Brief Report

Lack of Evidence of Myocardial Damage in Children with *Plasmodium falciparum* Severe and Complicated Malaria from an Endemic Area for Endomyocardial Fibrosis

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Summary

Malaria is among the factors thought to be involved in the pathogenesis of endomyocardial fibrosis (EMF), a restrictive cardiomyopathy of unclear etiology, with no specific therapy, which affects predominantly children and adolescents. In Africa, regions endemic with EMF are also areas with high prevalence of malaria. We studied 47 consecutive children aged 5- to 15-years old and concluded that myocardial damage and dysfunction are rare in severe and complicated *Plasmodium falciparum* malaria cases in children.

Key words: malaria, endomyocardial fibrosis, myocardial damage.

Introduction

The nature and course of cardiac involvement during and after *Plasmodium falciparum* malaria are not completely understood. Myocardial injury, reversible global hypokinesia and diffuse myocardial necrosis (evidenced by raised troponin-T, echocardiography and autopsy) have been associated with severe and complicated malaria [1], an impairment that does not seem to result from lowered hemoglobin levels [2, 3]. However, in a study in Ghana including children and adults, regardless of the severity of the infection, in which the diagnosis was based on clinical grounds and positive blood smears, myocardial damage detectable by cardiac troponin T (cTnT) was rare [4].

Malaria is among the factors thought to be involved in the pathogenesis of endomyocardial fibrosis (EMF), a restrictive cardiomyopathy of unclear etiology, with no specific therapy, which affects predominantly children and adolescents. Although the epidemiologies of malaria and endomyocardial fibrosis are not absolutely overlapping, in Africa the regions endemic with EMF are also areas of high prevalence of malaria [5]. This is also the case in Mozambique, where an endemic area for *P. falciparum* malaria has also high prevalence of EMF [6]. We therefore hypothesized that severe and complicated *P. falciparum* malaria could cause myocardial injury in children, and aimed at measuring the levels of troponin-T and performing echocardiography during episodes of severe and complicated *P. falciparum* malaria in children, from an endemic area for both malaria and EMF.

Patients and Methods

Study area

The study was undertaken in a tertiary hospital (Hospital Geral Jose Macamo) serving an extensive suburban area of the capital of Mozambique, where *P. falciparum* malaria is endemic with perennial transmission and moderate seasonality. The transmission rate is higher in the hot and wet season (from November to April).

The national malaria control program in Mozambique relies essentially on prompt diagnosis, effective treatment and strategies for vector control in peri-urban areas.

Study design and patients

From October 2007 to February 2008, we studied 47 consecutive children admitted to Hospital Geral Jose

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Macamo, aged 5- to 15-years old, with diagnosis of severe and/or complicated malaria. One of the inclusion criteria was *P. falciparum* mono-infection confirmed by both microscopy and the rapid test for *P. falciparum* antigen HRPII, in the absence of any other known disease, including complicating or associated infections. None of the children included in the study received blood transfusion or anti-malarials prior to blood collection for measurement of cardiac markers.

Severe and/or complicated malaria was defined using the criteria established by the World Heart Organization [7]. These include a slide confirming the existence of asexual forms of the parasite in circulation together with the presence of one or more of the following conditions: cerebral malaria, severe anemia, renal failure, pulmonary edema, hypoglicemia, circulatory collapse or shock, spontaneous bleeding, repeated generalized convulsions, acidemia or acidosis, macroscopic hemoglobinuria, impairment of consciousness, prostation or weakness, hyperparasitemia, jaundice and hyperpyrexia. Severe anemia was defined as hemoglobin level of $<8\,g\,dl^{-1}$, and hyperparasitemia as the presence of $>100\,000$ parasites μl^{-1}, or 2–5% red blood cells infected.

The Ministry of Health and the National Bioethical Committee for Health in Mozambique approved the study. Written and witnessed informed consent was obtained from the parents or guardians of children who participated in the study.

Laboratory methods

Blood samples were obtained through puncture of a peripheral vein, using tubes with lithium heparin. Semi-quantitative determination of cTnT was done using the CARDIAC reader instrument (Roche). This kit gives the following results: (i) NEGATIVE when cTnT levels are below $0.03\,ng\,ml^{-1}$; (ii) LOW when cTnT levels are between 0.03 and $0.1\,ng\,ml^{-1}$; (iii) POSITIVE when the quantitative measurement values are between 0.1 and $2\,ng\,ml^{-1}$; and (iv) HIGH when the values measured are above $2\,ng\,ml^{-1}$. The upper limit of normal cTnT blood levels was defined as $0.1ng\,ml^{-1}$ [8].

Results

Forty-seven children were eligible for the study. One did not participate owing to refusal of the parents. Another tested negative for *P. falciparum* antigen HRPII and was excluded from the study. We therefore studied 45 children, of which 27 (60%) were females. The mean age ($\pm$SD) was 7 ($\pm$3.5) years. Eleven children (28.9%) had severe blood parasitemia (F++++ or more). All patients had fever on admission (Table 1).

Ten children had severe malaria (26.7%). The most frequent complications were anemia [30 (66.7%)] and cerebral malaria [18 (40%)]. The mean ($\pm$SD) hemoglobin level was $9.3\,g\,dl^{-1}$ ($\pm$2.2). Only two children (4.4%) had severe splenomegaly.

TABLE 1
Frequency of symptoms and signs of severe malaria in the 45 patients studied

Symptoms and signs	Frequency	Percentage
Fever, chills and hyperpyrexia	45	100
Seizures	18	40.0
Vomiting	17	37.8
Severe anemia	10	26.7
Impairment of consciousness	5	11.1
Severe splenomegaly	2	4.4

The electrocardiograms did not show any signs of myocardial ischemia. On echocardiography, ventricular systolic and diastolic functions were preserved in all cases; the left ventricular dimensions indexed for body surface were abnormal in two children with severe anemia (4.4%).

All children evaluated had undetectable (negative) levels of circulating cTnT. Following diagnosis, all children were treated with intravenous quinine and they survived.

Discussion

cTnT was not detected in any child with severe and/or complicated *P. falciparum* malaria. Because this marker shows high specificity and sensitivity in the assessment of myocardial damage in children [8], our results indicate the absence of myocardial damage in association with severe and complicated *P. falciparum* malaria.

There are conflicting results regarding the incidence of myocardial damage in *P. falciparum* malaria. While circulating concentrations of cardiac proteins have been shown in patients with both complicated and uncomplicated *P. falciparum* malaria [2, 3], myocardial damage was rare when assessed by cTnT [4] in a retrospective study involving patients of all ages and degrees of severity of *P. falciparum* malaria. In our study, positive microscopic diagnosis was confirmed by the rapid test for antigenF through detection of the *P. falciparum* histidine-rich protein 2 (HRP-2), all children presented signs of severe and/or complicated malaria, and echocardiographic examination confirmed the absence of myocardial dysfunction.

Malarial infection is among the hypotheses that have been explored to explain the occurrence of EMF, with both conditions being highly prevalent in some endemic areas of Africa [6, 9, 10]. Despite suggestions of the role of malaria in pathogenesis and the good initial results in the development of an animal model [5, 11, 12], a causal relationship between malaria and EMF has never been proven.

Plasmodium falciparum has multiple myosins that are part of its motile apparatus, some highly divergent and smaller than conventional ones [13, 14] while others are similar to mammalian myosins [15]. A possible explanation for the role of malaria in the pathogenesis of EMF could be an autoimmune lesion due to molecular mimicry between *Plasmodium* myosins and heart muscle. If this is the case, a certain period of time is needed for the establishment of a humoral immune response against *P. falciparum* myosins and the following cross-reaction of antibodies with the host myocardium, and therefore myocardial injury, would not be simultaneous with acute episodes of *P. falciparum* malaria.

Follow-up study of patients after acute malaria has previously shown cardiac affection, as assessed by electrocardiography or bi-dimensional echocardiography [16]. Considering recent knowledge of the host response to *P. falciparum* and the progress made in identification of markers of endocardial and myocardial damage, future studies should have long-term monitoring of the pattern of antibody responses to *P. falciparum* malaria, as well as assess the development of auto-antibodies and the presence of myocardial damage.

In conclusion, our results clearly demonstrate that myocardial damage and dysfunction are rare in severe and complicated *P. falciparum* malaria in children, as measured by troponin-T and echocardiography. Further research is needed to explore the possible role of *P. falciparum* malaria in the pathogenesis of EMF.

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