Multiple Brain Haemorrhages in Falciparum Malaria

A Biswas*, PK Gangopadhyay**, D Guha***, T Roy****

Abstract
A young male with multiple intracerebral haemorrhages with presence of P. falciparum in peripheral smear and normal coagulation profile without features of encephalopathy managed successfully with antimalarial has been reported. The rarity of the clinical presentation has been highlighted and its possible pathogenesis discussed.

INTRODUCTION
Malarial infection of the central nervous system often leads to a severe neurological syndrome termed cerebral malaria. This is a rapidly fatal disease characterized by hemiplegia, aphasia, hemianopia, cerebellar ataxia, and other focal neurological sign. Cerebral malaria presenting as multiple intracerebral haemorrhages is an uncommon presentation. Here, we are reporting one such case in a young male patient from malaria endemic zone.

CASE REPORT
A 24 years old nonhypertensive male patient presented with high-grade remittent type of fever with chills and rigor, associated with severe holocranial headache, nausea and occasional vomiting for 3 weeks prior to hospitalization. There was no history of loss of consciousness, seizure or any other neurological symptom. He was admitted in a local hospital and treated with antibiotic (Ceftriaxone 2 gm IV OD), antimalarial (a course of Chloroquine) and cerebral anti-oedema measures for one week. His investigations performed at that hospital included a normal haemogram, negative Widal test, absence of malarial parasites in peripheral smear on repeated examinations, and normal blood biochemical parameters. A cranial CT scan (Fig. 1) showed multiple round increased attenuating lesions of varying sizes in both cerebral hemispheres mainly in white matter areas with perilesional oedema in few and without significant mass effect, suggesting petechial haemorrhages. Coagulation profile was performed to ascertain the cause. However, the bleeding time, clotting time, prothrombin time and platelet count were normal. He was referred to our hospital for further management.

On admission, the patient continued to have fever with severe headache associated with vomiting. However, he was fully conscious. His general physical examination was unremarkable except mild pallor. Systemic examination did not reveal any abnormality. His liver and spleen were not palpable on per abdominal examination. Nervous system examination revealed normal higher mental function, no cranial nerve deficit, and absence of meningeal sign, normal fundoscopic examination with no other neurodeficits.

His investigations were as follows: Hb - 11 gm/dl, TLC -
8700/cumm, with neutrophils 54%, lymphocyte 46%, and eosinophils 3%, peripheral smear drawn at the onset of fever revealed rings of *P. falciparum*. His blood sugar, renal function, liver function tests and urinalysis were within normal limit. We repeated the coagulation profile, which showed normal bleeding time, clotting time, prothrombin time, partial thromboplastin time, normal platelet count and platelet function. A repeat cranial CT scan showed resolved small areas of petechial hemorrhages with relatively larger areas of intracranial hemorrhage in right frontal, parietal, and parieto-occipital areas.

We treated the patient with Quinine 600 mg PO TID alongwith Doxycycline 100 mg PO BID for 7 days with other conservative measures. The patient responded well to the treatment and repeated attempt failed to demonstrate malarial parasite in peripheral smear. We discharged the patient with Primaquine 45 mg and he was followed up for next 2 months. A repeat CT scan done after 6 weeks did not reveal any abnormality. The MR angiogram had done at this time reveals normal cerebral vascular architecture.

**DISCUSSION**

Malarial infection of the central nervous system is an encephalopathy, which occurs in around 2% of patients infected with *P. falciparum* and characterized by unarousable coma. In patients with cerebral malaria (CM) loss of consciousness can develop very rapidly, most patients are already in deep coma by the time they reach to the hospital. Convulsions are frequent and are seen in 20 to 50% adult patients. It is much more common in children. Subtle or subclinical seizures detected with electroencephalography are also common in children. Localizing signs are infrequently observed. A variety of neuro-ophthalmological signs could be elicited. A disorder of conjugate gaze (internuclear ophthalmoplegia) is a common finding. The eyes are usually divergent with normal Doll’s eye movement. Ocular bobbing, horizontal and vertical nystagmus, sixth nerve palsy, and convergent spasm are infrequently seen. Papilloedema is rarely encountered. Retinal hemorrhages are also infrequently seen and are associated with poor prognosis. Corneal and conjunctival reflexes remain intact (may be absent in deep coma), the pupils are symmetrical and react normally to light stimulus. Motor system examination frequently reveals symmetrical upper motor neuron signs. The histological hallmark is widespread cerebral vasculopathy due to sequestration of parasitized erythrocytes in vascular endothelium with increase endothelial permeability, perivascular infiltrations and cerebral oedema. Other features include necrosis of vascular wall, petechial haemorrhages, ring haemorrhages, so-called “Drunk’s granuloma”, intravascular microthrombosis, perivascular demyelination and gliosis. This was termed by Poser in 1969 as “disseminated vasculomyelinopathy”. The petechial and ring haemorrhages in white matters result from the rupture of endarterioles proximal to the occlusive plugs of parasitized erythrocytes. The erythrocytes present in the ring haemorrhages remain unparasitized.

Immunohistochemical and electron microscopy studies have shown that widespread cerebral endothelial cell activation and morphological changes as well as endothelial cell damage and necrosis occur in cerebral malaria. The blockage of cerebral vessels due to attachment of infected red blood cells to endothelial cells through the knobs on RBC membrane is considered to be the major factor in the pathogenesis of cerebral malaria. The parasite derived proteins are present on the electron dense knob-like projections on the surface of parasitized erythrocytes and facilitate adherence of parasitized erythrocytes to brain capillary-venous endothelium through a ligand glycoprotein, for example, *P. falciparum* erythrocyte membrane protein (PFEMP)-1. In vitro parasitized erythrocytes bind to endothelial cells by specific receptor mediated interactions to host adhesion molecules such as “intercellular adhesion molecules” (ICAM-1) whose expression on cerebral endothelial cells is increased in cerebral malaria as part of systemic endothelial activation.

Agglutination of non-parasitized erythrocytes around red cells containing mature forms of parasite leads to rosette formation, which further aggravate the venular obstruction. The diffuse cerebral anoxia because of mechanical obstruction in microvascular blood flow is a possible cause of coma in CM. Induction of local neuroactive mediators such as nitric oxide and systemic cytokines like tumour necrosis factor (TNF) alpha has been considered to be responsible for rapidly reversible coma of cerebral malaria.

It has been argued that in endemic areas, a hyperergic state already exists because of recurrent infections. Thus when a fresh infection occurs, even of low grade, the burnt of the attack fall on the immunological pathway, which leads to vascular endothelial changes and an encephalopathy settles very rapidly.

Even though, some aspects of the pathogenesis have been explained, many things still remain obscure. The endothelial activation and consequent changes happen in all organs of the body. Nevertheless, in the absence of disseminated intravascular coagulopathy, petechial haemorrhages, and ‘ring haemorrhages’ are found exclusively in brain parenchyma. Recent attempts to study the pathogenesis in murine model might elucidate these unresolved issues.

Our patient presented with headache and vomiting at the spike of fever without loss of consciousness, seizure or any focal neuro-deficit for a long time, subsequently multiple petechial haemorrhages were detected in cranial CT and *P. falciparum* ring forms were demonstrated in peripheral smear. Patient did not have any feature of disseminated intravascular coagulopathy or any other organ dysfunction. Patient’s symptoms disappeared with proper antimalarial treatment and CT findings resolved gradually over time. The whole clinical profile suggested *P. falciparum* mediated vasculopathy as the cause of petechial haemorrhages. However, lack of features of encephalopathy and retained consciousness has made this case interesting. The use of chloroquine, probably had modified the clinical picture.
REFERENCES


---

Announcement

An International Update on Haematological Malignancy (Advances and gray zones), 21 - 22 January 2005, 9 am to 6.30 pm. S.P. Jain Auditorium, Bombay Hospital Institute of Medical Sciences, Marine Lines, Mumbai, India

International faculty : Dr. Eva Hellstrom-Lindberg, Sweden. Dr. Pierre Fenaux, France. Dr. Ghulam Mufti, UK. Dr. David Oscier, UK.

Registration fee : PG Students : Rs.300/-, Others : Rs.1000/-

To send registration fee by draft drawn in favour of “CME in Haematology-Bombay Hospital”

For details please contact : Prof. (Dr.) M.B. Agarwal, Programme Director, Haematology Centre, Vijay Sadan, 168-B, Dr. B. Ambedkar Road, Dadar TT, Mumbai - 400 014, India

Tel. 022-2411508; Cell : 098200-24850; Fax : 91-022-24140058; Email : mbagarwal@hotmail.com

---

Announcement

XX Annual Conference of Indian Rheumatology Association, Chennai, Tamilnadu, India.

to be held on November 26, 27 and 28, 2004

For further details contact : Dr. V. Krishnamurthy, Organising Secretary, New No.20, Old No.11, 4th Cross Street, Karpagam Gardens, Adyar, Chennai – 600 020 Tamil Nadu, India

Tel : 91-44-24469897; Mob: 98410 41717; Fax : 91-44-24469594;

Email : drvk1@vsnl.com/vk23@hotmail.com