

# Opsoclonus-myoclonus in *Falciparum malaria* infection

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## ABSTRACT

Involvement of the central nervous system in malaria is exclusively a feature of infection with *Plasmodium falciparum*. Neurological manifestations such as altered mentation, seizure, coma, extra pyramidal symptoms, peripheral neuropathy and neuropsychiatric illnesses have been reported in *Falciparum malaria* (*F. malaria*). We report a case of transient opsoclonus-myoclonus in a 40-year-old lady with *F. malaria*, a clinical entity described only once previously (opsoclonus) in the medical literature. The patient improved following anti-malarial therapy.

**Keywords:** *Falciparum malaria*, opsoclonus–myoclonus syndrome, cerebral malaria, cytoadherence

## INTRODUCTION

Many neurological manifestations have been described in *Falciparum malaria* (*F. malaria*) in the literature.<sup>1</sup> Cerebral malaria is one such commonly described entity. However other neurological manifestations including neuropsychiatric manifestations, extra-pyramidal syndrome and post malaria neurologic syndrome (PMNS) have also been reported. Some of the pathogenesis or mechanisms have yet to be fully understood. We report the case of a 40-year-old lady who presented with opsoclonus myoclonus as a rare manifestation of *F. malaria* and recovered well with anti-malarial therapy.

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## CASE REPORT

A previously well 40-year-old housewife from an urban area of Bangalore presented with fever and chills of seven days duration associated with diffuse abdominal discomfort and vomiting of two days duration. She had no significant past medical history. There had been no exposure to drugs, toxins or infectious contacts.

On physical examination, she was mildly tachycardic with a pulse rate of 104; blood pressure of 100/60 mmHg. Pallor and mild splenomegaly were present. She was afebrile and anicteric at the time of presentation. Neurological examination was remarkable for chaotic conjugate eye movements consistent with opsoclonus and presence of myoclonic jerks in the face, upper and lower limbs bilaterally. There were no cranial nerve pal-

sies, focal motor weakness, cerebellar signs or signs of meningeal irritation. Breast, gynaecological examination and the rest of the other systems were clinically normal.

Investigations revealed a haemoglobin level of 8.9g/dL (Normal: 12-15g/dl) and platelet count of 24,000 cells/mm<sup>3</sup> (1,50,000–4,00,000 cells/mm<sup>3</sup>). Liver function tests revealed a total bilirubin of 3.7mg/dl (up to 1 mg/dl), direct bilirubin of 2.7mg/dl (up to 0.2mg/dl), aspartate aminotransferase (AST) of 62 U/L (<37 U/L) and alanine aminotransferase (ALT) of 55U/L (<41 U/L). Serum creatinine was 2mg/dL (0.7–1.2mg/dl). The coagulation parameters were normal. Chest radiograph was normal. Serology for typhoid, dengue, leptospira and *Epstein-Barr virus* were negative. Peripheral blood smear was positive for ring forms and gametocytes (Figure 1) of *Plasmodium falciparum*. Cerebrospinal fluid (CSF) analysis showed two cells - all lymphocytes, protein of 27 mg/dl (15-45mg/dl) and glucose of 67 mg/dl (40-70mg/dl). A magnetic resonance imaging (MRI) of the brain (done to rule out posterior fossa lesions) was normal. Serum alfa-feto

protein (AFP) was within normal limits (less than 10 microgram/L) and toxicology screen was negative. Anti-Ri and anti-Hu antibodies were negative.

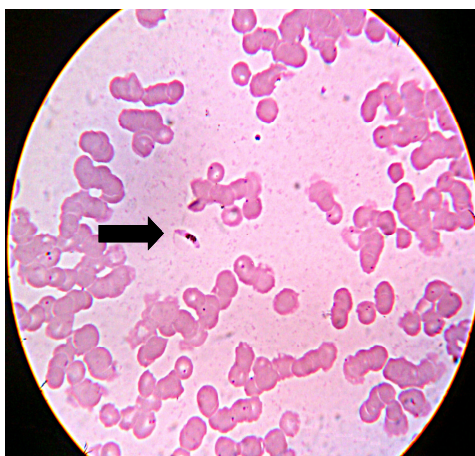
The patient was started on intravenous artesunate 4mg/kg per day for three days along with oral mefloquine 25 mg/kg as part of the hospital protocol for complicated malaria. Opsoclonus and myoclonus were managed with clonazepam with reduction of the amplitude of oscillations. The patient was discharged after 10 days of hospitalisation with full clinical and biochemical recovery. There was no opsoclonus or myoclonus at discharge.

## DISCUSSION

Of the known species of plasmodia causing human infections *Plasmodium falciparum* is implicated in most cases of severe malaria including those with neurological manifestations. Cerebral malaria is one of the most ominous presentations associated with a mortality of over 20%.<sup>1</sup>

The pathogenesis of neurological manifestations is multifactorial. Sequestration of infected erythrocytes in the cerebral capillaries or venules which allow the plasmodium to evade the host defense mechanisms and proliferate in a relatively hypoxic environment.<sup>2</sup> Adhesion of infected erythrocytes to endothelium of capillaries or venules, termed cytoadherence which occurs via the parasite ligand - P falciparum erythrocyte membrane protein-1 (PfEMP-1) and the endothelial receptors, CD36, E-selectin and Chondroitin sulphate.<sup>3</sup>

Increased circulatory cytokines, levels



**Fig. 1: Peripheral blood smear showing gametocytes of *Plasmodium falciparum* (arrow) (Giemsa stain, oil immersion, magnification x1000).**

of nitric oxide and impairment in the blood brain barrier system contribute to the neurological outcomes.<sup>4</sup>

Central nervous system (CNS) involvement in malaria can manifest in several ways of which the following have been described especially in children and non-immune adults- Cerebral malaria, defined by the World Health Organisation (WHO), as unarousable coma and the presence of asexual *Plasmodium falciparum* in blood film, with a Glasgow Coma Score of less than nine (<9), seizures, usually of the generalised tonic-clonic variety, psychiatric manifestations including psychosis, hallucinations, schizophrenia, delusions<sup>5</sup> and malarial retinopathy.<sup>6</sup> Neurological sequelae in malaria, although more common in children, are seen in <3% of adults, manifesting as hemiparesis, cranial nerve palsies, seizures and cortical blindness (Table 1).

Many such neurological sequelae categorised as post-malaria neurologic syndrome (PMNS) with ocular manifestations have been reported. One report described two cases (72-year-old female and a 20-year-old male respectively) with cerebellar ataxia and ocular flutter. Both patients responded to prednisolone.<sup>7</sup> Brain CT scans were normal in both cases. Another report described a 61-year-old man with encephalopathy (delirium), cerebellar ataxia and ophthalmoparesis.<sup>8</sup> MRI of the brain in this particular case showed extensive multi focal white matter abnormalities. This patient was treated with high-dose methylprednisolone with complete resolution of the neurological deficits. There were minimal residual lesions after nine months.

Opsoclonus is defined as a chaotic,

**Table 1: Reported neurological manifestations of *Falciparum malaria*.**

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- Cerebral malaria
  - Seizures
  - Cerebellar ataxia
  - Psychiatric manifestations including psychosis, hallucinations, schizophrenia, delusions
  - Malarial retinopathy
  - Hemiparesis
  - Cranial nerve palsies
  - Cortical blindness
  - Encephalopathy
  - Ocular paresis, ophthalmoplegia, opsoclonus
  - Post malaria neurologic syndrome (PMNS)
  - Opsoclonus – Myoclonus syndrome
- 

conjugate, multi-vector, back-to-back, saccadic eye movement without intersaccadic latency. Although the exact pathophysiology of opsoclonus remains unclear, findings of recent pathological and functional MRI studies have suggested that dis-inhibition of the fastigial nucleus of the cerebellum is involved. Opsoclonus myoclonus syndrome has also been described in encephalitis caused by *Epstein-Barr* virus, *Coxsackie* virus, enterovirus and varicella infections<sup>9, 10</sup>, Lyme's disease<sup>11</sup>, in association with certain neoplasms (notably, neuroblastoma in children and gynecological cancers in adults), and certain toxins (including organophosphates).

A case of post malarial opsoclonus-myoclonus-ataxia syndrome has been described in the paediatric age group.<sup>12</sup> The clinical syndrome of opsoclonus in malaria in adult has only been described once previously.<sup>13</sup> The case was a 24-year-old woman who presented with a two-week history of high-grade fever and lassitude. Blood smear showed ring forms of *P. falciparum*. The

patient developed opsoclonus and hand tremor on the day following therapy with quinine and tetracycline, which showed partial response to therapy. At discharge three weeks later, she had minimal opsoclonus.

Various therapies that have been tried with some success for opsoclonus–myoclonus are corticosteroids, intravenous immunoglobulins, immuno-suppressants, plasmapheresis, rituximab, clonazepam, baclofen, adrenocorticotrophic hormone (ACTH), valproate and 5-hydroxytryptophan.<sup>10</sup> Our patient responded well to clonazepam.

Artemisinin combination therapy is indicated as the first line treatment in endemic areas and our patient was treated with par-enteral artesunate 4mg/kg per day for three days in combination with oral mefloquine 25mg base/kg. Steroid was not used in our case.

In conclusion, our case is probably the first report of an adult patient with reversible opsoclonus–myoclonus syndrome that occurred during the acute phase of *F. malaria* infection. This responded to artemisinin combined with mefloquine and clonazepam. Opsoclonus-myoclonus syndrome should be included in the list of neurological manifestations of *F. malaria*.

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