Corticosteroid-Responsive Postmalaria Encephalopathy Characterized by Motor Aphasia, Myoclonus, and Postural Tremor

Hans Schnorf, MD; Karin Diserens, MD; Hans Schnyder, MD; Michel Chofflon, MD; Louis Loutan, MD; Virginia Chaves, MD; Theodor Landis, MD

Objectives: To study the clinical spectrum of an acute severe encephalopathy occurring in 2 patients after recovery from falciparum malaria infection and to compare it with the reported clinical features of the postmalaria neurological syndrome.

Design: Case report.

Setting: Tertiary care hospital.

Patients: Two patients presented with acute onset of fluctuating motor aphasia, severe generalized myoclonus, and postural tremor. Additional signs were cerebellar ataxia, and in 1 patient, generalized epileptic seizures. Magnetic resonance imaging of the brain revealed patchy white matter lesions in 1 patient. Clinically, the patients' conditions continued to worsen until corticosteroids were introduced, the use of which induced a rapid, albeit incomplete, recovery.

Conclusions: We describe a new, severe variant of the still poorly defined postmalaria neurological syndrome. We propose a preliminary classification of this syndrome, according to its clinical characteristics, as follows: a mild or localized form, characterized by isolated cerebellar ataxia or postural tremor; a diffuse, but relatively mild encephalopathic form, characterized by acute confusion or epileptic seizures; and a severe, corticosteroid-responsive encephalopathy that is characterized by motor aphasia, generalized myoclonus, postural tremor, and cerebellar ataxia.

Arch Neurol. 1998;55:417-420

A SMALL number of published observations on neurological disease following successfully treated Plasmodium falciparum malaria has increased awareness of the postmalaria neurological syndrome (PMNS).\(^1\)\(^-\)\(^3\) However, both the clinical spectrum and the etiology of this syndrome are still poorly defined. Isolated cerebellar ataxia following P falciparum malaria has been described in patients from Sri Lanka.\(^1\) More recently, a group from Vietnam observed an acute confusional state or generalized convulsions in a number of patients recovering from P falciparum malaria.\(^2\) These patients had complete recovery without specific therapy.

We report a new and severe variant of PMNS. Two patients who had recovered from a recent severe P falciparum malarial infection developed an acute encephalopathy with fluctuating motor aphasia, severe generalized myoclonus, and postural tremor. Clinical deterioration continued until the introduction of corticosteroids, the use of which induced a rapid, but incomplete, recovery. Possible pathomechanisms of this encephalopathy are discussed.

REPORT OF CASES

PATIENT 1

A 34-year-old woman was diagnosed as having mixed infection with P falciparum (45% parasitemia) and Plasmodium vivax 12 days after returning from a trip to Africa, where she took a homeopathic preparation as malaria prophylaxis. She was febrile (body temperature, 39.2°C), somnolent, disoriented, mildly icteric, and had otherwise normal results of the neurological examination. Her hemoglobin level was 8.7 g/L and platelets were 306 000 \(\times 10^9\)/L. She was treated with intravenous quinine sulfate (10 mg/kg 3 times per day for 3 days), clindamycin hydrochloride (10 mg/kg twice daily for 7 days), blood exchange transfusion (3.5 L), and fibrinogen. She developed complications of severe hemolysis, disseminated intravascular coagulation, and acute renal
failure necessitating hemofiltration and hemodialysis. Four days after admission there was no parasitemia and her mental status had gradually normalized. Twenty-one days after admission she became febrile again (body temperature, 38.2°C), irritable, restless, had important word finding difficulties, difficulties in naming objects, postural tremor of the arms, and mild cerebellar ataxia of gait and extremities. Examination of the cerebrospinal fluid (CSF) showed a white blood cell count of 0.01×10⁹/L (95% lymphocytes and 5% monocytes) and a protein level of 0.6 g/L without oligoclonal distribution. Results of extensive serologic studies and cultures, both in serum and CSF, were negative. Peripheral blood smears remained negative for malaria parasites. Results of cranial computed tomography (CT) were normal and cranial magnetic resonance imaging (MRI) showed hyperintense lesions in periventricular and supraventricular areas and in the cerebellum, some of which showed gadolinium enhancement (Figure). An electroencephalogram revealed mild to moderate slowing of background activity and intermittent dysrhythmic discharges. During the following days she developed generalized stimulus-sensitive myoclonus, continued to have expressive aphasia that fluctuated in severity, and had 2 tonic-clonic epileptic seizures. Treatment with phenytoin was started. Ceftriaxone sodium (2 g every 12 hours) and acyclovir (10 mg/kg every 8 hours) were empirically given for 6 days, with no clinical improvement. Treatment with intravenous methylprednisolone sodium succinate was started 9 days after the appearance of fever and neurological symptoms (100 mg/d for 3 days with subsequent tapering for 10 days). Twenty-four hours after the initiation of corticosteroid therapy the patient was afebrile, and had significant improvement of aphasia and myoclonus. When discharged 2 weeks later all of the patient's neurological abnormalities had resolved, except for postural tremor of the arms.

PATIENT 2

A 61-year-old man, who had spent several years working in Central Africa, was diagnosed as having *P falciparum* malaria (50% parasitemia) 5 days after returning from a business trip to Cameroon. He had taken no antimalaria prophylaxis. He consumed sustained moderate amounts of alcohol and was known for years to have intermittent mild tremor of the hands. He was febrile (body temperature, 39.2°C), somnolent, disoriented to space, dehydrated, mildly icteric, and had petechial lesions on both lower legs. His hemoglobin level was 13.5 g/L; platelet count, 7000×10⁹/L, and leukocyte count, 3.2×10⁹/L. Cytomegalovirus (CMV) serologic test results were positive (IgG, 2.7 g/L [normal, <15]; IgM, 0.74 g/L [normal, <0.6 g/L]). He was treated with intravenous quinine sulfate (10 mg/kg 3 times daily for 3 days) and doxycycline (200 mg/d), followed by mefloquine hydrochloride (1500 mg). A blood exchange transfusion (3 L) was given on day 1. Four days after admission blood smears were negative for parasites, he made an uneventful recovery, and he was discharged 1 week after admission. Ten days later he was readmitted because of irritability, word finding difficulties, and headache. He was
afebrile, restless, oriented, and had word finding and naming difficulties. He had postural tremor of the arms and rare myoclonic twitches of his face and extremities. Examination of the CSF showed a white blood cell count of 0.06 × 10^9/L (97% lymphocytes and 3% monocytes) and a protein level of 1.87 g/L (γ-globulin, 0.28 g/L without oligoclonal distribution). Blood serologic test results were positive for CMV (IgG, 7.4 g/L; IgM, 2.27 g/L), Epstein-Barr virus (EBV) (IgG >1:160; IgM positive) and varicella-zoster virus (VZV) (IgG, 0.6 g/L [normal, <0.2 g/L]; IgM negative). Test results for EBV were negative twice. His CSF was negative for antibodies against CMV, EBV, and mildly positive for VZV (IgG, 0.57 g/L; IgM negative). Repeated polymerase chain reaction testing, performed in 3 subsequent CSF specimens, revealed negative results for CMV, EBV, VZV, and herpes simplex virus. Cultures of blood, CSF, and urine were sterile. An electroencephalogram revealed mild slowing of background rhythm and theta-delta activity over the left temporo-central region. Findings of cranial CT and MRI scans were normal except for mild cerebral atrophy. On the day after readmission, body temperatures up to 38°C recurred. Repeated blood smears were negative for malaria parasites. Empirical treatment with halofantrine hydrochloride (500 mg 3 times daily) was given, with no benefit. The patient developed ataxia of gait, severe generalized myoclonus, which was sensitive to auditory and tactile stimuli, and continued to have expressive aphasia. A CSF culture was sterile, with a white blood cell count of 0.08 × 10^9/L (87% lymphocytes and 12% monocytes) and a protein level of 1.8 g/L, without oligoclonal distribution. Because of a positive serologic test result for schistosomiasis, praziquantel was given (60 mg/kg). Twelve days after the appearance of neurological symptoms, prednisone therapy was started at a dose of 60 mg orally and continued for 4 days. Twenty-four hours after initiating prednisone therapy the fever disappeared and the neurological abnormalities improved rapidly, which continued after the drug regimen was stopped. Another CSF culture 25 days after readmission was sterile, with a white blood cell count of 0.01 × 10^9/L (93% lymphocytes and 6% monocytes), and a protein level of 0.37 g/L (γ-globulin, 0.37 g/L with 3 oligoclonal bands). Levels of anti-VZV IgG were mildly elevated in CSF (0.35 g/L), while complement-fixation and anti-VZV IgM test results were negative. On the 26th day the patient was discharged after normal neurological examination results were obtained, with a residual postural tremor of the arms.

**COMMENT**

The neurological symptoms observed in these patients enlarge the clinical spectrum of PMNS. This syndrome has been defined as the acute onset of confusion or epileptic seizures, occurring in a patient without parasitemia, with a latency of several days to weeks, after recovery from successfully treated *P falciparum* malaria. Furthermore, postmalaria isolated cerebellar ataxia, which has been mainly observed in Sri Lanka, should be considered a mild variant of PMNS. Our patients’ encephalopathy was characterized by fluctuating motor aphasia, severe generalized myoclonus, postural tremor, and cerebellar ataxia. One patient had generalized epileptic seizures. While previously described patients recovered spontaneously and completely, our patients’ conditions deteriorated, showed clinical improvement only on the introduction of corticosteroid therapy, and had residual postural tremor. Three patients with isolated cerebellar ataxia described in Sri Lanka were transiently given corticosteroids with possible beneficial effects on the speed of recovery of their ataxia. The neurological involvement of PMNS thus ranges from limited and mild, as exemplified by isolated cerebellar ataxia or isolated postural tremor, to that of a diffuse encephalopathy, which is either mild and self-limiting or severe and necessitating corticosteroid treatment. We propose that PMNS be classified according to its clinical characteristics into (1) a mild or localized form characterized by isolated cerebellar ataxia or postural tremor; (2) a diffuse, but relatively mild encephalopathic form, characterized by acute confusion or epileptic seizures; and (3) a severe, corticosteroid-responsive encephalopathy that is characterized by motor aphasia, generalized myoclonus, postural tremor, and cerebellar ataxia. However, to some extent, clinical features may overlap between the 3 forms, as exemplified by our patients, in whom we observed cerebellar ataxia in addition to the clinical syndrome described earlier.

The etiology of PMNS remains unclear, but immune mechanisms may play a dominant role and have been implicated in postmalaria cerebellar syndrome. Neurological symptoms in most patients with PMNS, including ours, develop with a latency after acute malarial infection, similar to acute disseminated encephalomyelitis following a viral or mycoplasmal infection. Magnetic resonance imaging studies in patient 1 revealed several discrete white matter lesions (Figure) that have not been reported previously in PMNS, and which are reminiscent of the radiological abnormalities seen in mild cases of acute disseminated encephalomyelitis. The favorable clinical response to corticosteroid therapy witnessed in our patients supports the hypothesis of an underlying immune mechanism. It is unlikely that the initial bout of malaria resulted in the white matter lesions in patient 1, because during the period of acute malaria, her neurological status was normal except for initial mild somnolence.

Coinfection with a virus capable of causing encephalitis has been suggested as another possible mechanism implicated in the pathogenesis of some cases of PMNS. Patient 2 had elevated levels of IgG and IgM antibodies against CMV and EBV in serum, but not in CSF. He also had raised titers of anti-VZV IgG antibodies in serum and CSF and oligoclonal distribution of immunoglobulins in his third CSF examination. Although polymerase chain reaction repeatedly failed to detect genomic material for VZV, EBV, and CMV in the CSF, the possibility cannot be excluded that a reactivated herpesvirus, especially VZV, participated in the pathogenesis of the encephalopathy in this patient.

This report does not clarify the role of mefloquine in the pathogenesis of PMNS, which had been given to...
only 1 of our patients. Mefloquine has been identified as a risk factor for PMNS and may have adverse effects, such as acute confusion and generalized convulsions. Neither mefloquine nor halofantrine, which was given to patient 2, has been associated with the neurological symptoms seen in our patients.

We conclude that the clinical spectrum of PMNS is broader than previously recognized and includes a distinct syndrome of motor aphasia, generalized myoclonus, and postural tremor. This severe variant of PMNS should prompt early corticosteroid treatment, which induced rapid clinical recovery in our patients. Our proposed preliminary classification of this syndrome should alert the clinician that corticosteroid therapy, while not necessary in most cases of PMNS, is indicated in a severe, progressive variant, with patients being severely disabled by their symptoms and not showing any signs of spontaneous recovery.

Accepted for publication September 9, 1997.

Corresponding author: Hans Schnorf, MD, Central Hospital, Avarua, Rarotonga Island, Cook Islands.

REFERENCES


Announcement

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