

Plasmodium vivax cerebral malaria - a rare cause of multi organ dysfunction

Abstract

Cerebral malaria is the most severe complication of *plasmodium falciparum* infection. It is a clinical syndrome characterized by unarousable coma at least one hour after termination of seizures and asexual forms of the parasite in peripheral blood smear with no other explainable causes of coma. Usually cerebral malaria is caused by *P. falciparum*, but rarely it is seen as a complication of *plasmodium vivax* infection. We report a case of cerebral malaria caused by *Plasmodium vivax* complicated by seizures and multiorgan dysfunction. It was successfully treated with parenteral artesunate, mechanical ventilation and other supportive without any sequelae.

Keywords: cerebral malaria, *plasmodium vivax*, multiorgan dysfunction

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Abbreviations: *Pfalciparum*, *Plasmodium Falciparum*; PRVC+PS, pressure regulated volume control pressure support; PEEP, positive end expiratory pressure

Introduction

Plasmodium falciparum infection is most commonly associated with severe malaria although in the past few years many cases of severe malaria are being reported due to infection with *plasmodium vivax*.¹ Classically malaria caused by *P. vivax* is considered as "benign tertian malariae" and usually follows a benign course with few complications. However recent studies and reports have revealed the dangerous potential of *P. vivax* to cause severe malaria including cerebral malaria, renal dysfunction, respiratory distress and bleeding abnormalities.² We report a case of severe malaria due to *P. vivax* infection that presented to us with features of cerebral malaria with multi organ dysfunction.

Case report

A 57 year old male patient businessman by profession presented to our hospital with complaints of fever since five days. Fever was intermittent in nature and was associated with chills and rigors. Fever was associated with abdominal pain, generalized weakness and yellowish discoloration of sclera since three days. On the day of presentation he had an episode of vomiting and was found in a state of altered sensorium since morning. He gave no history of cough, breathlessness, chest pain, burning micturition, seizures or loss of consciousness. He gives a past history of two episodes of fever which he developed while he was visiting Tanzania, Africa where he was diagnosed with malaria and the fever subsided on treatment. Drug details are not known. The last episode of fever was six months back. He was apparently normal following that episode until one week ago. He was recently detected with diabetes mellitus and was on oral hypoglycemic therapy. He had no other significant past medical or surgical history and gave no history of drug or other allergies or any previous blood transfusions.

On presentation to our hospital, he was found to be conscious but disoriented. He was febrile with a temperature of 39°C rising to 40°C in between and was associated with chills and rigors. There was no evening rise of temperature. His pulse rate was 107 per minute, regular and all peripheral pulses were equally felt. His blood

pressure recorded was 120/70mmHg. Patient was icteric though rest of his general examination was unremarkable. His chest was clear to auscultation, heart sounds were normal with no audible murmurs. His abdomen was soft with no palpable organomegaly or ascites. He was disoriented though there were no signs of focal neurological deficit or signs of meningeal irritation and pupils were bilaterally equal and reactive to light.

His initial lab investigations showed a hemoglobin of 9.1g/dl, total count 8,200cells/cumm with predominant neutrophilia. Thrombocytopenia was present with a platelet count of 60,000cells/cumm. Renal function tests were deranged with a blood urea of 190mg/dl, serum creatinine 6.2mg/dl. Liver function tests showed unconjugated hyperbilirubinemia (total bilirubin 7.4mg/dl, direct bilirubin 3.6mg/dl, albumin 3.2 g/dl, ALP 262 IU/L, SGOT 31U/L, SGPT 47U/L). Serum LDH was elevated with values of 644 U/L, serum amylase was 30 U/L and serum lipase was 11U/L. His initial blood sugars, serum electrolytes and coagulation profile were within normal limits. Tests for Dengue and Leptospira were found to be negative. Peripheral smear showed normocytic, normochromic anemia, thrombocytopenia and positive for trophozoites of *plasmodium vivax* malarial parasite. 2DEcho showed moderate LV systolic dysfunction with global hypokinesia and an EF 40% suggestive of myocarditis. Ultrasound abdomen and CT Brain were within normal limits.

He was admitted to the intensive care unit for the problems of cerebral dysfunction, acute kidney injury, unconjugated hyperbilirubinemia, thrombocytopenia and peripheral smear positive for *plasmodium vivax*. He was started on iv artesunate 120mg once daily dosing, oral chloroquine 600mg on the first 2 days and 300 mg on the third day and other supportive measures. Central venous catheterization was done and fluids were administered to maintain normal CVP with ultrasound guided evaluation. He had adequate urine output and hence renal dysfunction was managed conservatively with appropriate hydration. He developed a single episode of generalized tonic, clonic seizure the next day. The seizure lasted for a few minutes and was promptly terminated with iv lorazepam 2mg. Neurologist's opinion was sought and advice followed. He improved on antimalarials and supportive therapy. However after 3 days in the ICU he started developing tachypnea and was gradually desaturating. ABG showed poor oxygenation (pO₂ 50mmHg) with metabolic acidosis (plasma bicarbonate 13 mmol/L). Chest x-ray showed diffuse bilateral

infiltrates. He was initially managed on non invasive ventilation. But considering ARDS, worsening ABG and multi organ dysfunction he was electively intubated and ventilated. He was maintained on PRVC+PS mode with PEEP 6-8, PS above PEEP 12-14, PC 14, VT target 6ml/kg of predicted body weight. His total counts were increasing for which antibiotics were hiked up and meropenem and clarithromycin were added. He was also started on primaquine 15mg once daily. Blood sugars were constantly monitored and any rise in blood sugars were controlled with insulin. Inotropic/ vasopressor support was not needed for hemodynamic stability. Nutritional support was provided enterally through a Ryles tube and caloric intake was stepped up. Other supportive measures like chest physiotherapy, limb exercises, general nursing care of the patient were continued. He did not require platelet or PRBC transfusion. He gradually improved and after five days of elective ventilation his chest became clear, renal function (creatinine decreased to 2.9mg/dl from 6.2mg/dl) and liver function (total bilirubin decreased to 2.4mg/dl from 7.4mg/dl, enzymes normal limits) improved, total counts and platelet counts were normalised. He was slowly weaned off the ventilator and was extubated on the 6th day. Once his general condition improved he was shifted out of the Icu. He was discharged home 4 days later and was advised to continue primaquine 15mg OD for a total of 14 days and to review with the physician 2 weeks later.

Discussion

Cerebral malaria is the most severe complication of *plasmodium falciparum* infection. It is a clinical syndrome characterized by unarousable coma at least one hour after termination of seizures and asexual forms of the parasite in peripheral blood smear with no other explainable causes of coma. India accounts for nearly 40% of all malaria cases outside Africa and 60-70% of cases in India are due to *vivax* infection.³ Though *P.vivax* malaria follows an uncomplicated course there are recent reports of severe malaria caused by *P.vivax*.² The WHO has established clinical and laboratory criteria for severe *P. falciparum* malaria which includes cerebral malaria (decreased consciousness, seizures), respiratory distress (non cardiogenic pulmonary edema), prostration, circulatory collapse or shock, acute kidney injury, clinical jaundice, abnormal bleeding, hyperglycemia, metabolic acidosis, hyperlactatemia, hemoglobinuria and severe anemia. Severe *vivax* malaria may also present with such similar symptoms and may be fatal.

This patient had features of cerebral malaria with multi organ dysfunction in the form of renal impairment, liver dysfunction and respiratory dysfunction. Cerebral malaria is the most severe neurological complication of malaria and presents as a syndrome of decreased consciousness, repeated seizures and coma.⁴ Focal neurological signs are not seen and meningeal irritation is unusual. It is thought to occur due to sequestration of infected erythrocytes in cerebral microvessels accompanied by perivascular leucocyte infiltrates, platelet thrombin deposition and activation of inflammatory cytokines. Neural injury is more with hypoglycemia and increased ICP. It is characterized by a diffuse symmetric encephalopathy. It occurs more commonly in children and are also associated with neurological sequelae in children. Early treatment causes early restoration of cerebral blood flow and recovery of neurological function. Neurological dysfunction makes patients prone to hypoxia, hypoventilation and aspiration.

Renal dysfunction manifests as acute tubular necrosis and is more common in adults. Sequestration of erythrocytes in the renal microvasculature is thought to be the cause and it resolves rapidly.

Starting renal replacement therapy early improves the chances of survival, though most cases respond adequately to conservative management. This patient did not require hemodialysis and serum creatinine levels returned to normal after 9 days.

Pulmonary manifestations occur late during the course of the disease sometimes even after patient seems to be recovering on antimalarial therapy. It usually occurs after other features of severe disease have manifested. It is believed that *P.vivax* undergoes cyto adherence to lung endothelial cells and gets sequestered in the pulmonary microvasculature.⁵ It increases capillary permeability leading to pulmonary edema, lung injury, respiratory distress and ARDS. Recovery is fast with institution of supportive ventilation. Our patient showed initial improvement with antimalarial therapy and developed respiratory distress after 3 days. This shows that patients need to be monitored carefully even if there are signs of initial improvement. Low tidal volume ventilation strategy was used in this patient to limit lung injury.

Daily ABGs, constant monitoring of oxygen saturation are equally important in early detection of severe acidosis, hypoxia, hyperlactatemia which are all poor prognostic indicators. Iv antimalarials must be started in severe malaria as early as possible. The WHO recommends IV artesunate 2.4mg/kg/dose stat iv followed by 2.4mg/kg at 12 and 24 hours and then daily if necessary as the drug of choice for severe malarial cases.⁶ It must be followed by full course of artemisinin combination therapy for 3 days to prevent the risks of relapse and resistance to artemisinin derivatives. It is more effective than quinine and without serious adverse effects. Quinine can also be given at a dose of 10mg/kg infused over 4 hrs. However side effects are more common.⁷

Conclusion

This case report highlights the severity of *P.vivax* infection. Although known to infrequently cause multi organ dysfunction and respiratory distress intensivists must be vigilant of such rare causes of multi organ dysfunction. Prompt recognition and institution of supportive therapy and early antimalarial therapy will increase the survival rates by many folds with minimum sequelae.

Future prospects

A poor understanding of the pathogenesis is a hindrance to research in cerebral malaria. Functional MRI to describe neural activity in coma and proton MR spectroscopy to measure levels of substrate and metabolites could be seen as future prospects.

Conflicts of Interest

The authors do not have any Conflict of interests.

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