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Can malaria lead to a broken heart?

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Take Home Messages

- Malaria remains a significant cause of morbidity and mortality worldwide.
- In recent years there has been increased recognition of the potential for cardiac involvement in malaria.
- Reported cardiac pathologies include myocarditis, heart failure, acute coronary syndromes, arrhythmias, and cardiac tamponade.
- The exact pathophysiology for cardiac involvement remains obscure.

Introduction

Malaria remains a long-standing and leading cause of morbidity and mortality worldwide. In the 20th century, malaria accounted for between 150-300 million deaths(1). In 2022, according to the WHO malaria report (2), there were an estimated 249 million cases of malaria and around 600,000 deaths in 85 countries (majority being low and middle income countries), highlighting the significant burden of the disease.

Malaria is caused by protozoan *Plasmodium* species typically transmitted by marsh mosquitoes and is endemic to Asia, Oceania, South and Central America. However, the highest burden of disease is in Sub-Saharan Africa (3). Severe and fatal malaria is generally caused by *Plasmodium falciparum* which is responsible for more than 90% of the world's malaria mortality (4).

While the malarial parasite can affect all organs, cardiovascular (CV) sequalae of malaria are poorly understood due to the paucity of published research on the area. A small prospective study has suggested that in patients with severe malaria (clinical or laboratory evidence of vital organ dysfunction including reduced conscious levels, severe anaemia and renal impairment), the incidence of CV involvement can be as high as 26% (5). In this editorial we explore the prevalence of CV compromise, the theories related to the pathophysiology of CV complications in malaria and the management of such patients.

Cardiovascular complications

In a systematic review and meta-analysis by Holm et al, 43 studies (a mixture of clinical studies, case reports and case series) including both paediatric and adult patients between 1950 and 2020 were analysed. The overall pooled prevalence of CV complications in adult populations was found to be around 7%, with the most common being myocarditis and acute coronary syndromes (6). In a Danish cohort study from 1994 – 2017 by Brainin et al, infection with *P. falciparum* malaria was associated with an increased risk of heart failure (HR: 1.64 [1.14–2.36], $P = 0.008$) (7). Case reports have also described cases of conduction disorders, arrhythmias, and cardiac tamponade in patients with complicated malaria (8,9).

Pathophysiology

Figure 1 describes the life cycle of Plasmodium parasites and how this leads to malaria. The mechanisms by which malaria causes CV complications has not been fully elucidated, though various theories have been postulated.

Elevated levels of proinflammatory cytokines such as tumour necrosis factor-alpha, interleukin-1, interleukin-6, and interferon-gamma are found in patients with severe malaria. These high levels of inflammatory cytokines lead to increased nitric oxide (NO) production (10). These high concentrations of NO induce production of cGMP which cause blockade of sacrolemic ca2+ channels which results in cardiac depression (11).

These proinflammatory cytokines also lead to endothelial dysfunction. Cytokines activate endothelial cells causing them to express adhesion molecules (such as intercellular adhesion molecule) on their surface. This promotes cytoadhesion of infected red blood cells to the endothelium (12). This sequestration leads to microvasculature obstruction and organ ischaemia. This theory has been strengthened by autopsy findings in cases of severe malaria, where myocardial capillaries were blocked with parasites and infected red blood cells resulting in ischaemic cardiomyopathy (13-14).

It has also been shown that glycosylphosphatidylinositol (GPIs), which are glycolipid anchors found in *Plasmodium* species, can act as a toxin. *In vitro* studies have shown they lead to upregulation of apoptotic genes (apaf-1, bax) leading to induced myocyte death (15).

Finally, it should also be noted that antimalarial drugs have been reported to cause cardiotoxicity by prolonging ventricular repolarization as evidenced by QTc interval prolongation. In a study by Func-Brentano et al, though treatment of malaria with dihydroartemisinin-piperaquine, artesunate-amodiaquine and artemether-lumefantrine therapies did prolong the QTc, there was no increased risk of proarrhythmia observed (16).

Management

The cornerstone of treatment remains the early detection of malaria and prompt initiation of appropriate antimalarial regimes to reduce the parasitaemia. Cardiac symptoms usually resolve once the infection is effectively treated, however, in severe cases of malaria haemodynamic support may be required.

Gutpa et al. highlight that early detection of cardiovascular complications from malaria is critical to improve patient outcomes. The authors have suggested a diagnostic algorithm involving the use of cardiac monitoring (ECGs, cardiac biomarkers) and the use of further imaging (transthoracic echocardiography - TTE/cardiac magnetic resonance imaging - CMR) in high-risk individuals (infection with *P. Falciparum*, high parasitaemia levels and severe malaria) (Figure 2) (17). However, there are some limitations to this diagnostic algorithm. Cardiac biomarkers lack specificity and can be raised in context of severe infection. Furthermore, to the best of my knowledge there is no scar pattern specific to myocarditis caused by malaria on CMR.

Conclusions

Malaria remains a deadly disease in endemic regions, with increasing evidence from small studies recognising cardiac involvement. Though rare, cardiac manifestations may be underreported in resource constrained endemic regions. Clinicians should therefore be aware of the possible CV consequences of malaria to allow for early detection and improve prognosis. Ultimately future research in the area is required to delineate the spectrum of cardiac complications of malaria.

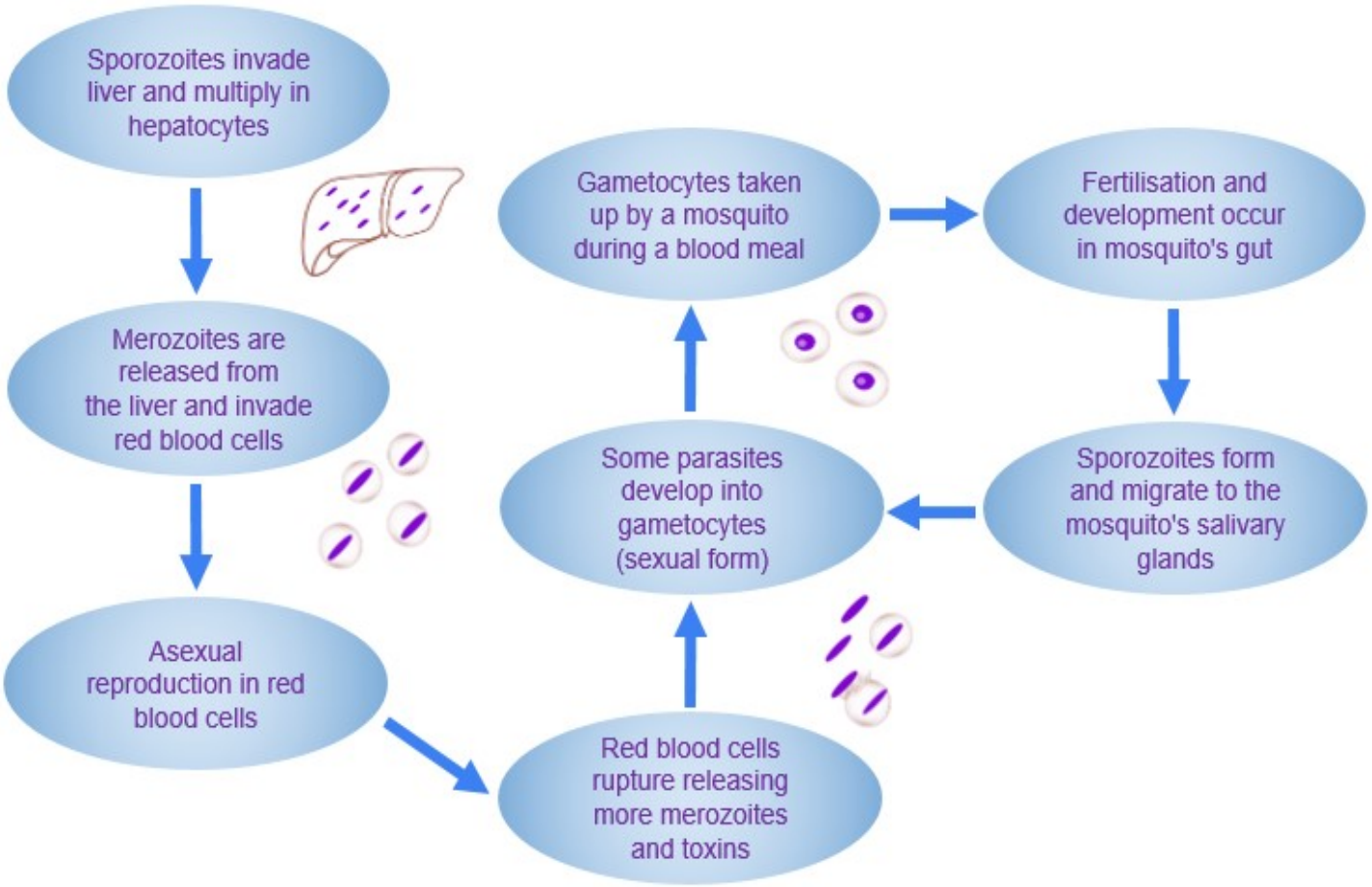

Figure 1: When an infected mosquito bites a human, it injects sporozoites (the infective form) into the bloodstream, which travel to the liver. In the liver, sporozoites mature into merozoites which are released into the bloodstream after liver cells rupture. Merozoites infect red blood cells, multiply, and cause the cells to burst, releasing more merozoites, leading to the clinical symptoms of malaria. Some merozoites differentiate into gametocytes (sexual forms). When a mosquito bites an infected human, it ingests gametocytes. Inside the mosquito, gametocytes mature, form zygotes, and develop into sporozoites. These sporozoites migrate to the mosquito's salivary glands, ready to infect another human. This cyclical process between humans and mosquitoes perpetuates malaria transmission.

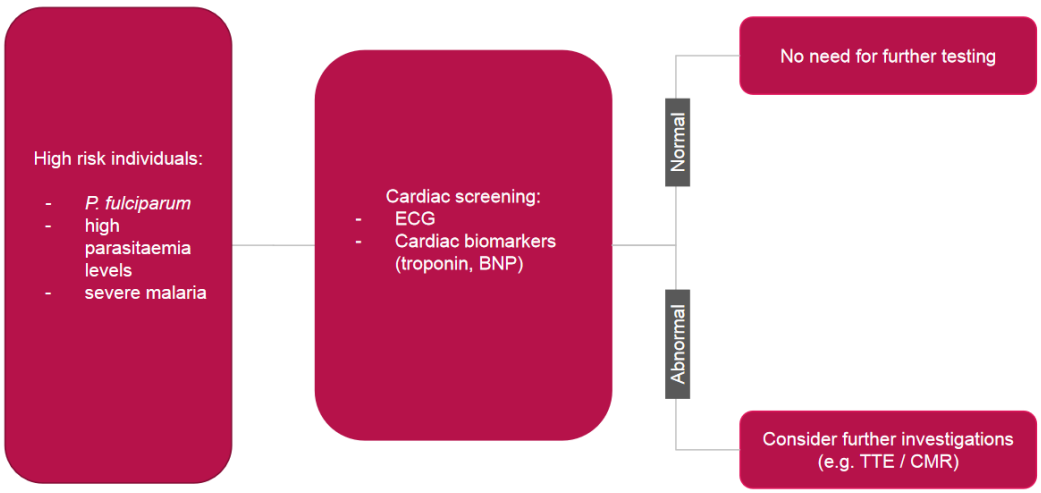

Figure 2: Diagnostic algorithm suggested by Gupta et al for screening of CV involvement. Adopted from Gupta et al (Gupta S., Gazendam N., Farina J.M., et al. "Malaria and the heart: JACC state-of-the-art review". J Am Coll Cardiol 2021;77:8: 1110-1121).

Disclosures

Nothing to declare.

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