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Cerebral hemodynamic in patients with major β-Thalassemia using transcranial Doppler sonography

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Abstract

Background: β-thalassemia, a severe form of anemia, is an inherited blood disorder characterized by growth retardation, splenomegaly, and bone abnormalities. Complications related to treatment-induced iron overload also affect the quality of life of patients with major β-thalassemia. Some recent studies indicated cerebral hemodynamic disorders and increased risk of stroke in these patients. The aim of this study was to evaluate mean flow velocity (MFV) in some cerebral arteries of patients with major thalassemia using transcranial Doppler ultrasonography.

Materials and Methods: In this cross-sectional study, 26 patients with major thalassemia were investigated. The definitive diagnosis was based on serum hemoglobin electrophoresis. Transcranial Doppler ultrasonography was performed in patients and MFV of internal carotid, anterior cerebral, and middle cerebral. Posterior cerebral arteries were measured. Demographic characteristics, duration of treatment, number of blood transfusions per month, the interval between the last blood transfusion, and the ultrasonography were recorded and analyzed statistically.

Results: Ten female and 16 male patients participated in this study. Results showed that 57.7% of patients had a hemodynamic abnormality in at least one vessel. The abnormality was significantly higher in the anterior and middle cerebral arteries ($p<0.001$ and $p=0.005$, respectively). Among the variables evaluated, age was significantly associated with hemodynamic dysfunction. This relationship remained significant after using the logistic regression analysis ($p=0.0267$).

Conclusions: Some patients with major thalassemia have a cerebral hemodynamic abnormality. Aging is associated with the higher frequency of this abnormality.

Keywords: Major thalassemia, Cerebral, Hemodynamic

Introduction

Major Beta-thalassemia is a type of anemia caused by a defect in the synthesis of β-globin chains of hemoglobin, and it has an autosomal recessive pattern of inheritance (1). Due to the dysfunction of red blood cells, the blood production in the bone marrow of these people increases, causing the bones to become deformed in the long run, especially the broad bones. These patients also require regular blood transfusions, which causes the patients to develop complications such as increased iron levels in various organs (2, 3, 4). Although bone problems, involvement of the heart and abdominal organs, and infections are more prevalent than other complications, studies have shown that these patients are also prone to thrombotic events, especially in the cerebral arteries (5, 6). Multiple factors such as impairment of coagulation inhibitors, thrombocytosis after splenectomy, and impaired function of liver or heart are predisposing factors for increased coagulation and eventually vascular events such as stroke (7, 8, 9, 10). Assessment of patients at a higher risk for stroke is considered as one of the important therapeutic goals. Target Doppler ultrasound is a non-invasive and accessible technique without any complications. Based on its findings, clinicians can

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evaluate the hemodynamic status of internal and external cranial arteries with high accuracy (11). The value of using a Doppler ultrasound has been demonstrated for years in strokes and diseases such as sickle cell anemia (12, 13, 14, 15). Some recent studies showed that Doppler ultrasound might be useful in the hemodynamic evaluation of patients with major beta-thalassemia and the screening of patients at risk of cerebrovascular events (10). Studies conducted in this regard are limited, and the factors associated with transfusion have not been evaluated in this field, yet. Therefore, in this study, the authors evaluated mean flow velocity MFV in some cerebral arteries of patients with major thalassemia using transcranial Doppler sonography.

Materials and Methods

Patient Selection

In this descriptive-analytical study, using simple sampling, the investigators selected 26 patients with major beta-thalassemia who had visited Shahid Sadoughi Hospital in Yazd. The patients were diagnosed with beta-thalassemia by an oncologist based on the complete blood count and hemoglobin electrophoresis tests (4). They were first examined by a physician in the thalassemia center, and those with another underlying disease, history of thrombosis or other vascular events, fever or use of sedatives in the last 24 hours, and any acute illness in the last two weeks were excluded. Informed consent was obtained from patients, and they participated voluntarily.

Ethical considerations

The ethics committee of Yazd Shahid Sadoughi University of Medical Sciences approved the study (IR.SSU.MEDICIN.REC 13950143).

Ultrasound

After selecting the patients, their demographic characteristics including age, duration of infection, number of transfusions, and the time interval between transfusion and ultrasound were recorded in the checklist. A neurologist performed transcranial and extracranial Doppler of cerebral arteries on all patients using a CW/PW bi-directional Doppler connected to a DWL digital box (Sipplingen, Germany). This device has two separate probes, one 4MHz for evaluation of the internal carotid arteries (ICA) and one 2MHz for evaluation of the anterior cerebral arteries (ACA), middle cerebral arteries (MCA), and posterior cerebral arteries (PCA). MFV was automatically calculated by the device. Other parameters such as pulsatility index (PI) could be also detectable, but given that the most reliable parameter is MFV (based on Alexandrov neurosonology reference), this item was selected for evaluation. The investigators measured the time-averaged maximum mean velocity in bilateral ICA, ACA, PCA, and MCA with a temporal window approach. The cases with a poor temporal window for the ultrasound were excluded. The criterion for an abnormal MCV was according to the reference book (16). Based on the previous study (17) and using the sample size calculation software of the PASS version11, the sample size was indicated as 26 patients.

Statistical Analysis

Data were analyzed by descriptive statistics, independent t-test, Chi-square test, Fisher exact test, and logistic regression analysis. The significance level was considered as $P<0.05$ in SPSS version 22.

Results

In this study, 26 patients were enrolled, of which ten patients (38.5%) were female, and the rest were male. The age range of patients was 6 to 31 years. The frequency of studied variables is shown in Table I. Of all patients, 57.7% had a hemodynamic abnormality in at least one of their arteries. The hemodynamic abnormality had a significantly higher incidence in anterior and middle cerebral arteries ($P<0.001$, $P=0.005$, respectively) (Table II). Among the studied variables, age had a significant relationship with hemodynamic disorders ($P = 0.013$) (Table I). This relationship remained significant after using the logistic regression analysis ($P=0.267$) (Table III).

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Table I: Relation between variables and hemodynamic status

Variables	Levels	Abnormal	Normal	P-value
		Mean± SD		
Age		22.47±6.50	15.82±6.32	0.013
Gender	Female	6	4	0.851
	Male	9	7	
Number of blood transfusions	15	2	2	0.907
	20	11	8	
	>20	2	1	
Duration of treatment	0-5	1	2	0.188
	6-10	0	1	
	>10	14	8	
Interval between blood transfusions and ultrasonography	0-15	10	8	0.576
	16-20	5	2	
	>20	0	1	

Table II: Comparison of hemodynamic status according to arteries

	Abnormal	Normal	
Arteries	Mean± SD		P-value
MCA	115.69±26.98	84.85±20.26	0.005
ACA	102.43±17.59	68.72±15.47	<0.001
PCA	28.67±8.28	25.25±8.29	0.285
ICA	55.93±11.48	57.95±14.96	0.760

MCA: Middle Cerebral Arteries; PCA: Posterior Cerebral Arteries; ICA: Internal Carotid Arteries

Table III: Results of univariate and multiple logistic regressions

	Crude			Adjusted		
Variables	OR	95%C.I for OR	P-value	OR	95%CI for OR	P-value
Age	1.18	1.01,1.38	0.037	1.206	0.87,1.68	0.267
MCA	1.073	1.01,1.14	0.028	1.215	0.95,1.55	0.121
ACA	1.126	1.02,1.23	0.012	1.102	0.96,1.27	0.175
OR: Odds Ratio; C.I: Confidence Interval						

MCA: Middle Cerebral Arteries; ICA: Internal Carotid Arteries

Discussion

This study evaluated the hemodynamic status of patients with major thalassemia using the Doppler ultrasound technique. The results showed that more than half of the patients with major thalassemia with no history of vascular events had hemodynamic abnormalities. This finding has several important clinical implications: First, a significant proportion of patients with major thalassemia secondary to the hemodynamic disorder are prone to vascular events, and the process of screening these patients can influence on their clinical condition. Second, similar to the patients with thalassemia (18,19, 20), Doppler ultrasound can be a useful, efficient, and non-invasive tool for screening high-risk patients. Third, this study is one of the few studies on patients under the age of 15 years and showed the existence of this abnormality at young ages. The authors also found the presence of these abnormalities in other limited studies conducted in this field. Shariat et al. conducted a hemodynamic evaluation of cerebral arteries in 54 patients with thalassemia (with or without

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thrombocytosis) and found that a large portion of studied patients had hemodynamic disorders. However, the incidence of this disorder was much higher in patients with thrombocytosis (10). In a case-control study by Karimi et al. on 60 patients with thalassemia major, they found a significant difference in cerebral arteries mean blood flow of these patients in comparison to healthy individuals (21). These changes have also been reported in other types of thalassemia, such as intermediate thalassemia, which indicates that pathophysiology is similar in all types of thalassemia (17, 21, 22). It is reported that multiple factors are involved in hemodynamic abnormality development in thalassemia patients such as impairment of coagulation inhibitors, thrombocytosis after splenectomy, and impaired function of liver or heart. These factors lead to hemodynamic abnormality by causing coagulation disorders (7, 8, 9, 10). Among the studied variables, age had a significant relationship with vascular disorders. This finding shows that as age increases, the risk of cerebrovascular events becomes greater. Because coagulation disorders are the leading cause of vascular events, (7, 8, 9, 10) this factor seems to become more important in older ages, and it should be considered in treatment and follow-up. In this study, the incidence of hemodynamic disorders in the anterior and middle cerebral arteries was significantly higher ($p < 0.001$, $p = 0.005$, respectively). This finding may indicate a greater susceptibility of some arteries to the incidence of abnormalities. Shariat et al. also reached this conclusion, however, among the patients they studied, the incidence of this disorder was higher in the vertebral arteries (10). In a case-control study by Ashja Zadeh et al., they found that this disorder was present in all arteries of patients with intermediate thalassemia, suggesting that the type of thalassemia also affects the rate and type of arteries involved (6). This study found no association between the time of transfusions and the time of the ultrasound. This finding showed that carrying out this method at any given time can be valuable for high risk patients screening. This study had some limitations that should be considered in future studies: First, the investigators did not consider anemia, thrombocytosis, and splenectomy in this study. Given that both anemia and thrombocytosis (caused by splenectomy) affect hemodynamic parameters, the results must be considered when interpreting them. Second, all arteries should be assessed. Due to the young age of some patients and their lack of full cooperation until the end of the ultrasound process, the investigators were not able to examine all arteries. Therefore, only those arteries were examined in all patients. Also, it is noteworthy that in an ultrasound, mainly proximal arteries were evaluated.

Conclusion

Findings showed that some patients with thalassemia major had the cerebral hemodynamic abnormality. Aging was associated with the higher frequency of these abnormalities.

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Conflict of interest

The authors declare no conflict of interest.

References

1- Viprakasit V, Ekwattanakit S. Clinical Classification, Screening and Diagnosis for Thalassemia. Hematol Oncol Clin North Am 2018; 32(2):193-211.

2- Origa R. β-Thalassemia. Genet Med 2017; 19(6):609-619.

3- Hadipour Dehshal M, Tabrizi Namini M, Hantoushzadeh R, Yousefi Darestani S. beta-Thalassemia in Iran: Things Everyone

[DOI: 10.18502/ijpho.v11i3.6566]

Needs to Know About This Disease. Hemoglobin 2019; 43(3):166-173.
4- Ansari-Moghaddam A, Adineh HA, Zareban I, Mohammadi M, Maghsoodlu M. The survival rate of patients with beta-thalassemia major and intermedia and its trends in recent years in Iran . Epidemiol Health 2018;40:e2018048-e2018052.
5- Borgna Pignatti C, Carnelli V, Caruso V, Dore F, De Mattia D, Di Palma A, et al. Thromboembolic events in beta thalassemia major: an Italian multicenter study. Acta Haematol 1998; 99(2) : 76 -79.
6- Ashjazadeh N, Emami S, Petramfar P, Yaghoubi E, Karimi M. Intracranial Blood Flow Velocity in Patients with β-Thalassemia Intermedia Using Transcranial Doppler Sonography: A Case-Control Study. Anemia 2012; 2012: 798296-798300.
7- Ataga KI, Cappellini MD, Rachmilewitz EA. Beta-thalassaemia and sickle cell anaemia as paradigms of hypercoagulability. Br J Haematol 2007; 139(1): 3 -13.
8- Karimi M, Khanlari M, Rachmilewitz EA. Cerebrovascular accident in beta-thalassemia major (beta-TM) and beta-thalassemia intermedia (beta-TI). Am J Hematol 2008; 83(1): 77 -79.
9- Panigrahi I, Agarwal S. Thromboembolic complications in beta-thalassemia: Beyond the horizon. Thromb Res 2007; 120(6): 783 -789.
10- Shariat A, Nazeri M, Abolhasani Foroughi A, Karimi M. Transcranial Doppler Ultrasonography in Beta-thalassemia Major Patients Without and With Thrombocytosis, Iran Red Crescent Med J 2013; 15(3):234-238.
11- Naqvi J, Yap K H, Ahmad G, Ghosh J. Transcranial Doppler Ultrasound: A Review of the Physical Principles and Major Applications in Critical Care. International Journal of Vascular Medicine Int J Vasc Med. 2013; 2013: 629378-629381.
12- Dorn AY, Thorpe S G , Canac N, Jalaleddini K, Hamilton R B. A Review of the use of Transcranial Doppler Waveform Morphology for Acute Stroke Assessment J Clin Neurosci 2020;81:346-352.
13- Naffaa L N , Tandon Y K, Irani N . Transcranial Doppler screening in sickle cell disease: The implications of using peak systolic criteria. World J Radiol 2015; 7(2): 52–56.
14- Lee MT, Piomelli S, Granger S, Miller ST, Harkness S, Brambilla DJ, et al. Stroke prevention trial in sickle cell anemia (STOP): extended follow-up and final results. Blood 2006;108(3):847–852.
15-Hamziee-Moghadam A, Iranmanesh F, Arabpour-Fathabadi A, Mohammadi F. Cerebrovascular Reactivity and Carotid Intima-Media Thickness in Opium Dependents: A Case-Control Study. Addict Health 2018; 10(2):131-136.
16-Alexandrov AV. Cerebrovascular Ultrasound in Stroke Prevention and Treatment.2th edition.2011;9-12
17- Kanavaki A, Kattamis A, Delaporta P, Papassotiriou I, Spengos K. Evaluation of Intracranial Cerebral Blood Flow Velocities in Splenectomised and Non-Splenectomised Patients with β-Thalassemia Intermedia Using Transcranial Doppler Sonography. In Vivo 2015; 29 (4): 501-504
18- Deane CR, Goss D, O'Driscoll S, Mellor S, Pohl KR, Dick MC, et al. Transcranial Doppler scanning and the assessment of stroke risk in children with HbSC [corrected] disease. Arch Dis Child 2008; 93(2): 138-141.
19- Bulas D. Screening children for sickle cell vasculopathy: guidelines for transcranial Doppler evaluation. Pediatr Radiol 2005; 35(3): 235 -241.
20- Neish AS, Blews DE, Simms CA, Merritt RK, Spinks AJ. Screening for stroke in sickle cell anemia: comparison of transcranial Doppler imaging and nonimaging US techniques. Radiology 2002; 222(3): 709 -714.
21- Karimi M, Haghpanah S, Ashjazadeh N. Cerebral Artery Velocity Determined by Transcranial Doppler Ultrasonography in Patients With β-Thalassemia Intermedia Compared to β-Thalassemia Major. Clin

[DOI: 10.18502/ijpho.v11i3.6566]

Appl Thromb Hemost 2013; 19(4):367-373.
22- Nassef S, Shenoufy M, Rawi R, Demerdash D, Hassan M, Mustafa H, et al. Assessment of Atherosclerosis in Peripheral and Central Circulation in Adult β Thalassemia Intermedia Patients by Color Doppler Ultrasound: Egyptian Experience. J Vasc Res 2020; 57: 206-212.

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