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Post-Malaria Neurological Syndrome: A Case and Review of The Literature

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Abstract

We present a case of a 38-year-old morrocan man recently returned from Niger, where he had been successfully treated for cerebral falciparum malaria infection with a high parasitemia of Plasmodium falciparum. He was admitted to our hospital since his consciousness level rapidly deteriorated with ataxia and a generalised tonic–clonic seizure despite the parasitemia was cleared by artesun by day 7. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis (69 cells/mL) and hyperproteinorrhachia (137 mg/dL). Brain MRI was unremarkable and EEG revelead focal epileptic anomalies in centrotemporal. PCR testing for neurotropic viruses was negative as were CSF and blood cultures. The patient was treated with ceftriaxone and acyclovir. Steroid therapy was initiated on day 8. Subsequently, the neurological manifestations improved and he was discharged on day 21 without any sequelae. We believe post-malaria neurological syndrome (PMNS), a rare self-limited encephalopathy, that should be strongly considered in patients with recent history of malaria and present with neuropsychiatric symptoms.

Keywords: Post-Malaria Neurological Syndrome (PMNS); Falciparum Malaria, Encephalopathy

Introduction

Malaria is a highly prevalent parasitic disease, clustring around tropical and subtropical areas, such as Africa, the Amazon region and Southeast Asia [1]. Falciparum malaria remains a common cause of morbidity and mortality, with an estimated 229 million cases and 409 000 deaths in 2019 [2]. In Morroco, imported malaria from travellers returning from endemic countries is still a revelant part of our clinical daily life. According to recently published data, there has actually been an increase in annual hospitalisations sue to malaria infections in Morroco [3]. This increase in incidence is important not only regarding the different systemic complications, but also because clinicians in general should be aware of more rare complications of such an infection [1]. Cerebral malaria is the most severe manifestation of Plasmodium falciparum malaria and usually induces a coma. Even in high-income countries, this is a medical emergency, and fatal cases still exist. Therefore, a precise diagnosis and prompt treatment are crucial for survival [4]. Specifically, in the past 20 years, there have been growing reports of a different clinical syndrome that presents after the clearance of parasites from blood [1]. There are three neurological syndromes that can occur following complete recovery from malaria, in particular Plasmodium falciparum and occurring after an interval of 2 days to 2 months [5,6]. These syndromes are an acute disseminated encephalopathy, known as post-malaria neurological syndrome (PMNS); a delayed cerebellar syndrome; and an acute idiopathic demyelinating polyneuropathy (AIDP). These syndromes may follow recovery from an attack of falciparum malaria with no parasitaemia, and more commonly occurs after treatment with mefloquine [4, 5, 6]. These diseases are difficult to diagnose, as their clinical findings often overlap, in which the magnetic resonance imaging findings and immunological etiology are so similar that ADEM is thought to be involved in PMNS [4]. PMNS is a self-limiting neurological complication characterized by a myriad of neuropsychiatric manifestations including mild neurological deficit to severe encephalopathy [6]. It is a rare complication of severe malaria that might be underreported. PMNS was first described in 1996 and since then there have been 48 cases reported in the English literature [6]. We report another case of PMNS in a 38-year-old healthy male and present a review of the disease entity.

Case presentation

A 38-year-old morrocan man, diabetic treated with oral antidiabetic drugs. He was a truck driver and flew routes between Morroco, Niger and the Republic of the Congo. In September 2020, he presented with fever, vomiting, headaches and drowsiness, with hepatic impairment (SGOT/ SGPT 179/224 U/L), hyperbilirubinaemia (93 µmol/L, normal range < 25 µmol/L) and positive thick drop for P. falciparum with 5 parasites/2 µL. Thereafter, the patient received treatment for cerebral malaria falciparum infection included intravenous artesunate (2.4 mg/kg, 5 doses for 3 days), and the patient improved quickly, both clinically and biologically (clearance of parasitaemia from the blood on day 3). In octobre 2020, his wife reported that, during a 3-day period, he showed ataxia, dysarthria, and his fever increased to 39 °C. He was also getting progressively more disoriented, agitated, irritable with confused speech, and exhibited clumsy movements, poor balance and started having visual hallucinations. He was seen at the emergency room, where he had a generalised tonic–clonic seizure prior to observation. On admission, his neurological examination, revealed psychomotor agitation, temporospatial disorientation, effortful speech with wordfinding difficulty and bilateral upper limb ataxia. There was a low fever (37.6°C) and no other symptoms. On admission, a third blood smear was negative for parasites. Laboratory results revealed a high white cell count with slight lymphocytosis (13×109/L leucocytes with 40% lymphocytes); C reactive protein was 0.3 mg/dL (normal: <0.5 mg/dL). Head CTrevealed no changes. Brain MRI performed at day 6 was also normal and an EEG performed at day 7 showed occasional left temporal slow waves. Lumbar puncture performed at day 3 revealed lymphocytic pleocytosis (69 cells/mL) and hyperproteinorrhachia (137 mg/dL). Subsequent results for cerebrospinal fluid (CSF) PCR for common neurotropic viruses (herpes simplex virus 1 and 2; cytomegalovirus; human herpes virus 6 and 7; varicella zoster virus) were negative, as were CSF and blood cultures. Thereafter, he was treated with intravenous artesun despite a negative blood smear, cefotaxime and acyclovir. Intravenous acyclovir was stopped after 6 days following the negative result for HSV PCR in CSF. A clinical diagnosis of PMNS was made and prednisone therapy was started at 1 mg/kg/day. His mentation began improving the second next day, and steroids were tapered over 15 days with full recovery. The patient was discharged with only a slight residual cerebellar ataxia on day 21 and had fully recovered on day 40. Subsequent follow-up at 3 months revealed normal neurological examination. The patient remains completely asymptomatic 6 months later and there have been no relapses or symptoms suggestive of central nervous system dysfunction.

Discussion

The malaria disease causes neurological impairment during its acute phase and cerebral malaria can provoke neurological sequelae. Additionally, a return of neurological signs after cure has been reported [7]. Considering the very large number of cases across the world, it is very surprising that PMNS was only first described in 1994 by Senanayake et al. [8], and since then there have been fewer than 50 cases reported in the literature, mostly as single case reports [5, 7]. The systematic review of the literature found 49 PMNS patient cases of which 43 involved P. falciparum alone, 4 P. vivax alone, and 2 P. falciparum and P. vivax together. No cases were described with P. ovale, P. malariae or P. knowlesi [7]. The incidence of PMNS in patients after falciparum malaria can range from 0.7 to 1.8 per 1000 and it is 300 times more common in patients with severe rather than uncomplicated malaria [9]. Twenty-four (49%) infections were contracted in Asia, 24 (49%) in Africa, and 1(2%) in the Dominican Republic [6]. It therefore appears to be an extremely rare complication but it may also be grossly underreported, since a large number of those affected are young children in the developing world and once recovered from malaria, patients may return home and the subsequent illness either not reported or not ascribed to a complication of malaria [5]. In the studied patient population, PMNS developed mostly in adults (mean age of 33), there were 36 males and 13 females with male:female ratio of around 2.76:1 [6]. PMNS occurred mostly in patients who had preceding severe falciparum malaria (85%), with cerebral malaria (50%), like our case. It was seen most frequently in people who live in, but also in those who travel to, malaria-endemic areas [7]. The exact pathogenesis of PMNS is not known. It appears that PMNS is a post-infectious syndrome probably due to various pathophysiological mechanisms [7]. Some authors suggest obstruction of cerebral microvasculature by parasitized red blood cell inducing cerebral hypoxemia [9, 10]. However, this mechanism is questionable as obstruction of microvasculature does not seem plausible due to the potentially long delay between malaria episode and PMNS [6]. Another postulated hypothesis is immunization against some cerebral antigens after a neurotropic infection, mediated by molecular mimicry and T cell-activated cerebral aggression [11]. The delayed onset, negativity of blood smear, association with fever, and sometimes elevated CRP, negative extensive screening of possible infectious or systemic causes may also suggest this inflammatory pathway, but no demonstration of that has been made to date [7]. An increment of serum and CSF concentrations of inflammatory cytokines such as TNF-alpha, IL 2 and IL 6 has been described in some cases of delayed postmalaria cerebellar syndrome, which decreased following steroid therapy [6]. The approximately 15-day symptom-free period is not without interest, since it corresponds roughly to the 2–3 weeks needed for the production of specific antibodies [7]. Some authors suggest that the PMNS can be related with ADEM, given that they share many characteristics: a postinfectious nature, with multiple neurological signs and symptoms (and multiple white matter changes in MRI in some cases), monophasic course and good overall response after steroid therapy [12], for this Plasmodium falciparum and Plasmodium vivax should be added to the list of pathogens causing ADEM [7]. There is also some evidence of possible molecular mimicry, whereby antibodies to antigens expressed by certain strains of P. falciparum cross-react with antigens in the CNS [6]. However, a study by Siriez et al. was unable to detect intrathecal IgG and specific P. falciparum antibodies in the CSF [6, 13]. The cerebral microvasculature could be the locus of this immunization process, since parasites and pigments are known to be sequestered there due to cytoadherence; this is the case even after P. falciparum clearance and even in non-neurological malaria [7]. The fact that cytoadherence is less significant, or at least less frequent, in P. vivax infection could explain why most PMNS cases follow P. falciparum infections [14]. Coinfection or reactivation of a viral infection capable of causing encephalitis has been suggested as another possible mechanism [4]. Schnorf et al. found elevated IgG and IgM antibodies against CMV and EBV in the serum but not the CSF of one of his patients, and positive IgG antibody against varicella zoster virus in the CSF and serum of the same patient albeit PCR repeatedly failed to detect genetic material of EBV, CMV, and VZV in the CSF. In fact, P. falciparum infection has been shown to induce polyclonal B cell activation and subsequent secretion of different antibodies, causing false-positive serological tests [15]. Risk factors for developing PMNS include severe P falciparum malaria and treatment with mefloquine [1, 5]. Nguyen et al. implicated Mefloquine as a possible cause of PMNS since 17 of 22 patients (77%) were treated with Mefloquine. However, altogether 54.3% PMNS in a litterature review were not taking Mefloquine, like our patient [6]. Additionally, Markley et al 4 also reported patients who developed PMNS after quinine treatment [1]. Cerebellar signs can be seen not only in severe malaria, where they respond to anti-malarial treatment, but also in PMNS, where the inefficacy of anti-malarials and the absence of parasites argue for a different, perhaps immune, mechanism [7]. The median duration of onset of PMNS is 4 days. However, the syndrome can occur anywhere from 0 to 60 days following clearance of

parasitemia [1]. The median duration of symptoms is 13 days (range 3–25 days) [6]. The clinical features of PMNS are compatible with post-infectious encephalitis, either ADEM or AIE [7]. The clinical features as defined in this and subsequent reports are several neurological changes such as aphasia, seizures, confusion, ataxia and psychosis [1, 6]. More rarely, cranial nerve palsy, visual impairment, sphincter disorders, and headaches were seen [7]. CSF findings in PMNS may be variable and may show risen opening pressure, pleocytosis and elevated protein like our case [6]. MRI brain can be unremarkable or reveal some signal changes in various parts of brain. Our patient had a normal MRI of brain [5]. MRI patterns underline a possible link with ADEM or auto-immune encephalitis [7]. The abnormalities consisted of nonspecific findings with increased signal uptake in various regions of brain, including the periventricular areas, brain stem, thalamus, corona radiata, internal capsule, and cerebellum [6]. EEGs, when realized, usually showed signs of encephalopathy [7]. PMNS usually does not require specific treatment [6], but steroids can be used in the most severe cases as they may have a role in the recovery process [7]. Corticosteroids do nonetheless appear to be a first-line treatment for PMNS, at least in severe cases and at least for now. The prognosis of PMNS seems to be good and corticosteroid treatment should be discussed for the most severe cases [7]. Hsieh et al. described persistent unsteadiness in their patient with PMNS for 2 weeks until the use of corticosteroids, which resulted in dramatic recovery [6]. If corticosteroids are not effective, first the diagnosis of PMNS should be reconsidered, and thereafter intravenous immunoglobulin or plasma exchange discussed [7]. The neurological signs and symptoms of PMNS in most of patients resolved within days to weeks [6]. Our patient's symptoms remitted 10 days after admission and he remained asymptomatic until discharge 21 days after admission [4]. In contrast to other infectious diseases causing a coma, most cerebral malaria survivors recover from unconsciousness without much delay; the median time to full recovery of consciousness is about 24 hours in children and 48 hours in adults [4, 5]. The frequency of any neurological sequelae is less than 1% in adults but more frequent in children [4].

Conclusion

PMNS is a rare complication of severe malaria that might be underreported. It can develop up to 2 months after clearance of parasitemia. Most of its characteristics can fit into the diagnosis of post-infectious encephalitis, ADEM or AIE. The addition of malaria due to P. falciparum and P. vivax parasites to the list of pathogens causing ADEM should be highly considered.

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