Postmalaria Neurological Syndrome: Two Cases from The Gambia

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We describe 2 patients with severe Plasmodium falciparum malaria whose convalescence was complicated by fever, with acute confusion and acalculia in one patient and a triad of myoclonus, tremor, and dysphasia in the other. Inflammatory changes were found in cerebrospinal fluid samples. Postmalaria neurological syndrome was diagnosed in each patient, and a therapeutic response to oral corticosteroids was seen in the second patient.

The 2 British, white adults described in the present report did not take antimalarial prophylaxis during vacations in The Gambia, West Africa, and both developed severe malaria after returning to the United Kingdom. Their clinical course was biphasic: after recovery from the initial parasitic illness and associated acute complications, they both developed recurrent fever accompanied by encephalopathy (figure 1). Herein we report the investigation and outcome of this late complication of Plasmodium falciparum malaria.

Patient A. Twenty-three days after returning from The Gambia, a previously healthy 44-year-old man was admitted to the Hospital for Tropical Diseases, London, with a 4-day history of febrile illness. P. falciparum malaria was diagnosed on the basis of blood-film examination; the initial level of parasitemia was 32% of RBCs. Acute complications included hemolysis, profound thrombocytopenia, mild coagulopathy, and malaria-induced hepatitis. Patient A was treated in the intensive care unit with intravenous quinine, a 6-unit exchange blood transfusion, and supportive measures. His clinical course was also complicated by adult respiratory distress syndrome (ARDS), for which he required mechanical ventilation from days 3 through 12. Furthermore, the development of acute renal failure necessitated hemofiltration from days 3 through 12. The parasitemia decreased rapidly, however, and had cleared by day 6, when the patient was treated with a single dose of sulfadoxine and pyrimethamine. From day 12 onward, the patient was independent of both respiratory and renal support and remained afebrile until discharged from the hospital on day 19.

One day after returning home, however, the patient developed incoherent speech and markedly disturbed and uncooperative behavior. He was readmitted to the hospital on day 22. On examination, the patient had a temperature of 37.8°C but no clinically detectable focus of infection, no meningism, and no abnormal neurological findings other than acute confusion and a Glasgow coma score of 12/15. Blood glucose, pH, and arterial blood gas measurements were normal. CT and gadolinium-enhanced T1- and T2-weighted MRI scans of the brain were also normal. Analysis of a CSF sample obtained by lumbar puncture revealed a clear and colorless fluid with 4 lymphocytes/mm³, a normal glucose concentration, and an elevated protein concentration of 0.89 g/L (normal range, 0.2–0.4 g/L). The patient was treated empirically with intravenous cefotaxime and aciclovir while additional test results were pending.

Subsequent investigations for viral, bacterial, and fungal infections in the patient’s CSF all had negative results; however, these tests included bacterial and viral cultures, PCR analysis for herpesviruses and Mycobacterium tuberculosis, and an assay of the cryptococcal antigen concentration. Results of blood-film examinations for malarial parasites and trypanosomes were negative. Despite a persistent low-grade fever (temperature range, 37.2°C–38.2°C), the patient did not develop a peripheral blood inflammatory response; the serum C-reactive protein (CRP) concentration remained <2.0 mg/L, and the total and differential WBC counts remained within the normal range. Cultures of blood, urine, and stool samples and a throat swab were sterile. There was no evidence of a transfusion-associated infection or an autoimmune process. Findings of biochemical screening were also normal, including analysis of blood electrolyte, urea, and creatinine concentrations and liver-function tests.

The patient was treated symptomatically, and the acute confusional state steadily improved over the course of a week. Thereafter, the patient remarked on a distinct inability to perform simple arithmetic calculations. The patient’s acalculia was not associated with dysphasia or other features of temporoparietal dysfunction. His fever persisted for 16 days before finally resolving, and he made a full recovery with no long-term
neurological sequelae. No clear diagnosis of the patient’s fever and neurological symptoms was made until the clinical course of patient B shed further light on the likely cause.

**Patient B.** One month after patient A was admitted, and 17 days after returning to the United Kingdom from West Africa, a 22-year-old woman was admitted to the intensive care unit with a 1-week history of febrile illness. *P. falciparum* malaria was diagnosed; the initial level of parasitemia was 22% of RBCs. Acute complications included hemolysis, profound thrombocytopenia, marked hemoglobinuria, and metabolic acidosis. The patient also developed ARDS and required mechanical ventilation from days 3 through 9. She was treated with intravenous quinine, a 6-unit exchange blood transfusion, and supportive measures. The parasitemia cleared by day 6, when the patient was given a single dose of sulfadoxine and pyrimethamine. From days 10 through 13 the patient was afebrile and independent of respiratory support, and she made good progress during inpatient convalescence.

On day 13, however, the patient’s fever recurred, and she developed neurological symptoms that were 3-fold: (1) myoclonus of the arms and legs that was sensitive to auditory and sensory stimuli, (2) postural tremor, and (3) nominal dysphasia that was not associated with other features of temporoparietal dysfunction. Findings of CT and gadolinium-enhanced T1- and T2-weighted MRI scans of the brain were normal. When CSF was sampled by lumbar puncture, the opening pressure was normal (12 cm of CSF), and subsequent CSF analysis revealed a markedly elevated protein concentration (2.39 g/L), 59 lymphocytes/mm³, and a normal glucose concentration. Cultures for viruses and bacteria were sterile, cryptococcal antigen was not detected, and PCR studies for herpesviruses and *M. tuberculosis* were negative. An electroencephalogram demonstrated slow-wave activity consistent with encephalopathy. Blood-film examinations were negative for malarial parasites and trypanosomes. Despite a persistent fluctuating fever (temperature range, 37.3°C–39.4°C), the patient had no peripheral blood inflammatory response; the serum CRP concentration remained ≤2.0 mg/L, and the WBC count was <4.5 × 10⁹ cells/L, with a normal differential count. Cultures of blood, urine, and stool samples and a throat swab were sterile, and serologic testing for HIV types 1 and 2 was negative. There was no evidence of a transfusion-associated infection or autoimmune process. Findings of biochemical screening were also normal, including measurements of blood electrolyte and glucose levels and acid-base status. A pharmacological review identified no prescribed medications that might have caused her symptoms.

A literature search, however, identified a case report by Schnorf et al. [1] describing an encephalopathic illness in a patient with an identical constellation of clinical features and investigational findings that occurred during convalescence from *P. falciparum* malaria. Schnorf et al. [1] made a diagnosis of postmalaria neurological syndrome (PMNS), and reported

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**Figure 1.** Diagram illustrating the biphasic clinical course of 2 patients (patient A and patient B) with *Plasmodium falciparum* malaria who developed postmalaria neurological syndrome during convalescence.
that both the fever and neurological symptoms responded rapidly to corticosteroid therapy. Having excluded other pathologic processes, a diagnosis of PMNS was made for patient B. She was treated with a 10-day reducing course of prednisolone with a starting dosage of 60 mg/day. Treatment was associated with a rapid diminution of fever and neurological symptoms, and these fully resolved 5 days after the start of treatment. Patient B made a full recovery with no long-term neurological sequelae.

**Discussion.** PMNS is a self-limiting, postinfective encephalopathy that occurs within 2 months after an episode of *P. falciparum* malaria [1–4]. This phenomenon is quite distinct from the acute neurological complications that are seen during cerebral malaria. There is some evidence to suggest that the pathogenesis of PMNS is mediated immunologically [5], possibly because of a process of molecular mimicry whereby antibodies to antigens expressed by certain strains of *P. falciparum* cross-react with antigens in the CNS. Both of our patients had inflammatory changes in the CSF but not in the peripheral blood, which is consistent with an inflammatory process confined to the CNS.

PMNS may present with a variety of neurological manifestations, which can be broadly classified into 2 main forms. The most frequently reported form is a mild localized encephalopathy that affects the cerebellum and presents with ataxia alone [3, 4]. Almost all of such cases have been reported from Sri Lanka, and it has been suggested that the geographic clustering of this form of PMNS might relate to certain local strains of *P. falciparum* [3]. The second form, a generalized encephalopathy that causes confusion with or without epileptic seizures, was the predominant form of PMNS found in a prospective study conducted in Vietnam [2]. The incidence of PMNS in that study was found to be ∼1 case per 1000 cases of malaria, although the findings were confounded by the fact that the risk of PMNS was also strongly associated with use of mefloquine, which has well-documented neuropsychiatric side effects [6]. There has been a previous report of a case of severe generalized encephalopathy in which myoclonus, tremor, and dysphasia were observed [1].

Our 2 cases presented considerable diagnostic difficulty, particularly in view of the inflammatory changes in the CSF, which are seen in a minority of reported cases of PMNS [1–4]. Arboviral encephalitides, which typically have a short incubation period, were extremely unlikely diagnoses given that the onset of encephalopathy in each patient occurred >1 month after they returned to the United Kingdom from West Africa. Lack of awareness of PMNS and its spectrum of clinical manifestations may result in considerable underdiagnosis of this complication of *P. falciparum* malaria. The clinical picture in patient A was consistent with PMNS, with diffuse encephalopathy and focal parietal lobe dysfunction, whereas patient B developed a severe generalized encephalopathy. As far as we are aware, patient B is only the second case of PMNS with the specific manifestations of myoclonus, tremor, and dysphasia, and our report suggests that this triad of neurological features is a distinctive presentation of PMNS.

PMNS is usually a short-lived, self-limiting condition with no long-term neurological sequelae. No randomized trials of corticosteroid treatment have been conducted. However, the apparent response of patient B to oral prednisolone supports the suggestion that corticosteroid therapy may be useful for patients with severe or protracted symptoms, as reported previously [1], and it provides further evidence that PMNS is an immunologically mediated phenomenon [5].

**References**