

CASE REPORT

CEREBRAL VENOUS SINUS THROMBOSIS IN SEVERE MALARIA

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Abstract. Cerebral venous sinus thrombosis has been reported to be associated with various systemic illnesses and infections, including severe malaria. We report here a 43 year-old Thai male presenting with fever and seizures. He was diagnosed as and treated for severe falciparum malaria. After gaining consciousness he developed focal neurological signs and evidence of increased intracranial pressure. Magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) of the brain revealed a mid-superior sagittal sinus thrombosis with venous infarction. Investigations for other infections and thrombophilia were negative. The patient denied anticoagulant treatment. The clinical status and radiologic findings improved gradually. Physicians who care for malaria patients need to be aware of this rare complication when a malaria patient presents with focal neurological signs.

INTRODUCTION

Malaria can cause various neurological symptoms. Malaria can cause not only cerebral malaria and seizures but can also present with rare manifestations, such as psychiatric symptoms, polyneuritis, Guillian-Barre syndrome and cerebral venous sinus thrombosis (Garg *et al*, 1999; Falchook *et al*, 2003; Krishnan *et al*, 2004; Idro *et al*, 2005). We report a case of cerebral venous sinus thrombosis in severe malaria patient.

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CASE REPORT

A 43 year-old Thai man, previously healthy presented with fever and nonspecific symptoms for 6 days. Two weeks prior, he travelled to and rafted in the jungle of Karnchanaburi Province, along the border between Thailand and Myanmar. He was admitted to a private hospital and subsequently referred to the Hospital for Tropical Diseases due to generalized seizures and coma [Glasgow Coma Scale (GCS) = 4]. The patients was comatose, not pale, but had moderate jaundice. His pupils were 2.5 mm diameter and reacted sluggishly to light bilaterally. There was no facial palsy, his reflexes were all 2+, he had a plantar response on Babinski, no neck stiffness and otherwise the exam was unremarkable. The blood smear revealed ring forms of falciparum

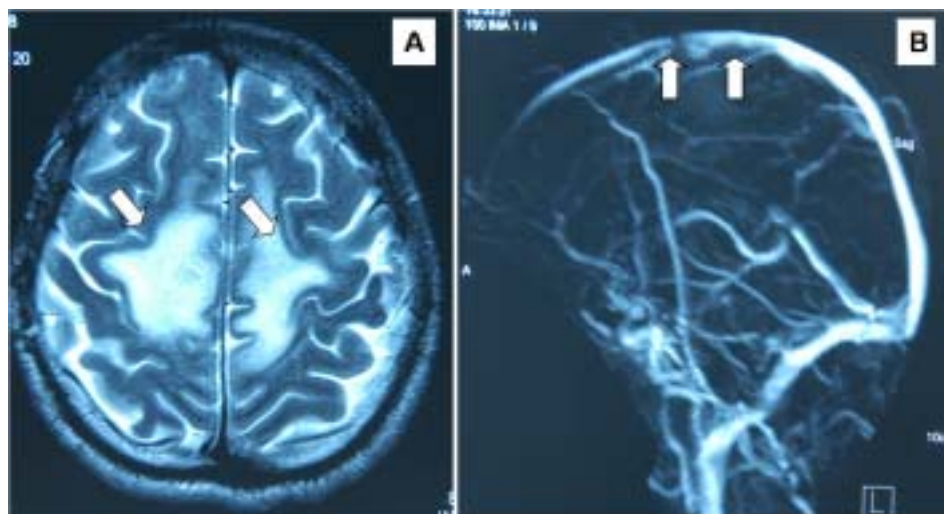


Fig 1–The first MRI/MRV of brain: (A) axial FLAIR MRI of brain reveals hyperdensity lesion in both parasagittal frontal area (arrows) suggesting cerebritis with venous infarction, (B) MRV demonstrates mild irregularity of the mid-superior sagittal sinus (arrow) and the left transverse sinus.

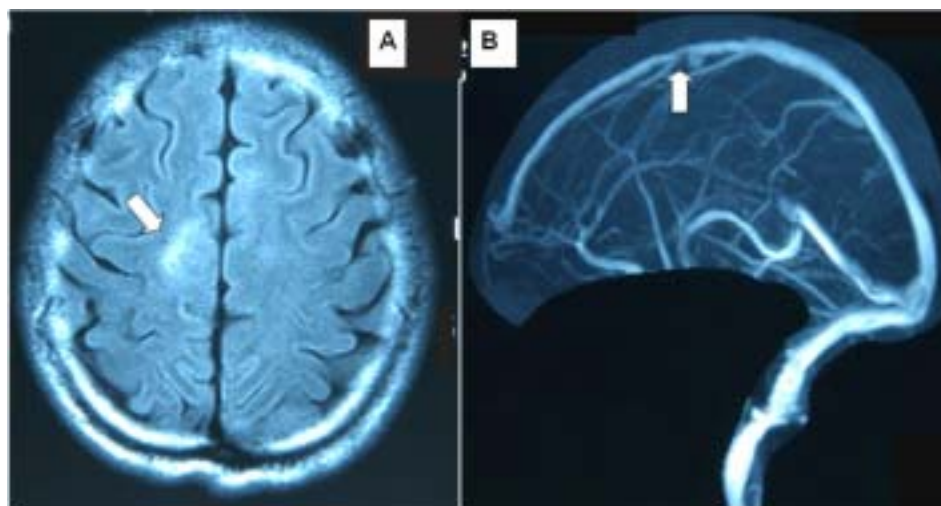


Fig 2–The second MRI/MRV of the brain one month after the first imaging: (A) axial FLAIR MRI of the brain shows reducing extension and degree of enhancement of previous subacute venous infarction involving bilateral superior frontal gyri more on the right side (arrow), suggestive of improvement. (B) MRV unchanged mild irregularity of the mid superior sagittal sinus with no definite filling defect.

malaria, with 8% red blood cells parasitized. Laboratory findings showed a hemoglobin of 12.5 g/dl, a white blood cell count of 13,900/ μ l (neutrophils 80%, lymphocytes 10%, monocytes 8%, eosinophils 1%, basophils 1%)

platelets 34,000 / μ l, a BUN of 29 mg/dl, a creatinine of 0.9 mg/dl, a blood sugar of 129 mg/dl, the electrolytes were normal, a total bilirubin of 26.3 mg/dl, a direct bilirubin of 18.5 mg/dl, an SGOT of 48 U/l, an SGPT

Table 1
Clinical and laboratory progression of patient.

	09/07/2008 (Admission)	16/07/2008 (Day 7)	22/08/2008 (Day13)	15/02/2009 (Month 5)	11/03/2009 (Month 9)
Consciousness and activity	Coma	Fully conscious, dependent	Minor handicap	Independent	Normal activity
GCS	4	15	15	15	15
EOM	-	80% bilateral lateral rectus palsy	Full	Full	Full
Muscle strength	-				
Right arm		III/V	V/V	V/V	V/V
Left arm		0/V	V/V	V/V	V/V
Right leg		0/V	IV/V	V/V	V/V
Left leg		0/V	III/V	IV/V	IV/V
Blood film for <i>P. falciparum</i>	8% parasitemia	negative	negative	-	-

GCS, Glasgow Coma Scale; EOM, extra ocular movements

of 46 U/l and an alkaline phosphatase of 91 U/l. Chest x-rays and urinalysis were normal. The hemoculture, leptospira antibody test, and immunofluorescens assays (IFA) for scrub typhus and murine typhus were all negative. An anti-HIV test was non-reactive.

He was initially diagnosed as having severe falciparum malaria (cerebral malaria and hyperparasitemia) and was treated with intravenous Artesunate 120 mg/day for 5 days, followed by Mefloquine 250 mg orally in 1 day. He developed acute renal failure (BUN 111 mg/dl, creatinine 8.1 mg/dl) and hemodialysis was initiated on Day 4 of admission. He gained consciousness and was extubated 1 week after admission but had headache and diplopia. On examination he had a high-grade fever, GSC =15, good consciousness, papilledema in both eyes, no nystagmus, no ocular dysmetria, bilateral lateral rectus palsy and could only move his right arm (motor strength III/V). Other findings were within normal limits. An MRI and MRV of the brain revealed focal cerebritis with venous infarction of both a parasagittal

frontal area and posterior left cerebellar hemisphere, mild irregularity of the mid-superior sagittal sinus and left transverse sinus consistent with venous sinus thrombosis (Fig 1). Investigations for other infections and thrombophilia (anti-thrombin III, protein C, protein S and serum homocysteine) were all negative. The patient refused anti-coagulant treatment. A corticosteroid and acetazolamide were not given in this case. The patient received only supportive treatment, hemodialysis, physical therapy, close observation and repeat imaging. An MRI/MRV one month later showed reduction of extension and degree of enhancement of the previous subacute venous infarction of the bilateral superior frontal gyri and unchanged mild irregularity of the mid superior sagittal sinus (Fig 2). He was clinically improving and could walk with support by 6 weeks (Table 1). His creatinine returned to normal by 2 months. At 9 months follow-up he had only mild weakness of the left leg (motor strength IV/V) and ataxia of the left side while walking. Other cerebellar signs

were normal. He returned to work as usual without cognitive impairment. The MRI/MRV showed no further changes.

DISCUSSION

Systemic or central nervous system (CNS) infections, are risk factors for cerebral venous sinus thrombosis (deVeber *et al*, 2001; Stam *et al*, 2005; Niyasom *et al*, 2006). Cerebral venous sinus thrombosis has been reported to be associated with severe falciparum malaria previously in three cases (Krishnan *et al*, 2004). Two of the three died and one had successful transcatheter thrombolytic therapy followed by oral anticoagulant treatment, who survived with mild deficits. Our patient had severe falciparum malaria complicated by cerebral venous sinus thrombosis, but recovered spontaneously without anticoagulant therapy.

The mechanism of thrombosis is still unclear and may be multifactorial (Krishnan *et al*, 2004). The hypotheses are hypercoagulable state activated by malarial infection and venous stasis due to increased intracranial pressure in cerebral malaria.

Altered phospholipid in malaria-infected red cells causes increased von Willebrand factor and other coagulation factors (Ghosh and Shetty, 2008). Endothelial damage by malaria-infected red cells also causes increasing tissue factor (Francischetti *et al*, 2007) and other cytokines, resulting in the hypercoagulable state of malaria infection.

Antithrombotic therapy and anticoagulant treatment in cerebral venous sinus thrombosis remain important issues and should be judged in the individual case. Randomized controlled trials demonstrated the benefit of anticoagulant treatment and are generally recommended for patients who have no other contraindications (Stam, 2005; Masuhr and Einhaupl, 2008). Some patients

in the control group had complete recovery (de Bruijn *et al*, 1999; Wasay and Kamal, 2008). Our case had recovery without anti-coagulant treatment.

No other risk factors for thrombosis, such as local or systemic infections other than malaria, drug or hereditary thrombophilia were found in our case. The patient improved after the malaria resolved so we hypothesize the severe malaria was associated with his cerebral venous sinus thrombosis.

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