Case report

Plasmodium falciparum malaria, bilateral sixth cranial nerve palsy and delayed cerebellar ataxia

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Abstract

We describe the case of a 14-year-old Caucasian male, a resident in the Democratic Republic of the Congo, who was observed in Portugal with severe *Plasmodium falciparum* malaria with high-level parasitemia and severe thrombocytopenia. The course was complicated by bilateral sixth cranial nerve palsy during acute malaria, followed by the appearance of delayed cerebellar ataxia during the recovery phase. This occurred after successful treatment with quinine plus doxycycline over seven days. Different levels of thrombocytopenia and C-reactive protein were observed during both neurologic events in the presence of HRP-2 positive tests for *Plasmodium falciparum* antigen. The patient recovered completely after three months.

Key words: *Plasmodium falciparum*; malaria; sixth cranial nerve palsy; delayed cerebellar ataxia

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Introduction

Plasmodium falciparum malaria is the most common imported parasitic disease in Portugal. Most often patients are infected in Africa [1]. Malaria should be suspected in anyone with fever or history of fever who has returned from or previously visited a malaria endemic area, regardless of whether prophylaxis was taken or not.

Typically, uncomplicated malaria presents as an undifferentiated febrile illness. However, several neurological complications are known. In 1994, in Vietnam, Nguyen described a post-malaria neurological syndrome (PMNS) in 1.8% of the patients after severe *P. falciparum* infection [2]. PMNS was defined in the presence of neurological or psychiatric symptoms within two months after recovery of acute illness. This implicates, in the case of symptomatic malaria infection with initial blood smear positive for asexual forms of the parasite, that parasites would have been cleared from the peripheral blood or, in the case of cerebral malaria, that the patient recovered complete consciousness [2]. Most cases described in the literature occurred in adults living in endemic areas for malaria, mainly in Asia and Africa, but additional cases were described in non-immune hosts (93%) who travelled to endemic countries without taking prophylaxis [3].

Cerebellar involvement in *P. falciparum* malaria can occur during the acute stage of fever, as sequels of cerebral malaria in survivors, in the form of delayed cerebellar ataxia (DCA) and as a side effect of drugs [4]. Two syndromes of cerebellar ataxia have been recognized: acute (or early) cerebellar ataxia and delayed (or late) cerebellar ataxia [5,6].

Acute cerebellar ataxia has been described in patients with cerebral malaria who were found to have cerebellar ataxia on recovery from coma. Cerebral malaria was defined as asexual parasitemia in a febrile patient with an unrousable coma of more than six hours for which no other cause was evident [6]; it was also described in patients with acute malaria and *P. falciparum* positive asexual parasitemia after treatment with chloroquine [7]. DCA refers to patients who developed cerebellar ataxia shortly after full recovery from an uncomplicated attack of malaria [6].

DCA was first described in 1984 in residents and regular visitors to Sri Lanka [8]. Since then more cases have been described in Asia [9] and Africa [6], mainly in adults. Only a few cases have been reported to occur in children (<18 years) [5,6,9]**.** Here we describe a case of PMNS in a child, a resident in a *P. falciparum* endemic area, who developed DCA. It is

also the first case described of bilateral sixth cranial nerve palsy and DCA.

Case report

A 14-year-old Caucasian male resident in Kinshasa, Democratic Republic of the Congo, was referred to our infectious diseases clinic with a five-day history of fever, chills, sweating, malaise and watery diarrhoea. Splenomegaly was the only abnormal finding upon physical examination. He had a past history of one episode *P. falciparum* malaria.

Peripheral blood analysis showed anemia (hemoglobin: 9.7 g/dL), leukopenia (3,900/mL), and thrombocytopenia (12,000/mL). C-reactive protein (CRP) was 20.21 mg/L. A blood smear revealed the presence of *P. falciparum* ring forms with a parasitemia level of 7%. Rapid antigenic tests were positive for *P. falciparum*.

Intravenous quinine sulfate plus doxycycline were administered over seven days. Intravenous ceftriaxone was started and maintained until negative blood culture results were available, because enteric fever (*Salmonella typhi* and *Salmonella paratyphi*) can be acquired in developing countries worldwide and may coexist with malaria but also bacteremia complicating severe malaria is not uncommon in infants and children and may cause any patient's clinical status to deteriorate abruptly. The next day, excessive sleepiness and diminished talkativeness was observed.

Peripheral blood analysis showed hyponatremia (124.6 mmol/L), hypoalbuminemia (2.1 g/dL), elevated lactate dehydrogenase (1043 U/L), alanine transaminase and, aspartate aminotransferase (82 U/L) values; arterial hypoxemia, hyperlactatemia (5.46 mmol/L), metabolic acidosis; blood level parasitemia of 14% and anemia (Hb-6.5 mg/dL).

He was transferred to the intensive care unit and transfused with packed red blood cells. On day 3, a bilateral sixth cranial nerve palsy was diagnosed. On day 4, parasitemia was negative; HRP-2 based rapid diagnostic test was positive. Electroencephalogram (EEG) showed the presence of bilateral slow-wave activity consistent with diffuse encephalopathy. Brain magnetic resonance imaging (MRI) and computed tomography (CT) scans showed no alterations. On day 9, he was discharged maintaining symptoms of double vision and signs of bilateral sixth cranial nerve palsy.

Twelve days later, he was readmitted because of sudden onset of fever (39.8ºC), somnolence, word-finding difficulty and postural tremor. He was easily rousable, conscious and oriented, and no meningeal signs were apparent; neurological assessment showed a truncal ataxia. He had one episode of generalized tonic-clonic seizure followed by a postictal state in the nursery. Blood analysis showed a CRP of 1.21 mg/L and thrombocytopenia (121,000/mL). Cerebrospinal fluid (CSF) analysis showed elevated protein content (44 mg/dL) and a pleocytosis of 92 mononuclear cells. Intravenous quinine and doxycycline were started and maintained for three days.

A provisional diagnosis of meningoencephalitis was considered. Meningoencephalitis due to *Listeria monocytogenes* may mimic herpes encephalitis. However, brain imaging, electroencephalogram, and polymerase chain reaction (PCR) results made a viral hypothesis less probable. Empiric treatment with ampicillin was started and maintained over 10 days, until CSF culture results were reported negative.

Repeated peripheral blood smears were negative for ring forms of *Plasmodium* sp. However, HRP-2 test positivity and thrombocytopenia was maintained until day seven after readmission. Brain tomography and MRI were normal. Electroencephalogram (EEG) showed slow-wave activity consistent with diffuse encephalopathy. PCR for herpes simplex viruses, varicella zoster virus, human herpesvirus type 6, and enterovirus were negative in the CSF. Serology for arboviruses, enteroviruses, syphilis, leptospirosis, Q-fever, toxoplasmosis, mycoplasma, cytomegalovirus, Epstein-Barr virus and HIV-1/2 were negative. Autoimmunity studies were negative. EEG alterations normalized and cerebellar ataxia disappeared after two weeks. The patient was discharged and was sent home.

Two months later, a complete recovery from the bilateral sixth cranial nerve palsy was observed.

Discussion

Cerebellar syndromes have been reported in both complicated and uncomplicated *P. falciparum* malaria and rarely after *P. vivax* infection [10,11]. Acute cerebellar ataxia is encountered during the recovery period after cerebral malaria and DCA occurs after uncomplicated malaria; the occurrence is estimated to be 0.25% [2]. Most of the cases (97%) were associated with severe malaria with a high (median, 16%) parasitemia. Time from the clearance of parasitemia to the first neurological symptom ranged from four to 15 days, while the median duration of the disease varied from 2.5 to 13 days [2]. The most common signs and symptoms are impaired

consciousness (77%), confusion (66%), fever (50%), generalized seizure (33%), aphasia (28%), tremor (23%), psychosis (17%) and myoclonus (11%), headache (8%), weakness (6%), catatonia (6%) and ataxia (6%) [3].

The pathogenic mechanisms associated with PMNS are not fully understood. Their rapid resolution makes a structural lesion unlikely and the clearance of parasitemia before symptoms onset make a cytoadherence mechanism less probable. EEG in our patient revealed diffuse background slowing, suggesting mild to severe encephalopathy. Brain MRI scans often show increased signal uptake in various regions. Brain CT scans are normal [3]. CSF analysis is abnormal in most patients with lymphocytic pleocytosis (50%) and elevated protein content (70%). Mild pleocytosis and increased protein content can also be the result of seizures; therefore, other causes of encephalopathy must be excluded [12]. CSF lymphocytic pleocytosis and elevated protein levels may support an immune mechanism at least in those patients without seizures. However, trigger factors for an immune mechanism after the successful treatment of an episode of malaria are currently unknown. No link between PMNS and different new strains of *P. falciparum* has been established so far.

Our patient had two simultaneous neurological manifestations: the bilateral sixth cranial nerve palsy sequel to severe infection, and DCA, a PMNS. These manifestations seem to be the result of the interplay involving different factors from the host (immunity, platelets and vascular endothelium) and from the parasite (*Plasmodium* adhesion molecules) leading to a state of inflammation either in the presence of infected erythrocytes (cranial nerve palsy) or in their absence (DCA).

The mechanism of immunity is still unclear. CD4+ T-cells play a central role in the immune response to malaria. They are required to help B-cells to produce the antibody that is essential for parasite clearance [13]. Acquired protection from malaria following natural exposure to *P. falciparum* parasites is mediated by IgG. Parasite-encoded, clonally variant surface antigens (VSA) are the main targets of protective IgG. They are organized into families, and the best-known antigen is *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), which is located in the knob structures on the infected erythrocyte surface [14]. VSA mediate the adhesion of the mature developmental stage (trophozoites and schizonts) infected erythrocytes to different receptors present in the host vasculature. Each parasite genome has multiple VSA-encoding genes for protein variants with different antigenic and adhesive properties. VSA diversity appears to be finite, as immune sera from African adults can recognize infected erythrocytes from different continents [14,15]. VSA associated with severe malaria are frequently and strongly recognized by antibodies in individuals with no or little pre-existing immunity. VSA associated with uncomplicated malaria and asymptomatic infection in semi-immune people are those that are rarely and poorly recognized by the immune system [14,15].

In areas of stable transmission, clinical immunity to mild malaria is acquired slowly, and it is not usually effective until early adolescence. Life-threatening disease is restricted to a much younger age group, indicating that resistance to severe infection is acquired more quickly [16]. This concept suggests that all the first *P. falciparum* infections should be the most severe.

The case presented is an argument against this concept because our patient had a previous episode of uncomplicated malaria in 1997 when he had no pre-existing immunity followed by the more severe and complicated infection we describe here. We believe that our patient was probably infected by a local strain for which he had no previous VSA-specific antibodies, either because immunity was lost by lack of stimulation since 1997 or because he became infected with a different new strain. In both cases the parasite took advantage of a "hole" in the immune repertoire of the patient that was closed by the ensuing disease. However, there is a lack of evidence for antibody mediation in DCA [17].

Overproduction of cytokines is associated with the activation of the vascular endothelium, a key component of cerebral malaria but not the only one [18]. The inflammatory cytokines (IL-1, IL-2, IFN-ϒ, and TNF-α) are all required for the development of experimental severe malaria (ESM). A marked elevation of serum TNF-α, IL-6, and IL-2 was demonstrated in DCA [19,20]. CD4+ T-cell activation leads to the production of pro-inflammatory cytokines, which up-regulate a variety of macrophage functions, one of which is the release of TNF-α in response to malaria antigens [21]. Also, sequestered leucocytes release TNF-α, leading to the amplification of a cytotoxic effect on endothelial cells, vascular wall damage and hemorrhagic necrosis. A clear role for TNF-α has been shown in parasite killing. At physiological concentrations, recombinant TNF-α is antiparasitic, synergizing with

IFN-ϒ to induce production of nitric oxide and other toxic radicals [22]. Differences in resistance and susceptibility to ESM in different strains of mice correlate with the development of inflammatory versus anti-inflammatory cytokines [20].

These data suggest that pre-existing immunity can modulate the severity of the disease. Our patient could have had some immunity to *P. falciparum* because he was living in a country endemic for malaria and he had had a previous infection, which probably accounted for his being partly protected against the development of cerebral malaria.

Our patient had elevated CRP during the acute phase of malaria and during DCA with values of 20.21 mg/dL and 1.21 mg/dL, respectively. These data suggest that different levels of inflammation occurred during both episodes. The severity of the clinical manifestations correlated with CRP and thrombocytopenia values. Thrombocytopenia is common in all forms of malaria. Platelet-mediated red blood cell agglutination has been associated with severe malaria and platelet binding to endothelial cells was associated with increased cell permeability [23]. CD36, a platelet receptor for infected erythrocytes, is also present in brain endothelium and may play a role in platelet activation. However, the exact mechanism for thrombocytopenia is not known [24].

Our case presented severe thrombocytopenia during acute malaria and during DCA with the simultaneous persistence of HRP-2 antigen until recovery from DCA. Histidine-rich protein 2 (HRP-2) is a water-soluble protein produced by asexual forms and young gametocytes of *P. falciparum*. HRP-2 based rapid diagnostic tests can stay positive for more than five weeks after successful treatment because of prolonged persistence of HRP-2 antigen in the circulation after parasite death and/or because of longer but limited persistence of immature gametocytes in the blood after successful therapy [25]. It is not known whether persistent HRP-2 antigenemia or the gametocytes have any role in the development of DCA.

Our patient was treated with blood-stage schizonticide drugs which are effective against multidrug-resistant parasites but do not eliminate gametocytes. However, PMNS was described after treatment with artemisins, which are gametocytocide drugs, suggesting that a clean-up mechanism of *Plasmodium* antigens could be involved. A synergic effect was found between mefloquine treatment and disease severity in inducing PMNS [2]. However, mefloquine is not the only risk factor. PMNS may occur in patients that had not received the drug and also may follow uncomplicated *P. falciparum* malaria [9].

To conclude, we describe a case of severe *P. falciparum* malaria with high-level parasitemia and severe thrombocytopenia, complicated by bilateral sixth cranial nerve palsy, and followed by delayed cerebellar ataxia during the recovery phase. Pathogenic mechanisms and associated clinical syndromes in *P. falciparum* malaria may result from the complex interplay between host-related factors in which previous immunity could be an important aspect. Also, parasite related factors could be involved, modulating the intensity of the immunological mechanisms and the degree of the associated brain damage.

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