

Neurological complications following *Plasmodium falciparum* infection

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ABSTRACT

Several neurological complications are associated with severe falciparum malaria. Cerebral malaria is one of the most life-threatening complications. A few patients may experience a neurological syndrome after complete recovery from *Plasmodium falciparum* infection. In the literature especially the postmalaria neurological syndrome (PMNS), acute disseminated encephalomyelitis (ADEM) and delayed cerebellar ataxia have been reported.

We describe a case of a 53-year-old woman who was re-admitted after an adequately treated *P. falciparum* infection with word-finding difficulties, confusion and tremor.

Peripheral blood smears were repeatedly negative for malarial parasites. The clinical features best fitted a PMNS. Because of the severity of the syndrome she was treated with high-dose prednisone. She recovered completely.

The possibility of ADEM is also discussed.

Aetiology of these syndromes is still unknown, but it could be mediated by an immunological mechanism. PMNS or ADEM must be considered when neurological signs and symptoms occur after recovery from a *P. falciparum* infection.

KEYWORDS

Malaria, neurological features, *Plasmodium falciparum*, postmalaria neurological syndrome

INTRODUCTION

Malaria affects 300 to 500 million cases worldwide with three million deaths each year.¹⁻³ In the Netherlands approximately 300 cases of malaria are reported annually.⁴ True incidence is estimated to be three times higher. Increasing incidence has been related to growing mobility,

resistance of the parasite to chemoprophylaxis, resistance of the *Anopheles* mosquito to insecticides, changes in the climate and failing of malaria reduction programmes.^{1,2}

Plasmodium falciparum is the most serious cause of malaria; it has a high mortality without treatment. *P. falciparum* invades erythrocytes of all ages, which can give parasitaemia levels of up to 50%.² Serious complications of *P. falciparum* infection include cerebral malaria, renal failure, pulmonary oedema, hypoglycaemia, anaemia, spontaneous bleeding and gastroenteritis. Cerebral malaria, an acute encephalopathy, is the most serious neurological disorder related to a *P. falciparum* infection. Symptoms are cerebral oedema and diffuse petechial bleedings with fever, severe headache, delirium and also stupor or coma with generalised seizures. Mortality is up to 20% and 10% of survivors still have neurological symptoms after discharge from the hospital. Malaria or quinine-induced hypoglycaemia can also lead to coma.^{2,3}

A few patients may experience a neurological syndrome after complete recovery from *P. falciparum* infection. In the literature especially the postmalaria neurological syndrome (PMNS), acute disseminated encephalomyelitis (ADEM) and delayed cerebellar ataxia have been reported.^{3,5-14}

We present a case of PMNS and will also discuss other possible causes of neurological complications following malaria, such as ADEM.

CASE REPORT

A 53-year-old woman was admitted to our hospital because of fever (body temperature up to 39°C), chills, headache and myalgia. She also mentioned severe tiredness, nausea, vomiting and nonbloody diarrhoea. Eleven days previously she had returned from a seven-day city tour in Kenya. She

had not taken any chemoprophylaxis for malaria. Her fellow travellers were all healthy. A peripheral blood smear showed 6% parasitaemia with *P. falciparum*.

Physical examination revealed a seriously ill woman. Blood pressure was 105/70 mmHg, pulse rate 120 beats/minute and body temperature 41°C. Except for right upper abdominal pain, there were no other abnormalities, and in particular no hepatosplenomegaly. Neurological examination was normal. Immediately after admission, her blood pressure dropped to 85/50 mmHg with a good reaction to fluid challenge.

Laboratory investigations (table 1) showed raised liver enzymes, mild renal dysfunction which recovered within two days and diffuse intravascular coagulation. Electrocardiography revealed a sinus rhythm with right bundle branch block and negative T tops in leads III, AVF and V₃. Chest X-ray was normal. She was treated for seven days with quinine 600 mg three times a day by intravenous infusion. Peripheral blood smear became negative on day 4 and blood cultures were all negative. Because of consolidation of the middle and lower segment of the right lung on the chest X-ray cefazolin (1 g three times a day) and ciprofloxacin (200 mg twice daily) were given for seven days. Abdominal echography revealed splenomegaly and some pleural effusion on the right side.

On day 5 she became afebrile. After 13 days she was discharged from the hospital in a good clinical condition. Five days later she was readmitted because of arthralgia and a body temperature of 38°C. She was tired, had diffuse pain in her body and a nonproductive cough. Physical examination revealed some crackles on inspiration, painful abdominal palpation and normal joints. Laboratory investigations (table 1) showed anaemia, mild transaminase elevations and negative peripheral blood smear for malaria. Chest X-ray was normal and she was readmitted for observation.

Table 1
Laboratory investigations

	DAY 1	DAY 18	DAY 21
Haemoglobin (mmol/l)	9.8	6.3	5.8
Leucocytes (10 ⁹ /l)	9.1	5.3	2.8
Thrombocytes (10 ⁹ /l)	22	276	166
CRP (mg/l)	184	6	6
Sodium (mmol/l)	128	139	137
Potassium (mmol/l)	4	4.8	4.5
Creatinine (µmol/l)	152	91	81
γ-GT (U/l)	141	88	52
Alkaline phosphatase (U/l)	110	138	101
ASAT (U/l)	160	68	55
ALAT (U/l)	75	93	65
LDH (U/l)	1412	919	932
glucose (mmol/l)	10.9	4.8	5.5
APTT (sec)	33	25	
D-dimer (mg/l)	25.3		
Blood smear (%)*	6	0	0

*Number of infected erythrocytes.

Three days after readmittance, she became confused and had progressive difficulty in finding words. Her blood pressure was 90/60 mmHg, pulse rate 100 beats/minute and body temperature 37°C. Physical examination showed shortness of breath. The neurological examination revealed a mixed aphasia, a position tremor, general restlessness and wide open eyes with mydriasis; pupil reactions to light and convergence were normal. Neck stiffness, paresis or abnormal reflexes were absent. The differential diagnosis included a parasitic infection (malaria, borreliosis or trypanosomiasis), bacterial infection (enteric fever), viral encephalitis, acute disseminated encephalomyelitis (ADEM), a postmalaria neurological syndrome (PMNS) or a drug-related disorder (quinine or ciprofloxacin). Laboratory investigations showed normocytic anaemia, leucopenia and decreasing liver enzymes levels (table 1). Peripheral blood smears were repeatedly negative for parasites.

Examination of the cerebrospinal fluid (CSF) showed 5 x 10⁶/l leucocytes (24% lymphocytes and 6% monocytes) and a protein level of 0.67 g/l. Results of extensive serological studies and cultures, both of serum and CSF, were negative except for *Rickettsia conorii* (IgM 1:128, IgG 1:64) and *Rickettsia tsutsugamushi* (IgM 1:32, IgG 1:128) in the serum. Brain computer tomography (CT) was normal. Magnetic resonance imaging (MRI) of the brain failed because of anxiety and dyspnoea. Electroencephalography showed diffuse slowing of the background activity with intermittent dysrhythmic discharges consistent with a diffuse encephalopathy.

On suspicion of severe PMNS prednisone was given intravenously (75 mg/24 hours for three days, and then tapered with 10 mg/day). We also started doxycycline 200 mg per day for a possible rickettsiosis, although clinical course, the absence of a rash or any other skin appearance and the long incubation period made this diagnosis improbable.¹⁵ Rapid recovery was seen within 24 hours. On day 33 she left the hospital. One month later she had recovered completely.

DISCUSSION

Our patient had neurological signs and symptoms that seemed to be related to the prior *P. falciparum* infection. We excluded cerebral malaria by negative peripheral blood smear and also other causes of infectious meningo-encephalitis as trypanosomiasis, viral or bacterial infections. Although *Salmonella typhi* infection can cause neuropsychiatric symptoms such as confusion, ataxia, meningitis, myelitis and acute psychosis,¹⁶⁻¹⁷ this diagnosis was thought to be less likely because of the relatively long incubation period, and the negative investigation of CSF and negative cultures of blood and faeces.

We did find positive Rickettsial serology suggesting a possible infection with *R. conorii*. *R. conorii* infections are frequently reported from Africa and are known in Europe

as Mediterranean spotted fever and in Kenya as Kenya tick typhus. This rickettsial infection can cause cerebral symptoms and severe myalgia.¹⁵ However, our patient developed her symptoms more than a month after returning from Kenya and did not show any signs of a rash or eschar. A rickettsial infection was therefore less likely to be the cause of the symptoms present during her second admission to the hospital.

Another explanation for the neurological symptoms of our patient could have been the earlier prescribed medication. Neurological symptoms induced by quinolones (such as ciprofloxacin) develop during the first days of treatment and disappear within 24 to 48 hours after discontinuation. So the time interval excludes a side effect of ciprofloxacin. A quinine intoxication was another option in our differential diagnosis. Calculated creatinine clearance on admission was 34 ml/min, which needed readjustment of the dosage of quinine. After rehydration creatinine clearance was 66 ml/min within two days, which justifies normal dosage. Quinine intoxication results in hypokalaemia, hypoglycaemia, cardiotoxicity, visual symptoms (also blindness) and neurological features as convulsions, coma and ataxia.¹⁸⁻²¹ Except for the neurological symptoms our patient did not have any of the symptoms mentioned above. Normally these symptoms develop during or shortly after the usage of quinine. In our patient the symptoms developed 14 days after the last gift of quinine, and therefore a quinine intoxication was less likely.

It was most likely that she had PMNS or ADEM. Both syndromes have been reported following complete recovery of *P. falciparum* infection.^{3,5-10,12}

In general, the inclusion criteria for PMNS are recent symptomatic malarial infection with parasites cleared from the blood, full recovery in cases of cerebral malaria and the development of new neurological or psychiatric symptoms within two months of acute illness.⁷

ADEM is an uncommon inflammatory demyelinating disease of the central nervous system with multifocal neurological symptoms, signs of an acute meningo-encephalopathy, depressed level of consciousness, focal or generalised seizures, and psychosis. The disease is usually preceded by a viral or bacterial infection or a vaccination and has occasionally been reported in the literature following *P. falciparum* infection.^{10,12}

PMNS was first described by Mai *et al.* in 1996.⁷ They found 22 cases with PMNS in 18,124 patients treated for a *P. falciparum* infection from Vietnam and Thailand of whom 1176 had severe infections; 21 patients with PMNS had had a severe infection. Incidence in this population was estimated at 1.2 per 1000 patients (95% CI 0.7 to 1.8). The true incidence is probably higher, because people with mild neurological signs and symptoms do not visit a hospital and could have been treated at home. PMNS has been described only after *P. falciparum* infections, not after infections caused by other *Plasmodium* species.⁷⁻⁹ At

the time of the diagnosis all patients were aparasitaemic. The median time from parasite clearance to the onset of neurological symptoms was four days (range 6 hours to 60 days).⁷ In our patient neurological symptoms were found 17 days after the first negative peripheral blood smear. In PMNS acute confusion or psychosis was seen in 13 cases, seizures in eight and a fine tremor of the extremities in one.⁷ Serum and CSF investigations showed no other cause such as metabolic disorders or infections that explains these features. A minor increase in the CSF protein level was found in 13 patients described by Mai *et al.*,⁷ both patients described by Schnorf *et al.*,⁸ the case of Mohsen *et al.*¹⁰ and in our patient. All patients described by Mai *et al.*⁷ recovered spontaneously within ten days. They suggested a relation with the use of mefloquine. Mefloquine may cause neuropsychiatric symptoms and seems to be a risk factor for developing PMNS, although five of 22 patients with PMNS were not taking mefloquine. In the randomised trial by Mai *et al.* ten patients out of 228 who were on mefloquine developed PMNS and one out of 210 treated with quinine developed PMNS.⁷ Both patients reported by Schnorf *et al.* were taking quinine⁸ as was our patient.

The clinical spectrum of PMNS was expanded by Schnorf *et al.*⁸ They classify PMNS according to the severity of symptoms:

1. Mild or localised form characterised by isolated cerebellar ataxia or postural tremor.
2. Diffuse, but relatively mild self-limiting encephalopathy characterised by acute confusion or epileptic seizures.
3. Severe, progressive corticosteroid-responsive encephalopathy, characterised by motor aphasia, generalised myoclonus, postural tremor, and cerebellar ataxia.

This classification includes cerebellar ataxia occurring after *P. falciparum* infection, which was first described in Sri Lanka by Senanayake in 1984.^{5,6} Senanayake and de Silva reported 74 patients with cerebellar ataxia after *P. falciparum* infection.⁶ All these patients were fully conscious and alert without any signs of cerebral involvement. They all had gait ataxia. One third of these patients still had a parasitaemia at the time the ataxia occurred in contrast to the patients with PMNS. Ataxia started 3 to 41 days (median time 13 days) after the last febrile period and there was no response on antimalarial therapy, which suggests that the *P. falciparum* infection was not the cause of the cerebellar ataxia.^{5,6}

Our patient with a progressive course of confusion, drowsiness, intention tremor and word-finding difficulties had a severe PMNS according to the classification by Schnorf *et al.*⁸ Rapid recovery was seen after starting prednisone 75 mg/day for three days, followed by tapering by 10 mg/day.^{6,8} Both patients described by Schnorf *et al.* were treated with prednisone 9 and 12 days respectively after development of the neurological features.⁸ Treatment with prednisone (60 mg/day for seven days, then tapered)

was given to three of 74 patients with cerebellar ataxia in the studies of Senanayake and de Silva. One patient recovered within seven days, while the symptoms of the others remained for two to 30 days.^{5,6} In summary, treatment with prednisone is suggested when there is a severe and progressive course of PMNS.

Aetiology of PMNS remains unclear. As in cerebellar ataxia and ADEM, it seems to have an immunological origin.^{3,5-8,10,11} The delay between the onset of the *P. falciparum* infection and the PMNS might also support an immunological mechanism, just as the rapid response to prednisone treatment.

Schnorf *et al.*⁸ and Mohsen *et al.*¹⁰ found normal brain CT scans, while MRI in two patients showed several discrete white matter lesions, which have also been described in mild ADEM. However, white matter lesions are far more prominent in most cases with ADEM including those with minor signs and symptoms.^{10,11} The hallmark lesions of ADEM are perivenular inflammation and surrounding demyelination which may be minimal or widespread, with coalescence of the multiple lesions. ADEM is characterised by the presence of hyperintense lesions in brain MRI or diffuse or scattered low-density lesions in the white matter. Recovery can begin within days, with complete resolution occasionally noted within a few days, but more often over the course of weeks or months.¹⁰⁻¹² In postmalarial cerebellar ataxia demyelinating lesions have been described in the pons and cerebellar peduncles which disappeared after resolution of symptoms, but in two other cases MRI was normal.¹²⁻¹⁴

Unfortunately, in our patient MRI scanning was not possible. CT scanning did not show any abnormalities. From the evolution of signs and symptoms we concluded that our patient was suffering from PMNS, but a relation between PMNS and ADEM remains possible.

CONCLUSION

The aim of this case report was to draw attention to neurological syndromes after *P. falciparum* infection, especially the postmalaria neurological syndrome, which has not been described before in the Netherlands. Patients with a severe *P. falciparum* infection can develop a neurological syndrome which is related to a prior adequately treated *P. falciparum* infection after an initial good and rapid recovery. What is important is the fact that no parasites can be found in the blood when these symptoms emerge. It can be difficult to distinguish between PMNS and ADEM, which are possibly related. Most patients show spontaneous recovery. Treatment with steroids may be considered when the features are severe and the course is progressive.⁸ Aetiology remains unclear, but an immune mechanism seems probable.^{5-8,11}

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