Malaria and Vascular Endothelium

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Abstract

Involvement of the cardiovascular system in patients with infectious and parasitic diseases can result from both intrinsic mechanisms of the disease and drug intervention. Malaria is an example, considering that the endothelial injury by Plasmodium-infected erythrocytes can cause circulatory disorders. This is a literature review aimed at discussing the relationship between malaria and endothelial impairment, especially its effects on the cardiovascular system. We discuss the implications of endothelial aggression and the interdisciplinarity that should guide the malaria patient care, whose acute infection can contribute to precipitate or aggravate a preexisting heart disease.

Introduction

Malaria is an acute febrile infectious disease, of vector transmission, caused by parasitic protozoans of the genus Plasmodium, whose following species infect humans: P. falciparum, P. vivax, P. malariae, P. ovale and P. knowlesi. The disease is characterized by high fever accompanied by shivering, sweating and headache, which occur in cycles from the second week of disease on, depending on the infecting parasite species. In 2010, 219 million cases of malaria and 660,000 deaths were registered worldwide, mainly among children living in Africa. Despite the overall reduction in the incidence of malaria, approximately 3.3 billion people were at risk for contracting the disease in 2011.

Some infectious diseases can have cardiovascular repercussions, which influences the patient’s prognosis. Because of the high prevalence of infectious diseases, cardiologists and infectious disease specialists should work together to better understand the prevention and treatment of complications of infectious diseases and/or the adverse events resulting from their treatment. It is worth considering an integrated approach to control infectious diseases, such as AIDS and malaria, in combination with chronic diseases, such as cardiovascular diseases, diabetes mellitus and cancer.

Although malaria complications are usually associated with P. falciparum, there are reports of severe disease caused by P. vivax, which is the most frequently found protozoan in Brazil. Its clinical complications are very similar to those reported for P. falciparum: severe anemia, acute renal failure, acute pulmonary edema, and algid malaria. In a series of patients diagnosed with P. vivax malaria, who evolved to death and underwent autopsy, pulmonary complications were the most frequently found. Most patients who died had other comorbidities (chronic liver disease, cardiovascular disease and G6PD deficiency), which might have contributed to that outcome. Series of severe cases of P. vivax malaria have also been reported in other endemic areas.

This study was aimed at discussing the relationship between malaria and cardiovascular complications, mainly endothelial impairment, based on a literature review.

Interaction of Plasmodium with vascular endothelium

In cardiovascular medicine, blood vessels were initially considered mere inert conductors that carried blood from the heart to the organs and vice-versa. The endothelium was understood as the innermost layer of vessels, separating the inner space from the smooth muscle layer and other elements immediately below. From 1980 on, several endothelial functions, such as the production of vasoconstricting and vasodilating substances responsible for vascular tone, have been discovered. Those discoveries have contributed to the understanding of endothelium as an endocrine organ, metabolically active and directly related to vascular relaxation and contraction, coagulation, thrombolysis and vascular growth, and also related to affections, such as arterial hypertension and coronary artery disease.

The abnormal adherence (cytoadhesion) of Plasmodium-infected erythrocytes to the endothelium, which occurs in malaria, is one factor that determines the severity of that disease’s progression. In addition to thrombophilic factors and platelet abnormalities, those erythrocyte changes can cause vascular thromboses, representing a new therapeutic target to be considered.

Malaria is a complex disease, which is difficult to control and involves an interaction between a host, a vector and Plasmodium. The molecular processes that coordinate cytoadherence or invasion of erythrocytes in malaria are related to specific receptors. Erythrocyte antigens are macromolecular structures located on the extracellular surface of the erythrocyte membrane, and have a wide structural and functional diversity. They can have several functions, such as transporters, adhesion molecule receptors, enzymes, and complement control. The glycoprotein of the Duffy blood group system, also known as Duffy antigen receptor for chemokine (DARC), has functions of reception and adhesion.
in *P. vivax* malaria, the major species causing malaria in Latin America, being expressed in several tissues in addition to the erythroid cell line, especially in endothelial cells. Duffy antigens function as *P. vivax* merozoite receptors in humans, as well as cytokines in erythrocytes, binding to several acute and chronic proinflammatory chemokines. They are also involved in hemolytic transfusion reactions and in the hemolytic disease of the newborn. In the Amazon state, the genotypes FYA/FYB and FYA/FYB of the Duffy antigen were associated with an increase in *P. vivax* infection.

Some properties of the pathogen should be considered. The *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1) is involved in the cytoadhesion process. Although the invasion of erythrocytes causes the common symptoms of malaria, erythrocyte cytoadhesion is also implicated in the disease’s severity. After erythrocyte invasion, the parasite modifies the host cell, changing its morphology and characteristics to cause adherence. The PfEMP-1 is a key molecule in the definition of the cytoadhesion properties of infected erythrocytes, which get close to non-infected erythrocytes to form rosettes, thus allowing binding to several endothelial receptors. That property has also been recently shown in *P. vivax*-infected erythrocytes, under static and flow conditions, in cells expressing endothelial receptors known as *P. falciparum* cytoadhesion mediators. That can change the old concept that *P. vivax* infection is benign and has no close relationship between infected erythrocytes and vascular endothelium.

There is scientific evidence relating endothelial dysfunction with the origin and aggravation of systemic diseases. The normal endothelium has anti-inflammatory, antithrombotic and vasodilating properties that allow maintaining blood flow, preventing thrombosis and leukocyte diapedesis. The reduction in the bioavailability of nitric oxide, a key molecule usually produced by the healthy endothelium, can cause endothelial dysfunction, represented by a change in the endothelium-dependent vasodilation.

Endothelial dysfunction can be also mediated by proinflammatory cytokines, whose circulating levels increase during both infections and sterile inflammations. Other factors, such as blood stasis, dehydration and increased coagulability can also contribute to that dysfunction.

Those functions characterize the endothelium as a biological sensor capable of detecting mechanical, physical or chemical stimuli, and of biological responses, making it a multifunctional tissue with an important role in human homeostasis.

The pathogenesis of severe malaria involves several processes, such as the rapid increase in the number of infected erythrocytes, destruction of those infected erythrocytes, inflammatory process, and microvascular obstruction by products released by cellular injury, leading to a reduction in tissue perfusion.

Two endothelial receptors participate in *P. falciparum* infection, intercellular adhesion molecule 1 (ICAM-1) and chondroitin sulfate A (CSA), which are also involved in the cytoadhesion of *P. vivax*-infected erythrocytes. Cytoadhesion is ten-fold smaller in *P. vivax*-infected erythrocytes than in *P. falciparum*-infected erythrocytes; however, after adhesion, the affinity of *P. vivax*-infected erythrocytes with CSA is as strong as that of *P. falciparum*-infected erythrocytes. The investigation of the role played by cytoadherence in spleen, lungs and placenta in chronic infection might reveal important molecular bases of the pathology of *P. vivax* malaria. If cytoadhesion in tissues, such as kidneys and bone marrow, is proved, observations about severe forms of disease and the cytoadhesion mechanism might be confirmed.

In *P. vivax* infection, other types of proteins are expressed on the surface of infected erythrocytes. That is a variant gene superfamily, called “VIR family”. Those proteins of the VIR family can mediate the cytoadhesion process. The subcellular localization and function of subtelomeric multigene families of the VIR genes in *P. vivax* remain unknown. Bernabeu et al., using transgenic lines of *P. falciparum* expressing VIR proteins, have shown that the VIR14 protein, which belongs to the C subfamily of a VIR multigene superfamily, is a ligand of the ICAM-1/endothelial receptor. The findings support the opinion that VIR proteins can have different subcellular localizations and functions. It is still a matter of investigation if *P. vivax* sequestration can occur in vivo and be involved in the disease’s pathogenesis.

**Clinical implications**

Malaria infection affects several organs and systems, which favors the development of the severe form of disease and appearance of complications. The lethality of malaria results from complications, such as central nervous system impairment, anemia and renal failure.

The *P. vivax* malaria, the most frequent in Brazil, is considered a benign disease, with few fatal cases. However, it causes a debilitating febrile syndrome. In more severe forms, it can present as cerebral malaria, severe anemia, severe thrombocytopenia, acute renal failure, and acute respiratory failure. The elevation in D-dimers and in fibrin degradation products (FDP) found in malaria confirms the rare complication of disseminated intravascular coagulation (DIC) and fibrinolysis. Even after complete clinical recovery, those markers can remain elevated, due to the residual cell damage caused by the parasite infection. Knowing this is important to avoid unnecessary diagnostic investigations and prolonged hospitalizations.

Further studies are required to assess the predictors of severe *P. vivax* malaria, cellular factors or host characteristics that can contribute to frequent complications.

Regarding heart impairment during the acute phase of disease, there is little information on the pathophysiology and clinical and laboratory findings of the myocardial lesion. In 1996, Bethel et al. suggested that, in cases of severe *P. falciparum* infection, the heart is one of the most intensely infected organs, although abnormalities in cardiovascular function have been rarely described.

Even considering the clinical and laboratory limitations at the time, in 1954 an uncommon case of *P. vivax* malaria was reported in association with cardiomegaly, anemia, hepatomegaly and renal impairment. Immunohistochimistry performed in five fatal malaria cases has detected the abundant presence of *P. falciparum* antigens, mainly in cerebral blood vessels, heart and pulmonary tissue.
reported a case of myocarditis associated with acute \textit{P. falciparum} malaria; they have also reported that classical studies on autopsies have revealed that, in the presence of parasitemia, there is sequestration of infected erythrocytes in the myocardial microvasculature and capillary blockade, which can cause myocardial ischemia.

Those data suggest that, during acute infection, myocardial lesion directly mediated by proteins released by the parasite can occur. Lacerda et al.\textsuperscript{12}, reporting two cases of shock syndrome due to \textit{P. falciparum} malaria, also known as algid malaria, have suggested that a reduction in cardiac inotropism with acute pulmonary edema can be a complication of the disease. The depression in myocardial function might be due to several factors, such as the release of inflammatory cytokines or presence of cardiodepressive components on the surface of parasite antigens, severe anemia, ischemia, and, myotoxicity induced by drugs used in the treatment\textsuperscript{23}.

Kim et al.\textsuperscript{34} have emphasized the importance of chest pain on the clinical exam of patients with \textit{P. vivax} malaria. Reporting a case of myocarditis associated with \textit{P. vivax}, those authors have described the clinical findings of a 27-year-old female patient complaining of substernal chest pain, suspected of having left ventricular anterior wall hypokinesia, with normal coronary arteries. The patient had elevated serum levels of CK-MB and troponin-I, and the possibility of chloroquine toxicity was ruled out\textsuperscript{35}.

In 2012, Bhat et al.\textsuperscript{35} reported a case of \textit{P. vivax} malaria in a 40-year-old male with no risk factors for coronary artery disease, who had typical precordial pain, thrombocytopenia, ST-segment elevation on electrocardiogram and increased serum levels of troponin-T and CK-MB. The echocardiogram showed left ventricular lateral wall hypokinesia. The patient was diagnosed with acute coronary syndrome as a complication of malaria or its treatment\textsuperscript{35}, Ahmad et al.\textsuperscript{36} have reported a case of acute pulmonary edema due to acute myocarditis in a 17-year-old female with \textit{P. vivax} infection.

Most studies on malaria have focused on the \textit{P. falciparum} species, because of its high mortality. However, the high morbidity and financial cost resulting from \textit{P. vivax} malaria require a more comprehensive understanding of that disease and the search for control strategies\textsuperscript{37}.

Patients with \textit{vivax} or \textit{falciparum} malaria have reduced gas exchange in pulmonary capillaries of similar intensities. However, after treating the infection, progressive alveolarcapillary dysfunction was observed in patients with \textit{P. vivax}, suggesting severe inflammatory response, probably due to the greater pulmonary vascular sequestration observed in the infection by that plasmodium species\textsuperscript{38}.

Janka et al.\textsuperscript{39}, assessing children with severe \textit{P. falciparum} malaria, have reported an increase in the pulmonary arterial pressure caused by endothelial dysfunction, resulting in increased right ventricular wall stress.

Such data emphasize that cardiologists should see malaria infection not only as an infectious disease, but also as a disease that may cause endothelial dysfunction, myocardial ischemia, myocardial contractility depression and pulmonary arterial hypertension, and that can aggravate the clinical conditions of previously healthy patients or those with an underlying heart disease.

**Conclusion**

Cardiologists usually have to manage patients with infectious diseases who are referred for the assessment of possible complications of those diseases or aggravation of a preexisting heart condition, as well as for the assessment of several therapies used in their treatment. Usually, cardiologists and infectious disease specialists do not interact to simultaneously manage the patient, which is quite often necessary, and can eventually change the disease outcome.

In face of current evidence, the clinical approach of patients with malaria, be it either \textit{P. falciparum} or \textit{P. vivax}, should be modified. This is particularly true regarding \textit{P. vivax} infections, wrongly considered to be benign and that can have late disease relapses, a fact that can cause repeated exposure of the endothelium to inflammatory factors. The pathophysiology of the cardiovascular complications of malaria due to that parasite has not been well defined.

The probable endothelial lesions in severe malaria with cardiovascular impairment require the simultaneous management of cardiology and infectology specialists. That is a new way to see an ancestral disease that continues to be an important public health problem, with no real perspective of eradication.

**Author contributions**

Conception and design of the research: Alencar Filho AC, Lacerda MVG; Acquisition of data and Analysis and interpretation of the data: Alencar Filho AC; Writing of the manuscript: Alencar Filho AC, Okoshi MP; Critical revision of the manuscript for intellectual content: Lacerda MVG, Okoshi K, Okoshi MP.

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