INTERNAL MEDICINE

□ CASE REPORT □

Steroid Pulse Therapy May Mitigate Prolonged Neurological Manifestations after Eradication of Severe *Plasmodium falciparum* Parasitemia

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Abstract

A 58-year-old Japanese man with a high parasitemia of *Plasmodium falciparum*, returning from Uganda, was admitted to our hospital since his consciousness level rapidly deteriorated after the initial dose of mefloquine. Despite the parasitemia was cleared by quinine by day 7, the coma remained unchanged and diffuse leukoencephalopathy was detected on magnetic resonance image. Steroid pulse therapy was initiated on day 8. Subsequently, the neurological manifestations improved and he was discharged on day 73 without any sequelae. Pathogenesis of *P. falciparum* causing cerebral malaria is diverse and complex. If neurological symptoms unusually prolong, steroid may be an effective treatment option.

Key words: cerebral malaria, PMNS, ADEM, steroid

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Introduction

In 2013, approximately 200 million people were infected with malaria, and 0.6 million people died (1). Cerebral malaria is the most severe manifestation of *Plasmodium falciparum* malaria and usually induces a coma (Glasgow coma scale <11) (2). In Africa, the cerebral malaria death rate is 20% (3). Even in high-income countries, this is a medical emergency, and fatal cases still exist. Therefore, a precise diagnosis and prompt treatment are crucial for survival.

In contrast to other infectious diseases causing a coma, most cerebral malaria survivors recover from unconsciousness without much delay; the median time to full recovery of consciousness is about 24 hours in children and 48 hours in adults (4). The frequency of any neurological sequelae is less than 1% in adults but more frequent in children, who typically have symptoms such as hemiplegia, cortical blindness, aphasia, and cerebellar ataxia symptoms at the time of discharge (5). Recently, late neurological disorders have also been reported following successful treatment and full recovery, including post-malaria neurological syndrome (PMNS) (6-8), acute disseminated encephalomyelitis (ADEM) (9-11), and acute inflammatory demyelinating polyneuropathy (AIDP) (12-14). These diseases are difficult to diagnose, as their clinical findings often overlap, particularly for PMNS and ADEM, in which the magnetic resonance imaging findings and immunological etiology are so similar that ADEM is thought to be involved in PMNS (15).

We herein report a case of cerebral malaria in which prolonged neurological disorders were successfully treated by steroid pulse therapy.

Case Report

The patient was a 58-year-old man. While travelling in Uganda for 6 days, he took medication for angina pectoris, a lipid metabolism disorder, and hypertension, but did not receive prophylaxis for malaria. He had not been vaccinated within the previous year and felt no preceding respiratory or

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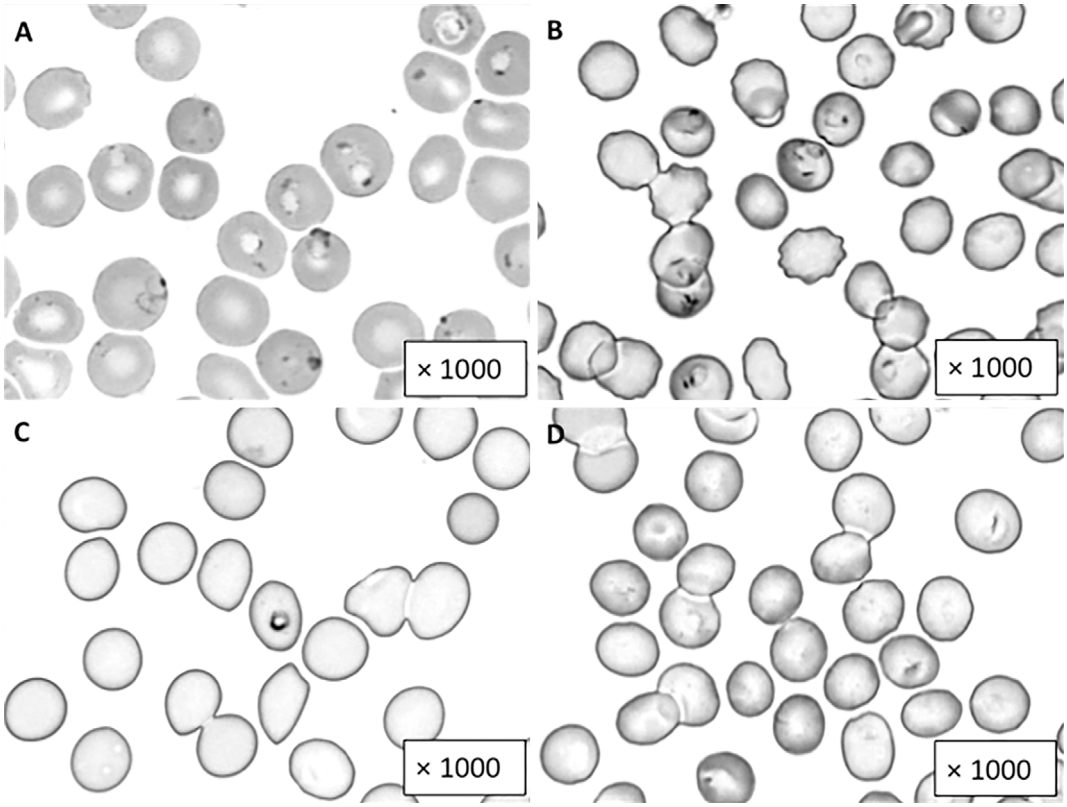

Figure 1. **Blood smears. Each sample was taken one day before admission (A), on hospital day 1 (B), day 3 (C) and day 7 (D) respectively. The ratios of paracitemia are 30% (A), 16% (B), 0.3% (C) and 0% (D) respectively.**

digestive symptoms. Five days after returning to Japan, which was five days prior to admission at our hospital, he began to feel feverish, dizzy, and nauseous. Two days prior to admission, he experienced severe fatigue and consulted a local clinic, where he was hospitalized with a diagnosis of fever of unknown origin. On the following day, one day prior to admission, the patient's general condition was good; however, malaria was suspected based on a blood smear, and the first dose of mefloquine (750 mg base at 1 pm, 500 mg base at 7 pm) was administered with clindamycin. To confirm a malaria diagnosis, photographs of the blood smear were sent to our hospital laboratory (Fig. 1A), and approximately 30% of the patient's red blood cells were found to be infected with *P. falciparum*.

By the evening of the day prior to admission at our hospital, the patient's blood pressure had decreased, and at midnight, he began to lose consciousness. He was therefore emergently transported to our hospital. Upon arrival, his level of consciousness was E1V1M1 (Glasgow Coma Scale), his light reflex was sluggish, his blood pressure was 114/78 mmHg, and his heart rate was 114 beats/min under noradrenaline administration. A blood examination indicated leukocytosis (white blood cell count, 18,970/μL), anemia (hemoglobin, 7.3 g/dL), thrombocytopenia (platelet count, 28,000/μL), a low nutritional level (total protein, 4.4 g/dL; albumin, 2.0 g/dL), increased transaminases (alanine transaminase, 243 IU/L; aspartate transaminase, 139 IU/L), renal dysfunction (creatinine, 3.4 mg/dL), and severe acidosis (pH, 7.100). Computed tomography revealed brain swelling with narrow ventricles and sulci. A peripheral blood smear using Giemsa stain revealed the presence of *P. falciparum* with a parasitemia level of 16% (Fig. 1B).

Based on the collective data, the patient was diagnosed with severe cerebral malaria and septic shock. Intravenous treatment with 500 mg quinine began immediately and was administered 3 times on the first day, twice on Day 2, and once on Days 3 through 7. The patient's respiration was managed by noninvasive positive-pressure ventilation (S/T mode), and his blood pressure was maintained by noradrenaline infusion with a transfusion of red blood cells and platelets. Hydrocortisone (200 mg/day) was administered for 5 days for septic shock. Continuous hemodiafiltration was performed for 8 days, and glucose was administered to treat the hypoglycemia caused by the infection and quinine treatment. As a result of these treatments, the parasitemia was reduced to 2% by Day 2 following admission (Fig. 1C), and no infected blood cells were detected on Day 7 (Fig. 1D). Quinine therapy was stopped after Day 7, and clindamycin treatment was begun.

Although the patient's hemodynamics stabilized on Day 4 without noradrenaline, his level of consciousness remained at E1V1M4 on Day 7; conjugate eye deviation to the right was present, with occasional roving eye movement. The Babinski reflex was negative. A cerebrospinal fluid (CSF) analysis revealed a normal cell count (2/3 μL) and a normal glucose level (70 mg/dL) but a high level of myelin basic

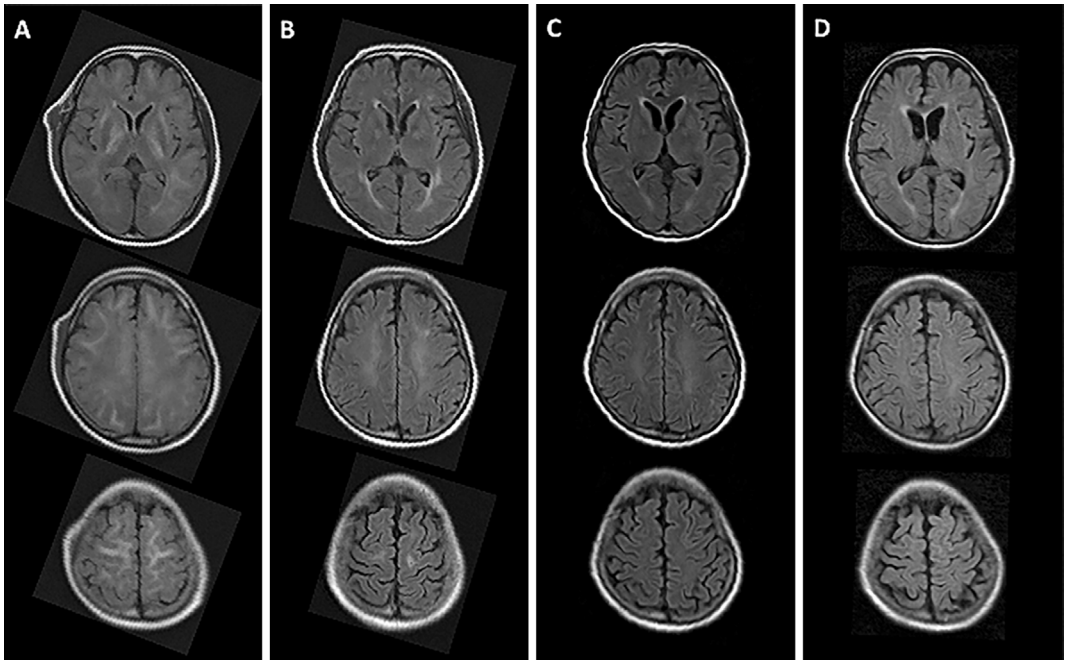

Figure 2. **Time course of MRI. Fluid-attenuation inversion recovery (FLAIR) images showed diffusely increased signal intensity in cerebral white matter on hospital day 7 (A) and this changes was improving gradually, on day 20 (B), day 36 (C) and day 48 (D).**

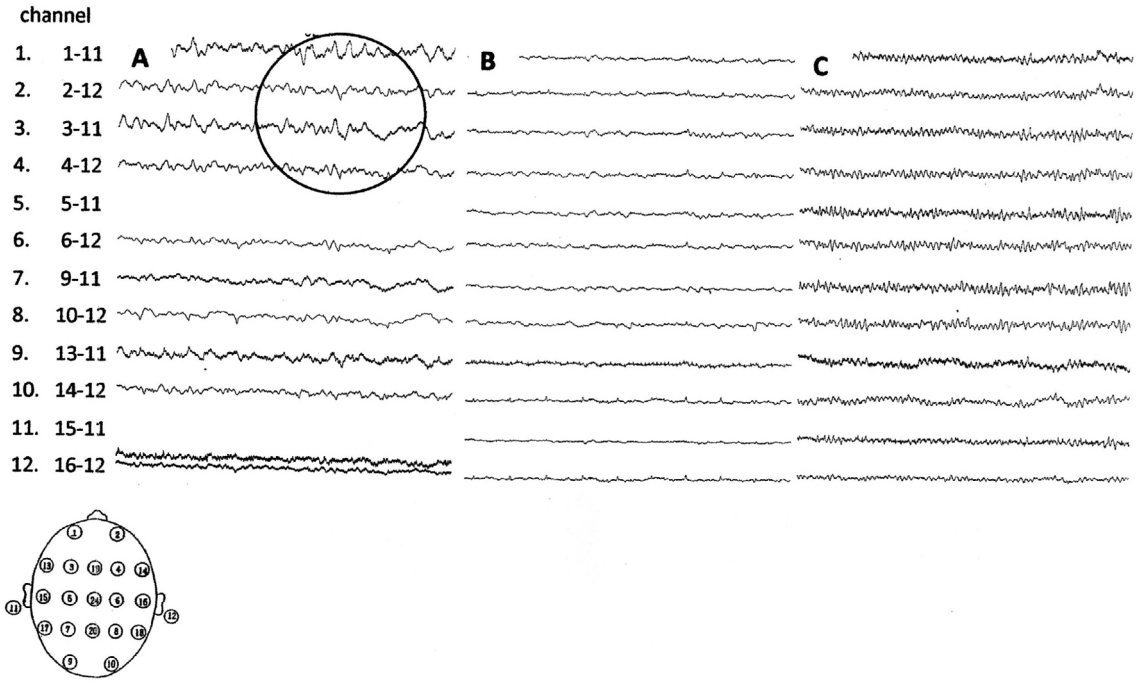

Figure 3. **Time course of electroencephalography (EEG: mono polar 1). EEG on hospital day 7 (A) revealed generally slow waves with theta waves in the frontal lobe (open circle) (channel 5 was not recorded due to recorder trouble). Theta waves in the frontal lobe disappeared on day 20 (B) and background frequency recovered on day 58 (C).**

protein (MBP) (637.7 pg/mL; normal limit, <102 pg/mL). Meningitis was excluded based on these data. On the same day, magnetic resonance imaging (MRI) and electroencephalography (EEG) were performed. T2-weighted and fluid-attenuation inversion recovery (FLAIR) images showed that brain swelling was slightly improved, but the signal intensity was increased in the patient's cerebral white matter (Fig. 2A). EEG revealed slow-wave activity in general, along with theta waves in the frontal lobe (Fig. 3A).

To treat the patient's neurological disturbances, including his unconsciousness, steroid pulse therapy was initiated on Day 8. Methylprednisolone (1,000 mg/day) was adminis-

tered for the first 3 days, followed by prednisolone (60 mg/day) for the subsequent 4 days, and then tapered. Following the initiation of steroid pulse therapy, the patient's level of consciousness steadily improved; the conjugate eye deviation disappeared, and he regained the ability to turn his head toward a voice on Day 9, nod his head on Day 14, and make simple conversation on Day 17. His quadriplegia remained until approximately Day 20, after which he began to regain movement in his legs and arms and was gradually able to sit, stand, and eventually walk without assistance. By Day 73, the patient regained his speech without disorientation and was discharged. Follow-up MRI and EEG on Day 20 confirmed that the leukoencephalopathy was improving (Fig. 2B), although an EEG showed that the slow waves remained; however, the theta waves in the frontal lobe were absent (Fig. 3B).

Discussion

In Japan, approximately 50-100 cases of malaria are reported annually, and all patients are infected abroad (16). Severe malaria cases are rare, however, making it difficult to accumulate evidence regarding the optimal treatment method in resource-rich settings (17). The cerebral malaria case presented herein deteriorated rather rapidly due to the extremely high parasitemia caused by a delay in consulting a physician after the onset of symptoms. This case was thought well worth reporting given the efficacy achieved with a high dose of steroid therapy, which was selected to treat the persistent neurological manifestations based on the MRI findings on Day 8. This treatment regimen ran counter to the WHO guidelines, which state that high doses of corticosteroids are contraindicated for severe malaria, as these therapies are associated with gastrointestinal bleeding, convulsion, and prolonged coma (2). However, those guidelines were developed on trials conducted in resource-limited countries, and steroid were administered in the acute phase without the guidance of any MRI findings. In the present case, by contrast, hydrocortisone administered on the first day of admission, in accordance with the Japanese Guidelines for the Management of Sepsis (18), was useful in treating the patient for septic shock, and the steroid pulse therapy administered on Day 8 apparently improved the neurological disturbances, including the patient's comatose state.

Despite the clearance of malaria parasitemia by Day 7, the level of consciousness improved only up to a Glasgow Coma Scale score of 6. Although there was no full-recovery period from the cerebral malaria in this case, post-malarial treatment neurological disorders such as ADEM and PMNS were considered as possible causes of the prolonged unconsciousness, since MRI T2/FLAIR showed increased signal intensity in the cerebral white matter, which is rather unusual in cerebral malaria (19). The present case showed unconsciousness, elevated MBP levels in the CSF, and slow wave activity on EEG, findings which are consistent with ADEM, but no increase in the cell count in the CSF and no signs of scattered hyperintense lesions in the white matter on MRI T2 images. PMNS was first described as a neuropsychiatric manifestation by Nguyen (6), but unlike with our case, PMNS occurs after a full recovery from a malaria infection and has normal MRI findings. Its clinical spectrum was recently expanded to include impaired consciousness, headache, myoclonus, cerebellar ataxia, acalculia, agraphia, and aphasia (20). Albuminocytologic dissociation and muscle weakness of the arms and hands are compatible with signs of AIDP. However, unconsciousness and changes in MRI findings are not present in AIDP.

Some immune-pathophysiological changes were suspected to play a role in the present case. The MBP levels were elevated, and diffuse leukoencephalopathy was present on MRI T2 images. Increased MBP levels in the CSF indicates inflammation of a demyelinatic lesion, which is often seen in demyelinatic diseases like multiple sclerosis or ADEM. Sharma et al. (21) and Mani et al. (22) showed that intravenous methylprednisolone (1 g/day for 3 days) was effective in treating ADEM after severe *P. falciparum* malaria. Wal et al. (23) reported the same therapy for PMNS treatment, and in the present case, we also administered a large dose of steroids after excluding the possibility of other infectious diseases. After the steroid treatment, the neurological disturbances, including unconsciousness, improved, and the patient was discharged without any sequelae. Of note, the patient was first treated using mefloquine. Nguyen et al. reported that PMNS was strongly associated with the oral treatment of mefloquine (6). In fact, artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids (quinine and quinidine) are recommended for use in treating severe malaria (2); in Japan, however, artemisinin derivatives are difficult to access, and patients are therefore typically treated with quinine.

The pathophysiological features of cerebral malaria are multifactorial. The sequestration of *P. falciparum*-infected erythrocytes in cerebral vessels is the most well-known feature (24). This sequestration is triggered by the expression of *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) on the cell membrane of malaria-infected erythrocytes, which binds to the cell adhesion molecules (CAMs) such as CD36, ICAM-1 (CD54), and colony-stimulating activity (CSA) on vascular endothelial cells. The sequestration subsequently leads to mechanical occlusion and abruptly disrupts blood circulation in the brain. However some patients are known to develop long-term neurological deficits despite responding well to antimalarial therapy; as such, other pathogenesis mechanisms are hypothesized. Cytokines are thought to contribute to the neurological symptoms. Indeed, tumor necrosis factor (TNF) receptor 2 or the LTβ receptor of TNF-related lymphotoxin (25), IL-12 receptor β (26), and protein kinase C-theta (27) are known to be involved in microcirculatory disturbances. A brain hemorrhage or infection are other mechanisms of prolonged neurological manifestations, but we observed no obvious hemorrhage on MRI to explain the altered consciousness in the present case.

Although the findings from numerous animal experiments have greatly contributed to the understanding of cerebral malaria, the observations regarding human cerebral malaria remain limited (24). MRI is expected to improve the understanding of cerebral malaria (28). However, a recently published prospective study of adult patients with severe malaria stated that the changes on brain MRI are mostly subtly and vary widely from case to case (19): the swollen areas which usually show a normal or high signal on T2/FLAIR were present in only one quarter of patients, and most had focal lesions in locations such as the basal ganglia and globus pallidus, unlike the diffuse leukoencephalopathy seen in the present case. This leukoencephalopathy was reversible (Fig. 2C and 2D), however, and may therefore be attributed in part to the severe brain edema in addition to the demyelinatic changes mentioned above.

In this case report, EEG was repeatedly performed throughout the patient's recovery from cerebral malaria, and our findings were compatible with those of a previous report (29). Slow waves, asymmetry, burst suppression, and interictal discharges on EEG have been associated with sequelae and mortality after recovery (30). In this case, all of the EEG channels (monopolar 1) showed slow-wave activity in general, along with theta waves in the frontal lobe on Day 7, despite the fact that no parasitemia was observed. As the patient's neurological condition improved, the delta waves disappeared on Day 20, and the background frequency improved to a normal rhythm on Day 58 (Fig. 3C). These findings support the above data that abnormal EEG findings are reversible with an improved disease state.

In summary, cerebral malaria is often fatal within 24 to 72 hours, but with an appropriate treatment, adult patients rapidly recover without sequelae. However, the pathogenesis of *P. falciparum* causing cerebral malaria is diverse and complex. For patients in whom neurological symptoms continue after eradication of parasitemia with diffuse leukoencephalopathy on MRI T2/FLAIR, steroid pulse therapy may be an effective treatment option, as reported herein.

The authors state that they have no Conflict of Interest (COI).

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