Editorial

Does Malaria Cause Hypertension?

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Is malaria a potential cause of hypertension? In this issue of the Circulation Research, Etyang et al1 offer a concise review of the epidemiological data and pathogenetic mechanisms that, according to the current status of knowledge, are thought to link Plasmodium infection to the growing burden of hypertension in the sub-Saharan Africa, some part of Asia and other low-income countries.1,2 They also suggest some research approaches to further explore this emerging issue.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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DOI: 10.1161/CIRCRESAHA.116.309013.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.116.309013

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Malaria, a devastating disease that is currently widespread in the tropics, is caused by at least 10 species, pathogen for humans, of the genus Plasmodium, large parasitic protozoa first described in 1885. The infection begins with inoculation of parasite sporozoite by infected mosquitoes. The sporozoites rapidly enter the hepatocytes (hepatic stage). In a few days, each sporozoite generates ≈40000 merozoites per each infected liver cell. The sporozoites of some Plasmodium species may generate hypnozoites, which may remain silent in the hepatocyte for months or years before generating merozoites. The blood stage of malaria starts when merozoites generated in the hepatocytes invade red blood cells (RBCs) and digest hemoglobin. Here, some derivative products of hemoglobin, including hematin, are lethal for the parasite. However, the parasite may convert hematin into the less toxic hemozoin, and this reaction is inhibited by chloroquine. The artemisinins, antimalarial drugs developed from the Chinese herbal remedy qinghaosu, are activated by intraparasitic heme iron, which catalyzes the cleavage of an endoperoxide bridge present in the drug, with resulting production of free radical intermediates that may kill the parasite by alkylating and poisoning essential malarial proteins.

Hemolysis of infected RBCs may lead to anemia. Infected RBCs tend to escape removal in the spleen through adhesion to endothelial cells at different levels, including brain and placenta, thereby causing important organ-specific syndromes. Cerebral malaria is particularly worrisome. Adhesion of infected RBCs to endothelial cells is mediated by some parasite proteins that are expressed on the surface of erythrocytes and interact with some host endothelial cell receptors, ultimately leading to sequestration of infected erythrocytes in the target organs. Unfortunately, resistance to antimalarial drugs, including chloroquine and artemisinins derivative, is rapidly developing in infected areas. This reinforces the need for new therapies and more effective preventive measures.

Although the estimates of malaria mortality may be imprecise,3,5 it is out of question that malaria is a devastating disease, which kills ≈1 million children per year in Africa and accounts for 25% of all childhood deaths.4 Fortunately, a modest reduction in the prevalence of malaria has been reported in sub-Saharan Africa over the decade, that is, 2000 to 2010, but the absolute numbers remain high.6 The growing burden of hypertension in sub-Saharan Africa2 and other low-income countries in which Plasmodium infection is endemic7 begins at younger ages than in more developed countries. In these low-income countries, the early development of hypertension is supposed to be an important factor underlying the excess risk of serious cardiovascular complications even in younger people.8,9 In their review, Etyang et al1 provide a summary of the mechanisms through which malaria exerts a detrimental impact on pregnancy. A synthesis of the entire scenario is reported in the Figure. Particularly in primigravid women,10 sequestration of Plasmodium merozoites in the placenta increases the risk of gestational hypertension, preeclampsia and eclampsia, which are the second leading cause of maternal death in those areas.11 At birth, infants with maternal malaria are smaller than those not exposed, and the rise in systolic blood pressure during the first year of life is greater than those not exposed, particularly among girls.12 Several mechanisms including a low birth weight, stunting and malnutrition in childhood, and chronic inflammation are reasonable pathogenetic pathways that may explain the potential role of maternal Plasmodium infection in the genesis of hypertension.

An additional potential mechanism linking malaria to hypertension includes the supposed effect of angiotensin II (Ang II) in limiting erythrocyte invasion by Plasmodium, as suggested from in vitro studies.13,14 Using monolayers of human brain microvascular endothelium, Gallego-Delgado et al15 found increased disruption of interendothelial cell junctions after incubation with erythrocytes infected with Plasmodium falciparum. Inhibition of Ang II type 1 or activation of Ang II type 2 receptors preserved the integrity of interendothelial cell junctions. This concept seems to be supported by the results of epidemiological studies. Indeed, 2 polymorphisms of the angiotensin-converting enzyme and angiotensin-converting enzyme-2 leading to increased circulating Ang II levels have been associated with lower risk of cerebral malaria in Indian women8 and individuals with African genetic background.17 Thus, although evidence is still scarce, an intriguing hypothesis is that Ang II polymorphisms may confer a survival
advantage to individuals with higher levels of Ang II and increased blood pressure.

Of course, the population-attributable risk of hypertension directly accounted for by malaria is still undefined. Also, undefined are the most appropriate research approaches to this issue. As outlined by Etyang et al,1 observational studies and randomized intervention trials have pros and cons that should be carefully considered. Conversely, Mendelian randomization studies based on the assumption that some hemoglobin polymorphism protect against malaria might offer a more promising approach. It is well known that human RBCs are subjected to genetic mutations that modify the structure of β-globins (hemoglobin S [HbS] and HbC), the expression of α- and β-globins (thalassaemias), or reduce the activity of important enzymes (glucose-6-phosphate dehydrogenase deficiency). RBCs may also be diversified by variations in surface antigens (ABO, Duffy, and Rhesus groups). The literature on the relation between hemoglobin polymorphisms and malaria is large, but results are not univocal. For example, it has been noted that HbS heterozygotes have a 10-fold less risk of malaria14 and that HbC homozygotes are also protected from malaria.15 In a recent prospective study from Mali, 4091 episodes of malaria were detected in 1543 children over a 4-year follow-up. HbS protected from malaria, but protection was attenuated after early childhood, and it was absent in teenagers, suggesting a declining protective effect of HbS with age in early childhood.20 In that study, HbA increased the risk of malaria, whereas α-thalassaemia, ABO group, and glucose-6-phosphate dehydrogenase A heterozygotes or hemizygotes did not provide protection from malaria.20

The hypothesis of a blood pressure difference between subjects with and without hemoglobin polymorphisms associated with malaria would reinforce, if clearly demonstrated, the causative role of malaria in the genesis of hypertension. The design of these studies, however, would require, as correctly suggested by Etyang et al,1 not only the inclusion of subjects with and without hemoglobin polymorphism from exposed areas but also of control groups with and without polymorphism from regions not exposed to malaria.

The malaria-high blood pressure hypothesis reviewed by Etyang et al3 has worldwide relevance that transcends the relation between Plasmodium infection and hypertension observed in sub-Saharan Africa and other low-income

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**Figure.** At least 3 lines of evidence suggest a possible association between malaria and hypertension: (1) malaria causes inflammation with final detrimental effects on the endothelial cells; (2) malaria in pregnancy leads to low birth weight as a consequence of impaired uteroplacental blood flow and maternal anemia; this may predispose to development of hypertension; and (3) malaria is associated with chronic malnutrition favoring loss of nephrons and premature senescence of the kidney. Finally, angiotensin II (Ang II) might modulate malaria severity through an inhibitory effect on the parasite growth. RAS indicates renin–angiotensin system.
countries. The detrimental impact of malaria in pregnancy and its consequences in terms of increased risk of hypertension and cardiovascular disease is a pathogenetic model that, added to other data linking disorders of pregnancy with cardiovascular disorders in adult life\textsuperscript{21–23} strongly supports the concept that prevention of cardiovascular disease is a social priority that should start early through preservation of health of mothers during pregnancy and of their babies during early and late childhood.

Disclosures

None.

References


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_Circ Res._ 2016;119:7-9
doi: 10.1161/CIRCRESAHA.116.309013

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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