

Case Report

Superior sagittal sinus thrombosis in a case of beta thalassaemia major

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Received: 13 February 2017

Accepted: 07 March 2017

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ABSTRACT

Patients with beta- thalassaemia major have a wide spectrum of clinical manifestations, from transfusion dependency to asymptomatic anaemia. Some may just have incidental finding of anaemia with splenomegaly during physical examination. Most of them require regular blood transfusion and their haemoglobin is maintained at an acceptable level. However they are at risk for multiple complications such as thrombo-embolic events which may be life threatening. We report here a case of beta- thalassaemia major complicated by cerebral sinus thrombosis, who had minimal clinical symptoms and signs at presentation. This case reiterates the importance of increased vigilance in the clinical management of this vulnerable group of patients.

Keywords: Beta thalassaemia major, Cerebral venous thrombosis, Headache, Hypercoagulability

INTRODUCTION

Patients with beta- thalassaemia major have a wide spectrum of clinical manifestations, from transfusion dependency to asymptomatic anaemia. Some may just have incidental finding of anaemia with splenomegaly during physical examination. Most of them require regular blood transfusion and their haemoglobin is maintained at an acceptable level. However they are at risk. However they are at risk of thrombo-embolic events which may be life threatening thrombo-embolic events which may be life threatening.^{1,2} We report here a case of beta- thalassaemia major complicated by cerebral sinus thrombosis, who had minimal clinical symptoms and signs at presentation. This case reiterates the importance of increased vigilance in the clinical management of this vulnerable group of patients.³

CASE REPORT

A 14-year-old female child was diagnosed to have beta-thalassaemia major disease at the age of 5. She presented with abdominal pain, pallor, jaundice and

hepatosplenomegaly. Investigations revealed anaemia. Haemoglobin level was 7.2 g/dl and there was hypochromia and microcytosis (MCV 72.8 fl). Haemoglobin electrophoresis confirmed beta-thalassaemia major. She underwent splenectomy at the age of 10 years. Her haemoglobin had been maintained at 9 to 10 g/dl without blood transfusion and her platelet count raised to around $700 \times 10^9/L$ after splenectomy.

At age of 14, she presented with headache for 4 days. The headache was described as constant tight feeling diffusely over bi-temporal region. It disturbed her sleep and she also developed vomiting. The headache was not relieved by simple analgesics. She could not recall any similar headache in the past. There was no history of trauma prior to this episode, nor family history of migraine. On examination, she was pale and jaundiced, but was fully alert and orientated. There were no focal neurological sign or evidence of meningism. Fundal examination was normal and examination of other systems was unremarkable. The results of investigations carried out on admission are shown in Table 1. Magnetic resonance venogram revealed absence of flow signal in bilateral

transverse sinuses and part of the superior sagittal sinus. These features were compatible with the diagnosis of venous thromboses (Figure 1).

Table 1: Laboratory investigations summary.

Complete blood picture	
Haemoglobin level	9.8 g/dL
MCV	84.7 fL
MCHC	30.8 g/dL
Coagulation profile	
Prothrombin time	13.1 sec
INR	2.36
Activated partial prothrombin time	47.7 sec
Biochemistry	
Sodium	132 mmol/l
Potassium	3.8 mmol/l
Urea	4.2 mmol/l
Creatinine	51 umol/l
Total protein	94 g/l
Albumin	45 g/l
Total bilirubin	113 umol/l
ALP	150 IU/l
ALT	64 IU/l



Figure 1: Magnetic resonance venogram (coronal view) showing absence of flow signal in bilateral transverse sinuses and part of the superior sagittal sinus.

The patient was started on low molecular weight heparin (LMWH) at 100 IU/kg every 12 hourly and warfarin 10 mg daily was added 4 days later. The dose was adjusted to keep the activated partial prothrombin time at 80-90

seconds. Warfarin was resumed at 5 mg daily 5 days after adequate heparinisation. Her symptoms began to subside. Heparin was tapered and then stopped. She was maintained on warfarin with a target INR between 1.5 to 2. Follow up magnetic resonance venogram on day 30 after the start of anticoagulation showed recannulation of bilateral temporal sinuses but the thrombi in the superior sagittal and straight sinus remained. After discharge, she remained clinically asymptomatic and examination did not reveal any neurological impairment. MRV performed at 6 months following the event showed persistent thrombosis of the above sinuses but without further progression.

DISCUSSION

Cerebral venous thrombosis in children is a serious but uncommon diagnosis. It has been reported after head and neck infection, trauma, severe dehydration, underlying prothrombotic state and in sick neonates. According to the Canadian Pediatric Stroke registry, the incidence of central venous sinus thrombosis was 0.67 per 100000 children per year.¹ It is well recognised that thalassaemia patients are prone to venous thromboembolism. According to an Italian multi-centre survey, 4% of thalassaemia major and 9.6% of thalassaemia intermedia of their study populations suffered from one or more episodes of venous thromboembolism.² Half of the thromboembolic events happened within the central nervous system.

Our patient's presentation is quite typical for central venous sinus thrombosis, with headache as the initial and only symptom. According to a Dutch series of 59 patients with cerebral venous sinus thrombosis, the most frequent symptom was headache (95%).⁵ It is usually of severe diffuse type in nature. It frequently precedes the development of other neurological symptoms.⁶ Focal seizures (with or without secondary generalisation), paresis (unilateral or bilateral) and papilloedema presented in 47%, 43% and 41% of patients respectively. Fifteen percent were comatose at presentation and thirty nine percent had impairment of conscious state. Severe alternation in consciousness level was a predictor for poor outcome.⁶ Another 20% presented with features of benign intracranial hypertension.

Much has been done to elucidate the mechanism for hypercoagulable state in thalassaemia, especially in those thalassaemia intermedia that does not require regular blood transfusion. Indeed, multiple mechanisms are involved. Eldor et al had published an excellent detail review and main points are summarised as follows.⁷

Abnormal platelet activation

There were various reports about evidences of platelet activation in thalassaemia patients. These included increased circulating platelet aggregates, shortened platelet lifespan associated with platelet consumption,

increased urinary thromboxane and prostaglandins metabolites, together with change of platelet morphology after splenectomy. All are suggestive of or leads to platelet activation. The increase in platelet count, however, may not contribute to the hypercoagulable state.⁸

Abnormal RBC morphology

The abnormal red blood cell is also a culprit for the hypercoagulable state. The usual membrane phospholipids distribution is disrupted due to the defective globin chain synthesis. Therefore, it may explain the enhanced RBC adherence to endothelial cells, thrombin generation and subsequent activation of platelets, monocytes, granulocytes and tissue factors. These are important members in pro-thrombotic cascade.

Cytokines profile

Alpha TNF and IL-1 beta are known pro-inflammatory cytokines.⁹ For alpha TNF, its thrombotic action is mediated through p55 receptor. Coupling of alpha TNF and p55 receptor leads to down regulation of thrombomodulin and then thrombomodulin-thrombin complex. The result is decreased protein C activation with an end result of a procoagulant state. Alpha TNF on the other hand up regulates tissue factors and so render endothelial surface prothrombotic. It also works with platelet activating factor (PAF) to exert angiogenic effect. IL-1 beta promotes neutrophil adhesion to endothelial surface while Alpha TNF promotes neutrophil degranulation. The anti-thrombotic properties of endothelial cells and mononuclear phagocytes are therefore modified on exposing to these cytokines. IL-6 acts as intermediate in endotoxin related coagulation cascade. In one Thai series, investigators measured various cytokine levels in beta thalassaemia/HbE individuals that were free from infections and had not received transfusion three months prior to measurement. They found that cytokine levels were raised in about 1/3 of patients while all controls had levels below upper limit by using conventional Elisa kits. By using hypersensitive kits, about 90% of patients had raised alpha TNF level and 50% had raised IL-1 beta.¹⁰

Treatment

It has been shown in adults that anticoagulation with heparin may reduce mortality for cerebral venous sinus thrombosis.¹¹ It is also an independent predictor for good cognitive outcome.³ Johnson reviewed 17 paediatric patients with sinovenous thrombosis and found that with various anticoagulant regimens (heparin followed by LMWH or warfarin, LMWH alone or with warfarin), about 60% of cases had complete clot resolution, while 35% had partial remission and 13% had static disease.¹² None of them had disease progression or recurrence. The advantage of LMWH includes a more predictable pharmacokinetics and requires less invasive

monitoring. Although both of them do not increase the risk of bleeding, it is not certain at this moment whether they are equally effective or which one is more effective. In our case indeed the thrombosis diminished on LMWH. Thrombolytic therapy with urokinase and rtPA either systemic or local are technically feasible. It is usually reserved for those severe diseases with high risk of heparin failure or those did not response to first line treatment.¹³

Implication

With the advance of medicine, we anticipate the prolonged survival of these patients and the complication of cerebral venous thrombosis may appear more frequently. Clinicians should be made aware of this complication during follow up. Smoking should be strongly discouraged as this will increase the risk for cerebro-vascular events. The patient should be warned against life styles that lead to development of diabetes mellitus or hypertension. We may need to advise female patient against the use of contraceptive pills. The need of prophylactic anti-coagulation during state of prolonged immobilisation or peri-operative period should be considered. The most important will be an enhanced vigilance towards the management of this group of patients.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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Cite this article as: Azad SM, Mukherjee A, Kapoor R, Bannerji R, Ray J. Superior sagittal sinus thrombosis in a case of beta thalassaemia major. *Int J Adv Med* 2017;4:585-8.