A Significant Association in Paediatric Emergency Department, Cerebral Sinovenous Thrombosis and Ulcerative Colitis; Review of Literature

M Acikgoz[1], A Guzel[1], K Aslan[2], F Korkmaz[1], E Yaman[1], C Albayrak[5], D Albayrak[5]

ABSTRACT

Aim: To discuss cerebral sinovenous thrombosis (CSVT), which is an important mortality and morbidity factor developing in progression of ulcerative colitis (UC) in childhood age, in the light of literature.

Materials and Methods: A review has been performed on database of Pubmed and Google Scholar Search on April 2014. The study retrospectively investigated the cases diagnosed UC with complication of CSVT below 18 years of age between years 1971 to 2014. The cases were analysed with respect to age, gender, disease duration and treatment, potential risk factors, clinical findings, location of thrombosis, thrombolytic therapeutical applications and clinical progressions.

Results: Twenty four paediatric cases aged between five and 18 years were included in the study. Cerebral sinovenous thrombosis had developed during active disease period in 23 (95.8%) periods. The most common application rationales were headache (79.1%) and emesis (29.1%). The most frequently detected risk factors for CSVT were anaemia (58.3%) and thrombocytosis (45.8%). Inherited thrombotic disorders were encountered 10 (41.6%) cases. The most common location sites for CSVT were transverse (33.3%) and sigmoid (33.3%) sinuses. It has been encountered that 19 (79.2%) cases were healed completely without a sequela whereas neurological sequelae remained in 3 (12.5%) cases and 2 (8.3%) cases died.

Conclusion: When a paediatric patient diagnosed with UC within apply emergency service with emesis, headache and mood changes during especially seizure; presence of CSVT should be certainly considered.

Keywords: Cerebral sinovenous thrombosis, child, emergency deparment, ulcerative colitis

From: [1]Department of Pediatrics, [2]Department of Radiology and [3]Department of Pediatric Hematology, Ondokuz Mayıs University Medical Faculty, Samsun, Turkey.

Correspondence: Dr M Açıkgöz, Specialist, Ondokuz Mayıs University Medical Faculty, Department of Pediatrics, Samsun, Turkey. **E-mail:** dracikgozm@gmail.com **Tel:** +90 362 312 19 19 (4063)**, Fax:** +90 362 457 60 41

INTRODUCTION

Cerebral sinovenous thrombosis (CSVT) developing secondary to obstruction in the veins functional in venous drainage of brain is an important morbidity and mortality factor that is quite rarely observed in childhood age. Its incidence is 0.25–0.67/100000 (1–2). Of CSVT cases in this age group; 5–12% show fatal progression while permanent neurological sequelae develop in 61–74% cases (2). Potential risk factors associated with CSVT in childhood age include prematurity, trauma, chronic inflammatory disorders, surgical operation, cardiac diseases, traumatic venous sinus damage, nephrotic syndrome, malignancy, head and neck infections and dehydration (2–3). Risk for cerebrovascular complication in inflammatory bowel disease (IBD), being one of the risk factors of CSVT, is 1.3–3.3% (3). The development of CSVT demonstrates a three-four-fold elevation in IBD (4). Its pathogenesis is considered associated with increased inflammatory response, genetic predisposition, loss of procoagulant factors through gastrointestinal system, temporary abnormalities in clotting system, increased levels of Factor V and VIII beside decreased levels of protein S and antithrombin III during disease progression (5).

This article aimed to discuss risk factors, clinical and laboratory findings, treatment and prognosis of CSVT that is an important and mortality factor in progression of ulcerative colitis (UC) during childhood age, in the light of literature review

MATERIALS AND METHOD

Review method

Pubmed and Google Scholar Search databases were screened in April 2014. This screening was performed using key words “cerebral venous thrombosis in childhood, thrombosis and/or thromboembolism and/or stroke, colitis, ulcerative colitis and/or inflammatory bowel diseases,

infant or child or adolescent or paediatric". All of these key words were screened in the databases without a language limitation and all of the potentially related articles were evaluated.

The study investigated the cases below 18 years of age diagnosed UC accompanied with developing CSVT between years 1971 to 2014. The cases were analysed with respect to age, gender, disease progression and treatment, potential risk factors for thrombosis, radiological findings, accompanying symptoms and findings, thrombolytic treatment applications and clinical progressions.

RESULTS

Demographic findings

The study included the 24 child cases followed-up with diagnosis of UC accompanied with developing CSVT (Table I). Mean ages of the cases were 13.0 ± 3.7 (ranging 5–18) years. The ratio between female/male was one. Incidence ages of CSVT in female and male children were 13.3 ± 3.9 and 12.7 ± 3.8 years. Llyod-Still *et al* (6) have reported the youngest case who was a five-year old female patient. Most of the cases (18/24, 75%) were in the adolescent age group (> 10–18 years old). The childhood age group (≤ 10 years old) included six (25%) cases (Table I). Age at diagnosis and time to development of thrombosis in four cases were not reported. Mean diagnosis age of the reported 20 cases was 11.7 ± 2.7 years and median value of time to development of CSVT after diagnosis of UC was 10.5 months [ranging 0.5–66.0 months] (Table I). The earliest time to development of thrombosis during disease progression was two weeks as reported by Barclay *et al* (7). The longest time to development of CSVT after UC was 66 months (5). Thrombosis developed during active stage of the disease in 23 (95.8%) cases whereas disease was not in the active stage in only one case. Of the cases; four (16.6%), three (12.5%) and 15 (62.5%) were receiving only 5-ASA, only steroid and combined therapy, respectively. The treatment protocol of two cases had not been reported (Table I).

Clinical findings

All patients were symptomatic (Table 1). Analysis of the baseline symptoms revealed the most common application rationales such as headache (19 cases, 79.1%) and emesis (7 cases, 29.1%). The accompanying clinical findings were summarized in (Table 2).

Prothrombotic Risk Factors

The most frequently observed risk for CSVT in the patients with ulcerative colitis was anaemia (14 patients, 58.3%) and thrombocytosis (11 patients, 45.8%). Thrombosis and anaemia were the only detectable risk factors for CSVT in three (12.5%) and two (8.3%) patients, respectively. Companionship of anaemia and thrombocytosis was present in eight (33.3%) of the cases. Incidence of risk factor for anaemia in the childhood age group (≤ 10 years old) was 33.3% (2/6) whereas that was 61.1% (11/18) in the adolescent age group. Incidence of risk factor for thrombocytosis in the childhood age group) was 33.3% (2/6) whereas that was 50% (9/18) in the adolescent age group. Among risk factors, inherited thrombotic disorders were detected in 10 (41.6%) cases. The most frequently observed inherited thrombotic disorders were mutation of methylene-tetra-hydro-folate reductase (MTHFR) [3 patients, 12.5%] and Anti-thrombin III deficiency (3 patients, 12.5%), respectively. Incidence of inherited thrombotic disorders in the childhood age group was 50% (3/6) whereas that was 38.8% (7/18) in adolescent age group. Risk factors of thromboembolism reported in the cases with UC were shown in the (Table 3).

Radiological findings

The number of the cases in whom CSVT was encountered in multiple locations was 12 (50.0%). In the cases with expressed location sites; CSVT was most commonly located in transverse sinus (8 patients, 33.3%), sigmoid sinus (8 patients, 33.3%) and superior sagittal sinus (7 patients, 29.1%), respectively (Fig. 1).

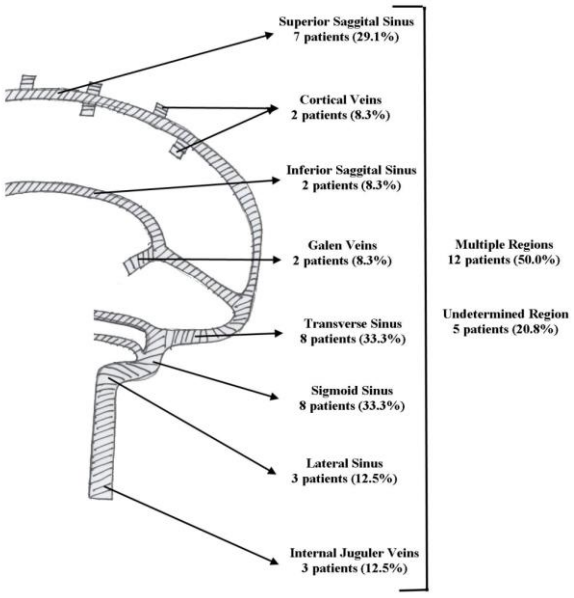

Fig: 1. Sites of cerebral venous sinus trombosis in patients with ulcerative colitis

The location site of the thrombus was reported as only CSVT in five [20.8%] (6, 8-11). The most common location in the adolescent age group was transverse sinus whereas the most common in the childhood age group was sagittal sinus.

Treatment and outcome

Heparin, low molecular weight heparin (LMWH), warfarin, aspirin and anti-factor Xa were administered in, respectively nine (47.3%), eight (42.1%), seven (36.8%), two (10.5%) and one (5.2%) of the 19 cases whose treatment protocols were expressed. Warfarin, LMWH and anti-factor Xa were administered after medication with heparin in seven (36.8%), two (10.5%) and one (5.2%) cases, respectively (Tables 1 and Table 4)

Table. 1: Pediatric case reports from patients with UC accompaied with CVST.

Author	Age	Sex	UC Diagnosis (month)	Treatment	Symptoms	Localization of Thromboemboli	Risk Factors	Anticoagulation	Outcome
Lloyd-Still et al.(6)	5	F	UR	Steroids Salisilazosulfapiridin	Pitozis Headache Loss of vision	CVST	Anemia	UR	CR
Kao et al.(14)	7	F	4	5-ASA	Headache, Aphasia	TS,SS,IJV	Anticardiolipin Ab	LMWH	Mild Right Pronator Drift
Lloyd-Still et al.(6)	7	M	UR	Steroids Salisilazosulfapiridin	Encephalopathy	Possible SSS	Anemia Thrombocytosis	UR	CR
Kutluk et al.(15)	9	M	24	Steroids 5-ASA AZA	Pitozis Papilledema, Headache	TS,SS	Anemia Thrombocytosis MTHFR gene muattion	Heparin LMWH	CR
Robison et al.(16)	10	M	36	Steroids	Headache, Vomiting	TS,SS GV,ISS	FVL Mutation, MTHFR gene muattion	LMWH	CR
Calderon et al.(8)	10	F	4,5	Salisilazosulfapiridin Steroids	Drowsiness, Dizziness, Headache,Vomiting, Asimetrik Pupil Nistagmus, Hemiparesis	CVST	AT III Deficiency Factor VIII	UR	Died 15 days later

Mahmoud Reza A et al.(4)	11	M	3	Steroids 5-ASA	Papilledema,Orbital pain Headache	SSS	Anemia Thrombocytosis	Heparin Warfarin	CR
Paradis et al.(12)	12	F	1	Steroids Salisilazosulfapiridin	Headache. Vomitig Facial Weakness, Right Hand And Foot Numbness	SSS	Anemia, Thrombocytosis	UR	CR
Schneiderman et al.(13)	12	F	12	Salisilazosulfapiridin Steroids	Headache,Seizures, Hemianopia, Diplopia Vomiting	short circumferential veins	Elevated Factor VIII	No	Died 2 days later
Keene et al.(11)	12	M	1	Steroids	Orbital Pain, Papilledema	CVST,SSS	Anemia Thrombocytosis AT III Deficiency	No	CR
Shaikh H et al.(49)	PT		2	Steroids 5-ASA	Headache, Nausea Confused, Altered Mental Status And Bilateral Lower Extremity Weakness	GV, ISS	Anemia	Heparin LMWH	CR
Barclay et al.(7)	13	M	0,5	Steroids Salisilazosulfapiridin	Sleep Headaches Vomits, Ataxia Hemiplegia	TS,ISS.	Anemia, Thrombocytosis immobile	Aspirin.	Hemiplegia
Kao et al.(14)	13	F	18	-	Seizures	SSS,TS,SS CV,IJV	Homocystinemia, G20210A	LMWH	CR
Al Tahan et al.(50)	14	F	5	Steroids 5-ASA	Headache, Seizures	SSS	Anemia Pro-S Deficiency	Heparin Warfarin	CR

Kao et al.(14)	14	F	36	-	Hemiparesis	SS,CV	No	Heparin, Warfarin	Left Hemiparesis
Markowitz et al.(17)	14	M	9	Steroids, 5-ASA	Headache, Hemiparesis Aphasia	LS,SS	Anemia, Thrombocytosis	Aspirin	CR
Ben Sassi et al.(32)	15	F	UR	5-ASA	Headache,Vomiting, Seizures	LS	Thrombocytosis	Heparin Warfarin	CR
Houissa et al.(9)	16	F	48	5-ASA	Headache, Confusion	CSVT	Thrombocytosis	LMWH	CR
Our Case	17	F	18	5-ASA	Headache, Aphasia	TS,SS, İJV	Anemia, Thrombocytosis MTHFR gene mutation	LMWH	CR
Macri et al.(51)	17	F	1	Steroids 5-ASA	Headache, Seizures, Aphasia, Hemiparesis	SSS,CV	Anemia, AT III Deficiency, OC	LMWH	CR
Diakou et al.(52)	17	M	18	Steroids, AZA	Headache	TS, SS	Pro-S Deficiency	Heparin Warfarin	CR
Cognat et al.(53)	18	M	60	Steroids, 5-ASA	Headache. Hemianopia	LS	Anemia	Heparin Warfarin	CR
Thorsteinsson et al.(5)	18	M	66	Steroids, AZA 5-ASA	Headache, Vomiting	TS	Anemia, Peritonsilitis İncision	Heparin Warfarin Fondaparinux	CR
Rousseau et al.(10)	18	M	UR	Steroids	Hemiplegia, Hemiparesthesia	CVST	Thrombocytosis	UR	CR

M, male; F, female; UR, unreported; AZA, azathioprine; 5-ASA, 5-aminosalicylic acid; CVST, cerebral venous sinus thrombosis; SSS, superior sagittal sinus; LS, lateral sinus; TS, transverse sinus; SS, sigmoid sinus; ISS, Inferior Saggital Sinus; İJV, internal juguler ven; CV, cortical veins; GV, Venous of Galen; Pro-S, protein S; AT III, antithrombin III; MTHFR, methylene-tetra-hydro-folate-reductase; FVLm, heterozygous for factor V Leiden mutation; OC, oral contraceptives; G20210A, prothrombin gene G20210A mutation; LMWH, low molecular weight heparin; CR, Complete recovery

Table. 2: Clinical findings in UC patients with CVST

Clinical presentations	n (%)
Headache	19 (79.1)
Emesis	7 (29.1)
Hemiparesis	6 (25.0)
Seizures	5 (20.8)
Aphasia	4 (16.6)
Papilledema	3 (12.5)
Hemiplegia	2 (8.3)
Pitozis	2 (8.3)
Hemianopsia	2 (8,3)
Orbital pain	2 (8.3)
Confusion	2 (8.3)
Diplopia	1 (4.1)
Facial weakness	1 (4.1)
Ataxia	1 (4.1)
Loss of vision	1 (4.1)
Droop	1 (4.1)
Dizziness	1 (4.1)
Drowsiness	1 (4.1)
Nistagmus	1 (4.1)
Numbness	1 (4.1)
Nausea	1 (4.1)
Encephalopathy	1 (4.1)

UC, ulcerative colitis; CVST, cerebral venous sinus thrombosis

Table. 3: Risk factors for thrombosis in patients with UC

Factors	n(%)
Anaemia	14 (58.3)
Thrombocytosis	11 (45.8)
Antithrombin III deficiency	3 (12.5)
MTHFR mutation	3 (12.5)
Protein S deficiency	2 (8,3)
Elevated FVIII	2 (8,3)
Factor V Leiden mutation	1 (4.1)
Anticardiolipin antibody	1 (4.1)
Prothrombin gene mutation (G20210A)	1 (4.1)
Homocystinemia	1 (4.1)
Immobilite	1 (4.1)
Peritonsilitis	1 (4.1)
Oral contraceptive use	1 (4.1)

UC, ulcerative colitis; MTHFR, methylene-tetra-hydro-folate-reductase

Table. 4: Therapy in Children with TE in UC

Treatment Protocol	**n (%)**
Only LMWH	6 (25.0)
Heparin+Warfarin	6 (25.0)
Heparin+ LMWH	2 (8.3)
Heparin+Warfarin +Anti Factor X	1 (4.2)
Only Aspirin	2 (8.3)
Unreported	5 (20.9)
Untreated	2 (8.3)
Total	24 (100.0)

TE, thromboembolism ;UC, ulcerative colitis; LMWH, low molecular weight heparin

During follow-up period under heparin therapy, one patient was complicated with heparin induced thrombocytopenia type II but recovered completely after exchanging the anticoagulant to fondaparinux (5). The treatment protocols of five cases were not expressed (6, 8, 10, 12) while it was expressed that anticoagulant therapy was not administered in two cases because of risk for bleeding (11, 13) (Tables 1 and Table 4). Only heparin or LMWH medication was preferred in the three patients whose treatment protocols were expressed in the childhood age group (14–16) [Table 1]. Of the patients who were treated heparin or LMWH; 86.6% (13/15) were healed completely while 13.3 (2/15) were recovered partially (14). Of the patients who received aspirin treatment; one patient remained hemiplegic (7) whereas the other patient was recovered completely (17).

It has been reported for the 24 cases followed with CSVT that 19 (79.1%) cases were healed completely whereas neurological sequelae (mild right pronator drift (14), hemiplegia (7), hemiparesis (14)) remained in three (12.5%) cases while two (8.3%) cases became exitus (8, 13). Grand Mal epilepsy was reported as cause of death (13) while development of sepsis after meningitis due to *Staphylococcus aureus* and *Enterobacter cloacae* was cause of death in the other exitus patient (8). Anticoagulant therapy was not given in one of the exitus cases (13) while treatment protocol was not reported in the other exitus case (8). Of the two cases who

were not given anticoagulant therapy because of bleeding risk; one died (13) whereas other cases was recovered completely (11).

Our Case

The 17-year-old female patient applied Paediatric Emergency Department with complaints of meaningless speech and extreme difficulty in expressing herself, understanding words and naming objects that continued for the recent two days, headache, bloody mucus in stool and fatigue that existed for the recent ten days. It has been informed that our patient was diagnosed 1.5 years ago, she has regularly used mesalazine and had two attacks of ulcerative colitis flares, with last one being four months ago, in her medical history. The physical examination of the patient revealed no abnormal finding except Wernicke's aphasia, headache and paleness. The laboratory tests resulted WBC: 13360/mm^3, Hgb:6.3 g/dL, Hct:%24, MCV:57.1 fL, RDW:%19, Thrombocyte:724.000/mm^3, Fe:9.7 ug/dL, TIBC:241.9 ug/dL, Ferritin:10.8 ng/mL, Sedimentation: 30 mm/hour, CRP: 31 mg/dL, PT:14.1 sec, aPTT:27.3. PT-INR: 1.17.

The other blood and urine findings were normal. Brain magnetic resonance imaging (MRI), diffusion MRI and MR-venography encountered thrombosis of left internal jugular vein, sigmoid sinus and transverse sinus and cytotoxic oedema with diffusion limitation in the left temporal lobe (Figs. 2–4). The LMWH and treatment of intravenous iron were initiated.

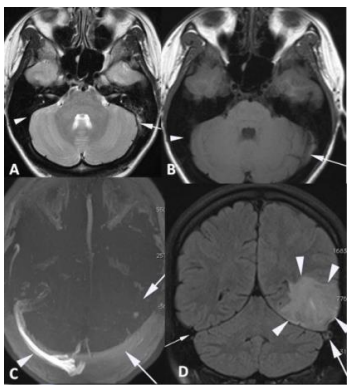

Fig: 2. Left sigmoid sinus thrombosis in T2 (A) and T1 (B) weighted imagings. Normal signal void patterns of right sigmoid sinus in T2 (A) and T1 (B) weighted imagings. (arrowhead). The interruption of left transverse and sigmoid sinus flows in time-of-flight MR angiography (C) (arrow). The normal right transverse and sigmoid sinus flows in time-of-flight MR angiography (arrowhead). Left sigmoid sinus thrombosis (thick arrow), hyperintensity

in temporal lobe cortical, subcortical and deep white matter in the areas due to venous infarction (arrowhead), and normal right sigmoid sinus flows (thin arrow) in fluid attenuated inversion recovery sequence (D).

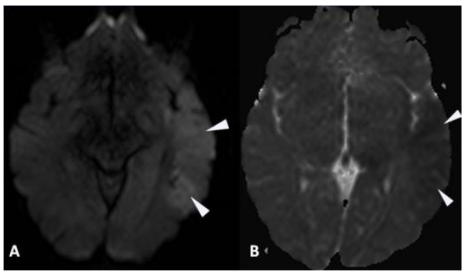

Fig: 3. The decrease of diffusion because of cytotoxic oedema in diffusion weighted imaging (DWI) (A-B) (arrowheads).

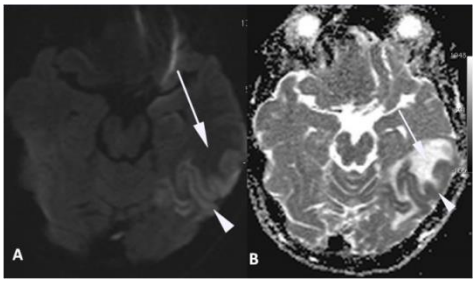

Fig: 4. Five days after LMWH treatment, the improving of diffusion because of cytotoxic oedema in DWI images (A-B) (arrowheads) and the appearance of increased diffusion areas secondary to vasogenic oedema (arrow).

Erythrocyte transfusion was performed. The tests for thrombosis demonstrated only positive heterozygous MTHFR mutation. The patient whose clinical and radiological findings improved due to treatment of LMWH was discharged to be followed-up in the polyclinic.

DISCUSSION

Cerebral sinovenous thrombosis that may be observed in progression of ulcerative colitis as one of the potential extraintestinal symptoms is an important mortality and morbidity factor (5, 18). Patterson *et al* (19) have reported the first thromboembolic complication due to IBD in

childhood age. Risk for venous thromboembolism (VTE) in case of IBD ranges between 1–8% in all age groups whereas that risk ranges between 39–41% in the cases applied post-mortem autopsy (20).

Beside this, rate of vascular complications that leads to thromboembolic events due to IBD also ranges between 1.3–3.3% in the paediatric age group (3). Venous thromboembolism occurs averagely 1.75 years (1–8 years) after onset of IBD (3). This situation is frequently during progression of UC in adulthood age group however it is quite rare and appears as case presentations. Venous thromboembolism, that involves also CSVT in the child patients with UC is observed in mostly early childhood period (21). It has been reported in the cohort study conducted by Nguyen ve Sam (21) in the childhood age group that VTE significantly increased (RR 13.7, 95% CI 4.1-45.3, $p < 0.001$) in children with UC in age range 0–10 years comparatively with non-IBD children diagnosed VTE and found 0.44%. It has been reported in the same study that risk for VTE in the children with UC showed no significantly increased risk (RR 1.3, 95% CI 0.7–2.2, $p < 0.3$) when compared with non-IBD children diagnosed UC in age range 11–20 years and found 0.25%. No correleation has been reported between gender and VTE in the children with IBD (3). It has been found in our literature review that development of CSVT was mostly detected in the adolescent age group (75%) and female/male ratio was determined equal differently from the cohort studies.

At the same time, time to development of CSVT was approximately, 10.5 months after onset of disease and this situation was similar to the reported values in the literature.

Clinical presentation of CSVT in paediatric population are nonspecific, most commonly including triad headache, emesis, and depressed mental status plus seizures (22). The symptoms of our study were also similar with the literature.

Risk for thromboembolism increases than normal population in IBD (3). The association between IBD and thrombosis is not yet completely clarified. Beside studies state that VTE is

more frequently seen than Crohn's disease (CD) in progression of UC (3, 20 –21, 23), some studies suggest that no significant difference was present (20, 24). Some studies consider VTE as a complication in progression of UC whereas some studies that accept VTE as a finding of the disease are also present (25). It has been considered that dehidratation, accompanying infections, anaemia, concomitant autoimmune diseases, presence of cyanotic heart disease, co-morbidity of nephrotic syndrome, corticosteroid treatment, use of oral contraceptive, immobility, inherited thrombotic diseases, previous surgical operations, activation of the disease, thrombocytosis, chromosomal disorders and metabolic circumstances such as homocystinuria play role in aetiology of CSVT which develops during progression of UC in the childhood (3, 22, 26–28). Its pathogenesis is accepted associated with increased inflammatory response, genetic predisposition, loss of procoagulant factors through gastrointestinal system, temporary abnormalities in clotting system, increased levels of Factor V and VIII beside decreased levels of Protein S and antithrombin III during disease progression (5).

Main causes of thrombocytosis which is accepted as a risk factor in development of CSVT in the patients with IBD are chronic inflammation, acute haemorrhage and use of corticosteroid (26–27). It has been stated that essential factor in pathogenesis of thrombocytosis is activation of thrombocytes due to endothelial damage in the wall of gastrointestinal system during acute exacerbations. It has been concluded that inflammatory mediators that increase during endothelial damage elevate potential of VTE as well as activation of thrombocytes (26).

On the other side, development of VTE in absence of thrombocytosis in the subjects with inflammatory bowel disease make us consider that thrombocytosis doesn't cause exclusively thromboembolic phenomenon (26–27). Another effective factor in development of CSVT through thrombocytes is use of corticosteroids in treatment of UC. It has been suggested

that these medicines inhibit synthesis of prostacyclin by reducing level of arachidonic acid in the vessel wall and create predisposition to thrombosis by making thromboxanes dominant (29).

On the other hand, corticosteroids have also inflammatory effect, reducing effect on hypercoagulability and increasing effect on efficacy of heparin as well as thrombogenic effect. Therefore, effect of steroid treatment in thrombosis is controversial. It has been also shown in the evidence-based studies conducted in the recent years (27, 30) that use of corticosteroids does not increase risk for thromboembolism in the patients with and without IBD (17, 27).

In our study, thrombocytosis was detected in 45.8% of the cases with UC and thrombocytosis was the unique detectable risk factor in only three cases (9–10, 31).

Nonetheless, development of thrombocytosis was present in 47% of the 17 cases who received corticosteroid treatment. The obtained data has shown that thrombocytosis can be rarely solely risk factor for CSVT and that use of corticosteroids doesn't lead to thrombocytosis.

It has been proposed that iron deficiency anaemia is another important factor in aetiology of CSVT and stroke in childhood age (32–33). It has been stated that presence of iron deficiency anaemia increases risk for development of vaso-occlusive stroke 3.8-10-fold in childhood age group (33–34). In the recent years, available reports conducted on this issue in the related childhood age group are in the form of case presentation (35–37). Despite this, role of iron deficiency anaemia in pathogenesis of CSVT is not yet certainly clarified (38). However, it has been emphasized that thrombocytosis accompany 81% of cases with severe anaemia and this accompanying thrombocytosis leads to CSVT (38). Risk for development of thrombocytosis is 10.5-fold more in the children with iron deficiency anaemia than the healthy children (34). On the other side, iron is known as the negative feedback agent for production of thrombocytes (35, 39). It has been emphasized that low serum iron level causes thrombocytosis by activating megakaryocytes with increased level of erythropoietin and that microcytosis

which develops due to iron deficiency contributes to formation of CSVT (35, 39–40). It has been emphasized in a research which analysed 65 cases with IBD and cerebral thrombosis that presence of anaemia was detected in approximately half of the cases while anaemia is the unique detectable risk factor in 31% of the cases (27). Stolz *et al* have determined in the case-control study including 121 cases with iron deficiency that CSVT was significantly higher than the control group in the cases with Hb level < 9 gr/dL. In this study, thrombocytosis is not found a significant risk factor in development of CSVT while presence of severe anaemia (Hb < 9 gr/dL) was reported as important and independent risk factor [RR 7.79, 95% CI 1.73–35.10, $p < 0.008$] (38). In our study, the most common risk factor for CSVT in the patients with ulcerative colitis were anaemia (58.3%) and thrombocytosis (45.8%). Thrombocytosis and anaemia were the unique detectable risk factors for CSVT in three (12.5%) and two (8.3%) patients, respectively. Co-morbidity of anaemia and thrombocytosis was present in eight (33.3%) of the cases.

In progression of inflammatory bowel disease, development of thrombosis usually occurs in the acute exacerbations (15, 26). It has been detected in the studies that 71–100% of cases with IBD accompanied thromboembolism (TE) were in the active disease period (3, 7, 26–27, 41). The researchers have pointed out that risk for development of VTE increases 2-3-fold in the patients with active IBD than the ones with IBD in the inactive period and that this risk increases during passage from moderate exacerbation to severe exacerbation (3). It is also considered that time duration is an important factor in development of thrombosis as well as disease activity. It has been reported that cases with medical history of IBD longer than two years generally carry higher risk of thromboembolism than other cases (3). The development of CSVT in the active stage of the disease is associated with increased levels of fibrinogen, prothrombin fragment F1+2, thrombocytes, plasminogen activator inhibitor-1 and soluble thrombomodulin (15). It has been reported that immobility and fluid loss also contribute in

addition to excessive clotting developing due to disease activity (15). In our study, 95.8% of the cases with UC accompanied with CSVT were found in the active exacerbation stage. Median value of time to development of CSVT was 10.5 months.

Another risk factor for thrombosis in the patients with UC is inherited thrombophilic disorders (26). In the childhood age; inherited thrombophilic disorders were determined as risk factors in 36%, 44% and 33% of the cases with venous thromboembolism, ischaemic stroke and IBD accompanied with venous thromboembolism, respectively (3). The most common inherited risk factors for thromboembolism in IBD patients Factor V Leiden mutation, G20220A mutation in the prothrombin gene, and homozygous C677T mutation in the methylenetetrahydrofolate reductase gene (42). The most frequently investigated factor among these disorders in the recent years was Factor V Leiden mutation. Jackson et al have reported incidence of Factor V Leiden mutation as 5% in the study with 52 cases who had IBD and thromboembolism (43). The risk of thrombosis increases approximately five-fold in IBD patients with heterozygous for Factor V Leiden mutation and G20220A mutation in the prothrombin gene (27). Some authors who do not accept these inherited thrombophilic disorders in IBD patients as a risk factor beside main risk caused by the main disease since the report showing the relationship between IBD and thrombophilia are mainly published as a case report (15, 26). They recommend this issue has to be studied by multicenters, that include a larger number of IBD patients with thrombosis, to clarify the relationship between IBD and inherited thrombophilic disorders (42). In this review, 41.6% of the cases with UC had inherited thrombophilic disorders.

It is an undeniable reality that risk for venous thrombosis increases in UC. Therefore, it is recommended to apply prophylactic treatment in the recent years to reduce risk for thrombosis in presence of additional risk factors such as immobility, thrombophilia, thrombocytosis (> 750.000/mm^3) and severe disease (Pediatric Ulcerative Colitis Activity Index > 45) that

accompany UC in the childhood age (3). Also recommendations for dipyridamole therapy as outpatient are available for the selected patients and ones who have these additional risk factors (3, 7). Prophylactic oral or IV iron therapy are involved in the other preventive recommendations for iron deficiency anaemia that plays a role in aetiology of CSVT.

Oral iron preparations are available for the patients with IBD in whom intravenous iron preparations are contraindicated (27). However, a consensus on iron prophylaxis has not been established yet.

There is a consensus between guides on administering anticoagulants in acute therapy of CSVT except neonates (44–46). The most important effect of the anticoagulants used in treatment of CSVT is prevention of newly developing venous infarction. The greatest conflict of the anticoagulant treatment is causing potential intracranial haemorrhage although it leads to improvement of pulmonary embolism and neurological findings (27).

In presence of acute ischemic stroke which developed after CSVT, ultra-fractionated heparin (UFH) and LMWH treatment were recommended as initial therapy after elimination of cardioembolism and craniocervical dissection by American Heart Association [AHA] (46) and American College of Chest Physicians [ACCP] (44). But this protocol is different from the guide by United Kingdom Royal College of Physicians [UK-RCP] (44) that they recommend to initiate therapy by using only aspirin. Among recommended acute treatment principles for CSVT; UK guide recommends to administer anticoagulant therapy until obtaining recanalization (44). According to Chest guidelines, UFH or LMWH were recommended to initiate and administer treatment of LMWH or warfarin for 3–6 months during follow-up period. This guide recommends thrombectomy or surgical decompression for the resistant cases while thrombolysis is suggested for the selected cases. It is stated that anticoagulant therapy should not be administered in presence of bleeding and that it can be tested if progression of thrombosis

is detected by the repeated imaging Methods (44). The AHA 2008 Protocol suggests UFH or LMWH as initial therapy while it gives treatment of only warfarin for 3–6 months differently from Chest ACCP Guidelines. Same initial therapy is recommended in also presence of CSVT accompanied with intracranial haemorrhage. The treatment of local thrombosis is suggested in the irresponsive cases to therapy (46). The more commonly preferred treatment protocol in our study was to initiate with UFH and LMWH and to continue with warfarin and LMWH. Except these, rate of the patients who received only LMWH was 25% whereas rate of the patients who received only aspirin was 8.3%. No treatment was given because of risk for bleeding in only two patients.

Paediatric stroke due to CSVT, being 10th leading factor in paediatric deaths, has a mortality rate of 10% (22, 47–48). Mortality rate in presence of CSVT accompanying IBD was reported 5.7% (3). Relapse rate for CSVT in childhood age was < %5 while this rate ranges between 15–20% in haemorrhagic stroke and arterial ischemic stroke (22, 47–48). A permanent neurological deficit develops in three-fourth of the surviving child cases with CSVT (22). The partial recovery rate in the cases with CSVT in presence of IBD is 34%. Early and late recurrence are observed in 11% and 10% of these cases, respectively (3). The reported recovery rate without a sequela in the cases with CSVT in presence of UC was 79.2%. Mortality rate was found 8.3% similarly with literature. The partial recovery rate was detected 12.5%.

As a conclusion, IBD is a risk factor for venous thrombosis. The risk for thromboembolism is higher than normal population because of predisposition to hypercoagulation in the active period in patients with IBD. Prevention of the facilitating factors such as infections during acute periods of the disease, dehydration, accompanying presence of anaemia and thrombocytosis are essential. Venous thrombosis should be considered in differential diagnosis when symptoms and findings such as headache, cranial nerve involvement, papilloedema and loss of motor function accompany with course of UC.

REFERENCES

1. deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345:417-423.
2. Bektas O, Teber S, Akar N, et al. Cerebral Sinovenous Thrombosis in Children and Neonates: Clinical Experience, Laboratory, Treatment and Outcome. Clin Appl Thromb Hemost 2014;18:1-6.
3. Lazzerini M, Bramuzzo M, Maschio M, Martelossi S, Ventura A. Thromboembolism in pediatric inflammatory bowel disease: systematic review. Inflamm Bowel Dis. 2011;17:2174-83.
4. Mahmoud Reza A, Firozeh H, Houman A, Mehri NS. Pseudotumor cerebri in a case of ulcerative colitis with sagittal sinus thrombosis. Iran J Pediatr. 2013;23:109-12.
5. Thorsteinsson GS, Magnussson M, Hallberg LM, et al. Cerebral venous thrombosis and heparin-induced thrombocytopenia in an 18-year old male with severe ulcerative colitis. World J Gastroenterol 2008; 14:4576–9.
6. Lloyd-Still J, Tomasi L. Neurovascular and thromboembolic complications of inflammatory bowel disease in childhood. J Pediatr Gastroenterol Nutr. 1989;9:461-66.
7. Barclay AR, Keightley JM, Horrocks I, Garrick V, McGrogan P. Cerebral thromboembolic events in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2010;16: 677-83.
8. Calderon A, Wong J, Becker L. Multiple cerebral venous thromboses in a child with ulcerative colitis. Clin Pediatr. 1993;32: 169-171.
9. Houissa F, Salem M, Bouzaidi S, et al. Cerebral thrombosis in inflammatory bowel disease: a report of four cases. J Crohns Colitis 2011; 5: 249–52.

10. Rousseau B, Bélanger C, Lacoursière Y, Bergeron MG, Saab M, Poncelet P. Colite ulcereuse et thrombose veineuse cerebrale. Union Med Can. 1975;4: 414-7.
11. Keene D, Matzinger M, Jacob P, Humphreys P, et al. Cerebral vascular events associated with ulcerative colitis in children. Pediatr Neurol. 2001;24: 238-43.
12. Paradis K, Berstein M, Adelson J. Thrombosis as a complication of inflammatory bowel disease in children: a report of four cases. J Pediatr Gastroenterol Nutr. 1985;4:659-62.
13. Schneiderman J, Sharpe J, Sutton D. Cerebral and retinal vascular complications of inflammatory bowel disease. Ann Neurol. 1979;5: 331-7.
14. Kao A, Dlugos D, Hunter JV, Mamula P, Thorarensen O. Anticoagulation therapy in cerebral sinovenous thrombosis and ulcerative colitis in children. J Child Neurol 2002;17: 479–82.
15. Kutluk G, Hacıfazlıoglu NE, Horozoglu H, Ertem D, Yılmaz Y. Cerebral venous thrombosis associated with childhood ulcerative colitis. Turk Arch Ped 2013;48: 160-4.
16. Robison NJ, Dawlabani N, Lastra CR, Dhall G. Cerebral sinus thrombosis in a child with active ulcerative colitis and factor V Leiden. Pediatr Blood Cancer 2009; 52: 867–9.
17. Markowitz RL, Ment LR, Gryboski JD. Cerebral thromboembolic disease in pediatric and adult inflammatory bowel disease: case report and review of the literature. J Pediatr Gastroenterol Nutr 1989; 8: 413–20.
18. Saboul C, Darteyre S, Ged C, Fichtner C, Gay C, Stephan JL. Inaugural Cerebral Sinovenous Thrombosis Revealing Homocystinuria in a 2-Year-Old Boy. J Child Neurol. 2014.

19. Patterson M, Castiglioni L, Sampson L. Chronic ulcerative colitis beginning in children and teenagers: a review of 43 patients. Am J Digest Dis. 1971;16: 289-97.

20. Magro F, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. World J Gastroenterol. 2014;20: 4857-72.

21. Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. Am J Gastroenterol. 2008;103:2272–80.

22. Simma B, Höliner I, Luetschg J. Therapy in pediatric stroke. Eur J Pediatr. 2013 Jul;172[7]:867-75.

23. Saleh T, Matta F, Yaekoub AY, Danescu S, Stein PD. Risk of venous thromboembolism with inflammatory bowel disease. Clin Appl Thromb Hemost 2011; 17: 254-258.

24. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 2011; 60: 937-943.

25. Tan VP, Chung A, Yan BP, Gibson PR. Venous and arterial disease in inflammatory bowel disease. J Gastroenterol Hepatol 2013;28: 1095-113.

26. Shannon Standridge, Emily de los Reyes. Inflammatory Bowel Disease and Cerebrovascular Arterial and Venous Thromboembolic Events in 4 Pediatric Patients: A Case Series and Reviewof the Literature. J Child Neurol 2008 23: 59-66.

27. Katsanos AH, Katsanos KH, Kosmidou M, Giannopoulos S, Kyritsis AP, Tsianos EV. Cerebral sinus venous thrombosis in inflammatory bowel diseases. QJM. 2013;106:401-13.

28. Dlamini N, Billinghurst L, Kirkham FJ. Cerebral venous sinus [sinovenous] thrombosis in children. Neurosurg Clin N Am. 2010;21: 511-27.

29. Tezel A, Demir M. Inflammatory bowel disease and thrombosis. Turk J Haematol. 2012;29: 111-9.

30. Richard S, Fairise A, Lacour JC, Ducrocq X. Cerebral venous thrombosis in inflammatory bowel diseases. Inflamm Bowel Dis 2010; 16: 366–7.

31. Ben Sassi S, Mizouni H, Nabli F, Kallel L, Kefi M, Hentati F. Cerebral venous thrombosis presenting with cerebellar ataxia and cortical blindness. J Stroke Cerebrovasc Dis 2010; 19: 507–9.

32. Beri S, Khan A, Hussain N, Gosalakkal J. Severe anemia causing cerebral venous sinus thrombosis in an infant. J Pediatr Neurosci. 2012;7: 30-2.

33. Maguire JL, deVeber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. Pediatrics. 2007;120:1053–7.

34. Azab SF, Abdelsalam SM, Saleh SH, et al. Iron deficiency anemia as a risk factor for cerebrovascular events in early childhood: a case-control study. Ann Hematol. 2014;93: 571-6.

35. Habis A, Hobson WL, Greenberg R. Cerebral sinovenous thrombosis in a toddler with iron deficiency anemia. Pediatr Emerg Care. 2010;26: 848-51.

36. Hartfield DS, Lowry NJ, Keene DL, Yager JY. Iron deficiency: a cause of stroke in infants and children. Pediatr Neurol 1997;16: 50-3.

37. Belman AL, Roque CT, Ancona R, Anand AK, Davis RP. Cerebral venous thrombosis in a child with iron deficiency anemia and thrombocytosis. Stroke. 1990;21 :488-93.

38. Stolz E, Valdueza JM, Grebe M, et al. Anemia as a risk factor for cerebral venous thrombosis? An old hypothesis revisited. Results of a prospective study. J Neurol. 2007;254:729-34.

39. Yager JY, Hartfield DS. Neurological manifestations of iron deficiency in childhood. Pediatr Neurol. 2002;27: 85-92.

40. Carvalho KS, Garg BP. Cerebral venous thrombosis and venous malformations in children. Neurol Clin. 2002;20: 1061-77.

41. Solem CA, Loftus EV, Tremaine WJ, Sandborn WJ. Venous thromboembolism in inflammatory bowel disease. Am J Gastroenterol 2004; 99: 97–101.

42. Papa A, Danese S, Grillo A, Gasbarrini G, Gasbarrini A. Review article: inherited thrombophilia in inflammatory bowel disease. Am J Gastroenterol. 2003;98:1247-51.

43. Jackson LM, O'Gorman PJ, O'Connell J, Cronin CC, Cotter KP, Shanahan F. Thrombosis in inflammatory bowel disease: clinical setting, procoagulant profile and factor V Leiden. QJM. 1997;90: 183-8.

44. Paediatric Stroke Working Group. Stroke in childhood: clinical guidelines for diagnosis, management and rehabilitation. London: Royal College of Physicians; 2004.

45. Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children. American College of Chest Physicians evidence based clinical practice guidelines, 8th ed. Chest. 2008;133:887-968.

46. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008;39: 2644–2691.

47. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics 2007; 119:495–501.

48. Sträter R, Becker S, von Eckard A, et al. Prospective assessment of risk factors for recurrent stroke during childhood a 5 year follow-up study. Lancet 2002; 360:1540–5.

49. Shaikh H, Pukenas BA, McIntosh A, Licht D, Hurst RW. Combined use of Solitaire FR and Penumbra devices for endovascular treatment of cerebral venous sinus thrombosis in a child. J Neurointerv Surg. 2014;00: 1-4.

50. Al Tahan A, Mageed SA, Al Momen A, Zaidan R, Daif A, Al Tahan F. Cerebral venous thrombosis as a complication of ulcerative colitis associated with protein-S deficiency: case report and review of literature. Saudi J Gastroenterol 1998; 4: 34–7.

51. Macri A, La Spina P, Terranova ML, et al. Ulcerative colitis complicated by dural sina venous thrombosis. Int J Colorectal Dis 2002; 17: 61–2.

52. Diakou M, Kostadima V, Giannopoulos S, Zikou AK, Argyropoulou MI, Kyritsis AP. Cerebral venous thrombosis in an adolescent with ulcerative colitis.Brain Dev2011; 33:49–51.

53. Cognat E, Crassard I, Denier C, Vahedi K, Bousser MG. Cerebral venous thrombosis in inflammatory bowel diseases: eight cases and literature review. Int J Stroke 2011; 6:487–92.