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Original Article PEDIATRICS

Transcranial Doppler ultrasonography in patients with hemoglobinopathy: An experience from a tertiary center

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ABSTRACT

OBJECTIVE: Patients with hemoglobinopathy are prone to cerebrovascular event. Our aim was to screen the peak systolic flow velocity (PSV) using transcranial Doppler ultrasonography (TCD) in terms of cerebrovascular event risk in patients with beta thalassemia (β-thal) and sickle cell anemia (SCA).

METHODS: PSV and resistive index (RI) values were determined at internal carotid artery (ICA) and middle cerebral artery (MCA)-from both temporal regions using TCD.

RESULTS: A total of 55 participants (40 patients and 15 healthy people) were included in the study. Thirty-three (60%) of the participants were female. Among 40 patients, 12 patients (30%) had NTDT, 14 patients (35%) had SCA, and 14 patients (35%) had TDT diagnosis. Bilateral ICA and MCA were open in all patients and had a normal flow pattern. PSV and RI were not significantly different between study and control groups in right and left MCA and ICA. Patients with high platelet level (>450.000/mm^3) had significantly higher PSV values in right MCA (96 vs.70 cm/s, p=0.05). Among patients with TDT, age of starting iron chelation and right ICA PSV values was significantly negatively correlated (r=-0.56; p=0.04). Clinical symptoms (headache and pain crisis), hydroxyurea, and chelation therapy did not effect PSV values.

CONCLUSION: Platelet level and age of starting iron chelation might be an influencing factor for PSV. Regular follow-up of patients, appropriate therapy and lack of other factors causing cerebrovascular events might be possible reason for these acceptable results.

Keywords: Beta thalassemia; cerebrovascular event; sickle cell anemia; transcranial Doppler ultrasonography.

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Hemoglobinopathies are the most common hereditary hemolytic anemia in the world [1]. Sickle cell anemia (SCA) is a genetic hemoglobinopathy that is characterized by hemolysis and vaso-occlusive crises. Sickled erythrocytes increase blood viscosity, slow blood flow, cause hypoxia in the vessels [2, 3]. Cerebrovascular event is common complication of SCA and causes of mortality. Its prevalence in the first 18 years varies between 1% and 10% [4, 5].

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Thalassemia is another hemoglobinopathy that is accompanied by a quantitative disruption of the globin chains. The presence of increasing thromboembolic episodes in patients with beta thalassemia (β-thal) has proven the hypercoagulable state in these patients [6]. The extravascular hemolysis can lead to severe complications such as pulmonary hypertension and thromboembolism [7]. Splenectomy status is also responsible for thrombosis by causing spontaneous platelet activation and thrombocytosis [8]. These characteristics put thalassemia patients in a risky position in terms of thrombotic events [9]. The prevalence of stroke varies between 0.1% and 1% in patients with β-thal [10–13].

Transcranial Doppler (TCD) is a non-invasive, easy-to-apply, relatively inexpensive ultrasonography method used to monitor blood flow rates in the proximal areas of the large intracranial arteries. It has been used for a long time to predict the cerebrovascular event in risky population [14]. In this study, we aimed to screen the cerebrovascular blood flow pattern in patients with β-thal and SCA who are prone to cerebrovascular event.

Highlight key points

- Patients with hemoglobinopathy are prone to cerebrovascular event.
- PSV values of bilateral ICA and MCA of patients did not differ compared to healthy group.
- Thrombocytosis and age of starting iron chelation might be related to high PSV values posing a risk for stroke.

MATERIALS AND METHODS

Participants

This study includes 40 patients between the ages of 4 and 41 years who were diagnosed with transfusion dependent (TDT) and non-TDT (NTDT) β-thal and SCA, w/o regular blood transfusion in Thalassemia center, Istanbul Faculty of Medicine. During 3 month study period, patient visiting outpatient clinic were asked to participate into study. Those of them willing to participate without hypertension and any acute infection were given written informed consent.

Ethical Approval

The approval from the Local Ethics Committee was obtained (protocol number 2018.1594).

Design of Study

TCD was performed by faculty radiologist to screen the cerebral blood flow. Internal carotid artery (ICA) and middle cerebral artery (MCA) vessels of both side (right and left) were evaluated to measure peak systolic flow velocity (PSV) and resistive index (RI) values using "Canon Aplio 500" ultrasound system. Once the circle of Willis was demonstrated above the zygomatic arch from the temporal window then the proximal segment of MCA and C1 segment of the ICA, then the insonation angle was set to <60 degrees and highest velocity signals were measured from the peak systolic and end diastolic stage. The accepted PSV values according to literature were as follows: Normal<200 cm/s, conditional 200–250 cm/s, and abnormal (high risk) >250 cm/s [15]. (We used PSV value in this study, however some other studies used time average mean of the maximum [TAMM] value and therefore their cutoff values were as follows: Normal<170 cm/s, conditional 170–200 cm/s and abnormal [high risk] >200 cm/s according to STOP trial [10] and normal<155 cm/s, conditional 155–180 cm/s, and abnormal [high risk] >180 cm/s according to McCarville et al. [16]).

Statistical Analysis

For the statistical analysis, SPSS (version 22, the IBM corp.) program was used. The Mann–Whitney U test was used to compare two groups of variables, correlation analysis was performed for showing the inter-variable relations. $P<0.05$ was defined to be significant.

RESULTS

A total of 55 participants (40 patients and 15 healthy people) were included in the study. Sixty percent of the participants were female (n=33). The mean age of the study group was 18.3±9.3 (4–41), while that of the control group was 20.1±9.4 (6–33) (p=0.51). When the study group was classified according to the diagnoses, 14 patients (35%) had SCA, 12 patients (30%) had NTDT beta-thalassemia (NTDT), and 14 patients (35%) had transfusion-dependent beta thalassemia (TDT). Eighteen patients (45%) were receiving chelation (deferasirox 15 and deferiprone 3). Seventeen patients (43%) were taking hydroxyurea. Six patients (15%) were splenectomized. Half of the patients with SCA were on transfusion program. Eighteen patients (45%) had clinical symptoms as headache or pain crisis in the past 6 months (Table 1).

Table 1. The sociodemographic data of patients

Characteristics	Study group (n=40)
Gender F (%)	55
Age (mean±SD years)	18.3±9.3
Diagnosis (%)	
NTDT	30
TDT	35
SCA	35
Disease duration (of all patients) mean±SD years	14.6±10.0
Age of diagnosis (of all patients) mean±SD months (median)	40.9±50.9 (18)
Age of starting regular transfusion (of TDT patients) mean±SD months (median)	19.5±25.2 (9)
Age of starting iron chelation (of TDT patients) mean±SD months (median)	55.8±27.0 (52)
Age of starting hydroxyurea mean±SD months (median)	150.0±81.6 (120)
Age of splenectomy mean±SD months (median)	104.8±43.5 (90)
Transfusion status (of SCA patients) (%)	
Not transfused	50
On transfusion	
<8/year	35
>8/year	15
Splenectomy (yes) (%)	15
Chelation therapy (%)	45
DFX	83
DFP	17
Hydroxyurea therapy (%)	43
NTDT	41
SCA	59

SD: Standard deviation; NTDT: Non-transfusion dependent beta-thalassemia; TDT: Transfusion dependent beta-thalassemia; SCA: Sickle cell anemia; DFX: Deferasirox; DFP: Deferiprone.

The mean hemoglobin level was 9.3±1.2 gr/dl, the mean platelet level was 382.000±233.000/mm^3, and the mean ferritin level was 828±1260 ng/ml in patients during TCD was performing.

All patients had normal (<200 cm/s) PSV value in the right and the left MCA and ICA, except one patient with TDT had abnormal PSV value in the right ICA (>250 cm/s), and conditional PSV value in the left ICA and MCA and the right MCA (200–250 cm/s).

Study and control group did not differ PCV and RI values in both vessels (Table 2). Females had non-significantly higher PSV value in right ICA (115 vs. 98 cm/s; p=0.15). Patients with increased platelet level (>450.000/mm^3) had significantly higher PSV value in right MCA (96 vs.70; p=0.05). The common symptoms (headache and pain crisis) did not differ in PSV values (Table 3).

There was no significant relationship between age, gender, chelation type, hydroxyurea usage, hemoglobin level, ferritin level, splenectomy status, and PSV values. Within SCA patients, transfusion status did not differ in PSV values. Among patients with TDT, age of starting chelation and right ICA PSV values were significantly negatively correlated (r=-0.56; p=0.04).

DISCUSSION

In this study, we screened the cerebrovascular blood flow pattern of patients with β-thal and SCA who are risky population for stroke. We did not find any difference in PSV values among patients and control group. None of our patients experienced stroke. We found that platelet level and age of starting iron chelation might influence the PSV values in hemoglobinopathy patients.

Table 2. The comparison of TCD values among patients groups

Diagnosis	Right ICA		Left ICA		Right MCA		Left MCA	
	PSV	RI	PSV	RI	PSV	RI	PSV	RI
SCA	115±30	0.56±0.06	106±26	0.56±0.06	70±29	0.58±0.07	79±33	0.56±0.07
NTDT	105±33	0.55±0.05	103±33	0.53±0.05	79±34	0.54±0.05	79±41	0.55±0.06
TDT	117±52	0.55±0.07	105±51	0.59±0.11	84±46	0.58±0.08	92±47	0.55±0.06
Control	99±13	0.57±0.05	105±21	0.54±0.07	83±19	0.54±0.05	79±23	0.57±0.07
	p=0.82	p=0.97	p=0.80	p=0.22	p=0.66	p=0.27	p=0.55	p=0.77

TCD: Transcranial Doppler; ICA: Internal carotid artery; MCA: Middle cerebral artery; PSV: Peak systolic flow velocity; RI: Resistive index; NTDT: Non-transfusion dependent beta-thalassemia; TDT: Transfusion dependent beta thalassemia; SCA: Sickle cell anemia.

Table 3. The TCD values according to clinical and laboratory subgroups

Characteristics	Subgroups	Right ICA PSV	Left ICA PSV	Right MCA PSV	Left MCA PSV
Ferritin	<1000 ng/ml (n=29)	111±42	106±40	81±41	81±42
	>1000 ng/ml (n=11)	115±32	102±32	68±22	90±34
		p=0.53	p=0.90	p=0.44	p=0.24
Platelet	<450.000/mm^3 (n=28)	110±33	102±34	70±29	80±33
	>450.000/mm^3 (n=12)	117±55	116±46	96±48	97±54
		p=0.91	p=0.53	p=**0.05***	p=0.34
Symptom	With symptom (n=18)	118±47	109±41	82±46	91±49
	W/o symptom (n=22)	108±32	102±35	74±28	77±30
		p=0.77	p=0.62	p=0.89	p=0.55
Splenectomy	With splenectomy (n=6)	139±62	114±59	106±61	87±69
	W/o splenectomy (n=34)	108±33	103±33	73±29	82±34
		p=0.19	p=0.97	p=0.10	p=0.59
Chelation	With chelation (n=18)	119±47	109±46	77±43	88±45
	W/o chelation (n=22)	107±32	101±30	78±32	79±36
		p=0.36	p=0.78	p=0.64	p=0.50
Hydroxyurea	With hydroxyurea (n=17)	112±31	107±31	81±33	90±38
	W/o hydroxyurea (n=23)	113±45	104±43	75±40	78±41
		p=0.93	p=0.54	p=0.44	p=0.28

TCD: Transcranial Doppler; ICA: Internal carotid artery; MCA: Middle cerebral artery; PSV: Peak systolic flow velocity.

Hemoglobinopathies are risky diseases for vascular occlusion. Impairment of the erythrocyte structure, anemia, hypoxia, disorders in the coagulation system, and inflammation can lead to silent and clinically apparent cerebral infarcts. Transcranial Doppler ultrasound (TCD) is recommended and relatively standardized method in SCA to predict the cerebrovascular event, however its use in thalassemia continues to be the subject of research [14, 17].

Adams et al. [18] showed that higher than 200 cm/s values of TAMM at two measurement was associated with risk of stroke (40%) within 3 years in patients with SCA. The risk of stroke in these children was reduced by 92% with the chronic transfusion program. In our study, we did not have any patient with stroke.

Ashjazadeh et al. [19] studied on thalassemia intermedia (TI) patients and showed higher intracranial ar-

terial blood flow velocity compared to healthy people. Higher blood flow velocity was associated with platelet count and splenectomy status. In our study, patients with NTDT did not have increased intracranial blood flow velocity and splenectomy status did not significantly alter the PSV values.

Karimi et al. [11] performed TCD in thalassemia major (TM) and TI patients. They revealed that the TAMM velocity was higher in TI patients than in TM. Splenectomy status was found as a risk factor for higher blood flow velocity and transfusion program was detected as protective factor. On the contrary, we found that TDT patients had non-significantly higher PSV values compared to NTDT patients. In their study, nearly half of the patients had splenectomy. We only had six (15%) patients splenectomized and this discrepancy might explain our results. On the other hand; we found that the age of starting iron chelation was related to PSV values in right ICA vessel among patients with TDT. Patients requiring iron chelation at early age showed higher PSV values in their follow-up.

Hankins et al. [20] studied the effect of hydroxyurea treatment on intracranial blood flow velocity in children with SCA. They followed patients along 10 months and observed a significant change in TAMM velocity with hydroxyurea treatment. They concluded that hydroxyurea reduced conditional velocities in children with SCA. In our study, no difference was found in flow velocities among patients receiving hydroxyurea or not.

It is known that thrombotic complications are high after splenectomy in patients with NTDT thalassemia (NTDT). To evaluate cerebral blood flow in β-thal patients, Kanavaki et al. [21] performed TCD on splenectomized and non-splenectomized β-TI patients and found TAMM velocity within normal limits in both patient groups. They concluded that cerebral events might be due to microangiopathy and venous thromboembolic events. Similarly, Siddiqui et al. [22] studied on patients with splenectomized SCA and found that prevalence of abnormal TCD did not increase after splenectomy. However, they noted that the cerebral blood flow increased within the 1st few years after splenectomy. Russo et al. [23] concluded no increased cerebrovascular involvement in adult neurologically asymptomatic beta-thalassemia patients using MRI analysis. We found higher non-significant PSV values in β-thal patients with headache symptoms (115 vs. 76 cm/s in the left MCA; p=0.53).

According to clinical recommendations, TCD should be performed routinely until the age of 16 in SCA and should be repeated annually [24–26]. There is also new educational program about TCD application in SCA patients under umbrella of European countries [27]. However, because of the presence of practice barriers in also developed countries such as western United States, the adherence to TCD implement fall by half [28]. In that survey [28], one third of medical centers was complaining of lack of support staff. In our center, we try to perform routine screening program for those patients. In our study, our patient with the highest PSV was in the TDT group, had splenectomy and thrombocytosis. Therefore, the treatment program was planned appropriately in our clinic to closely monitor the patient.

Conclusion

As PSV values are higher in patient's thrombocytosis. Patients requiring iron chelation at early age should also be followed up in terms of cerebrovascular event. Large cohort studies and more importantly studies with MRI analysis are needed to clarify the risk for stroke and to follow-up of patients.

Ethics Committee Approval: The Istanbul University Clinical Research Ethics Committee granted approval for this study (date: 23.11.2018, number: 2018.1594).

Conflict of Interest: No conflict of interest was declared by the authors.

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