Postmalaria Neurological Syndrome after Treatment of *Plasmodium falciparum* Malaria in the United States

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The neuropsychiatric manifestations of postmalaria neurological syndrome (PMNS) that have been described are highly variable and include an acute confusional state or acute psychosis with ≥1 of the following symptoms: clouding of consciousness, inappropriate speech or behavior, visual hallucination, catatonia with waxy flexibility, generalized convulsion, fine postural tremor, and decreased muscle tone. This postinfectious syndrome occurs after the clearance of parasitemia and is not a manifestation of cerebral malaria. We present the first identified case of and magnetic resonance imaging findings for a patient with PMNS in the United States.

**Case report.** The patient was a 50-year-old woman from Ghana with a medical history that included hypertension, chronic renal insufficiency, rheumatoid arthritis, and malaria, the last of which had been treated 30 years earlier. She presented with intermittent dyspnea during physical exertion, which had progressively worsened during the previous 7 days. She also reported dizziness, light-headedness, worsening orthopnea, and occasional chest pain associated with the dyspnea. She denied having had fevers, chills, night sweats, nausea, vomiting, and diarrhea. Her medications included felodipine, prednisone, furosemide, iron, vitamin B12, and folate. The patient lived in Ghana and was visiting family and friends in the United States.

During physical examination, she appeared anxious and noticeably dyspneic. Her blood pressure was 189/126 mm Hg, her heart rate was 114 beats/min, her respiratory rate was 28 breaths/min, her temperature was 37.8°C, and her oxygen saturation was 83% in room air. She had pale conjunctivae. Coarse rales were present bilaterally, and decreased breath sounds were heard at the base of the right lung. She had a regular tachycardia, with normal S1 and S2, an S3, and a grade 2/6 systolic murmur at the left upper sternal border radiating to the carotids. Trace edema in the bilateral lower extremities and sacrum was present.

Pertinent laboratory values included a sodium level of 122 mmol/L, a potassium level of 6.4 mmol/L, and a creatinine level of 2.5 mg/dL. Testing of arterial blood gases revealed a pH of 7.42, a partial pressure of arterial CO₂ of 23 mm Hg, and a partial pressure of arterial O₂ of 51.7 mm Hg. Results of a complete blood count revealed a hemoglobin level of 5.6 g/dL and a leukocyte count of 10,600 cells/μL. A peripheral blood smear revealed the presence of *Plasmodium falciparum*, with a parasitemia level of 0.2% of RBCs, or 4040 RBCs/μL. She underwent transfusion with 4 units of packed RBCs, which increased her hemoglobin level to 10.2 g/dL.

The episode of malaria was treated with oral quinine sulfate (650 mg po q8h) and doxycycline (100 mg po b.i.d.) during the first 5 days of the patient’s hospitalization. This regimen was discontinued when her blood sugar level decreased to 31 mmol/dL. The patient then completed a full 3-day course of atovaquone-proguanil (Malarone; GlaxoSmithKline) to cover any inadequately treated organisms. After treatment was completed, *P. falciparum* was not detected on a peripheral blood smear.

The hyponatremia that was present at hospital admission resolved several days before the onset of acute delirium. Epi-sodic hypoglycemia was considered secondary to quinine therapy and resolved after therapy was discontinued, well before the onset of delirium. Results of chest radiography performed at admission showed significant pulmonary edema. This was treated with large amounts of loop diuretics but did not respond well and, eventually, required endotracheal intubation on hospital day 6. An echocardiogram showed mild concentric left ventricular hypertrophy, mild mitral and tricuspid regurgitation, and moderate left and right atrial enlargement, with normal ejection fraction and normal left ventricular end diastolic pressures. The etiology of the pulmonary edema was deemed secondary to *P. falciparum* infection.

On hospital day 18, 11 days after the clearance of parasitemia and 9 days after completing antimalarial treatment, the patient was found to have an abnormal mental state and to be experiencing upper and lower extremity myoclonus, jerking, and tremors. She was awake but disoriented and was unable to answer questions or follow commands. Verbal responses consisted only of incomprehensible responses to pain. The lowest
Glasgow coma score was 10. She was neither hypoxic (oxygen saturation, 96% in room air) nor hypoglycemic (plasma glucose level, 83 mg/dL). A CT scan of the head showed multiple old lacunar infarcts in the right subinsular and right and left caudate nuclei, as well as periventricular small vessel ischemic changes. No acute changes were noted. Subsequent MRI of the brain (figure 1) revealed nonspecific increased signal in the pons, posterior internal capsule, thalamus, corona radiata, and periventricular areas. Laboratory testing of CSF samples obtained by lumbar puncture revealed 3 WBCs/µL, 2 RBCs/µL, a protein level of 31 mg/dL, and a glucose level of 52 mg/dL. CSF cultures for bacteria, fungi, and mycobacteria were sterile. CSF IgG levels were within normal limits (CSF IgG level, 5.5 mg/dL; serum IgG level, 3430 mg/dL; IgG index, 0.61 [normal value, <0.65], and IgG synthesis rate, 0.7 gm/day [normal range, –9.9 to 3.3 gm/day]).

Administration of all possibly offending medications, including gatifloxacin, clonidine, metoprolol, hydrocodone/acetaminophen, enalapril, magnesium oxide, and enoxaparin, was stopped the day after symptoms developed. The patient’s abnormal mental state became progressively worse, and the patient was transferred to the medical intensive care unit. Eight and 9 days after the onset of the abnormal mental state, the patient experienced both visual and auditory hallucinations. Ten days after the onset of the symptoms, her mental status began to improve, and the patient was able to understand and answer questions. The patient’s mental state returned to normal, with the exception of a slight expressive aphasia that resolved 2 days later. The patient developed no further episodes of confusion, myoclonus, tremors, or jerking movements.

**Discussion.** The clinical manifestations of postmalaria neurological syndrome (PMNS) in this case are consistent with the descriptions offered by Nguyen et al. [1]. The patient’s acute symptoms began 9 days after completion of antimalarial treatment. The patient was disoriented, intermittently awake, and obtunded but was arousable and unable to communicate. The neurological symptoms and signs lasted for 12 days, during which time no other new adverse events occurred.

It is unlikely that the patient’s symptoms were due to the toxic effect of antimalarial treatment. She was treated with quinine and doxycycline for 5 days, followed by a full course of atovaquone-proguanil to cover inadequately treated strains. The combination treatment of atovaquone-proguanil has rarely been associated with neuropsychiatric adverse reactions. These events usually occur in patients with predisposing neuropsychiatric medical histories [2]. The patient did not receive mefloquine, which has commonly been associated with neuropsychiatric side effects, including seizures and psychosis [3–6]. Other investigators feel, however, that when preexisting disorders of the CNS are excluded, the occurrence of significant neuropsychiatric adverse events associated with mefloquine is infrequent [7]. A correlation between mefloquine therapy and PMNS was noted by Nguyen et al. [1], although almost one-fourth of the patients who developed PMNS did not receive mefloquine. None of the patients in that series received atovaquone-proguanil [1].

The first description of PMNS appeared only recently, in 1996. Therefore, there is some speculation regarding whether PMNS is a true distinct clinical entity and not a consequence of malarial cerebral damage or neurologic sequel to antimalarial therapy [8, 9]. In this case, we found no evidence of cerebral malaria, and we administered no medications associated with significant neurologic adverse events [2].

The pathophysiology of the delirium associated with PMNS is not known. Proposed neuropathologic processes include immunologic damage and sequestration of parasite-infected erythrocytes in brain capillaries. Studies of another rare self-limiting postinfectious complication of malaria—delayed cerebellar ataxia (DCA), which was first identified in Sri Lanka in 1984—may provide clues to the etiology of the neuropathologic process responsible for PMNS [10]. In DCA, the serum and CSF concentrations of certain cytokines, including TNF-α, IL-2, and IL-6, are elevated, and a favorable response to corticosteroid therapy supports the possibility that an underlying immune mechanism is present. The selective focal cerebellar ataxia of DCA, however, is distinct from the diffuse constel-
lation of symptoms seen in cases of PMNS, which supports a lower, more subtle degree of antibody cross-reactivity in patients with PMNS [10].

To our knowledge, this patient’s MRI scan is the first such scan published in a study of a patient with PMNS. The clinical significance of the nonspecific changes is unclear, although the diffuse distribution of increased signal enhancement that was observed may be subtle clinical evidence for an immune-mediated process, as is implicated in the development of PMNS.

Additional studies are needed to ascertain the epidemiology and pathogenesis of PMNS. The epidemiology will only be revealed in developing countries with a high prevalence of malaria, such as Vietnam. The pathogenesis of PMNS will require further elucidation of the clinical characteristics and their relationship to other known postinfectious neurologic syndromes.

References