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Case Report

Severe Malaria Due to Vivax: The Underestimated Culprit

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ABSTRACT

The World Health Organization's (WHO) Southeast Asia Region bears a significant burden of *Plasmodium vivax* (*P. vivax*) malaria, accounting for approximately 53% of the global total. Notably, India alone accounted for 47% of this burden in 2018. Historically, *P. vivax* has been regarded as a relatively benign species, typically causing mild, uncomplicated and self-limiting disease. *Plasmodium vivax* is known to cause relapsing malaria, but rarely causes severe malaria with cerebral involvement. Only a few cases of cerebral malaria due to *P. vivax* monoinfection have been reported in the literature. The parasite's preference for attacking reticulocytes in the blood results in lower parasitemia levels, making it potentially undetectable in blood smears and requiring high-level microscopic expertise for accurate diagnosis. It is essential to identify *P. vivax* infections accurately, as the treatment approach differs due to the higher relapse rate compared to *P. falciparum* infections. We report a rare case of cerebral malaria caused by mono-infection with *Plasmodium vivax* in a patient originally from northern India, now residing in rural Bangalore.

Keywords: *Plasmodium vivax*, Cerebral malaria, Severe malaria, Bangalore Rural.

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INTRODUCTION

According to the World Health Organization's (WHO) World Malaria Report 2021, India accounted for 1.7% of global malaria cases and 1.2% of global malaria deaths. Notably, within the WHO Southeast Asia Region, India contributed a significant 82.5% of malaria cases. Furthermore, India bears a substantial 47% of the global *Plasmodium vivax* malaria burden.[1]

Few studies conducted in Karnataka have reported the prevalence of *Plasmodium falciparum, P. vivax* and mixed infections to be approximately 50%, 40% and 10%, respectively.[2]

Traditionally, *Plasmodium vivax* was regarded as causing mild and uncomplicated illness; however, in recent years, there have been reports of severe malaria and cerebral malaria associated with both mono-infections and mixed infections.[3,4]

Cerebral malaria is a form of severe malaria, defined as an encephalopathy presenting with impaired consciousness, delirium and or seizures.[4]

Given the endemic nature of malaria in India, obtaining a travel history is crucial in patients presenting with acute febrile illness and encephalopathy, as it can help suspect malaria and guide timely diagnosis and treatment.

CASE REPORT

A 19-year-old male from northern India, with no prior medical conditions, was brought to the emergency department with a 3-day history of fever, headache, dizziness and lethargy, followed by reduced responsiveness for the past day. On examination, he presented with tachycardia, irritability and failure to obey commands. Additionally, neck stiffness was noted and his Glasgow Coma Scale (GCS) score was 9/15. His Random Blood Sugar (RBS) level at the time of examination was 98 mg/dL. The clinical findings suggested meningoencephalitis. Details regarding previous history of hospitalization, recent travel or similar complaints were unknown as the patient was brought to the hospital by a coworker and no family members could be contacted to provide additional information. A Non-Contrast Computed Tomography (NCCT) scan of the brain was performed and revealed normal findings. He was admitted to the Intensive Care Unit (ICU) and empirical antibiotic therapy was initiated, consisting of intravenous Ceftriaxone 2 g. Relevant investigations revealed elevated blood urea nitrogen and serum creatinine levels, indicating renal dysfunction, accompanied by metabolic acidosis. Additionally, liver function tests showed deranged results and a Complete Blood Count (CBC) revealed thrombocytopenia with a platelet count of 29,000/microL. Due to the low platelet count, Cerebrospinal Fluid (CSF) analysis was deferred to avoid the risk of bleeding complications. Given the presence of hepatorenal involvement and thrombocytopenia, a workup for potential infectious causes, including dengue, malaria, leptospirosis and rickettsial infection, was conducted. However, diagnostic tests for dengue, leptospirosis and rickettsial infection yielded

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negative results. The malaria card test yielded a positive result and a thin blood smear revealed numerous trophozoite forms of *Plasmodium vivax*. Consequently, treatment was initiated with intravenous doxycycline and Artemisinin based therapy, consisting of IV Artesunate at a dose of 2.4 mg/kg. Primaquine therapy was planned to be initiated after assessing the patient's Glucose-6-Phosphate Dehydrogenase (G6PD) levels.

By day 3 of Artesunate therapy, clinical improvement was observed, with noticeable enhancement in the patient's mental status, although laboratory abnormalities persisted. Despite our efforts to convince the patient and his attendants to continue treatment, the patient was discharged against medical advice and we were told he was taken to a hospital in his hometown.

Although the patient was lost to follow-up, we were able to observe significant clinical improvement after initiating Artesunate therapy, highlighting the importance of early diagnosis and timely treatment.

DISCUSSION

Although cerebral malaria is most frequently caused by *P. falciparum*, it should not be assumed to be solely due to *P. falciparum* or mixed infections, as mono-infections with *P. vivax* have also been reported to cause cerebral malaria.[2,4,5]

As mentioned earlier, our patient had a *P. vivax* mono-infection that led to severe malaria. According to the World Health Organization (WHO), severe malaria is defined by the presence of one or more of the following criteria: parasitemia (with no specified parasite density threshold for *P. vivax*), Acute Respiratory Distress Syndrome (ARDS), impaired consciousness (characterized by seizures or a Glasgow Coma Scale (GCS) score <11), multiple convulsions, shock, abnormal bleeding or coagulopathy, macroscopic hemoglobinuria, Acute Kidney Injury (AKI), jaundice, hyperlactataemia, acidosis, hypoglycemia and severe anemia (haemoglobin <5 g/dL).[6] Our patient met five of the above criteria and a definitive diagnosis of *Plasmodium vivax* malaria was made based on the thin blood smear examination, which revealed numerous trophozoite forms of *P. vivax*.

Individuals at risk for cerebral malaria include children, the elderly, pregnant women, those who have undergone splenectomy, malnourished patients and people with HIV-positive status. However, our patient did not possess any of these risk factors.

The pathogenesis of cerebral malaria is affected by the parasite and host responses which include Blood Brain Barrier (BBB) disruption, endothelial cell activation and apoptosis, nitric oxide bioavailability, platelet activation and apoptosis and neuroinflammation.[7]

The standard treatment for *P. vivax* malaria is chloroquine (25 mg/kg divided over 3 days) combined with primaquine (15 mg/day for 14 days or 30 mg/kg for 7 days). Additionally, artemisinin combination therapy has shown effectiveness against blood-stage parasites, particularly in severe cases of *P. vivax* malaria. The regimen including primaquine is crucial to prevent relapse, as it targets the hypnozoites present in the liver.[8] However, poor compliance is a concern due to the prolonged duration of primaquine therapy (14 days). Studies on a new 8-aminoquinoline anti-hypnozoite, single-dose tafenoquine (300 mg and 600 mg), showed recurrence-free rates of 89% and 92%, respectively. Using this new FDA-approved drug can improve adherence to therapy, but similar to primaquine, it requires pre-administration estimation of blood G6PD activity to prevent post-treatment hemolysis. Notably, primaquine can be administered with 30% G6PD activity, whereas tafenoquine requires at least 70% activity, which is a disadvantage. Currently, chloroquine is the only recommended partner drug for tafenoquine in treating *P. vivax* malaria.[9,10]

We observed symptomatic improvement in our patient on day 3 of Artemisinin-based therapy, consistent with other case reports that have documented clinical improvement within 36-72 hr after initiating antimalarial therapy.[3-5]

Chemoprophylaxis against *P. vivax*, comprising doxycycline or mefloquine, is recommended for travelers moving from non-endemic to endemic areas. However, in pregnant women with a previous history of exposure to *P. vivax*, chloroquine remains the only recommended chemoprophylactic agent.[10]

CONCLUSION

We conclude that *Plasmodium vivax* mono-infection can also be associated with cerebral malaria, a rare occurrence in rural Bangalore areas. However, this case may represent a relapse, as the patient originated from northern India, where *Plasmodium vivax* infection is more prevalent. Early diagnosis and complete treatment are crucial to prevent mortality in such cases.

PATIENT CONSENT

Not required, as patient details have been kept anonymous.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

WHO: World Health Organization; ***P. vivax*:** *Plasmodium vivax*; ***P. falciparum*:** *Plasmodium falciparum*; **NCCT:** Non-contrast computed tomography; **ICU:** Intensive Care Unit; **CBC:** Complete blood count; **CSF:** Cerebrospinal fluid; **G6PD:** Glucose-6-phosphate dehydrogenase; **ARDS:** Acute respiratory distress syndrome; **GCS:** Glasgow Coma Scale; **AKI:** Acute kidney injury; **BBB:** Blood brain barrier.

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