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ORIGINAL ARTICLE

Frequency of silent brain lesions and aspirin protection evaluation over 3 years follow-up in beta thalassemia patients

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Abstract

Silent brain lesions might be associated with overt cerebrovascular accident over time in beta thalassemia major (BTM) and intermediate (BTI). Aspirin may be protective in these patients. We evaluated brain magnetic resonance imaging (MRI) in thalassemia patients to see whether aspirin is protective or not. A historical cohort study was conducted on 35 thalassemia patients, 22 BTI, and 13 BTM patients at Shiraz Hematology Research Center in 2018. Median age of the patients was 32 years and ranged from 8 to 42 years. Twenty-four patients (68.6%) were females. Overall frequency of white matter lesions (WMLs) in the first MRI was 10 patients (28.6%). After 3 years, 3 patients developed new lesions and the frequency of WMLs was 13 patients (37.1%) in the second MRI. Moreover, in 3 patients, number of WMLs increased. Patients with new lesions or more lesions compared to the baseline were significantly older than the other group (median age 36.5 years vs. 31 years, $P = 0.046$). Regarding aspirin consumption, only 1 patient (16.7%) of patients with new lesions was using aspirin compared to 10 (34.5%) of the other group ($P = 0.640$). The high-risk patients with thrombocytosis, splenectomy, severe iron overload, and older age (> 30 years) should be under close follow-up and evaluated on a regular periodic basis as well as brain MRI at least once every 3 years. Aspirin could be protective against new or progressive brain lesions so that low-dose aspirin is recommended in high-risk thalassemia patients.

Keywords Aspirin · Beta thalassemia · Silent brain lesions

Introduction

Thalassemia is the most common hereditary anemia in the Mediterranean and Asia regions [1, 2].

Beta thalassemia intermedia (BTI) presents with milder anemia than beta thalassemia major (BTM) patients and does not need regular transfusion although it may require blood transfusion later on in life [3, 4]. On the one hand, novel oral iron chelation medicines along with new treatment modalities in BTI lead to enhancing their life expectancy; on the other hand, this causes late compilations such as thrombotic events in these patients. Enhanced tendency to thrombotic events has been demonstrated in thalassemia patients [5]. Thromboembolic events (TEE) have been observed both in BTI and BTM patients although it is more common in BTI patients due to multiple risk factors such as the presence of circulating abnormal red blood cells causing increased thrombin generation [6, 7]. TEE can occur in different vital organs including the brain, causing neurological complications through different mechanisms [8]. There are many reports showing overt and silent brain involvement in thalassemia patients. Silent brain ischemia and white matter lesions might be associated with overt cerebrovascular accident (CVA) over time in BTM and BTI patients. In the previous studies, we showed the frequency of silent brain ischemia and white matter lesions in thalassemia major and intermedia patients [9–12].

On the other hand, aspirin prevents clots through decreased platelet aggregation, making them less likely to clump in the circulation, and is used to reduce the risk of a second thrombotic stroke in patients who have had an ischemic stroke. Aspirin is associated with the risk of bleeding which outweighs its benefits. Aspirin in a daily dose of 160 to 300 mg

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that started within 48 h of symptom onset leads to decrease in morbidity and mortality caused by acute ischemic stroke regardless of access to imaging [13]. There are a few studies that reported the benefit of aspirin in thalassemia, while silent cerebral ischemia may happen in thalassemia [11, 12, 14]. Moreover, aspirin may be protective in these patients, so we evaluated brain MRI in thalassemia patients who had already performed brain MRI in order to see whether aspirin is protective or not over 3 years.

Methods

In this historical cohort study, 44 thalassemia patients (22 BTI and 22 BTM) were randomly selected by simple random sampling method from 46 BTM and 49 BTI patients who had performed brain MRI at baseline [11] (3 years before the end of the study) at Shiraz Hematology Research Center in 2018. In BTM group, 9 patients were excluded due to the lack of some relevant information in this retrospective analysis. Finally, 22 BTI and 13 BTM patients were investigated. These patients underwent second MRI after 3 years follow-up. The dose of aspirin was 80–100 mg once daily. The indication for starting low dose of aspirin was high platelet count more than 500,000/mm^3. All of them had no overt neurological defects. All BTI patients were non-transfusion dependent and have been on hydroxyurea, 10–15 mg/kg once daily. The diagnosis of BTI and BTM was made by complete blood count, hemoglobin electrophoresis, and clinical history. Informed written consent was taken before starting the study, and the proposal study was approved by medical ethics committee of Shiraz University of Medical Sciences (code number 5092). A designed questionnaire was made to obtain all the laboratory parameters including serum ferritin levels, complete blood count, history of medications such as aspirin, presence or absence of the spleen, and family history. Patients who had heart failure, diabetes, and risk factors of thrombophilia or any thromboembolic events as well as patients with other medical causes of brain ischemic white matter lesions including vasculitis, migraine, multiple sclerosis, carotid stenosis, and atrial fibrillation were excluded from the study (evidence of prothrombin, factor V Leiden, or MTHFR mutations documented by genetic studies; as well as positive result of antithrombin III, protein C, protein S, lupus anticoagulant, or cardiolipin antibodies). The MRI was interpreted by an experienced neuroradiologist for all participants using a 1.5 T MR unit (Siemens, Avanto, standard four-channel head coil, diffusion-weighted imaging, Germany).

Statistical analysis

Data were analyzed by SPSS version 21. Shapiro-Wilk test was used to evaluate normality of data. Descriptive data were presented as median, range, frequency, and percentage. Comparison of qualitative data between two groups was done by Fisher exact test. Quantitative variables were compared by Mann-Whitney test between the two groups. A two-sided P value less than 0.05 was considered statistically significant.

Results

Median age of the patients was 32 years, and ranged from 8 to 42 years. Twenty-four patients (68.6%) were females. The median platelet count was 523,000/μL (min–max 80,000–644,400/μL). Eleven patients (31.4%) were using aspirin regularly. Table 1 shows comparison of clinical and laboratory characteristics between patients with TM and TI. There was not significant difference regarding, age, sex, and hemoglobin level between BTI and BTM patients. Serum ferritin levels were significantly higher in TM patients ($P = 0.001$).

Overall frequency of white matter lesions (WMLs) in the first MRI was 10 patients (28.6%). After 3 years, 3 patients developed new lesions (Fig. 1) and the frequency of WMLs was 13 patients (37.1%) in the second MRI. Moreover, in 3 patients, number of WMLs increased in new MRI (Fig. 2). All of them were ischemic type. All 3 patients with new lesions were splenectomized, and no one was using aspirin. In 3 other patients with more WMLs than before, 2 patients were splenectomized, and only 1 patient was using aspirin.

Frequency of WMLs in patients with TI was more than TM patients in both steps (baseline 36.4% vs. 15.4% and after 3 years 45.5% vs. 23.1%). However, the differences were not statistically significant (Table 1).

Three patients with new lesions at the second MRI and 3 patients with development of more lesions than baseline MRI were considered as one group with new lesions ($n = 6$) and were compared with other patients ($n = 29$) regarding platelet count, hemoglobin, age, sex, serum ferritin, splenectomy, and aspirin consumption (Table 2). Patients with new lesions were significantly older than the other group (median age 36.5 years from 32 to 42 vs. 31 years from 8 to 40 years, $P = 0.046$). Other parameters were comparable between the two groups. Regarding aspirin consumption, only 1 patient (16.7%) of patients with new lesions was using Aspirin compared to 10 (34.5%) of the other group. However, the difference was not statistically significant ($P = 0.640$).

Discussion

Stroke is the third leading cause of mortality worldwide. The American Stroke Association Stroke Council suggested an initial aspirin dose of 325 mg within 24 to 48 h of the onset of symptoms [15]. Successful benefit of aspirin in the treatment and prevention of recurrent cardioembolic events in

Table 1 Comparison of demographic and clinical characteristics of patients with beta thalassemia major and intermediate

Group variables	Thalassemia intermediate $N = 22$	Thalassemia major $N = 13$	P value
Age (year) (median, range)	31.5 (8–42)	35.5 (24–40)	0.534
Sex (male), N (%)	8 (36.4)	3 (23.1)	0.487
Hemoglobin (g/dL) (median, range)	9.05 (8.4–11)	10 (8.1–11.4)	0.057
Ferritin (median, range) (ng/mL)	597 (110–4000)	1800 (170–6000)	0.001
Platelet, N/μL	491,500 (80,000–1,030,000)	523,000 (171,000–644,400)	0.730
Splenectomy (yes), N (%)	14 (66.7)	6 (46.2)	0.296
Aspirin consumption (regularly used), N (%)	9 (40.9)	2 (15.4)	0.150
White matter brain lesion, N (%)			
Baseline	8 (36.4)	2 (15.4)	0.259
After 3 years	10 (45.5)	3 (23.1)	0.282

patients without hemoglobinopathies has been established. Moreover, thalassemic patients with hypercoagulability state may also benefit from the use of aspirin for treatment and prevention that justifies further investigation [14]. In our study, we compared baseline brain MRI with 3 years afterward in patients with BTI and BTM who were divided into two groups based on the patients who were taking low-dose aspirin (80–100 mg, not 325 mg) or those patients who were not taking aspirin. Our results showed over 3 years brain MRI follow-up, and only 1 patient (16.7%) of patients with new lesions or increase in number of lesions was using aspirin compared to 34.5% of other patients, while no overt neurological deficit was observed. Although the difference was not statistically significant, it was clinically important to underscore that taking low-dose aspirin might be protective in preventing asymptomatic brain lesions among thalassemia patients. There is a significant association between increased number of activated platelets with thromboembolic phenomena, including silent cerebral ischemia (SCI), in splenectomized patients with NTDT [5, 7, 16] which necessitates the use of anti-platelet aggregation such as aspirin in these patients.

The chronic and permanent hypercoagulable state has been demonstrated in thalassemia although the frequency of TEE seems to be higher in splenectomized and non-transfused patients [5, 7]. The frequency of cerebral TEE is associated with increasing age (> 20 years old), transfusion naivety, splenectomy, thrombocytosis, cardiomyopathy, and diabetes so that diagnostic brain MRI is recommended in high-risk groups to screen for early asymptomatic brain damage. If brain ischemia is detected, the use of antiplatelet aggregate is probably beneficial [7, 10, 11, 17]. Our study showed that new brain lesions occurred in older patients compared to non-new brain lesions (median age 36.5 vs. 31 years) highlighting that diagnostic brain MRI should be taken into consideration in high-risk patients over 30 years old. To the best of our knowledge, long-term assessment of protective effect of aspirin on silent brain ischemia and lesions using comparable brain MRI has not been demonstrated yet and this study was designed to determine whether aspirin has a protective effect or not. The current data showed that the brain lesions were increased in thalassemic patients who did not take aspirin although it was not significant due to small sample size. However, at this point, there is no readily available clear-cut guideline as to

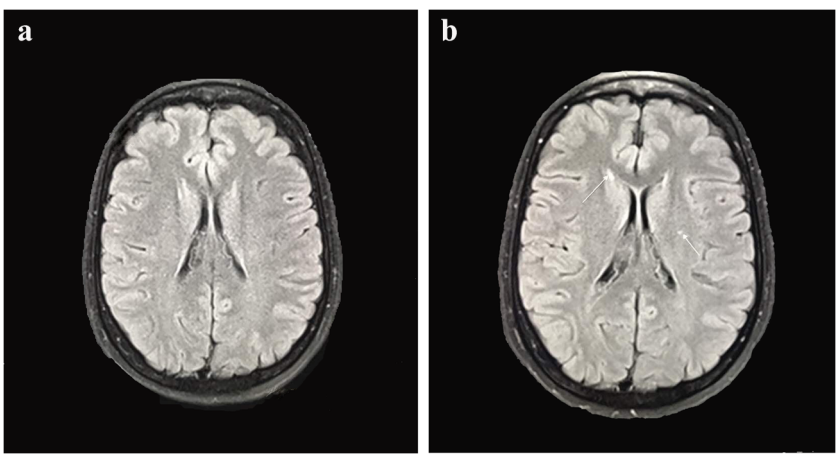

Fig. 1 The patient is a known case of thalassemia major. New developing white matter spots within 3 years are noted and marked in **b**. **a** Before aspirin therapy. **b** After aspirin therapy

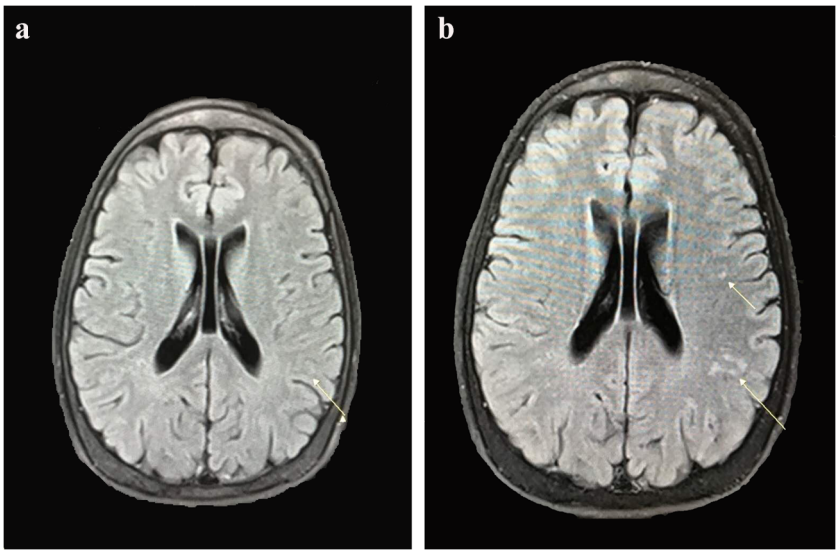

Fig. 2 The patient is a known case of thalassemia major. New developing white matter spots within 3 years are noted and marked in **b**. **a** Before aspirin therapy. **b** After aspirin therapy

who might benefit from antiplatelet aggregation to prevent silent brain ischemia or lesions before the appearance of clinical signs and symptoms. Although the benefit of taking low-dose aspirin was shown in our study, larger samples and more homogeneous population are needed to obtain a practical guideline on this issue.

We previously reported an overall frequency for asymptomatic white matter changes of 28% in 30 BTI and 15.8% in 95 BTI and BTM patients. These studies showed the positive correlation of the incidence of WML with thrombocytosis, splenectomy but not to regular blood transfusions which might be related to the treatment with hydroxyurea in non-transfused patients [10, 11]. However, another study reported a higher incidence (60%) of asymptomatic brain lesions in 30 adult splenectomized Lebanese patients and the probable protective effect of regular blood transfusions in decreasing WMLs [18]. Furthermore, the study on BTM compared to normal population in the same age-/sex-matched group confirmed the positive brain findings in patients with beta thalassemia, and the lesions are real and not an artifact [19].

BTM and BTI patients with older age and splenectomized (even with normal platelet count) have a higher incidence of SCI. The frequency of SCI in patients with β-TM was determined as 37.5%, while they have less circulating pathological RBC, underscoring that taking aspirin is recommend in high-risk group not only in non-transfusion-dependent but also in transfusion-dependent thalassemia patients [11, 12]. One more issue of debate is whether iron overload is a possible risk factor which was previously reported in patients with BTM or not? [20]. Free iron catalyzes the formation of reactive oxygen species (ROS) which causes oxidative damage to almost every part of the cell [21]. Our study showed that serum ferritin was significantly higher in BTM than BTI, but the frequency of brain lesions was not significant which might be due to regular transfusion and remarkably less pathologic circulating red blood cells in BTM patients.

On the basis of our study and reported data, SCI are asymptomatic, but since patients live longer, one might consider the possible conversion to overt cerebral ischemia or the increased number and size of these lesions [11, 12, 14] as we observed in our study, which emphasizes taking of aspirin in high-risk

Table 2 Distribution of risk factors in two groups of thalassemia patients with and without new lesions

Group variables	With new lesion $N = 6$	Without new lesion $N = 29$	P value
Age (year), median (range)	36.5 (32–42)	31 (8–40)	0.046*
Sex (male/female), N	0/6	11/18	0.146
Platelet, N/μL, median (range)	564,000 (80,000–1,030,000)	432,000 (144,000–644,400)	0.596
Hemoglobin (g/dL), median (range)	9.5 (8.5–11.4)	9.2 (8.1–11)	0.441
Ferritin (ng/mL), median (range)	597 (120–1950)	1200 (110–6000)	0.303
Splenectomy (yes), N (%)	5 (83.3)	1 (16.7)	0.364
Aspirin consumption (yes), N (%)	1 (16.7)	10 (34.5)	0.640

*Statistically significant

groups as well as follow-up of these patients by repeating brain MRI every 3 years. In addition, splenectomy should only be performed on patients where a large spleen results in severe pancytopenia. Effective iron chelation therapy to reduce iron overload should also be taken into consideration [21].

In conclusion, increased numbers of SCI are found both in BTI and BTM patients. The etiology and significance of this finding remain to be clarified. Therefore, the high-risk patients with thrombocytosis (platelet count > 500,000 mm^3), splenectomy, severe iron overload, and older age (> 30 years) should be under close follow-up and evaluated on a regular periodic basis as well as brain MRI at least once every 3 years. Aspirin could be protective against new or progressive brain lesions or ischemia so that low-dose aspirin is recommended in high-risk thalassemia patients since these lesions are asymptomatic, but, as the patients become older, one cannot foresee if and when they will become symptomatic.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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