Cerebral Venous Sinus Thrombosis in a 19 Year Old Female With Ulcerative Colitis: Long Term Follow-up and Review From the Literature

Anita Arsovska¹, Pietro Caliandro², Valeria Caso³, Florin Scarlatescu⁴, Marija Babunovska¹, Chiara Iakovelli⁵, Dennis Dietrich⁶

¹ University Clinic of Neurology, School of Medicine, “University Saint Cyril and Methodius”, Skopje, North Macedonia
² Fondazione Policlinico Universitario Agostino Gemelli, Unità Operativa Complessa di Neurologia, Rome, Italy
³ Stroke Unit, Division of Cardiovascular Medicine, University of Perugia, Italy
⁴ Floreasca’ Emergency Clinical Hospital-Neurology Clinic, Bucharest, Romania
⁵ Fondazione Don Carlo Gnocchi Onlus, Milan, Italy
⁶ Great Falls, MT and Department of Neurology, University of Washington, USA

ABSTRACT:
Background: Cerebral venous sinus thrombosis is a rare complication of ulcerative colitis.
Case presentation: We present a case report of a 19-year-old female patient with ulcerative colitis, who developed superior sagittal sinus thrombosis with haemorrhagic transformation. Despite the initial treatment with anticoagulant therapy, the patient became comatose, with symptomatic epileptic seizures and compromised cardiorespiratory function. She was transferred to the ICU and put on life-support for 3 weeks. She gradually improved and was discharged on low-molecular weight heparin and antiepileptic therapy. Oral anticoagulant therapy with warfarin was started 6 months later, when the subsequent D-dimers normalized. In the follow-up period, the patient experienced another series of symptomatic epileptic seizures and poorly regulated INRs. Therefore, antiepileptic and anticoagulation therapies were changed to oxcarbazepine and rivaroxaban.
Conclusion: Physicians should be aware that treatment of cerebral venous sinus thrombosis with haemorrhagic transformation in a patient with ulcerative colitis is very challenging and demanding. These patients need to be closely monitored for possible complications that might arise due to the concomitant presence of both diseases and possible drug interactions.

KEYWORDS: cerebral sinus venous thrombosis, ulcerative colitis, “thunderclap” headache, symptomatic epilepsy, anticoagulation

SAŽETAK:
Uvod: Tromboza vena sinus mozga je rijetka komplikacija ulceroznog kolitisa.
Prikaz slučaja: Prikazujemo slučaj 19-годишње bolesnice s ulceroznim kolitisom koja je razvila superiornu trombozu sagitalnog sinusa s hemoragičnom transformacijom. Unatoč početnom liječenju antikoagulantnom terapijom, pacijent je postao komatozan, sa simptomatskim epileptičkim napadajmi i kompromitiranom kardiorespiratornom funkcijom. Pacijentica je prebačena na jednicu intenzivnog liječenja tijekom narednih 3 tjedna. Postupno se poboljšava uz terapiju heparina niskih molekularnih mase i antiepileptičku terapiju. Oralna antikoagulantna terapija s varfarinom započela je 6 mjeseci kasnije, kada su se sljedeći D-dimeri normalizirali. U razdoblju praćenja pacijent je doživio niz simptomatskih epileptičkih napadaja i slabo reguliranih INR-ova. Stoga su antiepileptička i antikoagulacijska terapija promijenjene u okskarbazepin i rivaroxaban.
Zaključak: Liječnici trebaju biti svjesni da je liječenje cerebralne venske tromboze sa hemoragičnom transformacijom u bolesnika s ulceroznim kolitisom vrlo izazovno i zahtjevno. Također, te bolesnike treba pomno pratiti zbog mogućih komplikacija koje bi mogle nastati zbog istodobne prisutnosti bolesti i mogućih interakcija lijekova.

KLJUČNE RĲEĆI: cerebralna tromboza venskih sinus, ulcerozni kolitis, glavobolja, simptomatska epilepsija, antikoagulacija

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Correspondence: Anita Arsovska MD PhD anita7omk@yahoo.com

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**Introduction**

Cerebral venous sinus thrombosis (CVST) is a relatively rare condition compared to arterial disease. The estimated incidence is 3-4/100,000 in the adult population and up to 7/100,000 in children. It is more common in women than in men, and young women (age 20-35 years old) are more frequently affected. CVST can be caused by different conditions, such as collagen-vascular, infectious, structural, hypercoagulable states, hematological, hormonal, medication-related, and others (Table 1). Inflammatory bowel diseases, such as Crohn disease and ulcerative colitis (UC), have also been described as risk factors for CVST; it is suspected that hypercoagulable state occurring during the disease or the use of corticosteroids in the treatment could cause CVST.

**Case presentation**

We present a case of a 19 year old female patient, who was admitted at the University Clinic of Neurology due to strong generalized “thunderclap” headache resistant to analgesics that was followed by acute onset of right sided hemiparesis and hemiparesthesiae 3 days before. On admission the patient was conscious, blood pressure was 115/70 mmHg, with right-sided hemiplegia and motor dysphasia. Urgent computed tomography (CT) of the brain showed a hypodensity involving the left parietal cortical and subcortical region with hyperdensities within the affected area, suspicious for venous infarction with haemorrhagic transformation due to thrombosis of the superior sagittal sinus (Figure 1). She had been diagnosed with ulcerative colitis one year earlier and was on oral treatment with sulfasalazine and azathioprine. Therapy with low-molecular heparin (Clexane 2x60mg) was initiated.

Blood laboratory analysis showed increased levels of D-dimers (12 000 ng/ml), erythrocyte sedimentation rate-ESR (90 mm/h), CRP (136 mg/L) and decreased levels of RBC (2,51 10x12/L), albumin 27 g/L and Fe 3,7 mmol/l; other values were normal. Follow up CT of the brain two days after showed worsening of

![Figure 1. CT scan of a venous infarction with hemorrhagic transformation due to thrombosis of the superior sagittal sinus](image1)

![Figure 2. Control CT of the brain that showed massive venous infarction in the left parietal and left frontal region with compressive behavior towards the surrounding structures](image2)

**Table 1. Conditions that may cause CVST**

| Collagen-vascular | Infectious | Structural | Hypercoagulable states | Hematological | Medication-related | Inflammatory | Others |
|------------------|------------|------------|------------------------|---------------|-------------------|-------------|--------|
| Systemic lupus erythematosus | Sinusitis | Head trauma | Antiphospholipid syndrome | Paroxysmal nocturnal hemoglobinuria | Oral contraceptives | Crohn disease | Malignancies |
| Wegener granulomatosis | Surgery | | Protein S and C deficiencies | Thrombotic thrombocytopenic purpura | Corticosteroids | Ulcerative Colitis | Intracranial hypotension |
| Behçet syndrome | Lupus anticoagulant, Leiden factor V | | Antithrombin III deficiency, | Polycythemia | Epsilon-aminocaproic acid | Lumbar puncture | |
| | | | Pregnancy and puerperium | Sickle cell disease | Thalidomide | | |
| | | | | | Tamoxifen | | |
| | | | | | | | |

...continued
She came for regular visits every month, and was treated with gastroprotective, immunomodulatory and physical therapies.

During the hospitalization the patient had repeated focal complex motor symptomatic seizures with secondary generalization and antiepileptic therapy with carbamazepine was initiated. Despite treatment, the patient worsened, she became comatose, with right hemiplegia. The fourth day the patient developed additional symptomatic focal complex motor seizures with secondary generalization and compromised cardiorespiratory function.

She was transferred to the Intensive Care and Reanimation Unit and was intubated and ventilated. The 3 week course was complicated by aspiration pneumonia. Afterwards, she improved and was again transferred to the University Clinic of Neurology.

On admission she was conscious, with bilaterally weakened vesicular breathing in the basal parts on auscultation, with bronchitic noises in the middle parts bilaterally. Neurological examination showed motor dysphasia and right sided hemiplegia with spastic features, hyperreflexia and positive Babinski sign.

Routine laboratory blood analysis showed moderate secondary anaemia with decreased levels of RBC, HGB and SeFe, elevated WBC and sedimentation, all other values were normal. Coagulation studies showed increased levels of D-dimer and therapy with low-molecular heparin (Clexane 2x60mg) was continued.

EEG showed groups of delta waves over the left temporo-occipital region.

Follow up CT after 10 weeks showed massive hypodense zone in the left parietal and left frontal region without compressive behavior towards the surrounding structures, i.e. venous infarction in the phase of reabsorption (Figure 2). Through this zone smaller hyperdense punctuate zones were seen, that could represent smaller haemorrhagic formations.

Genetic mutation investigations for cerebrovascular diseases showed heterozygote for A1298C mutation in the gene for MTHFR, heterozygote for mutation V34L in the gene for factor XIII, homozygote for mutation eNOS-786 T>C, heterozygote for mutation 455 G>A in the gene for B-fibrinogen and heterozygote for mutation eNOS G894T and LTA. Other tests (levels of antiphospholipid antibodies, protein S and C, antithrombin III, lupus anticoagulant, and the Leiden factor V) were normal.

The previous finding, with venous infarction in the left parietal cortical and subcortical region, with dimensions 98mmx56mm and strong compressive behavior towards cerebral falx and left lateral ventricle, with haemorrhagic transformation with dimensions 16mmx9mm and several smaller punctate haemorrhagic changes (Figure 2). Antiedematous therapy with mannitol and steroids was administered.

Despite treatment, the patient worsened, she became comatose, with right hemiplegia. The fourth day the patient developed additional symptomatic focal complex motor seizures with secondary generalization and complicated cardiorespiratory function. She was transferred to the Intensive Care and Reanimation Unit and was intubated and ventilated. The 3 week course was complicated by aspiration pneumonia. Afterwards, she improved and was again transferred to the University Clinic of Neurology.

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The patients still had melena, so after gastroenterohepatologist consultation, proctocolectomy was recommended and anticoagulation therapy. The patient was discharged after 2 weeks in a stable condition, with mRS score of 4 and treated with anticoagulation, gastroprotective, immunomodulatory and physical therapies.

The dosage of carbamazepine was initially increased, but later switched to oxcarbazepine. Although the patient did not have any epileptic seizures in the following 6 months, she complained of transient side effects from oxcarbazepine (alopecia and skin rash on her back). Gradually, the side effects withdrew, and the patient did not experience them anymore. Nineteen months after the initial event, control INR showed poor regulation, mostly due to green salad intake and its interaction with warfarin.

Therefore, rivaroxaban of 15mg daily was recommended and warfarin was stopped.

**Discussion**

UC is a type of chronic inflammatory bowel disease (IBD) of unknown etiology that causes inflammation and ulcers in the colon and rectum. It is a consequence of complex interaction of environmental factors and genetic susceptibility. UC may affect any age group, but most commonly appears in age groups between 15-30 and 50-70 years. Approximately 40% of the patients have extra-intestinal manifestations in skin, joints, bones, lungs, blood, eyes, kidneys, liver, peripheral and central nervous system. Patients with IBD have high thromboembolic risk, with an annual incidence varying between 0,5 to 6,7%. Their risk for a thromboembolic event is increased 3-4 fold, compared to healthy controls.

CVST has been reported as rare, but severe complication of UC, with the annual incidence ranging from 1.3% - 7.5%. The clinical presentation of CVST, consisting of headaches, focal signs, seizures, or encephalopathy, and the sites of the venous occlusions are similar to the usual cerebral venous thrombosis.
It can appear from 2 months to 17 years after the first attack of IBD. Sometimes, the diagnosis of IBD is established only when CVST occurs. Katsanos et al. have retrospectively reviewed 65 case reports from IBD patients complicated with CVST, published in the period from 1967-2012. Sources included MEDLINE and EMBASE and they included only papers written in English. We searched MEDLINE for case reports published in the period 2012-2019 and found 13 papers describing total of 17 cases with UC and CVST (Table 2).

Mahmoud et al. (2013) have described an 11 year old male patient with 3 months history of UC who presented as pseudotumor cerebri due to superior sagittal sinus thrombosis during an acute exacerbation of his colitis, that was successfully treated with heparin and then warfarin.

Cojocaru et al. (2014) published cerebrovascular complications in 9 patients with IBD (6 with Crohn's disease (CD) and 3 with UC, 4 of them during acute disease at admission. Cerebrovascular complications were: CVT-7 cases (5 CD and 2 UC) and ischimic stroke-2 cases (1 CD and 1 UCC). Out of 7 cases with CVT 5 were superior sagittal sinus thrombosis (SSS), 2 SSS and transverse and sigmoid sinus thrombosis. Significantly high serum levels of homocysteine were observed in all patients. No correlation between high dose corticosteroids and its decrease, the activity of the IBD, the duration of the disease, and the onset of cerebrovascular complications was found. Tendency to hypercoagulability, even in the inactive state of the IBD was observed. The outcome of cases was favorable, with the remission of symptoms in CVT cases and with residual motor deficits in ischemic stroke patients.

Shaik et al (2014) presented a pre-teenager with newly diagnosed UC and acute headache, altered mental status and bilateral lower extremity weakness, with thrombosis in the vein of Galen and straight sinus, demonstrated on CT. Despite therapy with heparin, the patient clinically deteriorated and became unresponsive, and was therefore taken for endovascular treatment. A novel endovascular approach had been performed with combined use of Solitaire FR and Penumbra devices to enhance access to the straight sinus and to limit intra-procedural blood loss. The posttreatment CT demonstrated a decrease in hyperattenuation within the vein of Galen and straight sinus. The neurologic status improved within 24 h. The patient was discharged home with a normal neurologic examination.

DeFillipis et al, 2015 reported 6 IBD patients with cerebral venous thrombosis, of which 4 had active UC. The patients presented with hours to days of headache and were found to have venous thrombosis on imaging. All patients were treated with therapeutic anticoagulation. There were two deaths; one patient

| Author/year | Age  | Gender | Active UC | UC treatment | Neurological symptoms | CVST location | Risk factors | CVST treatment | Outcome |
|-------------|------|--------|-----------|--------------|----------------------|---------------|-------------|----------------|---------|
| Mahmoud et al. 2013 | 11 M | Yes | Prednizolon | Headache, orbital pain, phonophobia, transient blurred vision, vomiting | SSS | Increment of corticosteroid dosage, relapse of UC | Heparin/Warfarin | Completely recovered |
| Cojocaru et al, 2014 | 32 M | Yes | Sulfasalazine, Prednisolone | Headache, generalized convulsive seizures, drowsiness, papilledema | SSS, sigmoid S, Transverse sinus | Increased serum homocystein | LMWH | Completely recovered |
| Shaikh et al, 2014 | Preteenager M | Yes | Prednisone/ Mesalazine | Headache, altered mental status, bilateral lower extremity weakness | Vein of Galen, Straight sinus | / | Endovascular (Solitaire FR and Penumbra)/Heparin/LMWH | Completely recovered |
| DeFillipis et al, 2015 | 30 M | Yes | Corticosteroids | / | / | / | LMWH | Partially recovered |
| DeFillipis et al, 2015 | 12 M | Yes | Corticosteroids | / | / | / | LMWH | Completely recovered |
| DeFillipis et al, 2015 | 10 M | Yes | Corticosteroids | / | / | / | Heparin drip | Lethal outcome |
| DeFillipis et al, 2015 | 11 F | Yes | Corticosteroids | / | / | / | Heparin | Lethal outcome |
| Calcagno et al, 2015 | 22 M | Yes | Mesalazine, Prednisone | Headache, speech disturbance | Sigmoid sinus, superficial vein | / | Heparin/Warfarin | Completely improved |
| Meher et al, 2016 | 58 F | No | Oral steroids, 5-ASA, Sulfasalazine | Headache, nausea, vomiting, blurred vision, papilledema, photophobia, generalized tonic-clonic seizure | Sigmoid sinus, Transverse sinus | / | LMWH/Warfarin | Completely improved |
became comatose and died despite anticoagulation while the other recovered well from the sinus thrombosis but died after a bowel perforation 3 weeks later. Five patients were being treated with corticosteroids at the time of the occurrence of CVT. Three patients were on anti-tumor necrosis factor inhibitors, including two on infliximab and one on certolizumab. The most common locations for CVT were sagittal sinus and transverse sinus, both occurring in three patients. However, four patients had multiple cerebral thrombi involving both deep cerebral and superficial cortical veins. One patient had the heterozygous C677T mutation in the MTHFR gene. Three patients had elevated factor VIII activity attributed to ongoing inflammation. All patients were treated with therapeutic anticoagulation and subsequently maintained on low molecular weight heparin or warfarin for 6 months or longer. Altogether two patients died, in which one became comatose and died despite anticoagulation. The patient had a progression of infarcts in the left hippocampus, right internal capsule, right thalamus and right medial temporal lobe, with increasing edema, mass effect and midline shift. The other patient recovered well following the sinus thrombosis with only mild residual right-sided weakness and was discharged on low molecular weight heparin. She was readmitted to another hospital 3 weeks later after experiencing a few days of abdominal pain, rectal bleeding and respiratory distress. The patient was found unresponsive by the emergency medical services. A head computed tomography (CT) revealed no hemorrhage or evidence of ischemic stroke. The patient was found to have bowel perforation and underwent surgical intervention twice. She died from post-operative complications. Of the four patients who recovered, only one patient had any residual neurological deficits that were limited to trace right facial weakness, right-sided ataxia and mild sensory loss on the right hand and foot.

Calcagno et al, 2015 have described a case of a 22 year old male with UC in treatment with mesalazine and prednisone presenting with headache and speech disturbances. A magnetic resonance imaging of the brain showed a left temporal hemorrhagic infarct with thrombosis of the ipsilateral superficial vein and sigmoid venous sinus. No cause of thrombophilia was detected. Anticoagulation with heparin was started which was changed to low molecular weight heparin or warfarin. The patient was discharged on life-support for a period of 3 weeks. Her condition stabilized after this period and she became conscious, able to breathe on her own. Therapy with oral anticoagulant therapy with warfarin is continued with an INR target 2-3. When the patient is relatively stable, oral anticoagulant therapy with warfarin is continued with an INR target 2-3. Steroids reduce the intracerebral edema and are also indicated in the active cases of ulcerative colitis.

Our patient had an active form of UC with constant bleeding from its risks should be carefully weighed in light of possible hemorrhagic complications. When the patient is relatively stable, oral anticoagulant therapy with warfarin is continued with an INR target 2-3. Steroids reduce the intracerebral edema and are also indicated in the active cases of ulcerative colitis.

Various mechanisms have been proposed as possible explanations for thrombosis in UC, such as hypercoagulation (elevated FVIII, fibrinogen, decrease in antithrombin, protein S and protein C), hypofibrinolysis [elevated PAI-1 and lipoprotein (a)], platelet abnormalities, endothelial dysfunction (increased von Willebrand factor) and immunological abnormalities (antiphosphlipid antibodies). It has been suggested that the interaction between the coagulation cascade in the body and cytokine mediators of chronic inflammation and also the inflammatory process can itself activate the coagulation cascade. Beside inflammation, the drugs used in the treatment (corticosteroids and sulfonamides) contribute to the thrombophilic tendency. Some authors suggest that the majority of thrombotic events occur during the active phase of disease, however, others disagree. For example, Kristensen et al., reported a significant direct association of disease activity of IBD with increased risk of morbidity and mortality, while Katsanos et al., reported the presence of CVST in the active phase in 78.4% and in the inactive phase of the disease in 21.6%.

Risk factors and concomitant causes of CVST were systematically searched for in our patient. We found hypercoagulable state in our patient, with increased D-dimer levels. Also, biologic markers of inflammation such as elevated leucocyte count and CRP were registered and the patient was in an active phase of her UC (with continuous bleeding).

Genetic mutation investigations for cerebrovascular diseases showed (among other mutations), a heterozygote for A1298C mutation in the gene for methylenetetrahydrofolate reductase (MTHFR). Reports from the literature have also shown defective activity of MTHFR among patients with UC, which is linked to folate and vitamin B12 deficiency and causes hyperhomocysteinemia-related thrombosis. Data from the literature have shown that patients with UC have more frequently lower circulating protein S levels than normal controls and reduced levels of antithrombin III. But, in more than 50% of the patients with UC, no predisposing factor can be found. The values of protein C, S and antithrombin III in our patient were in normal range. The first-line treatment for CVST is adjusted-dose unfractionated heparin or low-molecular-weight heparin (LMWH), but its risks should be carefully weighed in light of possible hemorrhagic complications. When the patient is relatively stable, oral anticoagulant therapy with warfarin is continued with an INR target 2-3. Steroids reduce the intracerebral edema and are also indicated in the active cases of ulcerative colitis.
bleeding had stopped, we were able to switch her on oral anticoagulant therapy with warfarin with satisfactory level of INR. She has continued with oral anticoagulant therapy in the following period, without any side effects. However, when we encountered difficulty regulating the INR, with a possible risk for recurrent thrombosis, we made a choice to stop warfarin and introduce rivaroxaban. We searched MEDLINE for similar cases, and only found one case report, where rivaroxaban was prescribed to a 17 years old female with a CVST and Crohn’s disease. There were also other case reports regarding administration of rivaroxaban in patients with CVST, but without known UC.

Another problem that we have encountered was the recurrence of late onset epileptic seizures. The study of Kalita et al. showed that up to 5.6% of their patients with CVST had late recurrence of seizures. Recent study by the VENOST Study Group showed that epileptic seizures had no effect on prognosis of CVST.

Overall, the prognosis is usually good, but a few cases were fatal. There are recommendations for prophylaxis of thromboembolic phenomena (including CVST) in patients with IBD. The Canadian Gastroenterology Association and the British Society of Gastroenterology recommend pharmacological thromboprophylaxis in patients requiring hospitalization for moderate-severe IBD and without severe bleeding.

**Conclusion**

CVST is a devastating complication of IBD, especially, UC. This case report signifies the importance of considering the diagnosis of CVST in a case of IBD. Any sudden neurological symptoms such as headache, hemiparesis and seizures in a patient with UC should initiate urgent diagnostices in order to prevent the complications of the disease. Physicians should be aware that treatment of cerebral venous sinus thrombosis with haemorrhagic transformation in a patient with ulcerative colitis is very challenging and demanding. These patients need to be closely monitored for eventual complications that might arise due to the concomitant presence of both diseases and possible drug interactions. Our patient with CVST associated to UC is the first case reported in literature treated with rivaroxaban because of INR poor regulation.

**Author contributions:** All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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