with LMWH or UFH, followed by warfarin, recovered completely. The third group included six (10.17%) patients who received aspirin monotherapy. Therapy resulted in complete recovery in three patients, partial recovery in two patients, and death in one patient. Finally, in the fourth group, 18 (30.51%) patients who did not receive anticoagulants, seven recovered completely, seven partially recovered, three died, and one showed no improvement.

The decision to avoid anticoagulants in some patients was based on the presence of hemorrhagic infarctions or cerebral hemorrhages on brain computed tomography/magnetic resonance imaging and potential risk of intestinal bleeding. Overall, 41 (69.49%) patients, who were mostly administered UFH or LMWH (56.09%), recovered completely; 12 (20.34%) patients recovered partially; and five (8.47%) patients died, three of whom received no anticoagulant therapy. The outcomes of anticoagulant therapy are shown in Fig. 1.

## DISCUSSION

This study aimed to better describe the phenomenon of CVE in pediatric patients with IBD. We performed a wide search using several databases. This series of 62 cases of CVE in children with IBD provides an interesting basis for new research hypotheses. Most of our patients had UC (70.5%), were in the active phase of IBD at the time of CVE (87.93%), had a mean age of  $12.48 \pm 4.13$  years, and had a mean time interval between the onset of IBD and CVE of 20.84 weeks. The most frequent symptoms were headaches, sensory and



motor neuropathies, and seizures. The common sites of CVT were the transverse, superior sagittal, and sigmoid sinuses. The right and left MCA were the predominant sites of CAI. The predominant risk factor for CVE was IBD flares.

IBD is a known risk factor for thromboembolism. In a study by Nguyen and Sam [50], the incidence of thromboembolism was four to 20 times higher in children with IBD in comparison to children without IBD. CVE are the most common type of thromboembolism in children with IBD [51]. Similar to our review, several studies have highlighted a higher incidence of CVE in patients with UC than in those with CD, which could be due to the role of microvascular thrombosis in the disease process of UC. In other studies on adults and children, the incidence of thromboembolism was similar in male and female patients with IBD, which is in line with our findings [50-52].

The precise mechanism underlying thromboembolism in IBD is unknown. Thrombosis in PIBD consists of systemic thromboembolism events and focal microthrombi in the vasculature of the inflamed intestine [53]. Different aspects of IBD may be associated with the development of thrombosis. Specific factors may predispose patients to thrombosis. An IBD flare or activity was the most common risk factor (59.32%). Generally, chronic diseases associated with inflammation are risk factors for thromboembolism [4,54], and IBD is a disease with the highest degree of inflammation [4,55]. Although disease activity is a very important risk factor, there are reports of thromboembolism, even in patients with inactive UC or after colectomy [56-58]. In our review, most cases were in the active phase of IBD at the time of CVE, which is in line with the findings of Lazzarini et al. [51]. In this review, thrombocytosis (27.11%) was highlighted as a significant risk factor for CVE. Platelet activation and aggregation, in addition to thrombocytosis, increases the risk of thromboembolism [59,60]. Overall, 16.94% children experienced anemia. Anemia was the most common risk factor in a study by Katsanos et al. [1] on adult patients with IBD. However, the role of anemia as an independent risk factor for thromboembolism is controversial [4]. Moreover, inherited hypercoagulation disorders were detected in 32% patients. The detection rate of protein S deficiency, factor V Leiden gene mutations, prothrombin gene mutations, and MTHFR mutations were the same (5.08%). The detection rate of factor V Leiden gene mutation was similar in the studies by Katsanos et al. (7.6%) and Jackson et al. (5%) [1,61]. It appears that patients with IBD and thrombotic events are more heterozygous for factor V Leiden mutation than patients with IBD but without thrombotic complications [62]. Bernstein et al. [63] reported that factor V Leiden heterozygosity increased the risk of thrombosis by five- to eight-folds. In addition, MTHFR mutation was detected in 5.08% children in the literature. However, there are insufficient data regarding the association between MTHFR mutations and the risk of venous thrombosis [64-66]. Similar to the findings of our study, a previous study showed that prothrombin G20210A gene mutation was not common in patients with IBD compared to that in the general population; nevertheless, it caused a five-fold increase in the risk of thromboembolism [2].

There are no approved guidelines for the management of CVE in patients with PIBD; therefore, prevention needs to be prioritized. However, some important questions need to be addressed. One of these questions is related to the important risk factors for CVE in patients with PIBD, especially in outpatient settings. In total, 26.83% patients had CVE at presentation, and factors related to hospitalization, such as indwelling catheter and immobilization, were not involved. Although the disease was in remission in some cases, CVE were reported (12.07%). In addition, 16.95% patients had no risk factors, suggesting that

primary prevention should be considered. Moreover, according to a study by Lazzerini et al. [51], the risk factors for thromboembolism should be investigated in all patients. Therefore, early diagnosis and proper management of PIBD must be prioritized. Mucosal healing, which is the new goal of therapy for PIBD, may be more important than clinical remission. Further research must be conducted to determine whether early diagnosis, clinical and mucosal remission, and screening of risk factors together can prevent outpatient thrombosis.

During hospitalization, some important preventive measures include correction of anemia and dehydration, changing the treatment protocol or adjusting medications to control disease activity, avoiding immobilization, hypertension control, diagnosis and treatment of infection, and correct use and care of indwelling catheters. However, there are no definite guidelines for medical therapy with anticoagulants for either prevention or treatment. According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the management of severe acute colitis, prophylaxis is recommended for children with only one risk factor for thromboembolism; LMWH is the drug of choice [67]. Our findings revealed that nearly 83% patients had a risk factor for CVE, while almost 49% of them had more than one risk factor. In the latest guidelines for the management of stroke in children, the indications for primary or secondary prevention (after the first attack) are not recognized [68]. The best way to decide on long-term prophylaxis with anticoagulants is to consult with a hematologist. According to the new American Heart Association guidelines, medical therapy with aspirin or heparin (LMWH or UFH) is recommended within the first 5–7 days of admission for children with CVE if there is no contraindication [68]. Although a sample of 62 patients is not sufficient to compare the efficacy of medications, as shown in **Fig. 1**, heparin or heparin+warfarin is the most effective therapy to achieve the best outcomes. However, the outcomes of conservative management are poor in children. In addition, aspirin may not be as effective as heparin for CVE in patients with PIBD. Considering the differences in the treatment protocols applied to the patients, we could not determine the optimal dose or duration of therapy.

## CONCLUSION

To our knowledge, CVE are the most common type of thromboembolism events in patients with PIBD, resulting in life-threatening complications and even death. Healthcare providers should improve their knowledge and awareness regarding the diagnosis, risk factors, therapeutic agents, and preventive options for CVE to obtain better neurological outcomes and decreased mortality rates. Therefore, further research is needed to determine the best practices for CVE management in patients with PIBD.

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