

SHORT COMMUNICATION

Etiology and treatment of ischaemic stroke in patients with β -thalassemia major

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Background and purpose: Although hypercoagulability-induced thromboembolism is generally accepted as cause of cerebral ischaemia in thalassaemic patients, cardiogenic embolism has been recently suggested as another possible stroke etiology.

Methods: We present four adult β -thalassemia major patients with manifest cardiac involvement who suffered territorial strokes.

Results: In the presence of siderotoxic cardiomyopathy and arrhythmia, we assumed cardiogenic embolism as etiology of stroke and initiated oral anticoagulation as preventive medication. Two of our patients were the first β -thalassemia major patients who underwent successful thrombolysis with rtPA.

Conclusions: Cardioembolism seems to be the cause of stroke in cases of β -thalassemia major. Thrombolysis can be applied in the setting of acute brain ischaemia in such high risk patients.

Introduction

Thalassemia is an inherited hemoglobinopathy caused by a deficient globin chain synthesis leading to hemolytic anemia. Regular blood transfusions and effective iron chelation regimes have significantly prolonged survival in homozygous carriers of β -globin defects, who develop β -thalassemia major (β -TM), thus allowing the manifestation of a wide spectrum of serious complications as more patients reach adulthood. Heart disease is the leading cause of death [1,2]. Chronic iron overload in β -TM causes toxic dilated cardiomyopathy, resulting in heart failure and arrhythmia, mostly atrial fibrillation (AF) [3,4]. The existence of a chronic hypercoagulable state is solidly established and considered as another important cause of morbidity and mortality because of thromboembolic complications that affect several organs including the brain [5,6]. Ischaemic stroke has been reported in 0.25–0.46% of patients with β -TM in different endemic countries and is considered as a rare complication [6–8].

Clinical cases

We report on four cases of hemispheric ischaemic strokes in patients with β -TM. All patients had manifest cardiac disease, either myocardial siderosis or arrhyth-

mia and signs of dilative cardiomyopathy. They were all on antiarrhythmic drugs, but no one received prophylactic anticoagulation. Details about patients' history, demographics, and other relevant findings are presented in Table 1 and Fig. 1.

A 32-year-old woman (patient 1) with known severe myocardial siderosis accompanied by permanent AF and dilative cardiomyopathy presented with a residual left-sided hemiparesis (modified Rankin Scale – mRS-score = 3) 3 months after suffering right middle cerebral artery (MCA) infarction. Within the preceding 4 months before ictus, she had presented transient episodes of aphasia and cortical blindness. Based on the history of transient ischaemic attacks in different arterial beds, the acute onset of a severe stroke syndrome, the typical territorial infarction, and the prominent cardiac involvement, we assumed cardioembolism as cause of stroke and initiated oral anticoagulation as secondary preventive medication. Under warfarin, the patient remains free of any cerebrovascular events for 2 years.

A 34-year-old man (patient 2) with also known siderotoxic dilative cardiomyopathy and paroxysmal AF suffered left hemispheric stroke because of a partial MCA infarction. He improved significantly and left hospital on clopidogrel (mRS-score = 1). Eight months later, the patient reported a short lasting episode of homonymous hemianopsia on the left, which suggested transient ischaemia in the right posterior cerebral artery territory. The occurrence of signs of acute ischaemia in different vascular territories at different time points in the presence of left atrial dilatation

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Table 1 Patients' history and relevant findings

	Patient 1	Patient 2	Patient 3	Patient 4
Basic Demographics				
Gender	Female	Male	Female	Male
Age	32	34	43	41
Disease-related history				
Splenectomy	Yes	Yes	Yes	Yes
Chelation therapy	Yes	Yes	Yes	Yes
Regular transfusions	Yes	Yes	Yes	Yes
Cardiac involvement				
Cardiac hemosiderosis ^a	Severe	Severe	No	Moderate
T2* (msec) ^a	18	3.3	30.0	16.4
R2* (/s) ^a	544.8	303.0	33.3	64.9
Atrial fibrillation	Permanent	Paroxysmal	Permanent	No
Other arrhythmia	No	No	No	Ventricular tachycardia
Left atrium diameter ^b	48 mm	40.5 mm	48 mm	52 mm
Ejection fraction ^b	50%	50%	60%	45%
Taken medication at stroke onset				
Antiarrhythmics	Verapamil, Propafenone	Amiodarone, Betaxolol	Amiodarone, Metoprolol	Digoxin
Antiplatelets	No	No	No	Aspirin
Anticoagulants	No	No	No	No

^aEstablished by means of cardiac MRI.

^bAssessed by transthoracic echocardiography.

and paroxysmal AF indicates again cardiogenic embolism as cause of stroke. Under oral anticoagulation, the patient remains now free of any cerebrovascular event for a year.

A 43-year-old woman (patient 3) with no cardiac siderosis but known permanent AF presented acute left-side hemiplegia. She was immediately transferred to our hospital where a NIHSS score of 13 was documented. A dense MCA sign on the right side was demonstrated on CT. Intravenous thrombolysis with alteplase was initiated 90 min after symptom onset. A territorial MCA infarction was finally visualized on MRI, whereas MCA recanalization was demonstrated by means of transcranial Doppler. She was discharged 12 days later after having regained independence (NIHSS-score = 3; mRS-score = 2). Based on the above-mentioned facts and the absence of any vascular lesions, we diagnosed cardioembolic stroke on the grounds of AF and initiated oral anticoagulation. Six months later, the patient remains free of any cerebrovascular events and shows a minimal residuum (mRS-score = 1).

A 41-year-old man (patient 4) with a similar disease history and moderate heart siderosis presented right-side hemiplegia and global aphasia while being hospitalized for an episode of ventricular tachycardia. A dense MCA sign on the left side was visualized on CT. He was then transferred to our stroke unit with a NIHSS score of 24. Thrombolytic treatment was initiated at the end of the 4.5-hour time window [9]. He improved significantly and regained mobility within a few days (NIHSS-score = 9; mRS-score = 3).

Discussion

This work adds to the limited series of reported stroke cases among patients with β -TM [6,7]. Moreover, it presents the first two cases of β -TM patients with acute ischaemic stroke who were treated successfully with intravenous thrombolysis within the established time window of 4.5 h [9].

In a recent study in the Mediterranean area, thrombotic events and ischaemic strokes have been reported in 0.9% and 0.25% of patients with β -TM, respectively [7]. In an Iranian study, stroke was documented in 0.46% [6]. It should be noted that four of these five patients suffered large hemispheric infarcts involving the cortex and that three of them had also AF and cardiomyopathy. This constellation strongly indicated an underlying cardioembolic mechanism rather than a hypercoagulability-associated etiology for these probably territorial infarcts and raised important questions regarding stroke pathogenesis and prevention among these high-risk patients [6,8]. The specific clinical and imaging findings, the cardiologic features, and the preventive effect of oral anticoagulation in our case series clearly support this hypothesis, which suggests cardiogenic embolism as cause of severe stroke in patients with β -TM and seriously question the etiopathogenic relevance of the permanent hypercoagulable state that characterizes all thalassemias [5,10]. While patients with β -TM seem to suffer large hemispheric territorial infarcts in the presence of AF and cardiomyopathy [6,7], patients with sickle β -thalassemia and

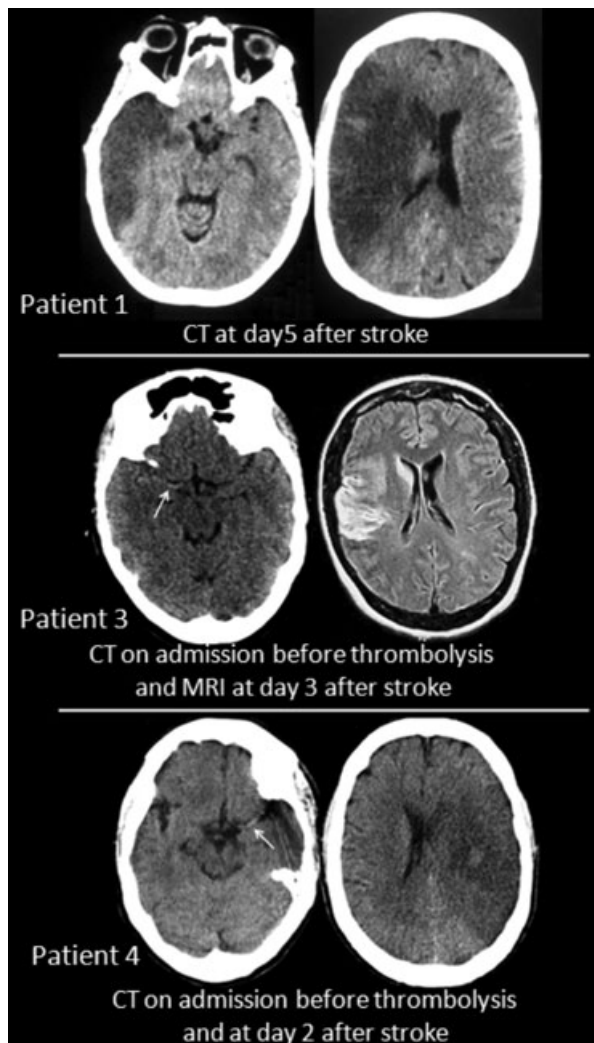


Figure 1 Admission CT scans reveal a dense MCA sign (arrows) indicative of an acute vessel occlusion in patients 3 and 4, whereas follow-up imaging studies demonstrate typical territorial infarcts indicative of an embolic stroke mechanism in all cases.

β -thalassemia intermedia present asymptomatic ischaemic lesions that are smaller and affect deeper structures while sparing the cortex [11–14]. These obvious differences indicate different pathogenetic mechanisms. Accordingly, β -TM patients with AF and dilative cardiomyopathy should be considered as being at higher risk. Preventive anticoagulation and extensive cardiologic evaluation at younger ages might be justified [4]. Finally, the multiple organ damage and morbidity of patients with β -TM should not prohibit the application of thrombolysis in cases of acute ischaemic stroke. However, owing to the fact that we did not demonstrate a definite cardiac source of embolism by

means of echocardiography, it should be acknowledged that our argumentation regarding stroke etiology remains assumptive, although it seems plausible and most likely to be true. Only prospective registries and large trials in patients with β -TM can provide solid evidence for the etiologic mechanism of stroke as well as the best diagnostic and therapeutic management of this highly sensitive and young population.

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