β-Thalassemia intermedia: morbidity uncovered

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Brain magnetic resonance angiography in splenectomized adults with β-thalassemia intermedia

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Abstract

Background: Hypercoagulability and venous thromboembolism are common in patients with β-thalassemia intermedia (TI), especially in the splenectomized adult. Although arterial involvement is not commonly reported, we have recently observed a high prevalence (60%) of silent brain infarction on brain MRI in 30 splenectomized adults with TI. The pathophysiology of these white matter lesions remains unknown. *Methods:* In this work, we evaluated magnetic resonance angiography (MRA) scans of the same cohort of 30 patients. Data collected were the presence or absence of vascular lesions, their locations, and severity. Correlations between MRA abnormality and patients/disease characteristics were evaluated. Comparisons between MRA and previous MRI findings were made. *Results:* Of 29 evaluable patients, 8 (27.6%) had evidence of arterial stenosis on MRA. The majority of lesions had mild narrowing and mostly involved the internal carotid artery. Five patients (17.2%) had evidence of aneurysms. Low total hemoglobin and high non-transferrin-bound iron levels independently characterized patients with evidence of stenosis on MRA. Among the 18 patients with silent brain infarction on MRI, three had evidence of stenosis on MRA with only one patient having lesions that could explain the silent infarcts. *Conclusions:* Cerebral vasculopathy is common in splenectomized adults with TI. However, large-vessel disease does not explain the occurrence of silent brain infarction. The combined use of MRA and MRI better identifies splenectomized TI adults with neuroimaging abnormalities.

Key words thalassemia intermedia; splenectomy; brain; silent stroke; magnetic resonance angiography

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Significant advances have been attained toward the understanding and management of stroke in patients with sickle cell disease (SCD) (1). However, data on patients with thalassemia syndromes remain limited. A hypercoagulable state has been recognized in thalassemia (2). It is mainly attributed to the procoagulant activity of hemolyzed red blood cells and activated platelets, especially in splenectomized patients, as well as coagulation factor abnormalities and endothelial inflammation (3). The largest epidemiological study to date examined data from 8860 patients in the Mediterranean area and Iran and showed that thromboembolic events occur 4.38 times more frequently in patients with β-thalassemia intermedia (TI) than in patients with β-thalassemia major (TM) (4). Thromboembolic events in patients with TI are mostly venous, and their occurrence increases with age (4–6). The risk of thromboembolism is also higher in splenectomized and never-transfused patients (4, 6–8).

Strokes, on the other hand, are less frequent in patients with TI compared with TM patients (28% vs. 9%, respectively) (4). This could be attributed to the higher rate of iron overload-mediated morbidity (diabe-

tes mellitus, cardiac dysfunction and arrhythmias) in patients with TM, which could increase stroke risk (9). Nevertheless, one study showed that 37.5% of patients with TI have evidence of silent brain infarction on magnetic resonance imaging (MRI) (10). More recently, we (11) and others (12) conducted brain MRI screening studies on patients with TI who had no history of neurological events. In our 30 splenectomized adults with TI, the rate of silent brain infarction was as high as 60% and involved the subcortical white matter in all patients (11). Such a high rate reflected a pathological finding, as no more than 10% of healthy individuals show incidental ischemic lesions on brain MRI. Moreover, other neurological pathologies causing white matter lesions were excluded (11). However, the mechanisms contributing to silent brain infarction in patients with TI remain unknown. We herein evaluate magnetic resonance angiography (MRA) scans of the same 30 patients to determine whether large-vessel pathology can account for the high rate of silent brain infarction in splenectomized adults with TI.

Patients and methods

Patients

This was a cross-sectional study conducted on all splenectomized adult (≥18 yr) patients with TI attending the Chronic Care Center (Lebanon) over a period of 6 months. All patients were diagnosed with TI based on previously described criteria (13). None of the patients had Hb-S-thalassemia, C-thalassemia, E /β-thalassemia or $\delta\beta$-thalassemia, co-inheritance of α-thalassemia or co-inheritance of determinants associated with increased γ-chain production.

A total of 43 patients were screened for exclusion criteria: neurological and/or gross cognitive signs or symptoms (abnormality detected during medical history taking, neurological exam or mini mental status exam performed by a qualified neurologist); history of anticoagulant or antiplatelet therapy; diabetes (use of antidiabetic drugs or a fasting blood sugar ≥ 126 mg/dL); hypertension (use of antihypertensive drugs or a blood pressure ≥ 140/90 mm Hg on two readings 6 wk apart); cardiac disease (any abnormality on electrocardiography or echocardiography including: arrhythmias, valvular disease, dysfunction, presence of atrial or ventricular thrombi, or pulmonary hypertension); thrombophilia (evidence of factor V Leiden, prothrombin, or methylenetetrahydrofolate reductase gene mutations or abnormality in protein C, protein S, antithrombin III, Lupus anticoagulant, or cardiolipin antibody levels); and smoking (any current or previous history of smoking). Thirty eligible patients were included in the study. The study was approved by the Institutional Review Board of the center, and written consents were obtained from all patients.

Patient charts were reviewed for demographics (age and gender) and any history of transfusion therapy. Blood samples were obtained for assessment of total hemoglobin level, nucleated red blood cell (NRBC) and platelet counts, and steady-state serum ferritin levels. Levels of non-transferrin-bound iron (NTBI) were also measured as previously described (14). Direct determination of liver iron concentration (LIC) was performed by R2 MRI using established methodology (15).

Brain imaging

All patients underwent MRI of the brain followed by MRA of the extracranial and intracranial circulation. Two neuroradiologists blinded to the clinical data reviewed the studies.

Brain MRIs were performed on a 3.0 Tesla, eight channel head coil, Achieva Philips Scanner using axial T1-weighted images (TR/TE, 450/10), T2 gradient-echo weighted images (TR/TE, 731/16), fluid-attenuated inversion recovery (FLAIR) images (TR/TE, 11 000/125) and diffusion-weighted imaging (TR/TE, 2312/68). Coronal FLAIR images (TR/TE, 11 000/125) as well as coronal and sagittal T2-weighted images (TR/TE, 3000/80) were also obtained. No contrast material was administered. Infarction or ischemic lesions were defined as areas of abnormally increased signal intensity on the T2- and FLAIR-weighted sequences and were classified by anatomic location and size. The size of lesions was classified into small (< 0.5 cm), medium (0.5–1.5 cm), and large (> 1.5 cm). For patients with multiple lesions, the largest lesion was used to define size.

Brain MRA was performed using three-dimensional time-of-flight (TOF) angiography of the circle of Willis with maximal intensity projection (MIP) reconstruction. Sequence parameters used were TR = 23 ms, TE = 3.453 ms, 200 slices, 0.8 mm thick and a directional field of view of 20 cm. Both the MRA source images and the MIP derived from the MRA data were evaluated. Data collected were the presence or absence of vascular lesions, their locations, and severity. The internal carotid arteries (ICA), middle cerebral arteries, anterior cerebral arteries (ACA), posterior cerebral arteries (PCA), as well as the vertebral and basilar arteries were rated from normal to occluded. Arterial segments were defined to be normal or to be mildly (≤50%), moderately (51–75%), or severely (> 75%) stenosed, or totally occluded (100%) (16). The presence of aneurysm was also recorded. All MRAs were reviewed by two neuroradiologists who were blind to the patient's clinical history. After that, the two results' forms were compared

and discrepant findings were reviewed until a consensus was reached.

Statistical analysis

Descriptive data are presented as means ± SD or percentages. Bivariate correlations between MRA abnormality and study parameters were evaluated using the independent samples *t*-test, the Chi-square test, and the Fisher's exact test. Multivariate regression models were constructed to determine the variables independently associated with MRA abnormality. All *P*-values were two-sided with the level of significance set at < 0.05.

Results

MRA findings

A total of 30 patients were included in this analysis (Table 1). One patient had a non-evaluable MRA scan. In the remaining 29 patients, 8 (27.6%) had evidence of arterial stenosis. Two patients (25%) had more than one artery involved (one had two and the other had four arteries) (Fig. 1), while the remaining 6 (75%) had a single stenosed cerebral artery. The ICA was the most commonly involved artery (in six of eight patients, 75%). Among the 12 identified stenotic lesions, two were severe (16.7%), one was moderate (8.3%), and the remaining 9 (75%) were mild (Table 2).

Moreover, five patients (17.2%) had evidence of aneurysms. Three patients had a single aneurysm: one in the left ICA (2 mm), one in the right superior cerebellar artery (3 mm), and one fusiform aneurysm of the right PCA. The other two patients had multiple aneurysms: the first patient had two aneurysms in the right ICA (3 mm) and the other patient had four aneurysms. In this last case, three aneurysms were located in the right ICA ranging from 2 mm to 1 cm and one fusiform aneurysm was located in the A1 segment of the right ACA (Fig. 2).

Table 1 Patients' characteristics

Parameter	Value
Mean age ± SD (range), yr	31.9 ± 11 (18–54)
Men : women	13 : 17
Transfusion, *n* (%)[1]	
None	18 (60)
Occasional	12 (40)
Mean total hemoglobin ± SD (range), g/L	86.4 ± 20.8 (49–131)
Mean NRBC count ± SD (range), $\times 10^3/mm^3$	367.4 ± 319.8 (0–1366)
Mean platelet count ± SD (range), $\times 10^9$/L	791.2 ± 355.3 (189–1602)
Mean serum ferritin ± SD (range), μg/L	1176 ± 641.9 (116–3158)
Mean NTBI ± SD (range), μM	3.4 ± 3.4 (–2.1 to 10)
Mean LIC ± SD (range), mg Fe/g dw	11.3 ± 7.8 (1–32.1)

NRBC, nucleated red blood cell; NTBI, non-transferrin-bound iron; LIC, liver iron concentration; dw, dry weight.

[1]Patients were occasionally transfused during infections, surgery, or pregnancy. None of the patients were on iron chelation or hydroxyurea therapy.

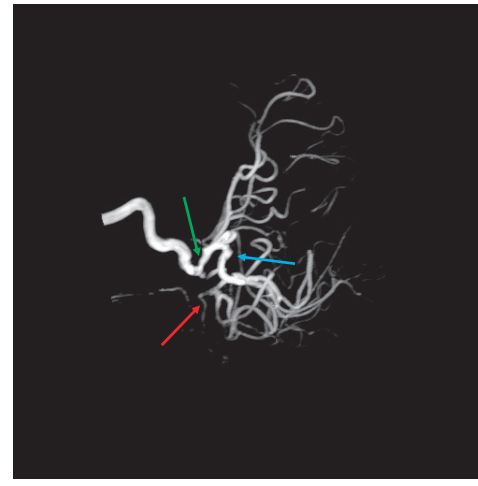

Figure 1 A 37-yr-old female patient. Coronal oblique maximal intensity projection of the magnetic resonance angiography of the anterior circulation demonstrated severe stenosis and almost occlusion of the cavernous segment of the left internal carotid artery (ICA) (red arrow) and mild narrowing of the cavernous portion of the right ICA of <50% (green arrow). There was also irregularity and fusiform enlargement of the A1 segment of the right anterior cerebral artery (blue arrow).

Risk factors for MRA abnormality

There was no statistically significant correlation between evidence of stenosis on MRA and any of age, gender, transfusion history, NRBC count, platelet count, serum ferritin level, or LIC. However, the mean total hemoglobin level was significantly lower in patients with evidence of stenosis on MRA than those without (71.3 vs. 91.1 g/L, $P = 0.018$). Moreover, the mean NTBI level was significantly higher in patients with evidence of stenosis on MRA than those without (6.4 vs.2.3 μM, $P = 0.002$).

Using both total hemoglobin level and NTBI level as independent variables in a generalized linear model, both variables were significant in explaining the dependent categorical variable stenosis on MRA ($P = 0.046$ for total hemoglobin and $P = 0.039$ for NTBI). A logistic

Table 2 Patients with evidence of stenosis on MRA and their corresponding brain MRI findings

Patient	MRA stenosis		MRI infarction		
	Location	Severity	Location	Number	Size (cm)
1	Right ICA	Mild	Bilateral frontal	23	<0.5 (21), 0.5–1.5 (1), >1.5 (1)
	Left ICA	Severe	Bilateral parietal	21	<0.5 (20), >1.5 (1)
	Left MCA-M3	Mild	Bilateral occipital	3	<0.5 (3)
	Left PCA	Severe	Bilateral EC	3	<0.5 (3)
2	Right ICA	Mild	Bilateral frontal	8	<0.5 (8)
			Left occipital	1	<0.5 (1)
			Left EC	1	<0.5 (1)
3	Left ACA	Mild	Bilateral frontal	4	<0.5 (4)
4	Right ICA	Mild	None		
5	Right MCA-M2	Moderate	None		
6	Right ICA	Mild	None		
7	Left ICA	Mild	None		
	Left PCA	Mild			
8	Right ICA	Mild	None		

MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; EC, external capsule.

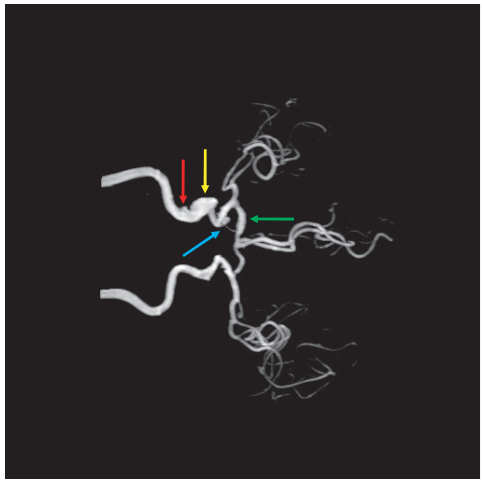

Figure 2 A 45-yr-old female patient. Coronal oblique maximal intensity projection of the magnetic resonance angiography of the anterior circulation demonstrated fusiform aneurysm of the petrous portion of the right internal carotid artery (ICA) (yellow arrow) and a tiny saccular aneurysm of the same segment (red arrow). Also noted were a third 4-mm saccular aneurysm of the cavernous portion of the right ICA (blue arrow) and a fusiform enlargement of the A1 segment of the right anterior cerebral artery (green arrow).

regression model was also performed to estimate the probability of stenosis on MRA using total hemoglobin level and NTBI (Fig. 3). The model was significant ($P < 0.001$) and had a predictive value of 82.76%.

MRA vs. MRI

Among the 30 patients, 18 (60%) had evidence of silent brain infarcts on MRI, all within the subcortical white matter. Fourteen (77.8%) had evidence of multiple white matter lesions (2 to >40). The frontal ($n = 17$, 94.4%) and parietal ($n = 9$, 50%) lobes were the most commonly involved. Patients mostly had small ($n = 10$, 55.5%) or medium ($n = 7$, 38.9%) lesions, with only one patient (5.6%) having a large lesion.

Among the 18 patients with MRI abnormalities, three had evidence of stenosis on MRA (patients 1–3 in Table 2), with only one patient having extensive lesions that could explain the silent infarcts (patient 1 in Table 2). The remaining two patients (patients 2 and 3 in Table 2) had large-vessel involvement that does not geographically explain the silent infarcts. MRA identified five additional TI patients with vascular abnormalities that have normal MRIs (Table 2).

Discussion

This is the first MRA study of patients with TI. It demonstrates that although large-vessel disease is a common finding in splenectomized adults with TI, it does not explain the occurrence of silent brain infarction at high rates. These findings could constitute the first step toward understanding cerebral vasculopathy in this patient population.

Around one-third of patients in this report had evidence of stenosis in at least one major cerebral artery. High levels of NTBI characterized this subgroup of patients. NTBI is a low-molecular-weight form of iron that is directly detected when transferrin becomes fully

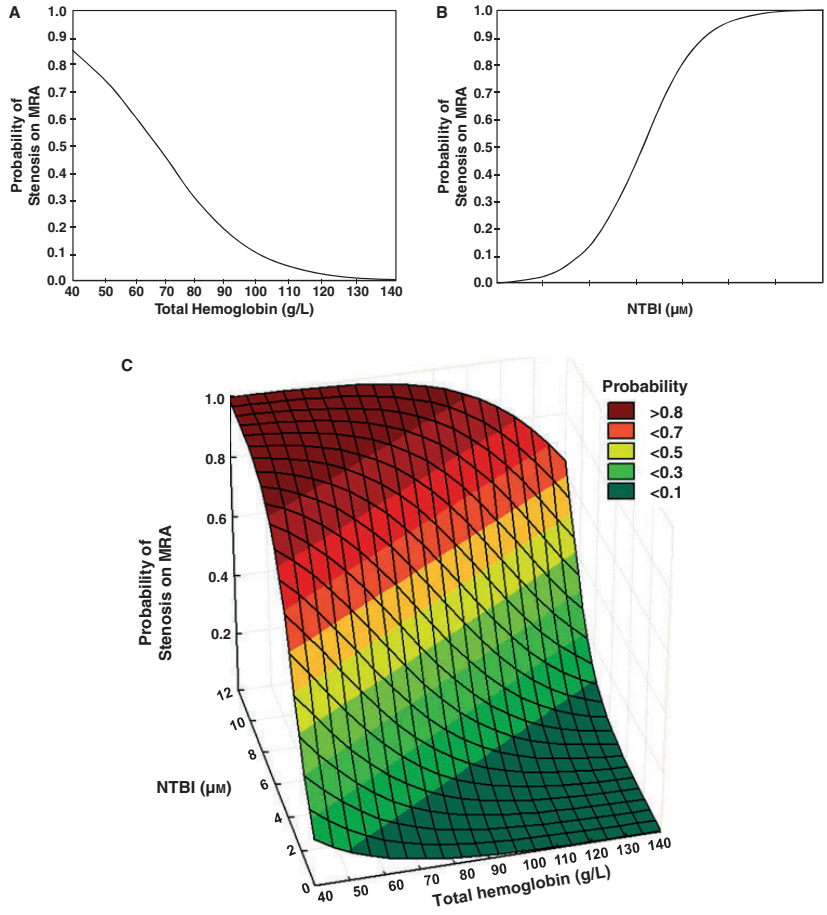

Figure 3 Logistic regression curves showing the probability or stenosis on magnetic resonance angiography as a function of (A) total hemoglobin level, (B) non-transferrin-bound iron (NTBI) level, and (C) both total hemoglobin and NTBI levels.

saturated and is unable to bind excess iron (14). It has been demonstrated that the presence of NTBI in serum can cause oxidative vessel injury (17). Free radicals act directly on the endothelial cells and have a close interaction with lipid peroxidation, causing a modification of low-density lipoprotein and facilitating its deposition, with the consequent formation of atherosclerotic plaques (18). Thus, iron-mediated endothelial dysfunction and a secondary atherosclerotic process may explain cerebral large-vessel disease in patients with TI and echo recent studies supporting the idea that patients with TI exhibit a proatherogenic biochemical phenotype (19, 20). Such large-vessel injury could occur early on with direct iron toxicity (there was no correlation between MRA abnormality and age in our study) and does not require chronic accumulation of iron over time (absence of correlation with LIC or serum ferritin). Whether thrombosis, in this disease with hypercoagulability, is a secondary process or incremental in vessel narrowing warrants investigation. This could be achieved by further study using Doppler/duplex sonography, which can give a better understanding of the morphology (etiology) of stenosis. It should also be noted that five patients (17.2%) had evidence of aneurysms, a prevalence that is higher

than that documented in the healthy adult population (approximately 1–2%) (21) and that is similar to observations in patients with SCD (22, 23). The aforementioned assumptions of vessel wall pathology could be extended to explain the occurrence of these aneurysms.

An association between anemia and cerebrovascular stenosis has never been documented. The association of lower hemoglobin levels with stenosis on MRA in our study may be reflecting an indirect link between phenotype severity and vascular abnormality. Although transfusion status did not correlate with stenosis, most patients in our study were only occasionally transfused in special circumstances, and the role of regular transfusion therapy in ameliorating this large-vessel disease requires further investigation.

Only one of 18 TI patients with silent brain infarction had relevant stenosis on MRA, indicating that large-vessel disease is not a contributing factor in the pathophysiology of these silent white matter lesions. The situation is similar to what have been often described in patients with SCD. It is now established that the majority of symptomatic strokes in patients with SCD are secondary to large-vessel disease. However, the absence of large-artery disease is especially apparent in the context of silent infarcts (24). Whether these infarcts are, thus, secondary to hypercoaulability and smaller arteriolar pathology merits further evaluation.

Silent infarcts observed on brain MRI are associated with a high risk, subsequent overt stroke, and neurocognitive deficits, as evident from several reports on children and adults with SCD (25–31). Furthermore, SCD patients with abnormal MRA findings are at higher risk for stroke (16). Our study demonstrated that the addition of MRA to MRI identifies a greater proportion of TI patients with silent neuroimaging abnormalities. As these abnormalities maybe associated with increased risk of overt stroke or neurocognitive dysfunction, performing both modalities in any diagnostic setting is recommended. Prospective evaluation of a risk assessment model for the development of these abnormalities may help develop a cost-effective screening program of high-risk patients (e.g., patients with severe anemia or iron overload). Such models should also accurately predict which patients are at higher risk of subsequent events and require therapeutic intervention. The role of transfusion and antiplatelet therapy in this regard merit further investigation.

Our study carries several limitations. Using three-dimensional time-of-flight angiography, both high flow and low flow can result in signal void, and high-grade stenoses might, therefore, be misclassified as complete occlusions. A more reliable distinction could be achieved with contrast-enhanced MRA. However, no cases of complete occlusion were detected in this report, making the aforementioned limitation irrelevant. Further, TOF angiography does not provide any information on the etiology (i.e., atherothrombotic vs. embolic vs. dissection, etc.) of the stenosis. Assuming that large-vessel disease in patients with β-thalassemia intermedia might be due to arteriosclerosis as discussed by the authors, it would be desirable to support this hypothesis by imaging data. The MR data should, therefore, be supplemented by Doppler/duplex sonography. Besides precise information on the morphology of stenosis, the suspected degree of stenosis could then be verified. Moreover, our study did not include age-matched healthy individuals as controls. However, in one review of 2000 healthy persons with a mean age of 63.3 yr, the rate of major-vessel stenosis found incidentally on MRI was only 0.5% (95% CI: 0.2–0.8) (32). In another MRA-based study, the rate of mild stenosis ($< 50\%$) on MRA was only 4% (95% CI: 1.4–6.6) in 225 healthy individuals with a mean age of 63 yr (33). Recent large studies in the general population with mean age between 20 and more than 70 yr of age found prevalences of intracranial aneurysms to be 0% (34, 35), 0.1% (95% CI: 0–0.2) (35), 0.2% (95% CI: −0.1 to 0.5) (36), 1.8% (95% CI: 1.2–2.4) (32), and 2% (95% CI: 1.7–2.3) (37). Together, these findings indicate that the vascular abnormalities identified on MRA in our report [large-vessel stenosis 27.6% (95% CI: 11.3–43.9) and intracranial aneurysms 17.2% (95% CI: 3.5–30.9)] are pathological rather than normal variations; especially that the mean age in our cohort (32 yr) is much younger than that reported in the aforementioned references from healthy individuals.

Our study demonstrated that cerebral vasculopathy, evident from large-vessel disease, is common in splenectomized adults with TI. However, it does not explain the occurrence of silent brain infarction. The combined use of MRA and MRI could, thus, better identify splenectomized TI adults with neuroimaging findings that are commonly associated with a high risk for future stroke or functional neurologic deficits.

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Conflict of interests

ATT is a member of Novartis Speakers' Bureau.

Authors' contributions

Study design: KMM, AB, ATT; data collection and assembly: KMM, RH, RR, SK; data analysis and interpretation: KMM, AB, WN, ATT; analysis review and

manuscript preparation: KMM, AB, RH, WN, ATT; final approval for submission: KMM, AB, RH, WN, RR, SK, ATT.

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