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Original Article

Cerebral venous sinus thrombosis in children: Clinical, imaging, laboratory findings and evaluation of relation to the platelet indices

Dilek Saglam

Malatya Education and Research Hospital, Clinic of Pediatric Radiology, Malatya, Turkey

Abstract

Aim: The aim of this study is to present clinical, imaging and laboratory findings of pediatric cerebral venous sinus thrombosis (CVST), and to evaluate any relationship between the platelet indices and CVST in children.

Material and Methods: Clinical, laboratory and imaging findings of fifteen children with detected CVST on MRI examinations were recorded retrospectively. Fifteen controls were included in the study. All patients and controls were evaluated and platelet indices including; MPV, PDW, PC and MPV/plt ratio were compared.

Results: There was no difference in age and gender distribution between patients and controls. The most common symptom in patients with CVST was headache and fever. Platelet count, PDW, MPV and MPV/plt ratio were slightly higher in controls, however there was no significant difference between two groups (p=0.2, p=0.486, p=0.47, p= 0.595, respectively). Prothrombotic state was found in 33% of our patients and all had increased homocysteine levels. The most common localization of thrombosis was transverse sinus with 50% involvement.

Conclusion: This study presented clinical, MRI and laboratory findings of children with CVST and showed no difference in PC, MPV, PDW and MPV/plt ratio between patients and controls. Platelet indices may not be used to support the diagnosis of CVST in children.

Keywords: Sinus thrombosis; intracranial; child; mean platelet volume.

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) in children is very rare with an incidence of 0.67 in 100.000 children (1). Cerebral venous sinus thrombosis is a major problem causing death and morbidity with neurological deficit (2). Clinical findings are various and can be nonspecific including headache, nausea and vomiting. Obvious neurological findings may not be found in all patients and the presentation may be very subtle especially in infants and children (3). Because of the rare incidence and non-specific clinical findings in children, CVST may be misdiagnosed easily.

Thrombosis starts with aggregation of erythrocytes, fibrin and platelets (plt). Platelets play a major role in the pathogenesis of the thrombooclusive diseases. Platelets release proinflammatory molecules with prothrombic activities.These molecules cause pathological thrombosis and progression of thrombosis (4-6). Mean platelet volume (MPV) and platelet distribution width (PDW) are the two parameters showing platelet activity. These parameters are shown to detect the coagulation activation process better when they are co-evaluated (7). Studies had reported the relationship of platelet indices; MPV, PDW and platelet count (PC) in CVST in adults. To the best of our knowledge, there isn't a study evaluating the platelet indices in children with CVST in the literature.

The aim of this study is to present clinical characteristics and MRI findings of pediatric CVST, and to evaluate any relationship between the platelet indices and CVST in children.

MATERIAL and METHODS

The Local Ethics Committee granted approval for the study. The archives were evaluated retrospectively for the period of 2005-2016 (11 years). Fifteen children (0-18

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Corresponding Author: Dilek Saglam, Malatya Education and Research Hospital, Clinic of Pediatric Radiology, Malatya, Turkey.
E-mail: dilekuzman@hotmail.com

years old) with detected cerebral venous sinus thrombosis on cranial MRI or cranial MR venography examinations were included in this study. Patients with CVST were also divided into two groups as intra-parenchymal brain lesion positive and negative according to the initial MRI. In control group, 15 children who admitted to our hospital and were evaluated with cranial MRI or cranial MR venography examinations, which ended with negative results for any intracranial pathology, were included. Patients in control group didn't have any remarkable history of medical illness. None of the individuals in study group was using any medication including anticoagulants or platelet aggregation inhibitors, which may influence the platelet indices.

The previous medical history of patients was recorded. For all patients and the control group; platelet count (PC), MPV, PDW, hemoglobin (Hb), hematocrit (Htc) levels were recorded. The exclusion criteria were lack of any information in the laboratory data. Follow-up cranial MRI/MRI venography and prothrombotic laboratory panel (including; antinuclear antibody, anti-double-stranded DNA, lupus anticoagulant, antiphospholipid antibodies, protein C and S, anti-thrombin III and factor V Leiden mutation) were also recorded and evaluated in available patients.

Statistical analyses were done with SPSS software, version 21 (IBM Corporation, Armonk, NY, USA). The data is expressed in the mean ± standard deviation (SD) and the median (minimum-maximum). Saphiro-Wilk test was used to determine the normality in the distribution of the quantitative data. To compare two independent groups Student's t-test was used for normal distributed data and Mann Whitney U test for non-normal distributed data. A p value less than 0.05 was considered statistically significant.

RESULTS

The mean age of patients were 9.4±7.3 years old, the mean age of controls were 9.2±7.1 years old with no significant difference (p= 0.967). Also the distribution of gender didn't differ between patients and controls (p=0.645).

Table 1. Clinical presentation and medical history of patients

Patient	Clinical presentation	Medical history
1	Headache	-
2	N/A	Prenatal history of cerebral venous sinus thrombosis
3	Fever, seizure	-
4	Dizziness, left 6 th cranial nerve palsy	-
5	Headache	-
6	Headache	Behçet's disease
7	Trauma	-
8	Headache	-
9	Blurred vision	Functional heart murmur
10	Headache	Migraine
11	Headache, fever	-
12	Vomiting, fever	Acute myeloblastic leukemia
13	N/A	History of respiratory depression in neonatal period
14	Headache	-
15	Headache	Burkitt's lymphoma

Table 2. Demographic and laboratory data of the study population

	Intraparanchymal lesion (+) patients(n=4)	Intraparanchymal lesion (-) patients (n=11)	All patients (n=15)	Controls (n=15)	p
Age (years) mean-SD (min-max)	6.5+7.2 (0.3-17)	10.3+7.3 (0,1-18,8)	9.4±7.3 (0.1-17)	9.2 ± 7.1 (0.22 – 18.2)	0.967
Gender (female/male)	3/1	3/8	6/9	9/6	0.645
Platelet Count (10^4/µL) mean-SD (min-max)	364.25 + 72.8 (265-425)	261.18 + 94.97 (83-409)	288.66±99.01 (83-425)	338.84 ± 110.19 (185.000-582.000)	0.2
PDW (%) mean-SD (min-max)	40.8±3.5 (38.2-46.1)	51.1±6.9 (39-63)	48.3±7.68 (38.2-63)	67.2±83.9 (32.8 – 373)	0.486
MPV (fL) mean-SD (min-max)	6.9±0.6 (6.2-7.8)	7.5±0.89 (6.2-9.1)	7.42±0.86 (6.2-9.1)	7.63±0.72 (6.5-9.1)	0.47
Hb (g/dL) mean-SD (min-max)	10.9±0.69 (10.2-11.7)	12.3±1.94 (10-17)	11.98±1.8 (10-17)	12.0±1.41 (10-14.8)	0.744
Htc mean-SD (min-max)	33.9+2.1 (31.1-35.8)	37.6±6.3 (31.8-53.3)	36.6±5.7 (31.1 ± 53.3)	36.6±4.87 (27-43)	0.461
MPV/PLT mean-SD (min-max)	0.02+0.006 (0.02-0.03)	0.03 +0.02 (0.02-0.11)	0.03 ± 0.02 (0.02- 0.11)	0.2 ± 0.007 (0.01-0.04)	0.595

PDW: platelet distrubition width, MPV: mean platelet volume, Hb: Hemoglobin, Htc: hematocrit
p= comparision between patients vs controls.

The most common symptom in patients with CVST was headache and fever (Table 1). There was no remarkable medical history in 9 patients with CVST. The remaining 6 patients had a medical history including; Burkitt's lymphoma, functional heart murmur, acute myeloid leukemia, Behçet's disease, migraine and prenatal history of CVST. At the time of CVST presentation, 4 patients had fever consistent with infection and one patient had history of trauma.

Table 3. Prothrombotic state of evaluated patients

Laboratory data	Tested (n)	Abnormal (n)	%
ANA	9	0	0
Ads-DNA	7	0	0
C-ANCA	4	0	0
P-ANCA	4	0	0
ASMA	2	0	0
Anti-cardiolipin Ig G	7	0	0
Anti-cardiolipin Ig M	10	0	0
Anti-B2 glycoprotein	3	0	0
Activated protein C resistance	6	0	0
Antithrombin 3 deficiency	9	0	0
Homocystein	9	5	55
Protein S deficiency	8	0	0
Protein C deficiency	10	1	10
Factor 5 Leiden mutation	4	0	0
Factor 7	2	1	50
Factor 8	4	3	75
Factor 9	3	1	33
Factor 10	1	0	0
Factor 11	3	1	33
Factor 12	5	0	0
Fibrinogen	2	1	50
Sedimentation	4	4	100
C reactive protein	8	3	37
Von Willebrant factor antigen	1	1	100

ANA: anti-nuclear antibody, Ads-DNA : anti-double stranded deoxyribonucleic acid, ANCA: anti-neutrophil cytoplasmic antibody , ASMA: anti-smooth muscle antibody

Platelet count, PDW, MPV and MPV/plt ratio were slightly higher in controls (Figure 1), however there was no significant difference between two groups (p=0.2, p=0.486, p=0.47, p= 0.595, respectively) (Table 2). Platelet count, PDW, MPV and MPV/plt ratio of intra-parenchymal lesion positive patients, lesion negative patients and the control group were also compared. The only significant difference was in PDW (p= 0.01) between lesion positive patients and control group (p=0.03).In some patients with CVST, prothrombotic factors were also evaluated (Table 3). Protein C was abnormal in 1/10 patients evaluated. None of the patients had Protein S abnormality or Factor 5 Leiden mutation. Von Willebrant factor antigen was positive in one patient. Homocysteine was high in 5/9 patients with being the most common prothrombotic abnormality.

The most common localization of thrombosis was transverse sinus with 50% involvement (Table 4). Seven of the patients had just one cerebral venous sinus involved, whereas 5 patients had 2, and 3 patients had 3 of the cerebral venous sinuses involved (figure 2). Eleven patients were free of any intracranial finding beyond CVST in initial brain MRI. Four patients had additional intra-parenchymal brain lesions; one patient had bilateral thalamic diffusion restriction, one patient had parenchymal hematoma in parietooccipital lobe, one patient had leptomeningeal enhancement and the patient with lymphoma had an intracranial mass in right frontal lobe extending to the right orbit.

Table 4. Localizations of cerebral venous sinus thrombosis in patients

Cerebral venous sinus involved	Number of patients	Percent (%)
Superior sagittal sinus	6	23.07
Straight sinus	1	3.84
Transverse sinus	13	50
Sigmoid sinus	6	23.07

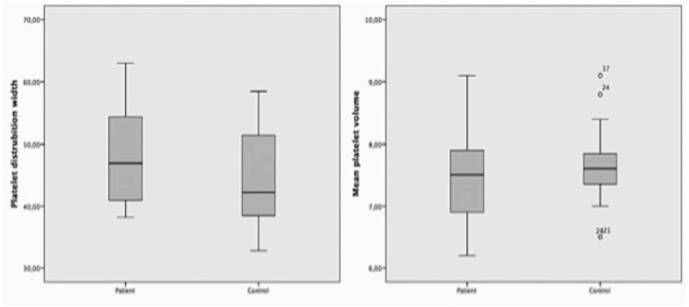

Figure 1. Boxplot histogram of PDW and MPV value of patients and controls.

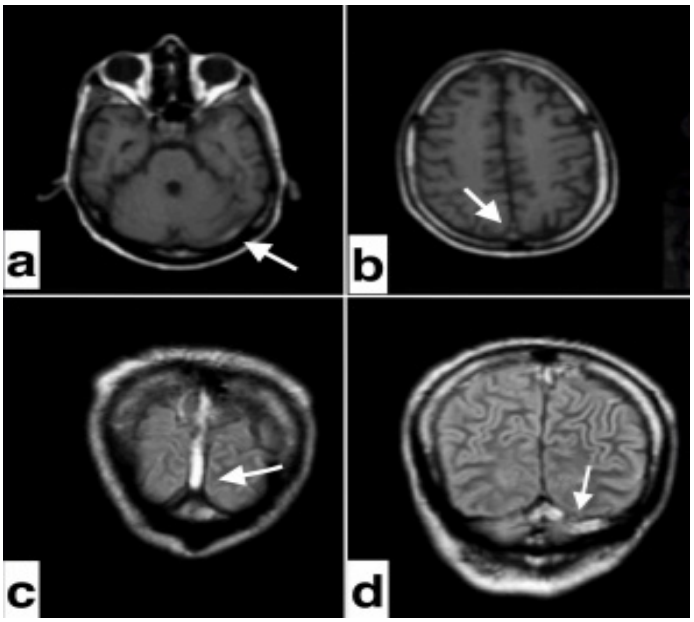

Figure 2. Patient (5 year old, boy) with superior and left transverse cerebral sinus thrombosis. Axial T1 weighted images (a,b) and coronal FLAIR images show hyperintense signal at left transverse (arrows in a and d) and superior sagittal sinus (arrows in b and c) consistent with thrombosis

Fourteen patients had follow up cranial MRI/MR venography examinations. Five patients had normal cranial MRI on follow up. Three patients had reanalyzed thrombus and two patients had chronic thrombus without recanalization. The patient with thalamic diffusion restriction in initial MRI developed bilateral thalamic encephalomalacia and the patient with hematoma in parietooccipital lobe developed parietooccipital encephalomalacia. The patient with lymphoma had new onset white matter lesions consistent with progression of lymphoma. In one patient leptomeningeal enhancement seen on first MRI was still positive on follow up.

DISCUSSION

In the present study, the most common symptom was headache (53%) in children with CVST and only 6% of our patients presented with seizure. In the literature; the two most common clinical presentation of CVST in children is reported as headache and seizures. Se´bire et al. presented headache (68%) as the most common and lethargy (45%) as the second common presenting symptom among 42 children with CVST (8). In the study of Heller et al. the main presenting symptom was seizure (37.9%) among 149 children with cerebral venous thrombosis including internal cerebral veins (9). Fitzgerald et al. reported 57% of neonates with CVST were presented with seizures (10). Carvalho et al. presented seizures in 55% of 31 children with CVST (11). In Bolayır et al.'s study, papilledema (85.2%) was the most and headache (74.1%) was second common symptom among 54 adults with CVST(12). Kamışlı et al. reported headache in all patients with CVST in their study evaluating 53 adults with CVST and the following symptom was papilledema (43%) (13). Karadaş et al. also presented headache in 80.4 % of 23 adults with CVST(14).

Nine patients (60%) with CVST in the present study were previously well, which is consistent with the reported literature. In our study, 33% of the patients had a recent triggering event; infection or trauma, at the time of CVST. In the study of Sedire et al., 59% of 42 children with CVST was previously well, however they had reported a recent triggering event in all patients at the time of CVST; including infection or dehydration (8). Bolayır et al. reported 44.4% of 54 CVST positive adults and Karadaş et al reported 39.2% of 51 CVST positive adults with no previous medical illness (12-14).

Prothrombotic state was found in 33% of our patients and all had increased homocystein levels. Protein C deficiency was detected in one and Von Willebrant factor antigen positivity was detected in another patient. None of our patients had Factor V mutation. Wasay et al. reported prothrombotic state in 13/20 (65%) children with CVST; three patients with homocystinuria, one with Protein C and two with protein S deficiency (15). Heller et al. reported factor V mutation in 14.8% of children with CVST (9). Fitzgerald et al. reported 13% factor V mutation(10).

This study showed no difference in PC, MPV, PDW and MPV/plt ratio between total CVST patients and the control group. However PDW was significantly higher in control group when compared to lesion positive CVST patients, which was unexpected. Our results do not corroborate with most of the reported literature, which presented increased platelet indices in patients with CVST. Tutak reported only significant difference in MPV/plt ratio, and presented no significant difference in MPV and PDW in adults with CVST compared to controls. Kamışlı et al. found increased PDW in adults with CVST compared to controls. They also presented increased MPV in CVST patients with parenchymal brain lesion on MRI compared to controls (13). Bolayır et al. found both increased MPV and PDW value in adults with CVST compared to controls (12). Our study population is composed of children, which may have affected our results. Although normal ranges of platelet indices in adults and children are accepted same; there are also studies, which had reported difference in platelet indices between age groups. Giovanetti et al. showed increase in MPV and decrease in PDW values with the increasing age (16). Mean platelet volume also decreases with the increasing PC, except in patients under 1 year old (17) (18).

In our study, the most common localization of CVST was transverse sinus (50%) with superior sagittal and sigmoid sinus both being the second (23.07%). Involvement of more than one sinus was present in 53% of the patients. Our results were consistent with some of the reported literature. In the study of Heller et al. evaluating the CVST in children; the most commonly involved sinus was the superior sagittal sinus (62.4%) and transverse sinus (14.1%) was the following (9). In Heller's study more than one cerebral venous sinus was involved in 13.4 % of 149 children with CVST. Fitzgerald et al. found more than one sinus involvement in 50% of 42 neonates with CVST, who also reported superior sagittal sinus and transverse sinus as the most common involved sinuses, with 67% and 55%, respectively (10). Carvalho et al. also reported more than one sinus involvement in 41% of CVST positive children (11). In the study of Bolayır et al., transverse sinus was the most commonly involved sinus (72.2%) among 54 adults with CVST (12). Kamışlı et al. also reported superior sagittal sinus (34%) as the most and transverse sinus (23%) as the second commonly involved cerebral venous sinus among 53 adults with CVST (13).

In the present study 26 % of patients had intraparanchymal brain lesion in initial MRI. However Fitzgerald et al. reported a higher incidence; 48% of children with CVST had intraparanchymal brain lesion including hemorrhage and infarction, which could be because of higher percentage of neonates in their study population, which had comorbidities (10).

The present study has some limitation. The study group is small because of the low incidence of CVST in children. Retrospective nature of the study restricted detailed clinical information of patients and all patients were not evaluated for prothrombotic state. Although MPV and PDW are known parameters to show platelet activity,

turbidimetric platelet aggregation is the gold standard test for platelet function (19). In the present study we didn't perform the gold standard test for platelet function. It's also reported that ethylene diaminetetra acetic acid (EDTA) used for anticoagulation in blood tubes increases MPV values when the time between venipuncture and measurement increases (20). We don't know the exact time between venipuncture and complete blood count for each patient in the study. Also the standardization errors of laboratory instruments may also have caused data errors in detected PDW and MPV values.

CONCLUSION

In conclusion, this study presented clinical, MRI and laboratory findings of children with CVST and showed no difference in PC, MPV, PDW and MPV/plt ratio between patients and controls. According to our results, platelet indices may not be used to support the diagnosis of CVST in children. However, further studies with larger population evaluating CVST positive children, with standardization of the blood sampling and the platelet indices will have additional value to the literature.

Competing interests: The authors declare that they have no competing interest.
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Dilek Saglam ORCID:0000-0002-5778-6847

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