

Association of ulcerative colitis and cerebral venous thrombosis a case report and review of the current literature

Nicoleta Tohanean¹, Andrei Bibirigea², Vlad-Ioan Suciuc³, Iulia Coroian⁴,
Lacramioara Perju-Dumbrava¹

¹Neurology Department, "Iuliu Hatieganu" University of Medicine and Pharmacy,
Cluj-Napoca, Romania

²Neurology Clinic, Academic Emergency Hospital Cluj-Napoca, Romania

³Neurology Clinic, Academic Emergency Hospital Sibiu, Romania

⁴Oncology Institute Cluj-Napoca, Romania

ABSTRACT

There is a rare association regarding inflammatory bowel diseases and cerebral venous thrombosis that can have a potential unfavourable outcome. Here we report a 29 year-old female patient with a severe form of pancolitis autoimmune disease and an incomplete superior sagittal sinus and bilateral transverse sinuses thrombosis with a clinical response of motor deficit in the right upper limb. With the implication of a multidisciplinary medical team and anticoagulant therapy the patient had a good neurologic outcome and we want to compare our case to the few other reported cases regarding associated pathologies, risk factors, treatment and outcome.

Keywords: inflammatory bowel diseases, cerebral venous thrombosis, anticoagulant therapy

Abbreviations (in alphabetical order)

IBD – inflammatory bowel disease

UC – ulcerative colitis

CVT – cerebral venous thrombosis

LMWH – low molecular weight heparin

y – years

no – number

s.c. – subcutaneous

CT – computer tomography

MRI – magnetic resonance imaging

INTRODUCTION

The cerebral venous thrombosis (CVT) is a more rare cause of stroke, which involves the occlusion of one or multiple cerebral veins or dural sinuses. The pathogenetic mechanism can be divided into two broad categories – infectious and non-infectious. In non-infectious CVT, the state of hypercoagulability plays an important role and can be met in coagulopathies, sickle cell disease, cancer, thrombocytosis and autoimmune disorders (Behcet's disease, Ulcerative colitis and other In-

flammatory bowel diseases). The clinical onset is acute or subacute with slower progression than other stroke syndromes and the general outcome seems to be favourable. Venous infarctions with hemorrhagic complication develops frequently in such cases (1,2).

CASE REPORT

A 29-year old female patient, race – caucasian, was diagnosed at the age of 25 years in a clinical gastroenterology service, with a severe form of

Corresponding author:

N. Tohanean

E-mail: nicoleta_alex@yahoo.com

Article History:

Received: 8 February 2019

Accepted: 24 February 2019

pancolitis autoimmune disease. Her family history only revealed father with Vitiligo. After diagnosis, she started treatment with Prednisone 40 mg per day for 3 weeks with progressive decrease of the dose, simultaneous with Mesalazin 3 grams per day (which is continued until present). After just 3 months, she presents a new episode of acute colitis for which in 2014, treatment with Azatioprin 100 mg per day was established for seven months. This treatment was stopped after the seven months because of a severe neutropenia (grade 4 neutropenia). Later she received a biologic therapy with Infliximab iv 5 mg/kg/dose every 8th week for approximately one year (until 2015) until the appearing of anti-Infliximab antibodies. A switch of the therapy was made from Infliximab to Adalimumab s.c. 40 mg per dose every second week. After 10 months, the anti-Adalimumab antibodies were positive and the treatment was stopped.

Furthermore, the patient presented two episodes of infectious colitis with *Clostridium difficile* in 2017 which were treated with oral antibiotic medication (Metronidazol 500 mg every 8 hours and Vancomycin 125 mg every 6 hours for a period of 14 days).

Subsequently, along with Mesalazin 3 grams per day by mouth and 1 gram with local application, treatment with Imuran 100 mg per day was reintroduced, with good toleration. Since may 2018 treatment with Budesonide MMX 9 mg by mouth was initiated along with VLS#3 1 bag per day for 10 days.

In June 2018, during a very stressful period of time, she present a right upper limb motor deficit, difficulty in movement coordination of the right upper limb and vertigo feeling, for which she was admitted in a territorial Neurology service. Native head computer tomography (CT), native head magnetic resonance imaging (MRI) and head angio-CT with arterial acquisition, described a left parietal lobe small infarction raising the suspicion of an arteriovenous malformation of the left parietal lobe. 3 days after the motor deficit installed, the patient presented during a 12-hour period of time 2 episodes of conscious loss with a tonico-clonic appearance of approximately 1 minute duration, for which was administered Carbamazepine 400 mg and transferred in our Neurology department.

At admission in our service, patient presented a light motor deficit of the right upper limb (with a 4/5 segmentary muscular strenght).

At the imaging reevaluation of the head using angio-MRI examining with both arterial and venous components, an incomplete superior sagittal sinus and bilateral transverse sinuses thrombosis was described (Fig. 1), alongside with a venous infarct of the left postcentral gyrus associated with a minimal local hemorrhage and also an ischemic lacuna located in the head of the right caudate nucleus (Fig. 2, 3).

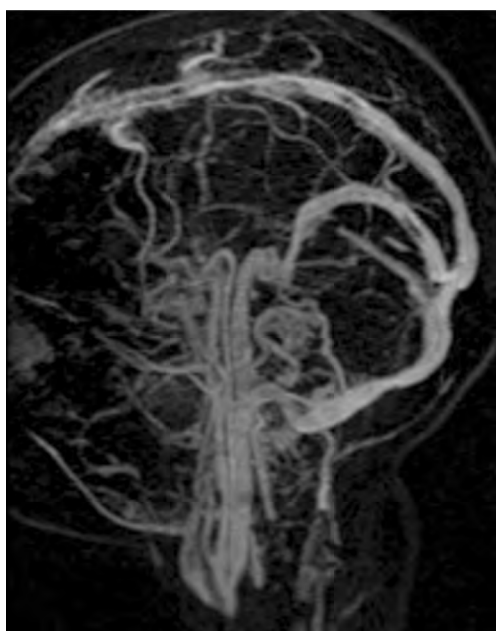


FIGURE 1. Angio-MRI of the head showing an incomplete superior sagittal sinus and bilateral transverse sinuses thrombosis

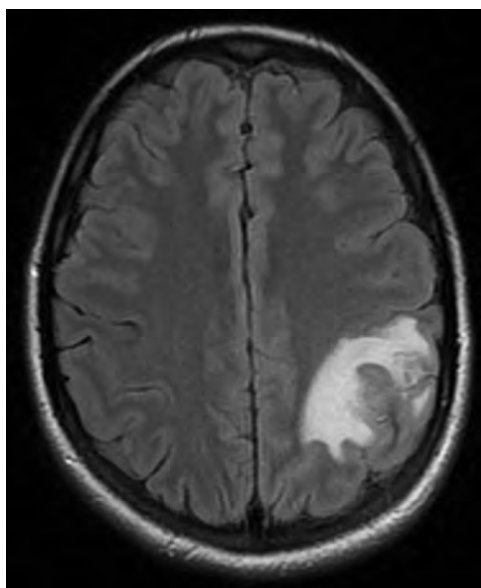


FIGURE 2. Angio-MRI of the head, FLAIR sequence, axial section showing venous infarct of the left postcentral gyrus

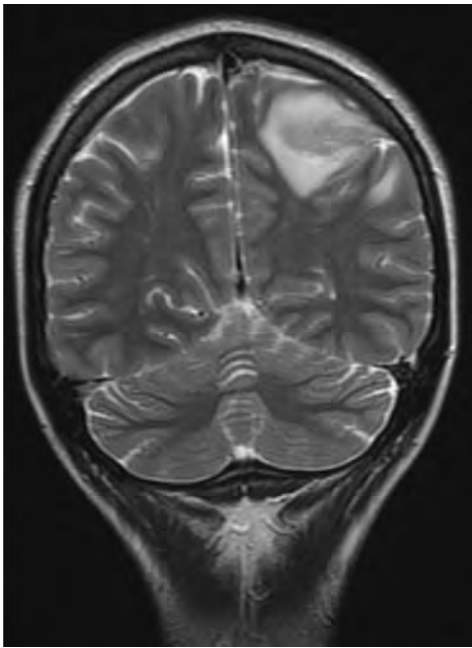


FIGURE 3. *Angio-MRI of the head, T2 sequence, coronal section showing venous infarct of the left postcentral gyrus*



FIGURE 4. *Angio-MRI of the head showing the superior sagittal sinus and bilateral transverse sinuses with normal blood flow*

Anticoagulant s.c. (enoxaparin sodium – 0,3 mg every 12 hours), therapy was started and Carbamazepine was replaced with Levetiracetam in progressive doses till 1,000 mg per day. After hyperventilation the electroencephalogram shows a risen amplitude of the waves alongside with isolated peaks and wave-peak complexes in the bilateral frontal lobes but more on the left side.

Biological findings consists in a severe anemic syndrome (hemoglobine 7,3 mg/ dl) and an inflammatory syndrome (Erythrocyte Sedimentation Rate 21 mm/h and a C-reactive protein of 4,64 mg/dl). The extended immunological tests were positive

for c-ANCA antibodies (and negative at the reevaluation) and IgM Borrelia (uncertain result was obtained for IgM Borrelia). There was also blood collection for thrombophilia in the idea of excluding a prothrombotic intrinsic state and there were found: Antitrombin III (147,61% activity), C protein (154,6% activity), mutation of PAI-1 gene (mutation in 844 A>G genotype GG), mutation of MTHFR gene (mutation 1298 A>G heterozygote) and mutation of the 5th factor Leiden (mutation 1691 G>A heterozygote). No pathological findings at Doppler ultrasound of the neck arteries and in the cardiologic examination.

Inflammatory Bowel Diseases Multidisciplinary team's report, supported the s.c. anticoagulant therapy suggesting the possibility of initiating a new therapy with anti-integrin monoclonal antibodies (Vedolizumab).

Abdominal ultrasound revealed liver hilar lymphatic nodules with a reactive aspect, splenomegaly, a segmentar spleen vein thrombosis and left colitis with the aspect of an active ulcero-hemorrhagic colitis, pericolic and mesenteric reactive lymph nodes.

The patient had a good clinical evolution, haemoglobin levels ranged 10 mg/dl and the upper right limb motor deficit became unnoticeable.

After a 6-month period of time, the angio-MRI investigation of the head shows that there are no more blood flow defects in the venous head system and there can be seen only the old venous stroke lesion in the left parietal lobe, all compared to the initial angio-MRI investigation of the head; clinically no motor deficit.

DISCUSSIONS

Our case presented multiple common features with the cases reviewed in this paper. We have compared 9 cases of patients suffering from ulcerative colitis (UC), who during the course of their illness presented cerebral venous thrombosis.

There were 44% women and 56% men. The mean age was 22 years, while the oldest patient was 35 years old. At the onset of the CVT, epileptic seizures were present in 4 patients. Headache was present in 5 patients (1 woman, 4 men), while other neurologic abnormalities were present in 6 patients (2 women, 4 men). Fever and diarrhea were present in 2 patients (all men), while lower gastrointestinal bleeding was described in 5 patients (3 women, 2

TABLE 1. Case reports from patients with ulcerative colitis complicated with cerebral venous thrombosis

Reference*	Derdeyn and Powers ¹	Keene, Matzinger, Jacob and Humphreys ²			Adrish and Rios ³	Lee, Hwang, et al ⁴	Taous, Berri, et al ⁵	Menon, et al ⁶	Srivastava, et al ⁷
Case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age	26	5	13	12	unknown	35	22	35	29
Gender	F	M	F	M	M	M	F	F	M
Seizures	yes	yes	yes	no	no	no	no	yes	no
Headache	no	no	no	yes	yes	yes	no	yes	yes
Other neurologic signs	yes	yes	no	no	yes	yes	yes	no	yes
Fever	no	yes	no	no	no	yes	no	no	no
Diarrhea	no	yes	no	no	no	yes	no	no	no
Blood in the stools	no	no	yes	no	no	yes	yes	yes	yes
Abdominal pain	no	no	no	yes	no	no	yes	yes	no
Prior Immunosuppressive medication	yes	no	yes	yes	yes	no	no	no	no
Prior corticotherapy	no	no	yes	yes	yes	no	no	no	no
Prior UC medication	Mercaptopurine, Dipentum	-	Prednisone	Prednisone, Asacor	Certolizumab, Mercaptopurine, Prednisone	-	-	-	-
Risk factors for CVT	1 (history of DVT)	2 (thrombocytosis, dehydration)	1 (corticotherapy)	2 (corticotherapy, anemia)	1 (corticotherapy)	2 (dehydration, anemia)	2 (dehydration, anemia)	1 (anemia)	1 (dehydration)
Abdominal surgical intervention	no	no	yes	yes	no	no	no	no	no
UC flare	no	yes	yes	yes	no	yes	yes	yes	yes
Neurologic outcome	good	negative	good	good	good	good	good	good	good
Anticoagulation	yes	no	no	no	yes	yes	yes	yes	yes
Imaging diagnostic value	yes	indirect signs	indirect signs	yes	yes	yes	yes	yes	yes
Solitary or Multiple CVT	solitary	multiple	multiple	solitary	multiple	multiple	multiple	multiple	multiple

*please consult the references

**Note: These cases refer only to ulcerative colitis (UC) complicated with CVT.

men). 7 patients had an UC flare (3 women, 4 men), while only 4 had prior UC medication. Despite the fact that 7 patients had multiple venous thrombosis sites (3 women, 4 men), and all had at least one risk factor for CVT (5 patients with 1 risk factor and 4 patients with 2 risk factors), good outcome was reported in 8 patients (9 total). The most common risk factors were anemia and dehydration, both present in 4 cases each. One patient recovered incompletely having residual neurologic abnormalities at follow-up. Anticoagulation was prescribed in 6 patients (3 women, 3 men) (1-7).

TABLE 2. Risk factors for CVT in the 9 case reports (1-7)

Risk factor	Number of cases present
Anemia	4
Dehydration	4
Corticotherapy	3
Thrombocytosis	1
History of deep venous thrombosis	1
Total	9 (100%)

TABLE 3. Statistical summary of different parameters in the reviewed case reports (1-7)

	Present (n)	Women (n)	Men (n)
Convulsions	4	3	1
Headache	5	1	4
Other neurologic signs	6	2	4
Fever	2	0	2
Diarrhea	2	0	2
Bloody stools	5	3	2
Abdominal pain	3	2	1
Prior Immunosuppressive medication	4	2	2
Prior corticotherapy	3	1	2
Abdominal surgical intervention	2	1	1
UC flare	7	3	4
Anticoagulation	6	3	3
Good neurologic outcome	8	4	4
Total (n)	9	4	5

The data we collected from these case reports and our own clinical case was compared to the data of one review of 65 patients, which analyzed both

Crohn's disease and ulcerative colitis associated with CVT. This review revealed that CVT was present in 1,3-6,4% of cases with IBD (both Crohn's disease and UC). In most cases (78,4%), the CVT complicated an IBD flare. The mean age was 29 years (the youngest patient being 7 years old). The association of CVT and IBD was frequent in younger female patients. They have found anemia to be the most common risk factor for CVT (49,2%), having the mean hemoglobin 9,08 g/dL. Other risk factors were also thrombocytosis (26,1%) and coagulopathies (23%). A positive history of non-cerebral venous thrombosis was present in 10,7% of patients. No identifiable risk factor was found in 13,8% of patients. The most common neurologic symptom was headache (80%), while the most common location of the CVT was the superior sagittal sinus (50,7%). Also multiple sites of concomitant CVT were common (50,7%). The overall prognosis was favorable with complete recovery in 64,6%, despite various management approaches (LMWH alone, LMWH followed by warfarin or aspirin, aspirin alone, thrombolysis with anticoagulation or no therapy at all) (8).

CONCLUSIONS

Our case was similar to the typical patient with this particular association. Many similarities were

found: female gender, age (similar to the mean age in the reviews), headache, seizures and hemiparesis as neurologic symptoms; the IBD was active, blood in the stools was present, multiple CVT sites were involved and the mean hemoglobin value 8-9 g/dL. Also anemia was found to be a major risk factor in our patient.

We challenge the fact that anemia can be a risk factor for CVT and comment on the validity of the pathogenic mechanism that can explain the link between anemia and thrombosis.

The fact that young female patients are more frequently affected by CVT while suffering from IBD could be explained by the hormonal factor.

Katsanos and coworkers (8) commented on the fact that steroid therapy is not a risk factor for CVT because these compounds are believed to decrease bowel inflammation, thus controlling the UC flare. This could be indeed true, but further research is still necessary for confirmation.

As a final comment, we believe that the neurologist faced with a patient suffering from IBD who presents stroke symptoms, should take into consideration the possibility of CVT, even if the incidence is very low. Also a multidisciplinary team of experts in medicine is needed to diagnose and treat such complex cases.

Conflict of interest: none declared

Financial support: none declared

REFERENCES

1. Derdeyn CP, Powers WJ. Isolated Cortical Venous Thrombosis and Ulcerative Colitis. *AJNR Am J Neuroradiol* 1998; 19:488-90.
2. Keene DL, Matzinger MA, Jacob PJ et al. Cerebral Vascular Events Associated With Ulcerative Colitis in Children. *Pediatr Neurol* 2001; 24:238-43.
3. Adrish M, Rios R. Intracranial hemorrhage and extensive cerebral venous thrombosis associated with ulcerative colitis. *Can J Gastroenterol Hepatol* 2014; 28:299-300.
4. Lee J, Hwang SW, Lee J et al. A case of ulcerative colitis presenting with cerebral venous thrombosis. *Intest Res* 2018; 16(2):306-11.
5. Taous A, Berri MA, Lamsiah T et al. Cerebral venous thrombosis revealing an ulcerative colitis. *Pan African Medical Journal* 2016; 23:120. doi:10.11604/pamj.2016.23.120.9186
6. Menon B, Goyal R, Nihal L et al. Cerebral venous thrombosis in ulcerative colitis. *J Neurosci Rural Pract* 2013; 4(1):84-6.
7. Srivastava AK, Khanna N, Sardana V et al. Cerebral venous thrombosis in ulcerative colitis. *Neurol India* 2002; 50:215-7.
8. Katsanos AH, Katsanos KH, Kosmidou M et al. Cerebral sinus venous thrombosis in inflammatory bowel diseases. *Q J Med* 2013; 106:401-13.