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Cardiac involvement in malaria: An overlooked important complication

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Severe malaria is a unique disease where many organs may be affected simultaneously or sequentially. It is still an enigma why one, or more or even none of the organ is affected. It is also not clear yet, when and which organ will be failing. Even persons from one geographical area may have different presentations. There are a lot of heterogeneity and unpredictable consequences.

World Health Organization[1] has outlined the criteria for severe malaria depending upon the available data, mostly from Africa. While severe anaemia, cerebral malaria[1–4], acute kidney injury[5–6], multiple seizures, acute lung injury, circulatory collapse, etc. are included, several other complications are still important, viz. jaundice or hepatic involvement[7–8], black water fever or haemoglobinuria, rhabdomyolysis[9], acral gangrene, etc. However, only a few studies have been carried out regarding the cardiac function in severe malaria[10–12]. In this article, we attempt to review briefly the published data on cardiac involvement of malaria. It may stimulate the clinicians to ponder over for future studies.

Hypotension, shock and circulatory collapse with impaired hemodynamic function have been observed in severe malaria patients[1]. Though it occurs occasionally in the severe malaria cases and it occurs frequently in sepsis. The role of the heart in severe malaria has not received due attention. In 2004 and 2005, Ehrhardt *et al*[13–14] have demonstrated raised cardiac enzymes in complicated malaria. Similarly, Yacoub *et al*[15] assessed ejection fraction by echocardiography which significantly reduced on admission compared with discharge.

Pathogenesis

The mechanism for hypotension and shock in sepsis are: reduced pre-load, myocardial suppression as well as reduced after-load contributing to hyperdynamic but insufficient cardiac function resulting in tachycardia and hypotension. Both, direct toxic effects of bacterial agents as well as excessive production of cytokines and immune mediators have been identified to cause this dysfunction[16, 17]. In contrast, parasite sequestration in small capillaries along with capillary leakage leads to oedema in patients with malaria. Some features are similar, viz. compromised microcirculation and lactic acidosis as well as excessive production of pro-inflammatory cytokines in malaria and bacterial sepsis[18–19].

The mechanisms for cardiac dysfunction are related to impaired pre- or post-cardiac circulatory parameters or results from myocardial dysfunction itself. Intravascular fluid depletion associated with severe malaria leads to impaired microcirculation. Moderate volume depletion may contribute to reduced cardic output (CO) by reducing the pre-load, but not the most prominent reason for reduced CO. Other factors leading to rapid fluid loss in children are fluid loss caused due to relatively high body surface of children, high fever, diarrhoea, vomiting and limited intake of fluids.

The peripheral vascular resistance was significantly increased in patients with malaria. The increased after-load might contribute to the decreased CO. Major pathophysiological processes typical for *Plasmodium falciparum* malaria are the parasite adhesion to the endothelium, rosetting, the sequestration of parasitized and unparasitized red blood cells (RBCs) in peripheral small vessels, and the decreased deformability of RBCs resulting in impaired microcirculation and lactic acidosis.

Finally, malaria may affect cardiac function itself. N-terminal probrain Natriuretic peptide (NT-proBNP) is a sensitive marker for impaired left ventricular (LV) function and is significantly elevated predominantly in severe malaria patients. Parasite toxins or host immune mediators or both may have a suppressive effect on myocardial function. It has been shown that plasmodial toxin glycosylphosphatidylinositol (GPI) augments apoptosis rates in cardiomyocyte culture. On the other hand, the host immune reaction against malaria parasites involves pro- and anti-inflammatory cytokines as well as immune mediators like nitric oxide (NO). While pro-inflammatory cytokines and immune mediators have been shown to exert a suppressive effect on myocardial function. Cardiovascular biomarkers have been reported as good prognostic markers for outcome in septic and critically ill patients. Recent publications support myocardial sup-

pression in malaria although other evidence is still contradictory. In addition, antimalarial treatment may add to cardiotoxic effects.

Cytokines

All cytokines assessed are significantly elevated in malaria patients compared to controls, especially IL-17A in complicated malaria. It has been described that pro-inflammatory cytokines like tumor necrosis factor—TNF-α can impair myocardial function via negative-inotropic effects which may play a role in malaria patients.

High-output failure is typical for bacterial sepsis and large amount of fluid substitution is established as life-saving therapy, but, pathophysiological processes appear to be more heterogenic in malaria leading to (mild) low-output failure in a subset of patients. Yet, findings could be interpreted in that moderate and careful volume and substitution may be preferable over strict volume depletion in this highly febrile disease as it may not only improve cardiac output but also may have a beneficial effect on microcirculation, tissue perfusion and lactic acidosis. However, there is no evidence derived from randomised clinical trials that volume substitution improves mortality in severe malaria.

Toxic effects due to cytokines such as the TNF plays an important role. Plasmodial GPI—either free or linked to surface antigens—have a direct effect (independent from cytokine production by monocytes) on cardiac myocytes. An upregulation of apoptotic genes and of a myocardial damage marker NT proBNP suggests that GPI might induce myocyte apoptosis and can cause malarial myocarditis.

In 2010, Janka *et al*[11] demonstrated increased pulmonary pressures and myocardial wall stress among children with severe malaria. These complications are consistent with NO depletion from intravascular haemolysis, and these indicate that the pathophysiologic cascade from intravascular haemolysis to NO depletion and its cardiopulmonary effects are activated in children with severe malaria.

In severe malaria, there is a significant increase in the level of NT-proBNP, heart-type fatty acid-binding protein (H-FABP—A marker of acute myocardial injury), myoglobin and creatine kinase-muscle brain (CK-MB) both established markers of myocardial injury and necrosis even in patients who did not display significant electrocardiogram (ECG) abnormalities. But, in another study in 2011, the serum concentration of cardiac troponin-T was found to be elevated only in a very low (0.6%) proportion of patients. ECG-specific abnormalities such as, delayed conduction and/or T or ST alterations were observed in 14.3% of the patients, suggesting that the electrophysiology of cardial myocites can be altered before myocytolysis occurs[12].

Autopsy data support the view that the mechanical blockage of capillaries exerted by malarial parasites and parasitized red blood cells (PRBCs) can lead to ischaemic cardiomyopathy, the severity of clinical features was thus put in relation with the high burden of PRBCs, which exhibited an increased ability to sequester in the deep microvasculature. However, in two fatal cases of *P. falciparum* infection the only significant finding detected at post-mortem evaluation was an acute lymphocytic myocarditis. More recently, myocarditis was also observed as a complication of *P. vivax* infection. The pathological finding of active lymphocytic myocarditis usually correlates with either acute myocardial infarction-like syndrome (with normal coronary arteries) or heart failure, with normal-sized or dilated left ventricle and haemodynamic compromise.

In summary, at the present state of knowledge myocardial damage appears to retain a multifactorial pathogenesis, being probably the result of mechanical (microcirculatory obstruction), metabolic (systemic acidosis and related tissue hypo-oxigenation), and humoral mechanisms. However, cardiac side effects related to therapy should also be considered.

Clinical implication

The clinical implication can be immediate which leads to features of myocarditis, ECG changes ectopics, conduction defects, tachy-brady-arrhythmias, or reduced cardiac output. Long-term cardiac dysfunction is rare. Franzen *et al*[20] studied 22 patients without previous history of cardiac disease. They prospectively evaluated cardiac involvement during acute malaria and 9 ± 5 months after recovery using non-invasive methods including resting electrocardiogram (ECG) and two-dimensional (2D) echocardiography. During the acute phase ECG abnormalities were common (5/22); pericardial effusion was found in two patients and global left ventricular hypokinesia in one patient infected with *P. falciparum*. At the follow-up of 19 patients, the resting ECG and echocardiography were normal or had normalized in all patients. The results suggest that persistent cardiac damage following malarial infection seems to be rare.

Investigations

ECG non-specific ST-T changes can occur. There may be arterial or ventricular ectopics due to the disease or the drugs. Continuous EKG monitoring may be useful to find out the incidence of conduction defects and arrhythmias.

Echocardiography: Several markers of haemodynamic compromise were noted by Yacoub *et al*[15] on admission, including severe tachycardia, low stroke volume index, and high inferior vena cava collapsibility index, which improved subsequently. The indices at admission and discharge respectively are: ejection fraction (63.1 ± 5.2% vs 71.9 ± 2.8%; $p < 0.001$) and left myocardial performance index (0.32 ± 0.16 vs 0.25 ± 0.08; $p = 0.03$). Acidotic patients had worse haemodynamic indicators, with a significantly higher inferior vena cava collapsibility index on Day 0 than non-acidotic patients (52.1 ± 21 .9 vs 37.7 ± 15.4; $p = 0.03$), plus lower stroke volume index and worse cardiac function with higher left myocardial performance index (0.38 ± 0.18 *vs* 0.26 ± 0.11; $p = 0.05$).

Heart specific biomarkers

In an unmatched case-control study of 63 non-immune European patients with uncomplicated (n = 52) and complicated (n = 11) falciparum malaria, serum levels of NT-proBNP, H-FABP, myoglobin, troponin-T and CK-MB were compared. Elevated levels of NT-proBNP and H-FABP indicated myocardial impairment in complicated but not in uncomplicated falciparum malaria[13].

In an another study in 2005[14], plasma levels of NT-proBNP, H-FABP, myoglobin and CK-MB were compared in 400 African children with severe and mild falciparum malaria. Plasma levels of these markers were correlated with lactate and glucose blood levels, indicators for hypovolemia, and with clinical outcome. Children suffering from severe malaria and children who died (n = 22) exhibited high to higher levels of cardiac markers, respectively.

Myocardial dysfunction in severe falciparum malaria was presented in two adults by Kumar *et al*[21] from Hyderabad, India. Günther *et al*[22] included 161 patients with falciparum malaria in the study, troponin-T was elevated in one case (0.6%), no CK-MB elevations were found, myoglobin was elevated in 10 out of the 161 patients (6.2%), all of whom were elderly and had concomitant elevated serum concentration levels of cystatin C and ECG abnormalities were seen in 23 patients.

A study published in 2011 by Herr *et al*[10] reported impaired myocardial function in patients with falciparum malaria. Cardiac output was significantly decreased in malaria patients compared to healthy controls. The increase in heart rate, however, was not sufficient to compensate for the lower stroke volume in malaria patients.

Herr *et al*[10] correlated 2D echo with cytokines and biomarkers: CI with pro-BNP, myoglobin, etc. in a prospective case-control study, where 28 patients with uncomplicated and complicated *P. falciparum* malaria were included and compared with 26 healthy controls. Cardiac function parameters were assessed by an innovative non-invasive method based on the re-breathing technique. In addition, cardiac enzymes and pro- and anti-inflammatory cytokines were measured and assessed with respect to clinical symptoms and conditions of malaria. CI as a measurement of CO was 21% lower in malaria patients than in healthy controls (2.7 l/min/m^2 vs 3.4 l/min/m^2; $p < 0.001$). In contrast, systemic vascular resistance index (SVRI) was increased by 29%; $p < 0.001$). This correlated with increased cardiac proteins in patients *vs* controls: pro-BNP 139.3 vs 60.4 pg/ml ($p = 0.03$), and myoglobin 43.6 vs 27.8 µg/l ($p < 0.001$). All the measured cytokines were significantly increased in patients with malaria. However, CI, SVRI as well as cytokine levels did not correlate with blood parasite density. The results support previous reports suggesting impaired cardiac function contributing to clinical manifestations in *P. falciparum* malaria.

Cardiao toxicity of drugs

Quinine is known to evoke arrhythmias, angina, and hypotension, potentially causing circulatory failure and or cardiac arrest. However, these effects generally occur when the drug is injected as a bolus. To date, there is no direct evidence for significant cardiovascular effects of artesunate. Co-morbid conditions attributing to cardiac dysfunction, especially in adult patients are: obesity, smoking, diabetes, hypertension, advanced age and previous CAD, or cardiomyopathy.

CONCLUSION

In severe *P. falciparum* malaria, the frequency of primary cardiac complications may be underestimated and unrecognized. Some cases of pulmonary complications may be due to cardiac component too. Sudden cardiac deaths can also occur due to cardiac involvement. It is not feasible to assess the cardiac indices in resource poor settings, and moreover not possible among the very sick patients who cannot be shifted also. It is hoped that large studies may be conducted with biochemical markers and echocardiography to establish the cadiac involvement. Autopsy studies will give more insight.

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