Case Report/Relato de Caso

Postmalaria neurological syndrome: a case report

Síndrome neurológica pós-malária: relato de um caso

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ABSTRACT

Described here is a case of postmalaria neurological syndrome in a patient who presented infection by *Plasmodium falciparum* two months earlier. The patient received empiric use of acyclovir for herpetic meningoencephalitis, but neuropsychiatric symptoms improved only after administration of methylprednisolone.

Keywords: Postmalaria neurological syndrome. Methylprednisolone. *Plasmodium falciparum.*

RESUMO

Descrição de um caso de síndrome neurológica pós-malária em paciente que apresentou infecção por *Plasmodium falciparum* dois meses antes. O paciente fez uso empírico de aciclovir para meningoencefalite herpética, mas a melhora dos sintomas neuropsiquiátricos só ocorreu após administração de metilprednisolona.

Palavras-chaves: Síndrome neurológica pós-malária. Metilprednisolona. *Plasmodium falciparum.*

INTRODUCTION

The postmalaria neurological syndrome was first described by Nguyen and colleagues in 1996, when the criteria for its diagnosis were defined[1-9]. The syndrome features an acute onset of neuropsychiatric or neurological symptoms in patients recently treated for malaria due to *Plasmodium falciparum* and who have no parasitemia when the symptoms appear[1-2]. The signs and symptoms (and frequency by which they occur) are decreased level of consciousness (77%); confusion (66%); fever (50%); generalized seizures (33%); aphasia (28%); tremor (23%); psychosis (17%); myoclonus (11%); headache and ataxia (each at 8%); and weakness, catatonia, and acalculia (each at 6%)[3]. The postmalaria neurological syndrome, described only after malaria by *P. falciparum*, has not yet been reported after malaria by other species[7].

A principal aspect distinguishes postmalaria neurological syndrome from cerebral malaria (one of the manifestations of severe malaria): the timing of appearance. While the former entity arises after the disappearance of the parasitemia, in a variable time that has been described as lasting up to two months[4-5], the later entity arises during the existence of parasitemia.

Postmalaria neurological syndrome occurs 300 times more frequently in severe malaria than in non-complicated cases of malaria[1,4]. Its overall incidence is 0.1% in patients with malaria due to *P. falciparum*[1,4].

CASE REPORT

JCSC, 24 years old, married, a member of the Brazilian military, was admitted on August 15, 2010 at the Emergency Unit of the Army Central Hospital (Hospital Central do Exército, HCE) in Rio de Janeiro, six days after returning from a peacekeeping mission in Haiti that had lasted six months.

During his stay at the Department of Infectious and Parasitic Diseases, he presented fever (38°C), chills, malaise, dizziness, headache, nausea and vomiting, jaundice (+/4), and superficial abdominal pain on palpation in the right upper quadrant. Laboratory tests revealed mild thrombocytopenia (100,000/mm^3), anemia (hematocrit: 35.4%; erythrocytes: 4,3x10^6/mm^3; hemoglobin: 12.1g%), elevated transaminases (aspartate aminotransferase: 129 units/L; alanine aminotransferase: 150 units/L), and total bilirubin at 2.4mg% with predominance of the conjugated fraction. Chest radiography, abdominal ultrasound, urinalysis, and electrocardiogram showed no abnormalities.

The peripheral blood smear evidenced the presence of *P. falciparum* parasitemia with qualitative 3+ (corresponding to 21-200 parasites/field). Endovenous quinine (500mg every 8h) and endovenous clindamycin (600mg every 6h) were administered. After three days, the patient was still febrile and thrombocytopenic (54,000/mm^3). His medication was changed to endovenous artesunate (2.4mg/kg as attack dose, followed by 1.2mg/kg every 12h) for three days plus five doses of artesunate/mefloquine (200/440mg) every 12h for three days. On the 12th day of hospitalization, the patient was discharged because of his good health condition. The post-treatment control of parasitemia, performed by the Fundação Nacional de Saúde (FUNASA), was negative in seven times it was carried out.

On October 16 (51 days after discharge) the patient returned to the Emergency Unit of HCE, presenting tonic-clonic seizures and mental confusion. He had delirium plus visual and auditive hallucinations, generalized spasms, and misleading and cerebellar syndrome, evolving to psychomotor agitation and decreased sensorium. Due to the seriousness of the case, the patient was admitted to the Intermediate Care Unit of the hospital.

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The next day, the cerebrospinal fluid examination revealed 30cells/mm^3 (99% of mononuclear cells and 1% of polymorphonuclear cells), protein at 82mg%, and glucose at 67mg%. The search for malaria was negative in peripheral blood smear. Acyclovir was administered endovenously (250mg every 8h) on this same day on the possibility that it was a herpetic meningoencephalitis.

On October 20, a second cerebrospinal fluid examination revealed 160cells/mm^3 (93% of mononuclear cells and 7% of polymorphonuclear cells), protein at 269mg%, glucose at 58mg%, and chloride at 115mEq/L, and direct examination for acid-fast bacilli and *Cryptococcus neoformans* was negative. A tuberculostatic scheme (rifampin/isoniazid/pyrazinamide/ethambutol) was empirically introduced on this date. The results of a computed tomography scan on October 23 were normal.

Methylprednisolone was administered for three days from October 21 at a dosage of 1g/day on the possibility that it was a postmalaria neurological syndrome. There was significant improvement in neurological disorders after one day of the onset of corticosteroid therapy.

The tuberculostatic scheme was discontinued on the eighth day of use because of liver toxicity. An encephalic magnetic resonance imaging done on November 6 revealed no changes. Acyclovir was continued for 15 days.

The patient was discharged on November 12, 2010, in the absence of motor or cognitive sequelae.

DISCUSSION

The postmalaria neurological syndrome can present various clinical forms. The postmalaria cerebellar ataxia with only the involvement of cerebellum is the variant that has been described in the literature since 1984[2]. Other clinical presentations are encephalopathy and acute disseminated inflammatory demyelinating polyneuropathy[3].

The pathogenesis of postmalaria neurological syndrome, occurring in the absence of parasitemia, appears to be due to the presence of cytokines (tumor necrosis factor-α, interleukin-2, and interleukin-6) produced during the episode of malaria, which remain even after efficacious treatment[1,8]. Studies based on postmalaria cerebellar ataxia have evidenced elevations of these cytokines in both serum and cerebrospinal fluid, as well as a favorable clinical response to corticosteroids, suggesting an immune mechanism as the cause of the syndrome[8].

A review of 36 cases of postmalaria neurological syndrome described in the literature up to 2009 shows that 64% of reported cases occurred in patients in Asia and 33% in patients in Africa. The remaining 3% is accounted for by one patient in the Dominican Republic[3]. The case presented in this article seems to be the first reported in Brazil.

Among thirteen patients cited in ten studies found in the literature, the encephalic computed tomography scan evidenced no change in any of the cases[1-10]. An encephalic magnetic resonance imaging performed in eleven patients was altered in four cases, with inflammatory and demyelinating lesions[1-2,8]. The electroencephalogram was the complementary examination that better evidenced the changes, with signs of encephalopathy in all eleven patients who underwent this examination[1-7,9-10]. The results of the computed tomography scan and magnetic resonance imaging of the patient in the present case report were normal.

The same thirteen patients mentioned earlier underwent lumbar puncture, and the most frequent changes were increased number of cells (ten cases) at the expense of lymphocytes and increased protein levels (11 cases)[1-10]. Our patient also showed a slight increase in the number of mononuclear cells and proteins in cerebrospinal fluid.

Mefloquine may cause neuropsychiatric symptoms and appears to be a risk factor for the development of postmalaria neurological syndrome[7]. However, only three of the 13 patients in the studies cited by the authors used this medication. Neuropsychiatric symptoms (hallucinations, confusional syndrome, acute psychosis, depression, anxiety, etc) occur in 1% of cases and may appear later (after 2 to 3 weeks) due to the prolonged half-life of this drug.

The patient's clinical case presented here was empirically treated for tuberculous and herpetic meningoencephalitis, before beginning corticosteroid therapy. Of the 13 patients in the studies found in literature, five of them used acyclovir[4-5,9-10] due to the characteristics of cells and biochemistry of the cerebrospinal fluid. Despite the rapid improvement with the use of methylprednisolone, acyclovir was continued for two weeks.

Finally, corticosteroids are indicated for the more severe forms and more prolonged evolutions of postmalaria neurological syndrome[2-4]. The use of prednisolone was described for three to ten days[2,9-10] and of prednisone for three to seven days[3,7,10]. We administered methylprednisolone for three days, with a significant improvement of neurological symptoms from the first day of drug use.

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REFERENCES

1. Mohsen AH, McKendrick MW, Schmid MJ, Green ST, Hadjivassiliou M, Romanowski C. Postmalaria neurological syndrome: a case of disseminated encephalomyelitis? J Neurol Neurosurg Psychiatry 2000; 68:388-399.
2. Matias G, Canas N, Antunes I, Vale J. Síndrome neurológico agudo pós-malária. Acta Med Port 2008; 21:387-390.
3. Markley JD, Edmond MB. Post-malaria neurological syndrome: a case report and review of the literature. J Travel Med 2009; 16:424-430.
4. Mizuno Y, Kato Y, Kanagawa S, Kudo K, Hashimoto M, Kunimoto M, et al. A case of postmalaria neurological syndrome in Japan. J Infect Chemother 2006; 12:399-401.
5. Prendki V, Elzière C, Durant R, Hamdi A, Cohen Y, Onnen I, et al. Short report: post-malaria neurological syndrome - two cases in patients of african origin. Am J Trop Med Hyg 2008; 78:699-701.
6. Marsala SZ, Ferracci F, Cecotti L, Gentile M, Conte F, Candeago RM, et al. Post-malaria neurological syndrome: clinical and laboratory findings in one patient. Neurol Sci 2006; 27:442-444.
7. Van der Wal G, Verhagen WIM, Dofferhoff ASM. Neurological complications following *Plasmodium falciparum* infection. Netherlands J Med 2005; 63:180-183.
8. Falchook GS, Malone CM, Upton S, Shandera WX. Postmalaria neurological syndrome after treatment of *Plasmodium falciparum* malaria in the United States. CID 2003; 37:e22-24.
9. Lawn SD, Flanagan KL, Wright SG, Doherty TF, Godfrey-Faussett P. Postmalaria neurological syndrome: two cases from the Gambia. CID 2003; 36:e29-31.
10. Schnorf H, Diserens K, Schnyder H, Chofflon M, Loutan L, Chaves V, et al. Corticosteroid-responsive postmalaria encephalopathy characterized by motor aphasia, myoclonus, and postural tremor. Arch Neurol 1998; 55:417-420.