

## CASE REPORT

# *Plasmodium vivax* Malaria Presenting with Multifocal Hemorrhagic Brain Infarcts in a School-going Child

by Santosh Kumar Rathia,<sup>1</sup> Jhuma Sankar,<sup>1</sup>  
Devasenathipathy Kandasamy,<sup>2</sup> and Rakesh Lodha<sup>1</sup>

<sup>1</sup>Department of Pediatrics, AIIMS, 110029 New Delhi, India

<sup>2</sup>Department of Radiology, AIIMS, 110029 New Delhi, India

Correspondence: Rakesh Lodha, Department of Pediatrics, Academic Block AIIMS, 110029 New Delhi, India. Tel: 01126593209.

E-mail: <rloodha1661@gmail.com>

### ABSTRACT

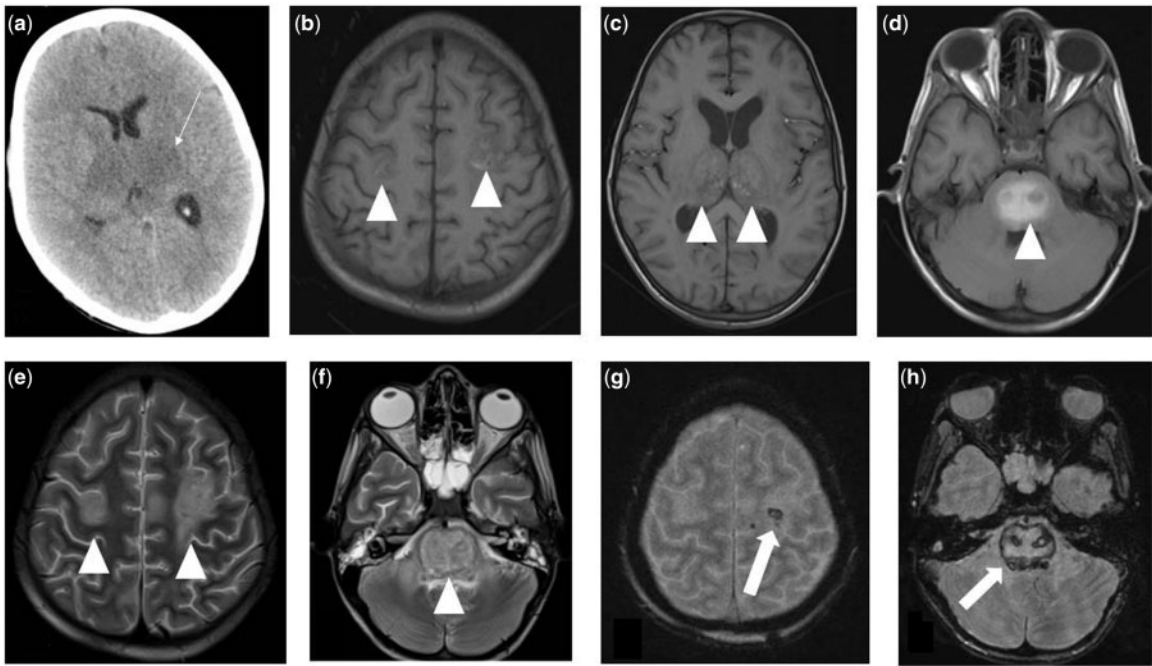
Cerebral malaria is a well-known complication of *Plasmodium falciparum* malaria. Over recent years, however, *Plasmodium vivax* also has been reported to cause cerebral malaria with or without coinfection with *P. falciparum*. Here, we report a boy aged 10 years presenting with acute febrile encephalopathy with raised intracranial pressure to the emergency, who was later diagnosed to have *P. vivax* malaria. His neurological status improved gradually during 6 weeks of pediatric intensive care unit stay. We report this case to highlight the unusual radiologic findings in the patient, such as multifocal hemorrhagic infarcts in the brainstem, bilateral thalami, frontal cortex and basal ganglia, which have not been reported with *P. vivax* malaria.

### INTRODUCTION

Malaria is still a global health problem. India accounts for 40% of all malaria cases with *Plasmodium vivax* infection, contributing to two-third of them. *Plasmodium vivax* is usually presumed to cause only uncomplicated malaria, but in the past few years, there have been several reports of complicated malaria, including cerebral malaria [1–5]. Here we report a case of cerebral malaria due to *P. vivax* in a boy aged 10 years. This case was unique radiologically, as the magnetic resonance imaging (MRI) showed multifocal hemorrhagic infarcts that have only been reported with *Plasmodium falciparum* till date.

### CASE REPORT

A 10 year old boy presented with fever with chills and rigors for 5 days duration, vomiting and multiple episodes of generalized tonic clonic seizures followed by altered sensorium since past 12 h with left nasal bleed since past 6 h. After being managed at three different hospitals, the child was brought to the pediatric emergency of our hospital. At admission, the child was comatose, having unequal sluggishly reacting pupils and jerky respiration with gasping efforts. He was intubated in view of low Glasgow Coma Score (E1V<sub>Tube</sub> M2) with poor breathing efforts and started on mechanical



**Fig. 1.** NCCT of head (A) shows subtle bilateral symmetrical hypodense areas involving thalamus (thin arrow) without any evidence of bleed. T1 weighted images (B–D) show bilateral symmetrical areas of hyperintensities involving frontal cortex, thalami and pons (arrow head). These areas are seen as hyperintensities (arrow head) on T2 weighted images (E and F). On SWI (G and H) these areas are showing profound hypointensity (blooming) (thick arrow) confirming the presence of bleed. These findings are suggestive of multifocal hemorrhagic infarcts involving cortex, thalamus, mid brain and pons. As illustrated here, the findings of hemorrhagic infarcts are much better seen on MRI than on CT.

ventilation. On examination, the child was afebrile with stable vital signs (heart rate—90 bpm, capillary refill time <2 s, blood pressure—92/54 mmHg and SpO<sub>2</sub>—98%) on mechanical ventilation. Neurologically, fundus examination was normal, corneal reflex and Doll's eye movement were absent, deep tendon reflexes were not elicitable with generalized hypotonia and plantars were extensor. Rest of the systemic examination revealed no abnormality except mild hepatomegaly. His left nasal passage was packed for epistaxis, but there was no evidence of bleeding from other sites and he had no pallor, petechiae or jaundice.

#### Investigations

The initial laboratory investigations showed hemoglobin of 11.9 g/dl, total leukocyte count of 10,600/mm<sup>3</sup> and thrombocytopenia with platelet count of 13,000/mm<sup>3</sup>. Quantitative Buffy Coat (QBC) for malarial parasite showed 200 copies/μl of *P. vivax*

(while both antigen/card test and QBC smear were negative for *P. falciparum*), and repeat smear examinations showed total clearance of parasite by the third day on antimalarial therapy. Other possible conditions such as dengue, herpes simplex virus (HSV) and Japanese encephalitis were ruled out by serology. During pediatric intensive care unit (PICU) stay, initial laboratory parameters were suggestive of severe malaria with anemia, thrombocytopenia and hepatic dysfunction (serum bilirubin = 0.3 mg/dl, total protein/albumin = 4.6/2.7 g/dl, aspartate aminotransferase/alanine aminotransferase = 878/480 IU/ml, Prothrombin time (PT) = 36.1 s Test (T)/11.6 s Control (C), International Normalised Ratio (INR) > 3). Non contrast computed tomography (NCCT) brain on first day showed bilateral hypodensities in midbrain, thalamus and basal ganglia without evidence of bleed or cerebral edema. MRI of brain with susceptibility weighted images (SWI) on Day 16 confirmed multifocal hemorrhagic

infarcts in bilateral thalami, frontal cortex, pons and midbrain (Fig. 1) in the same areas that were hypodense on initial CT scan.

### Course in hospital

The child was initially managed as a case of febrile encephalopathy. He was started on injections of Ceftriaxone, Vancomycin and Acyclovir to cover for viral and possible bacterial infections. He was also started on Artesunate (2.4 mg/kg/dose Intravenous (IV) 12 h for three doses, then once daily) and Clindamycin (10 mg/kg/dose IV 12 h) for 7 days in view of possibility of cerebral malaria, which was confirmed after Buffy Coat examination. On Day 3 of hospital stay, the patient developed features of raised Intra cranial pressure (ICP) in the form of worsening of sensorium with non-reacting pupils and papilloedema, and electroencephalogram revealed diffuse cerebral dysfunction. For these features, he was started on therapy for raised ICP. His hospital course was further complicated by ventilator-associated pneumonia and septic shock for which he was managed with supportive care. In the third week of PICU stay, the child underwent elective tracheostomy in anticipation of prolonged ventilatory support. He was subsequently weaned from ventilator over the next 2 weeks and showed some improvement in his neurologic status. He was finally shifted to the ward after 6 weeks of ICU stay with tracheostomy tube *in situ*, from where he was subsequently discharged. At discharge, he had some neurologic sequelae in the form of increased tone and minimal conscious state but was otherwise well preserved and parents were confident of managing him at home.

### DISCUSSION

Severe malaria if not adequately treated leads to multiple organ dysfunction affecting renal, hepatic, hematologic, neurologic and cardiovascular systems. Neurological manifestations occur in about 2% of all cases. A study by Kocher *et al.* [1] confirmed that *P. vivax* can cause both sequestration- and non-sequestration-related complications of malaria as seen with *P. falciparum* infection. In cerebral malaria, vascular sequestration of parasitized erythrocytes and functional blockade of the microcirculation lead to diffuse/bihemispheric dysfunction due to ischemia.

Cerebral malaria, which can occur in upto one-third of patients with severe malaria, is often reported with *P. falciparum* infection, but till date more and more cases are being reported with *P. vivax* infection too [1–5], and of all the cases of cerebral malaria due to *P. vivax* reported worldwide, about half have been reported in children [3]. Autopsy studies on cerebral malaria cases reveal variable histopathological changes, for example, cerebral edema with diffuse petechiae (ring hemorrhages mostly scattered around small vessels), parasitized Red blood cell (RBC's) occluding vessels and Durck granulomas (perivascular aggregates of RBCs, astrocytes and necrotic tissues) [6, 7]. The hemoglobin by-product, hemozoin, often discolors the brain surface [6]. Sequestration may lead to impaired perfusion and local release of inflammatory factors [8–10]. The systemic response to cytokine release can manifest with hyperpyrexia, seizures, hypoglycemia and even as multiorgan dysfunction (MODS). Bleeding risk with malaria-associated angiopathy and thrombocytopenia may be enhanced by platelet dysfunction, hepatic damage and resulting coagulopathy with MODS [9, 10].

In our patient with *P. vivax* malaria, MRI of brain with SWI confirmed multifocal hemorrhagic infarcts in bilateral thalami, brainstem and frontal cortex, in the same areas that were hypodense on CT scan. These findings were also consistent with MRI or CT findings previously reported, though mostly in cases of *P. falciparum* infection [4,11–13]. The major close clinico-radiological differentials for hemorrhagic encephalopathy that were ruled out by appropriate investigations were dengue, HSV encephalitis, Japanese B encephalitis and acute disseminated encephalomyelitis (ADEM) [4, 5].

Although central nervous system (CNS) imaging is infrequently obtained in malaria, variable MRI pictures have been described in literature and mostly with *P. falciparum* malaria. *Plasmodium vivax* mono infection is still under-reported because of cerebral malaria and even less with CNS imaging [3, 5]. Only few case reports earlier had shown MRI findings of focal edema or infarcts in cortex, thalami and pons in acute phase of cerebral malaria. Koch *et al.* [4] reported a case of acute psychosis occurring 2 weeks after successful therapy of *P. falciparum* malaria whose MRI revealed multiple hyperintensities on T2

weighted image (T2WI) suggestive of an immune-mediated ADEM. Potchen *et al.* [11] compared MRI findings of 152 children having cerebral malaria (with and without retinopathy) and reported more specific findings among retinopathy confirmed cases such as basal ganglia involvement, increased brain volume, diffuse cortical abnormalities, periventricular leucomalacia, thalamic and brain stem abnormalities, cerebellar and corpus callosal changes on T2/Diffusion weighted image (T2/DWI).

Usually the patients with cerebral malaria reveal cerebral microbleeds on histopathological analysis but lack findings on conventional MRI and CT. Recently, however, SWI, a novel in MRI, has been found to have high sensitivity to microbleeds, thereby improving the diagnostic accuracy of this finding [12, 13].

Through this report we would like to highlight the possibility of cerebral malaria with *P. vivax* mono-infection and also the superiority of MRI with susceptibility weighted imaging in detection of hemorrhagic infarcts, which were not seen on CT imaging. Ideally, PCR testing should be performed to rule out *P. falciparum* infection genotypically. This was not possible owing to logistic reasons in our case, although QBC and smear examination both obtained twice did not show *P. falciparum* species. Thus, though *P. vivax* is a rare cause of cerebral malaria in children as well as in adults, clinicians should be aware of its atypical imaging features, which may mimic a number of conditions so that patients can be treated at the earliest for better outcome.

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