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CASE REPORT

A high PCT level correlates with disease severity in *Plasmodium falciparum* malaria in children

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SUMMARY

Most clinicians in developed countries have limited experience in making clinical assessments of malaria disease severity and/or monitoring high-level parasitemia in febrile patients with imported malaria. Hyperparasitemia is a risk factor for severe *P. falciparum* malaria, and procalcitonin (PCT) has recently been related to the severity of malaria. In developed countries, where not all hospital have skilled personnel to count parasitemia, a rapid test might be useful for the prompt diagnosis of malaria but unfortunately these tests are not able to count the number of parasites.
In this context, PCT might have a prognostic value for the assessment of severe malaria, especially in children with cerebral malaria. We describe two children with severe cerebral malaria, who were directly admitted to the ICU with a high level of PCT and extremely high (>25%) parasitemia. Our conclusion is that PCT may also be a measure of severity of *P. falciparum* malaria in children.

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INTRODUCTION

The identification of patients with severe malaria due to *Plasmodium falciparum* in areas non-endemic for malaria is a key factor to manage these patients with the best approach. Globally, approximately 3.2 billion people are at risk of being infected with malaria, and 1.2 billion are at high risk (>1 in 1000 chance of getting malaria in a year). According to the World Malaria Report 2015, there were 214 million cases of malaria in 2015 with 438000 deaths, corresponding to 37% and 60% less than the malaria cases and deaths since 2000. The most dramatic setting is in sub-Saharan and pluvial Africa, where an estimated 90% of all worldwide malaria deaths occurred, and children aged under 5 years accounted for more than two thirds of all deaths (www.who.int/gho/malaria). Therefore, malaria in children is challenging because mortality might be higher.
Most clinicians in developed countries have limited experience in making clinical assessments of malaria disease severity and/or high-level monitoring in febrile patients with imported malaria. Hyperparasitemia (defined as more than 2% parasitized red blood cells or 100,000 parasites/μL) may be very useful to rule out patients with severe malaria. Overall, hyperparasitemia correlates with poor outcomes (Tangpukdee *et al*., 2012).

Key words:
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In non-endemic countries, the diagnosis and treatment of malaria is usually referred to specialized hospitals, but many travellers may present to any institution or even to general practitioners. Therefore, not all the laboratories may have the expertise for a proper diagnosis of malaria using thick and thin blood smears, and for the assessment of parasite load. Thus, these non-specialized centers often rely on rapid diagnostic tests for the diagnosis of malaria (Stauffer *et al*., 2009) but these tests are still unable to count parasites.
The clinical criteria for the severity of malaria include coma status, shock, acidosis, severe anemia, acute respiratory distress syndrome, renal failure, hypoglycemia, disseminated intravascular coagulation, and hemoglobinuria (Marsh *et al*., 1995).
The most life-threatening form is cerebral malaria (CM) caused by *P. falciparum*. CM only affects individuals naive for a specific and established immunity against *P. falciparum* and is characteristic of the first phase of invasion (Wah et al., 2016).
Many authors distinguish two principal forms of CM:

1) The *"African children pattern"*, very rapid to settle and worsen the neurological status, characterized by secondary seizures in >80% cases, involvement of brainstem, involvement of retina in >60% cases, brain swelling on CT scan in 40% of cases and a high ratio of death and neurologic sequelae;
2) The *"Thai adult pattern"* characterized by a slower involvement of the central nervous system and more rarely the onset of seizures, retinal damage and brain swelling) (Idro *et al*., 2005).

Characteristic anatomopathological fields are generally represented by: macroscopic edema, characteristic "pink

brain" and "spotty hemorrhages", whereas the most common microanatomopathological aspects are: red blood cells with "knob-like protrusions", capillaries blocked by parasitized blood cells, iron stores, "ring hemorrhages" and Durk's nodules and granulomas.

The principal pathogenetic theory is the sequestration of red blood cells by parasites with a reduction of cerebral vascular flow, "blood-brain-barrier dysfunction" and the theory of metabolic, immunologic and cyto-chemokine modifications (Idro *et al*., 2005; World Health Organization, 2010; 2015).

However, sometimes patients may not show these symptoms, but in a few hours their condition may deteriorate. At this time, identifying the risk level is fundamental. The fist-line therapy for uncomplicated and severe malaria is ACT (*"artemisinin-based combination therapy"*) (World Health Organization 2010 and 2015).

Artesunate, the pharmacological form used to treat our cases, is rapidly hydrolysed to dihydroartemisinin that has a major antimalarial effect throughout a rapid lethal effect on blood malaria parasites. Artemisinin-derived drugs caused a hyperperoxide-heme complex in the phagosoma's parasites with a potent antioxidant effect and a large production of the oxidant radicals and death of the protozoan (Idro *et al*., 2005; World Health Organization 2010 and 2015).

Although the assessment of parasitemia levels still represent a key parameter to determine malaria severity, its diagnostic efficacy depends on technical expertise which is very uncommon in non-endemic areas (Righi *et al.*, 2016). For prompt identification of patients with severe malaria, soluble easy to measure markers such as reactive protein C (CRP), neopterine, and especially procalcitonin (PCT) have been evaluated (Witt *et al*., 2010; Righi *et al.*, 2016).

We describe two cases of children born in Italy from African parents and presenting with severe cerebral malaria on their return from Africa in Italy. Both children were directly admitted to the ICU, with extremely high levels of PCT and parasitemia.

CASE REPORTS

Case 1. A 20-month-old girl born in Italy, travelled to Ghana from 4th to 16th August 2016 without prophylaxis. Once in Africa, she was treated empirically for fever. Four days after her return to Italy she developed fever and was referred to another hospital. The baby had a seizure and, suspecting cerebral malaria, was transferred to our hospital. At presentation, the patient was prostrated, with a positive rapid test for malaria GCS 14, therefore she was admitted to the ICU. *Table 1* summarizes her laboratory results. The baby was treated with red blood cells, benzodiazepine, ceftriaxone and artesunate iv 3 mg/kg every 12 hours for the first three doses and every 24 hours thereafter for a total of three days. On admission, parasitemia was 27%, total parasite count 726,000 parasites/μL; PCT was 6.33. After 24 hours of therapy, a considerable drop in parasitemia and lower values of PCT were observed. On the third day, the baby was transferred to the ID ward and discharged two days later, healed.

Case 2. The second patient was a five-year-old boy born in Italy. He travelled in Burkina Faso with his parents from July 31st to 30th August. In the evening of August 30th he began to have fever in Africa. Twenty-four hours after his return to Italy, on September 1st, he had confusion and high fever, therefore he was at first transported to another hospital and than transferred to our clinic with suspected cerebral malaria. It was the first time he travelled to Africa and prophylaxis was not performed. In the ER, the patient was comatose, rapid test was positive for PF malaria and he was admitted to the ICU. He was treated with red blood cells, ceftriaxone and artesunate fl iv 3 mg/kg every 12 hours for the first three doses and every 24 hours thereafter for a total of three days. On admission, parasitemia was 35%, total parasite count 798,000 parasites/μL, PCT was 100 (*Table 1*). After 24 hours a rapid decline in parasitemia and PCT was demonstrated and the patient was first admitted to the ID ward and then discharged without any adverse events.

Blood culture, Septifast®, urine culture and a search for parasite in the stool were negative in both children.

Table 1 - *Time course of parasitaemia, procalcitonin, hemoglobin and red blood cell count in two patients.*

Patient 1	*Day 1*	*Day 2*	*Day 3*
% parasitized red blood cells	27%	2%	0%
Number of parasites/μL	726,300	50,000	0
PCT	6.33	4.4	3.18
Hb	7.1	6.5	7.2
GR	2,690,000	2,500,000	2,730,000

Patient 2	*Day 1*	*Day 2*	*Day 3*
% parasitized red blood cells	35%	10%	0%
Number of parasites/μL	798,000	349,000	0
PCT	100	25.6	4
Hb	5.7	9.3	8.7
GR	2,280,000	3,490,000	3,280,000

COMMENTS

Nowadays, CRP and PCT have been investigated extensively for different types of infection in paediatric populations of industrialized countries (Milcent *et al.*, 2015). In addition, a few studies have evaluated the diagnostic and prognostic value of these biomarkers in African settings where infection profiles are different and malaria is endemic (Carrol *et al*., 2009; Díez-Padrisa *et al*., 2012; Erdman *et al.*, 2011).

In malaria-endemic areas the presence of malaria parasites should be taken into consideration, using PCT or CRP to differentiate viral from invasive bacterial pneumoniae (Díez-Padrisa *et al*., 2010) because "chronic" malaria leads to increased levels of nonspecific markers of inflammation especially in children under 1-year of age (Hurt *et al*, 1994).

Interestingly, PCT levels, currently considered an effective tool to diagnose systemic bacterial infections, have shown promising results in predicting malaria severity (Erdman *et al.*, 2011), especially in settings with a limited experience in the treatment of malaria (Hesselink *et al*., 2009; te Witt *et al.*, 2010). However, in children from malaria-endemic areas, the role of PCT as a marker of complicated malaria is still not clear (Braun *et al*., 2003).

Recently, Righi *et al.*, in a non-endemic malaria area, reported that severe malaria correlated with levels of PCT higher than 5 ng/ml, with good sensitivity and specificity. Their study included a total of 30 consecutive travellers diagnosed with *Plasmodium falciparum* malaria over a 2-year period. The study indicated that PCT and CRP may be useful predictors of complicated forms of malaria. None of the patients with complicated malaria showed PCT levels within normal limits (<0.5 ng/ml) while subjects with complicated *Plasmodium falciparum* malaria showed higher levels of parasitemia and PCT compared with patients with uncomplicated forms. In our study, we observed that both PCT and CRP correlated with parasitemia (Righi *et al.*, 2016). Furthermore, Chiwakata *et al.* identified a high mortality risk in patients with permanent PCT concentrations >25 ng/ml (Chiwakata *et al*., 2001).

In conclusion, these two cases demonstrated that PCT might be a useful tool for the diagnosis of severe malaria in children and for follow-up of clinical evolution, even in a non-specialized hospitals in non-endemic malaria areas. In our cases, we were able to count parasitemia, because we are the reference hospital in Naples for the Campania region, in Italy, but even in settings lacking expertise to count the rate of parasitized red blood cells, PCT plus a rapid test for malaria may be useful for the correct management of malaria patients, including children, and for disease follow-up. Early diagnosis and treatment are the most important factors contributing to a favorable outcome in severe cerebral malaria.

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