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Plasmodium vivax cerebral malaria complicated with venous sinus thrombosis in Colombia

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ABSTRACT

Complicated malaria is usually due to *Plasmodium falciparum*. Nevertheless, *Plasmodium vivax* is infrequently related with life-threatening complications. Few cases have been reported of severe *Plasmodium vivax* infection, and most of them from Southeast Asia and India. We report the first case of cerebral malaria due to *Plasmodium vivax* in Latin America, complicated with sagittal sinus thrombosis and confirmed by a molecular method.

1. Introduction

Malaria is one of the most prevalent parasitic infections in the world[1], with 225 million cases and 0.78 million deaths in 2009, mainly in Africa, Asia and South America. Four species of *Plasmodium* affect humans, but more recently *Plasmodium knowlesi* was described in Southeast Asia as a fifth species in primates that rarely affects men[2]. However, the most important species that contribute to increased morbidity and mortality in humans are *Plasmodium falciparum* (*P. falciparum*) and *Plasmodium vivax* (*P. vivax*)[1].

After *P. falciparum*, infection with *P. vivax* is the second most common cause of malaria in the world. It is difficult to treat *P. vivax* because of the hypnozoites and frequent relapses after initial management[1,3]. The previous old paradigm of *P. vivax* as "benign tertian malaria" has been challenged recently by reports of severe disease with complications such as acute respiratory distress syndrome, acute renal failure, severe thrombocytopenia, retinal hemorrhage, toxic shock, and cerebral malaria[4-10]. The purpose of this report is to describe a case of cerebral malaria as a complication of *P. vivax* infection.

2. Case report

A 22 year old male professional soldier was referred from the South Pacific coast of Colombia to Hospital San Vicente de Paúl (Medellín, Colombia), a high complexity referral hospital, with 1 week of subjective fever, malaise and headache. At admission to the emergency room, he was stuporous and febrile without neck stiffness or focal motor signs. Later, he presented two generalized tonic-clonic seizures. With Glasgow Coma Scale of 7/15 in the postictal

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state, he required mechanical ventilation support and was transferred to the intensive care unit.

Initial laboratories showed 55.300 platelets/mm^3, creatinine 1.34 mg/dL, serum glucose 142 mg/dL, lactate 2.7 mmol/L, aspartate aminotranferase 98 U/L, alanine aminotranferase 81.9 U/L, total bilirubin 1.6 mg/dL, indirect bilirubin 1.2 mg/dL, activated partial-thromboplastin time 35.1 s (control of 26 s), and hemoparasite test reported 3.280 parasites/ μ L of *P. vivax*. Treatment was started with intravenous quinine plus clindamycin under suspicion of mixed infection with *P. falciparum*. The different tests ruled out metabolic disorders as a cause of seizures and blood cultures for bacteria were negative. No additional study was performed to rule out coagulopathy.

Cerebrospinal fluid analysis was normal. Brain computed tomography was normal but magnetic resonance imaging with gadolinium showed suggestive images of incipient meningeal inflammatory process and partial thrombosis in superior sagittal sinus (Figure 1). Seriated hemoparasite tests were performed and we only found *P. vivax* gametocytes. The polymerase chain reaction (PCR) for malaria ruled out mixed infection. The patient completely recovered and had negative thick for hemoparasites after treatment.

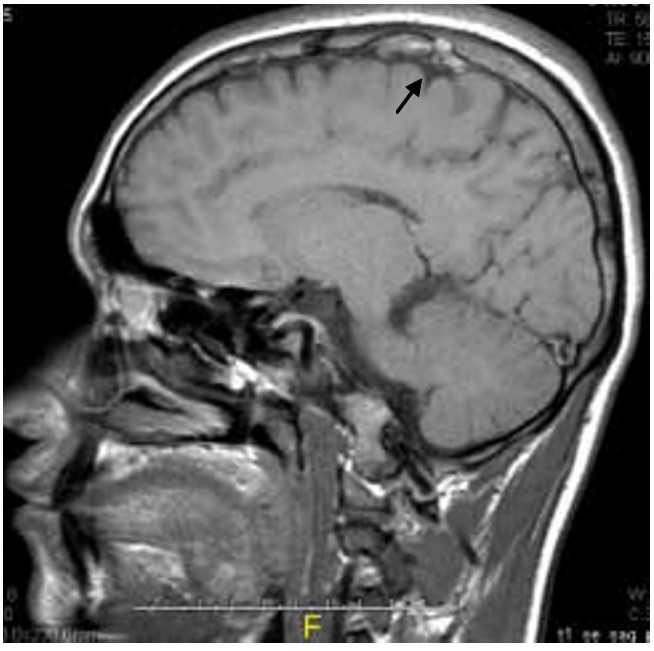

Figure 1. Saggital T1 slice.
Signal hyperintensity in superior sagittal sinus suggestive of venous sinus thrombosis (arrow). Evidence with the contrast of filling defect in the posterior portion of the sagittal sinus.

3. Discussion

Severe malaria is associated to *P. falciparum* and accounts for increased mortality worldwide[1]. *P. vivax* has been neglected in clinical studies of severe malaria and the incidence and cause of complications are unknown[11]. Previous studies believed that *P. vivax* was unable to produce cytoadherence with microvascular sequestration, therefore, it was considered impossible to cause organ dysfunction like in *P. falciparum* malaria. Recently, sequestration of *P. vivax* in the pulmonary vasculature has been noted and it is believed that organic dysfunction can be generated by an inflammatory response amplified by the release of cytokines[12,13].

However, there is little known about this presentation with *P. vivax* and its relation with individual immune status. Cerebral complications have been described in 45 patients, the majority in children from India and Pakistan. In 1921, Rossle described a lethal hemorrhage in the cerebellum of a 21 year old patient during a course of tertian malaria[14]. In 1932, Bruetsch reported a 61 year old woman with fatal tertian malaria induced as treatment for syphilitic psychosis; at autopsy "numerous parasitized red blood cells and young plasmodia" were observed in brain tissue[15]. Other complications mentioned are mainly seizures, altered consciousness reaching even coma, acute inflammatory demyelinating polyneuropathy and facial paralysis. Only four of these cases were single infections of *P. vivax* documented by PCR[16,17].

Cerebral malaria manifested by isolated bilateral sixth cranial nerve palsy is rare in adults but more commonly described in children[18-23]. Vinod and Talari recently reported a 13 year old girl with intermittent fever for 20 d, repeated generalized tonic clonic seizures and unconsciousness for 1 d; her brain enhanced CT showed diffuse cerebral oedema; peripheral blood film did not show parasites, but quantitative buffy coat technique revealed *P. vivax*; and *Plasmodium* LDH immunochromatographic test was also positive for *P. vivax*[24,25]. Krishnan *et al*. described three adults with *P. falciparum* malaria with fever, altered consciousness and focal neurological deficits (one of whom also had seizures); brain CT scan showed haemorrhagic infarction of the cerebral cortex and subcortical white matter with surrounding oedema suggestive of venous infarction in all of them; the diagnosis of cerebral venous thrombosis was missed in the first case and was detected only at autopsy; in the other two patients, superior sagittal sinus thrombosis was confirmed angiographically, one patient survived and the other died due to increased intracranial pressure, two of them had *P. vivax* co-infection[26,27]. Another report by Sarkar and Bhattacharya shows three adult patients with *P. vivax* malaria complicated by seizures and symptoms of diffuse meningoencephalitis[10]. More recently, the same author presented the first case of *P. vivax* malaria with left thalamus haemorrhage which is an unusual site of bleeding even more in the absence of severe thrombocytopenia or

disseminated intravascular coagulation[28].

This clinical scenarios show how *P. vivax* infection could lead to involvements other than the commonly described ones with different outcomes and should call our attention in order to rule out this co-infection when severe malaria appeared even if routine test shows *P. falciparum*; besides, we must watch closely patients with neurological findings because they could have sinus thrombosis, like our case who is the first confirmed by PCR in Latin America. Although we do not clarify the cause of the superior sagittal sinus thrombosis in this patient and there were no clear consequences of this event, we believe that this information can be added to future studies to enable a better understanding of the disease.

Conflict of interest statement

The authors declare no conflict of interest.

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