Evaluation of Intracranial Cerebral Blood Flow Velocities in Splenectomised and Non-Splenectomised Patients with β-Thalassemia Intermedia Using Transcranial Doppler Sonography

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Abstract. Background: A high incidence of clinically-silent cerebral ischemic events has been reported in splenectomised patients with β-thalassemia intermedia (βTI). These could be due to cerebral large-vessel disease. Based on the example of sickle cell disease, we applied transcranial Doppler sonography (TCD) to evaluate cerebral vessels velocity as a possible indicator of cerebral vasculopathy. Patients and Methods: In our study, we included 17 splenectomised and 13 non-splenectomised (control group) patients with βTI. Non-imaging TCD was performed and the time-averaged mean velocity (TAMV) values of cerebral arteries were measured. Results: There was no statistically significant difference between the two groups concerning age, gender, hemoglobin and hematocrit levels, nor in the TAMV values for all examined vessels (p>0.05). A statistically significant difference was found in platelet count (PLT) (p<0.01) that was higher in splenectomised patients. Conclusion: Our results do not support the presence of large-vessel vasculopathy in splenectomised βTI patients and agree with recent studies reporting that cerebral ischemic events in these patients might be due to microangiopathy or venous thromboembolism.

Beta-thalassemia is a congenital hemolytic anemia caused by reduced or absent synthesis of β-globin (hemoglobin subunit beta) chains. The clinical phenotype of β-thalassemia intermedia (βTI) is between that of β-thalassemia major (βTM) and β-thalassemia minor and presents a wide spectrum of clinical manifestations (1, 2). Patients with a mild form of βTI have mild anemia and may require for occasional transfusions, while those with more severe forms, although usually not in need of regular transfusions, may exhibit growth impairment and decreased stamina. β-Thalassemia intermedia is usually characterized by moderate anemia with hemoglobin levels of 7-10 g/dl, varying degrees of splenomegaly and skeletal changes (1).

Complications of βTI include pulmonary hypertension, extramedullary hemopoietic pseudotumors, leg ulcers, gallstones, iron overload, hepatic and endocrine dysfunction (3). Patients may exhibit hypercoagulability, especially if they gave been splenectomised, and suffer from thromboembolic events (1-5). Thromboembolism may manifest as deep venous thrombosis, pulmonary embolism, portal vein thrombosis, superficial thrombophlebitis and ischemic strokes.

Although overt strokes are more frequent in patients with βTM than in those with βTI, recent studies have shown a high incidence of clinically silent cerebral ischemic events (CIEs) in splenectomised patients with βTI (6-10). The pathophysiology of infarction in these patients has not been clarified yet. It was recently reported that splenectomised patients with βTI are prone to cerebral large-vessel disease, mostly intracranial artery stenosis (11). However, microangiopathy and venous thrombosis have also been suggested as an etiology of silent infarcts in such patients (2, 3, 11).

The purpose of this study was to evaluate cerebral vessel circulation in splenectomized patients with βTI in order to investigate the presence of cerebral vasculopathy by means of transcranial Doppler sonography (TCD). TCD has been proven to be of great value in screening of cerebrovascular...
disease in patients with sickle cell disease (12, 13). However, only few studies on TCD in patients with βTI have been reported, with variable results (10, 14, 15). Based on previous data, we hypothesized that splenectomised patients with βTI are likely to have cerebral large-vessel disease and thus, in the case of sickle cell disease, TCD might be a useful tool in detecting abnormal cerebral vessel velocities, implying cerebrovascular disease in βTI (1).

Patients and Methods

This was a prospective study conducted during an 18-month period (November 2011 to April 2013) at the Hematology Unit and the Department of Neurology of our tertiary University Hospitals. The Ethical Committee of our hospital approved the study (Approval Number: 17550/05-08-2011, Ethical Committee of Aghia Sophia Children’s Hospital).

Splenectomised patients with βTI, nine males and eight females, who presented for routine follow-up, were included in this study (group A). Their age ranged between 16 and 47 years (median=34, mean=32.2 years). A control group consisted of 13 non-splenectomised patients with βTI (group B).

Diagnosis of thalassemia intermedia was made according to the criteria described by Kattamis et al. (16). For all patients, laboratory data included hemoglobin, hematocrit and ferritin levels, and platelet count. All patients were transfusion-independent during this study and had no recent history of transfusion. Patients with known thromboembolic events, cerebrovascular or cardiovascular ischemic attacks, hypertension and diabetes mellitus were excluded from the study.

All TCD examinations were performed by an experienced investigator (K.S) using a non-imaging TCD device (RIMED Inc., Israel) with a 2-MHz transducer. The anterior (ACA), middle (MCA) and posterior (PCA) cerebral arteries were insonated through a temporal window approach and the basilar (BA) artery through a suboccipital window. Patients with an inadequate window for TCD were excluded from the study. For each vessel, the highest value of the time-averaged mean velocity (TAMV) was registered. We compared the TAMV between the two groups and with normal values. We also compared hematocrit and hemoglobin trends, and platelet counts between the two groups. Mann–Whitney and Chi-square tests were used for the statistical analysis using tools freely-available at http://www.socscistatistics.com.

Results

We included 30 patients with βTI in our study; 17 (56.6%) had undergone splenectomy, while the remaining 13 non-splenectomised patients comprised the control group.

No statistically significant difference was found between the two groups concerning age, gender, hemoglobin and hematocrit levels (Table I). All patients in the non-splenectomised group had a platelet count within the normal range (150,000-400,000/μl), while all splenectomised patients had counts above 400,000/μl. This difference between the two groups was statistically significant (p<0.01) (Table I).

As for cerebral vessel velocities, the mean and median values of the TAMV for the ACA, MCA, PCA and BA arteries were within the normal range (17, 18) in both groups (Table II). Contrary to our initial hypothesis, there was no statistically significant difference in the TAMV values for all examined cerebral arteries between the non-splenectomised and splenectomised patient groups, indicating the absence of intracranial large vessel disease (p>0.05).

Discussion

One of the major complications of βTI is thromboembolic events. Patients with βTI exhibit hypercoagulability (thrombophilia). Damage to circulating red blood cells, resulting in increased thrombin generation, chronic platelet activation and endothelial activation, and co-inheritance of defects in the coagulation system are considered possible causes (1-3, 5). Hypercoagulability is more common in splenectomised than in non-splenectomised patients with βTI (2, 19), manifesting as deep venous thrombosis, pulmonary embolism, portal venous thrombosis, superficial thrombophlebitis and ischemic strokes (2, 4, 5, 20).
In a recent study including 8,860 patients with β-thalassemia, thromboembolic events occurred 4.38-times more often in patients with βTI than in those with βTM (1).

Cerebral ischemic infarcts have been recognized as one of the major complications of βTI, especially in splenectomised patients. In contrast to βTM, they seem to be clinically silent and can only be detected on magnetic resonance (MR) imaging (3, 7, 8, 10, 11, 21). The exact cause of this cerebral ischemia remains uncertain (2, 3, 11).

According to a recent study by Musalam et al., splenectomised patients with βTI presented with cerebral vasculopathy (11). The application of MR Time of flight (TOF) angiography showed large-vessel disease, mostly intracranial artery stenosis. It is interesting, however, that these stenotic lesions did not correspond to the distribution of silent infarcts in the same patients.

In the present study, we used TCD to evaluate blood flow velocity in cerebral vessels as a possible indicator of cerebral vasculopathy. The mean intracranial blood vessel TAMVs were within the normal range for both groups (17, 18). There was no statistically significant difference in TAMVs of intracranial cerebral vessels between splenectomised patients and non-splenectomised ones. Thus, these findings do not support the hypothesis of cerebral vasculopathy in splenectomised patients with βTI, as was previously shown mainly based on studies using MR TOF angiographic sequences for the evaluation of cerebral arteries. This discrepancy may be due to false-positive results obtained by the MR TOF. It is well-known that imaging of stenosis on MR TOF angiographic sequence is based on the fact that turbulent flow caused by stenosis results in de-phasing of moving spin and, as a consequence, in signal loss or signal reduction. Non-transfusion-dependent patients with βTI have low hematocrit. Decreased hematocrit is related to increased cerebral blood flow velocities (22). We hypothesize that in patients with βTI, a low hematocrit results in turbulent flow that is falsely interpreted as stenosis on MR TOF angiography. The same explanation has been proposed for patients with sickle cell disease, where cerebral vasculopathy was unable to explain the distribution of silent infarcts (23).

The failure to support our initial hypothesis that splenectomised patients with βTI exhibit intracranial large-vessel disease supports recently published data showing that cerebral infarction in patients with βTI is not attributed to large-vessel arteriopathy but, instead, might be due to microangiopathy or venous thromboembolic events (2, 3, 11).

The limited number of patients and the absence of imaging findings to confirm or exclude the presence of silent infarcts are the major limitations of our study. Furthermore, TCD itself has many limitations, thus more robust and reliable examination of the cerebral circulation in patients with βTI may be required in order to clarify whether these patients do indeed suffer from intracranial arteriopathy.

References


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