Research Papers

Arterial thrombosis in Hb E - beta thalassaemia intermedia patients at Yangon General Hospital

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Background

Thalassaemia intermedia (TI) patients are extremely diverse in phenotypic expression and there is a wide variation in clinical complications[1]. Thromboembolic events are among the clinical complications of TI that were found to occur at a higher rate than in patients with thalassaemia major (TM)[2, 3].

Hb E beta-thalassaemia disease is the commonest of the thalassaemia syndromes presenting with clinical symptoms of anaemia in Myanmar[4, 5].

The incidence of thromboembolic events in Myanmar Hb E beta - TI patients has never been reported.

Aims and Objectives

To find out the occurrence of arterial thrombosis in Myanmar Hb E - Beta TI patients and to study clinical and laboratory parameters of these patients in a single center - the Department of Clinical Haematology, Yangon General Hospital.

Method

The case records of the Department of Clinical Haematology, Yangon General Hospital (YGH) from January 2008 to December 2014 were retrospectively analyzed. The clinical and laboratory parameters of patients with arterial thrombosis were thoroughly reviewed.

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Results

Among two hundred and three Hb E - Beta thalassaemia intermedia patients admitted to the Department of Clinical Haematology, Yangon General Hospital (YGH) from January 2008 to December 2014, only four patients (1.97%) had arterial thrombosis.

Age at the time of arterial thrombosis ranged from 22 to 39 years (mean = 30 years). Three patients were male patients and only one patient was female, with male: female ratio of 3:1.

Below knee amputation was observed in two patients and above knee amputation was observed in another two patients. Among two patients who had above knee amputation, one was initially treated by below knee amputation followed by above knee amputation due to recurrence of arterial thrombosis in infected amputated stump. All patients were non-diabetics, non-alcoholics and non-smokers. No one had family history of hyperlipidaemia and peripheral vascular disease. No one had family history of arterial or venous thrombosis.

All four affected patients had non-transfusion-dependent thalassaemia (NTDT). Only one patient had past history of one unit packed cell transfusion before arterial thrombosis and other three patients had no transfusion before arterial thrombosis. All patients received perioperative blood transfusion variably from 2 to 22 units (mean = 8 units). None of the patients was splenectomised.

Haemoglobin phenotypes were AEF in three patients and EF in another one patient. Fetal haemoglobin quantification results were found in three patients only and ranged from 8 to 21.7% (mean = 16.57%). Baseline Hb at the time of arterial thrombosis ranged from 3.1 to 8.4 g/dl (mean = 6.075 g/dl) and all patients had low mean corpuscular volume (MCV) (range = 56.3 - 79 fL, mean = 65.25 fL), low mean corpuscular haemoglobin (MCH) (range = 16.8 - 24 pg, mean = 19.8 pg). Mean corpuscular haemoglobin concentration (MCHC) ranged from 27.2 g/dl to 35.6 g/dl (mean = 30.425 g/dl). Red blood cell count ranged from 1.84 to 4.19 x 10^3/μL (mean = 3.06 x 10^3/μL).

Reticulocyte count ranged from 0.0305 to 0.0661 x 10^6/μL (mean = 0.0538 x 10^6/μL), total white cell count from 7.37 to 24.6 x 10^3/μL (mean = 14.72 x 10^3/μL) and platelet from 75 to 542 x 10^3/μL (mean = 355 x 10^3/μL).

Serum ferritin level ranged from 1146 to 2000 ng/ml (mean = 1355.33 ng/ml). All had raised nucleated red cell on blood film and normal coagulation parameters.

All patients were negative for Hepatitis B, C and HIV serology. Thrombophilic screen results were not found in all four patients.

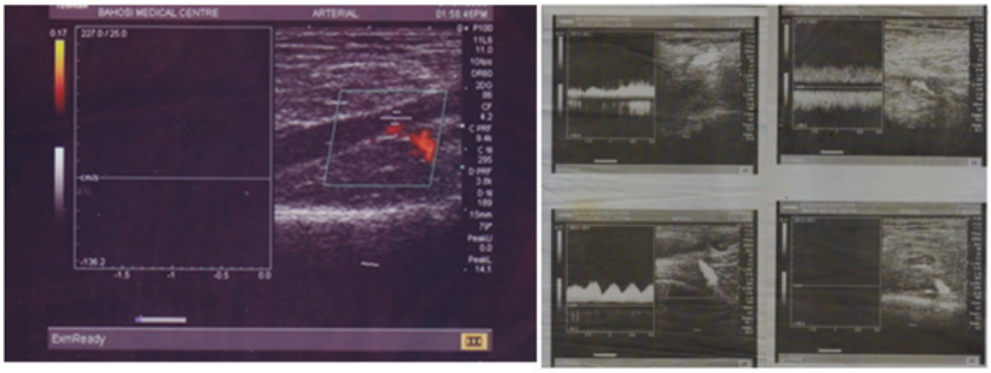

Figure (1) Doppler ultrasound scan showing thrombus in left femoral, popliteal and posterior tibial arteries

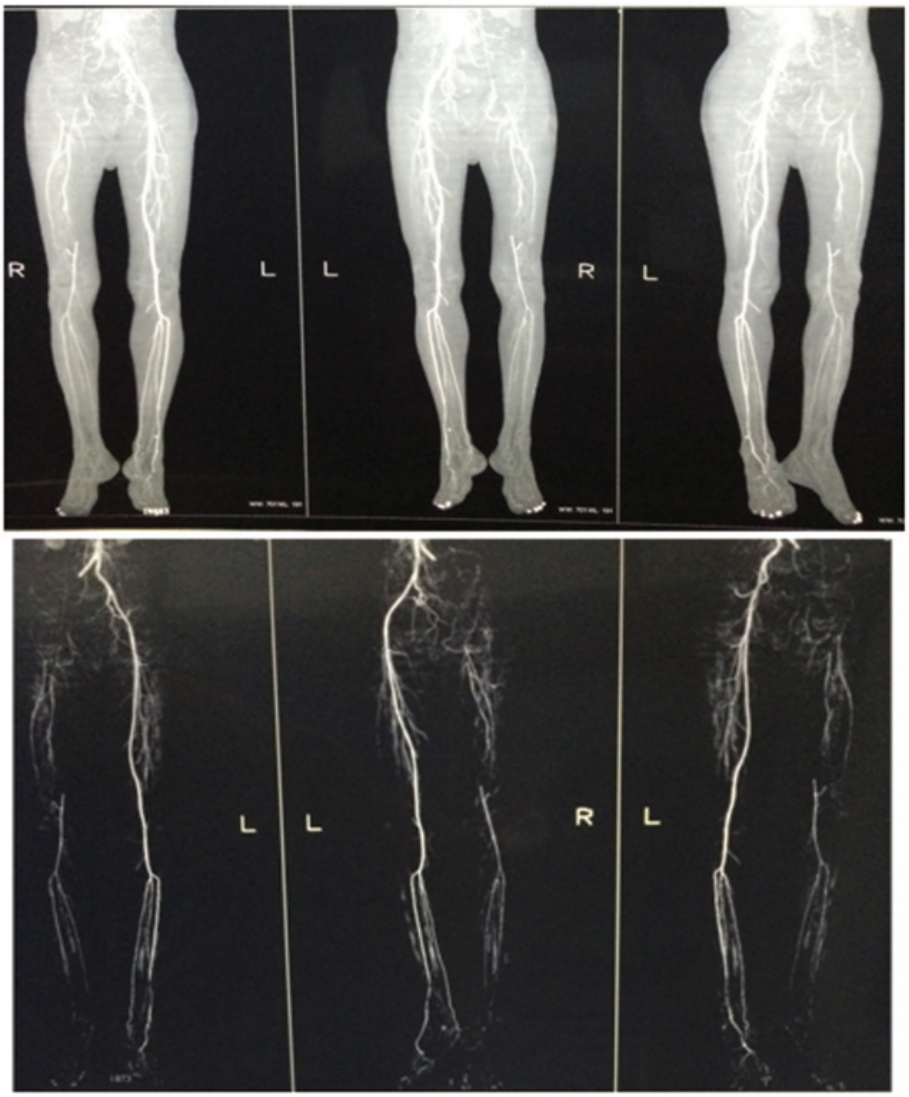

Figure (2) Computed tomography (CT) angiogram showing occlusion of right common iliac and femoral artery

Table (1) Clinical and laboratory parameters of HbE beta thalassaemia intermedia patients with arterial thrombosis

	Case 1	Case 2	Case 3	Case 4	Mean
Age (years)	33	22	39	26	30
Sex	M	M	M	F	
Past Transfusion	1	0	0	0	
Peri-op Transfusion	22	4	4	2	8
HB Phenotype	EF	AEF	AEF	AEF	
HB F (%)	20	8	NA	21.7	16.57
Hb (g/dl)	3.1	6	6.8	8.4	6.075
MCV	60.9	79	64.8	56.3	65.25
MCH	16.8	24	18.4	20	19.8
MCHC	27.2	30.5	28.4	35.6	30.425
RBC	1.84	2.51	3.69	4.19	3.0575
Retic Count (%)	1.66	2.5	1.62	1.64	1.855
Absolute Retic Count (x 10^6/μL)	0.0305	NA	0.0661	0.0649	0.0538
WBC (x 10^3/μL)	7.37	24.6	11.1	15.81	14.72
PLT (x 10^3/μL)	75	476	327	542	355
Ferritin (ng/ml)	1320	1600	2000	1146	1355.333

Discussion

A hypercoagulable state has been identified in NTDT patients, especially those with β-thalassemia syndromes[6-8]. The hypercoagulable state in patients with NTDT has been primarily attributed to abnormalities in platelets and pathological red blood cells. But other several factors are also believed to be involved. Patients with thalassaemia have activated platelet with increased platelet aggregation, and increased expression of activation markers (CD62P, CD63). Red blood cells have formation of reactive oxygen species, enhanced cohesiveness and enhanced aggregability which can be reduced to normal range after blood transfusion[9].

Inherited thrombophilic disorders have not been reported to play a role in the hypercoagulable state of NTDT[10], but low levels of anti-thrombin III, protein C and protein S have been documented[11]. The presence of hepatic or endocrine dysfunction in older patients with severe iron overload may also contribute to hypercoagulability[11].

Thrombosis, pulmonary hypertension, extra-medullary haematopoiesis, leg ulcers and cholelithiasis are specific complications more frequently seen in TI patients compared to TM patients[1].

The epidemiological data on overall frequency of thromboembolic event in patients with thalassaemia are relatively few[12]. In nine Italian pediatric thalassemia centers, 4% of the 683 patients with TM and 9.6% of the 52 patients with TI had experienced thromboembolic events[13]. The largest study conducted in Mediterranean area and Iran found that 1.65% of thalassaemia patients had thromboembolic events. Thromboembolism occurred 4.38 times more frequently in TI than TM ($P < 0.001$), with more venous events occurring in TI and more arterial events occurring in TM. Thrombosis in thalassaemia was also more common in females, splenectomized patients and those with haemoglobin < 9 g/dl. The authors also identified age above 20 years, splenectomy, family history of thromboembolic events and previous thromboembolic events as the main risk factors for developing thrombosis[3].

In the OPTIMAL CARE study which evaluated 584 patients with TI from six care centers (Lebanon, Italy, Iran, Egypt, United Arab Emirates and Oman), thrombosis was identified as the fifth most common complication, affecting 14% of the patient population. A higher risk of thromboembolic events was associated with age more than 35 years, splenectomy and serum ferritin level ≥ 1000 µg/l. Conversely, a positive history of transfusion and a hemoglobin level ≥ 90 g/l were found to be protective against thromboembolic events[1].

In this study, arterial thrombosis was observed in 1.97% of HbE - beta TI. All affected patients were age above 20 years, and male : female ratio was 3:1. All four patients had haemoglobin less than 9 g/dl. None of the patients with arterial thrombosis in this study had undergone splenectomy. All four patients had serum ferritin level ≥ 1000 µg/l. None of the patients had family history of thromboembolic events. One out of four patients had experienced recurrent thromboembolic events. All patients had non-transfusion-dependent thalassaemia (NTDT).

Blood transfusion, by reducing the number of pathological red blood cells with damaged membrane, may decrease the rate of thromboembolic events[14].

Conclusion

Arterial thrombosis is a rare, less-recognized, disabling complication in Myanmar non-transfusion-dependent HbE - beta TI patients. Although all four patients in this study were non-splenectomised patients, splenectomy which was proved as one of the main risk of developing thrombosis should be restricted to patient with massive splenomegaly and patients with hypersplenism. This is the first report of the occurrence of arterial thrombosis in Myanmar HbE - beta TI patients. Multicenter studies to detect the incidence of thromboembolic events in both TI and TM should be carried out.

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