

Acute disseminated encephalomyelitis after treatment of *Plasmodium vivax* malaria

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Key words Acute disseminated encephalomyelitis; malaria; MRI; *Plasmodium vivax*

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disease occurring 1–3 wk after viral infection or vaccination^{1,2}. Although most patients with ADEM make a full recovery, corticosteroids can be of help in severe cases. Generally, the diagnosis of ADEM is made by clinical history, neurological manifestations and magnetic resonance images (MRI) of the central nervous system. Neurological manifestations can occur both during and after malarial infection, particularly *Plasmodium falciparum* infection. These are infrequently encountered in *P. vivax* though post-malaria neurological syndrome (PMNS) has been reported from India³. ADEM has not been recognized as a common neurological complication of malaria. To the best of our knowledge only one case of ADEM following treatment of *P. vivax* malaria has been reported in literature⁴.

Case report

A female child aged 18 months, weighing 7.1 kg was admitted with history of high grade fever and convulsion for one day. Convulsion was generalized tonic, clonic in nature, lasted for about 10 min. On arrival to our institute, the temperature was 38.5°C, pulse rate was 130/min, respiratory rate was 30/min and blood pressure was 90/60 mm of Hg. Respiratory, cardiovascular and pre-abdominal examination was normal. On CNS examination, the child was irritable with hypertonia which was spastic in nature with more involvement of upper limb than lower limb and babinski's response. Laboratory investigations showed Hb 10.3 g/dl, white blood cells (WBC) $23 \times 10^3/\mu\text{l}$ and platelets $350 \times 10^3/\mu\text{l}$. Serum biochemistry including C-reactive protein and blood sugar was normal. Rapid malaria antigen test was positive for *P. vivax* and peripheral smear revealed ring form of *P. vivax* with >5% parasitemia. The cerebrospinal fluid (CSF) examination at that time was normal. Child was started on Injection Artesunate 2.4 mg/kg/dose repeated after 12 and 24 h as per guidelines of the National Vector Borne Disease Control Programme, India for treatment of severe malaria⁵. Child became afebrile after 24 h. Her neurological examination

was also normal. Repeat peripheral smear after 24 and 48 h was negative. Child was discharged on artesunate combination therapy (ACT) for 3 days. She was also advised to take primaquine 0.25 mg/kg/day for 14 days.

After 7 days child was readmitted with fever and loss of consciousness. Her Blantyre coma scale was 4 at that time. She was also having right sided hemiparesis. Her cranial nerve examination was found to be normal. Laboratory investigation showed mild anemia with Hb of 9.1 g/dl, and normal WBC and platelet counts. Peripheral smear was negative for malaria parasite on three occasions. Serum biochemistry including blood sugar and electrolytes were found to be normal. CSF examination showed pleocytosis (70 cells/ μl) with mild elevation of protein (50 mg/dl). CSF culture was sterile. Serology for herpes simplex, Japanese encephalitis, measles and mumps virus was found to be negative. Polymerase chain reaction (PCR) analysis of viral nucleic acid in CSF was not done as the facility for the same is not available at our centre. Acyclovir (10 mg/kg/dose 3 times per day) and broad spectrum antibiotics Ceftriaxone (100 mg/kg divided in 2 doses) was started keeping in view of the possibility of viral encephalitis or bacterial meningitis. Her consciousness level was deteriorated and Blantyre coma scale was 2 in spite of treatment. MRI brain was done after 72 h which showed diffuse white matter hyper-intensities on T2 weighed images, involving subcortical, deep and periventricular white matter and both external capsules (Fig. 1). She was diagnosed as ADEM after *P. vivax* malaria based on her clinical course, negative viral serology and MRI findings. She was given methyl prednisolone 30 mg/kg/day for 3 days which was tapered to oral prednisolone and stopped after 2 wk. Ceftriaxone and acyclovir was stopped after MRI report. She showed marked improvement after steroid, her consciousness level as well as hemiparesis were improved. Repeat MRI showed significant resolution of cortical and deep white matter signal abnormality (Fig. 2). At the time of discharge she was conscious, without any focal neurological deficit but unable to walk. After 6 months follow up child gradually started walking.

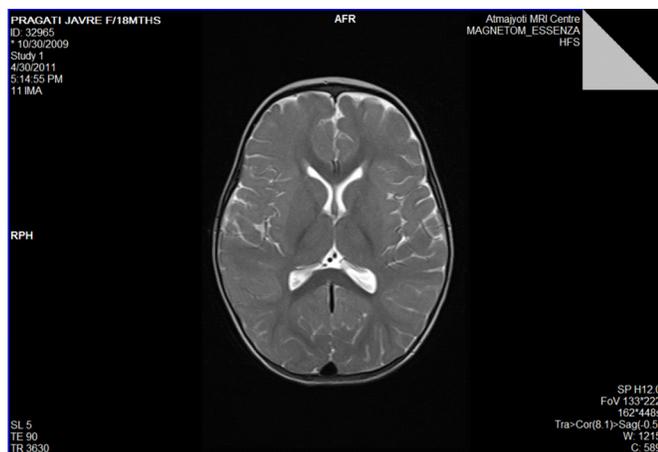


Fig. 1: T₂ weighed image showing bilateral symmetrical altered signal intensity involving subcortical white matter.

DISCUSSION

Severe and complicated malaria is usually caused by *P. falciparum* but it has been observed that *P. vivax* malaria can also lead to severe disease. The reported cerebral and non-cerebral complications included cerebral malaria, hepatic dysfunction, renal dysfunction, severe anaemia, ARDS, shock, pulmonary oedema, hemoglobinuria, and multiple organ involvement^{6–8}.

Because of negative peripheral smear and sterile CSF, initially, we suspected viral encephalitis in our patient. The neurological symptoms resolved so rapidly after giving steroid in our patient so diagnosis of viral encephalitis was very remote possibility. In ADEM patients, CSF protein is moderately elevated (50 to 150 mg/dl) and lymphocytic pleocytosis is generally present. MRI findings showed diffuse hyper-intensities involving subcortical white matter, corpus callosum and brain stem. The findings of these patient's CSF and MRI as well as clinical course were compatible with those of ADEM⁹. *Plasmodium vivax* infection seemed to be a direct cause of ADEM from the observed time course of her symptoms. Multiple sclerosis (MS) is difficult to differentiate from ADEM. But as per Pediatric MS Study Group child fits in ADEM as the disease was monophasic with clinical and MRI improvement on follow up.

ADEM can be regarded as a complication of severe malaria. Elevated level of neurotoxic cytokines in cerebrospinal fluid, tumour necrosis factor- α , interleukin 2 and 6 have been seen in a patient with severe malaria and PMNS¹⁰. The latency of neurological involvement after eradication of parasite and response to steroid treatment in our patient support an immunological mechanism.

“PMNS is defined as symptomatic malaria infection

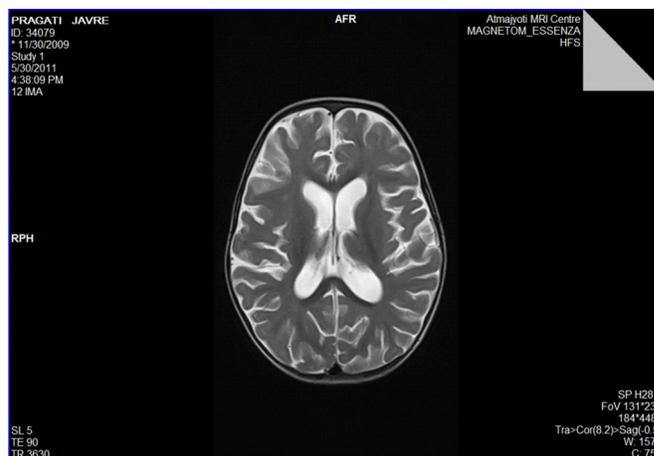


Fig. 2: T₂ weighed image showing significant resolution of cortical and deep white matter signal abnormality.

(initial blood smear positive for asexual forms of the parasite), whose parasites have cleared from the peripheral blood and, in cerebral cases, had recovered consciousness fully, who developed neurological or psychiatric symptoms within two months of acute illness”. It is, therefore, distinguished from cerebral malaria which occurs during parasitemia. Patients with PMNS exhibit impaired consciousness and multiple signs of cerebral involvement like impaired consciousness, confusion, generalized seizure, myoclonus, aphasia, tremor, and psychosis. PMNS is self-limited, lasting 2–14 days, and requires no specific treatment¹¹.

Several key features differentiate PMNS from delayed cerebellar ataxia (DCA). PMNS is preceded by severe malaria infection in most of the cases. Patients with PMNS have impaired consciousness and multiple signs of cerebral involvement, while patients with DCA are fully conscious and alert at onset. Nearly one-third of patients with DCA still had parasitemia at onset, while PMNS patients do not have parasitemia. Patients with PMNS rarely develop ataxia¹².

Some authors draw parallels between ADEM and PMNS². We also consider possibilities that ADEM following *Plasmodium* infection explains the pathogenesis of some cases of PMNS. We report a case of ADEM following *P. vivax* malaria. Further studies are required to identify these two diseases. This case highlights the importance that *P. vivax* malaria should be added to the list of infections able to precipitate ADEM.

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Received: 20 December 2011

Accepted in revised form: 17 April 2012

Acknowledgement

The Editor, the Editorial Board and the Editorial team of the *Journal of Vector Borne Diseases* thank all the authors, contributors, reviewers, and support staff for their constant support over the years in uplifting the journal and in achieving the **First Impact Factor of 1.177 for the Year 2011.**