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Review

Acute kidney injury in malaria: An update

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ABSTRACT

Malaria is a mosquito-borne infectious disease with active transmission in the tropics. Malaria is becoming a global threat with the increasing number of cases of 'imported malaria'. According to the World Health Organization, half of the world's population is at the risk of malaria. Severe malaria is associated with high mortality. There has been a change in the spectrum of manifestations of severe malaria over the past two decades. Acute kidney injury (AKI) in malaria is being frequently reported. AKI is commonly caused by *Plasmodium falciparum*. However, *Plasmodium vivax* and *Plasmodium knowlesi* are also shown to cause AKI. A combination of hemorheological, inflammatory and humoral responses has been implicated in the pathogenesis. AKI in malaria is frequently oliguric and hyper-catabolic. Cerebral malaria and jaundice are often associated with acute kidney injury and portend a poor prognosis. The KDIGO criteria enable earlier detection of acute kidney injury in malaria. Acute tubular necrosis is the most consistent histological feature. A lot of uncertainty surrounds fluid management in severe malaria. A conservative approach to fluid replacement is recommended. Artesunate is the recommended first choice antimalarial for the treatment of severe malaria. Prompt recognition and early institution of renal replacement therapy reduces the mortality.

1. Introduction

Malaria is a mosquito-borne infectious disease transmitted by the bite of an infected female anopheles mosquito. Five species of the genus *Plasmodium* are known to cause human disease namely *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi*. Globally a significant progress has been achieved in malaria control with a reduction in the incidence of malaria of 37% between 2000 and 2015. Severe malaria is associated with high mortality. There has been a recent change in the spectrum of manifestations of severe malaria. The incidence of acute kidney injury in malaria is on the rise. *P. malariae* causes nephrotic syndrome due to immune-complex mediated glomerular disease and is referred to as 'quartan malarial nephropathy'. Most cases of malarial acute kidney injury are attributable to *P. falciparum* infection. However, vivax malaria which was historically hailed to be a benign form of malaria is now recognized to give rise to a whole spectrum of pathological changes resulting in high morbidity and mortality.[1] Early recognition of renal impairment in malaria is of profound importance. Prompt institution of antimalarial therapy and renal replacement therapy has been shown to improve the prognosis.[2]

This review gives an overview of the epidemiology and pathogenesis of acute kidney injury in malaria and highlights the recent developments in diagnosis and management.

2. Epidemiology

2.1. Geographical distribution

Malaria occurs predominantly in the tropics. This tropical distribution is attributable to the favorable conditions for parasite survival in the vector. However, malaria is becoming a global threat with the advent of cases of 'imported malaria'.[3–5] The various species of genus *Plasmodium* have varying geographical distribution with *P. falciparum* predominating in Africa whereas *P. vivax* infection occurs in high frequency in the South East Asian Region (SEAR). More than 50% of the malaria cases outside Africa are caused by *P. vivax* and it constitutes more than 80% of the cases occurring in Ethiopia, Pakistan, and India.[6] *P. malariae* and *P. ovale* are largely restricted to the African continent. The fifth malarial parasite which has assumed recent importance is *P. knowlesi*. The first large focus of *P. knowlesi* infection was described in the Island of Borneo, Malaysia.[7] Since then *P. knowlesi* infections have been

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reported inThailand,[8,9] Philippines,[10] Myanmar,[11] Singapore,[12] Vietnam,[13] Indonesia,[14] and Cambodia.[15] The long-tailed and pig-tailed macaques act as reservoir hosts for *P. knowlesi*. The discovery of *P. knowlesi* infection in humans has led to a paradigm shift in the generally held view that zoonotic malaria was an extremely rare event.[16]

2.2. Global trends

In the year 2015, it was estimated that nearly half of the world's population was at risk of malaria. There were 214 million cases and 438,000 deaths globally.[6] The year 2015 marked the final year for achieving the targets set by the world health assembly and the roll back malaria program to reduce malaria incidence and mortality.[17] It also marked the end of Millennium Development Goals and the beginning of sustainable development goals. Significant progress has been made over the past 15 years in malaria control. Globally, the number of cases of malaria has decreased by 18% between 2000 and 2015 with the majority of the reduction happening in Africa (88%).[6] The incidence of malaria has dropped by 37%. The malarial mortality rate has fallen by 60%.[6] The Millennium Development Goal 6C to have halted and reversed the incidence of malaria was achieved. Out of the 106 countries which had active malaria transmission, 57 countries had recorded more than 75% reduction in the incidence of malaria and a further 18 reduced by 50–75%.[6]

2.3. Epidemiology of malarial acute kidney injury

Acute kidney injury (AKI) in malaria is often caused by *P. falciparum*. However, among the other species, *P. vivax* and *P. knowlesi* are notable for causing acute kidney injury. The incidence of malarial acute kidney injury varies from 15 to 48% in different studies.[18–22] The varying incidence in different populations is attributed to its dependence on age and the presence of antimalarial immunity. Naturally acquired immunity (NAI) to falciparum malaria occurs among people living in the hyper and holoendemic regions of malaria transmission. This immunity confers protection against the severe manifestations of malaria and death.[23] Nonimmune adults from areas of low transmission and older children are susceptible to develop acute kidney injury. Renal failure was as common as cerebral malaria in non-immune Europeans with falciparum malaria.[24] AKI has been reported from Austria and Netherlands and most of these cases were imported.[4] The incidence of malarial AKI in Africa seems to be low due to the hyperendemicity of the region which confers naturally acquired immunity. Waller et al. found that none of the 180 Gambian children with severe malaria had acute renal failure.[25] However due to the difference in the transmission rates, certain regions of Africa seem to have a high incidence of AKI. In a study done in Addis Ababa, it was found that malarial AKI contributed to 21% of the 136 consecutive treated adult AKI patients. The case fatality rate was as high as 37.9%.[26] AKI is a common manifestation of severe malaria in the South East Asian Region. Malarial AKI is being reported in increasing numbers from Kampuchea, Vietnam, Thailand, and Singapore. The overall incidence of malarial acute kidney injury in India varies between 4 and 17.2%.[27] In the pediatric population, the incidence of malarial AKI was found to be 7.7% in the under-5 year age group and 18.4% in the 5–14 year age group.[28] A recent upsurge in the number of cases of *P. vivax* associated AKI from India is also notable.[29]

3. Life cycle of the malarial parasite

Malaria is transmitted by the bite of an infected female anopheles mosquito. Four hundred different species of *Anopheles* mosquito have been identified of which 30 are of major importance. The mosquito inoculates the sporozoites which then traverse through 2 phases in the humans. In the pre-erythrocytic or intrahepatic phase, the inoculated sporozoites reach the liver and invade the hepatocytes. After the invasion, they may either remain dormant (as in the case with *P. vivax* and *P. ovale* infections) or undergo asexual reproduction to produce the merozoites. An increasing number of merozoites causes the hepatocyte to burst and release the merozoites into the circulation. In the circulation, merozoites invade the red blood cells (RBC's). In the case of *P. falciparum*, reticulocyte binding protein homologue 5 (PfRh5) and the corresponding erythrocyte receptor Basigin (CD147) are involved.[30] *P. vivax* invades the erythrocytes *via* the Duffy antigen Fy^a and Fy^b and the absence of this antigen in the West African population renders them resistant to the infection with *P. vivax*.[31] The merozoites feed on the RBC's hemoglobin and develop into the schizont. The RBC ruptures to release the merozoites which then invade another RBC to repeat the cycle. Some of the merozoites transform into the sexual forms, gametocytes. The circulating male and female gametocytes are taken up by the vector during a blood meal. The gametocytes then form the zygote in the insect's midgut which then transforms into the ookinete. The ookinete ruptures to release the sporozoites which reach the insect's salivary gland ready to be inoculated into another host.

4. Pathogenesis

P. falciparum is responsible for the majority of the mortality associated with malaria. However, *P. vivax* and *P. knowlesi* can also cause severe illness. The pathogenesis of malaria associated acute kidney injury is not clearly understood. A combination of hemorheological, inflammatory and humoral responses has been implicated in the pathogenesis. Recent studies have thrown insights into the pathogenesis of the clinical manifestations of malaria caused by these 3 species of *Plasmodium*.

4.1. Falciparum malaria

Three processes are central to the pathogenesis of Falciparum malaria: cytoadherence, rosetting, and agglutination.[32] These processes culminate in microvascular clogging and tissue hypoxia.

4.1.1. Cytoadherence

P. falciparum infected erythrocytes can bind to a diverse array of receptors on different cell types including endothelial cells, uninfected RBC's, platelets, dendritic cells, B cell, monocytes, and macrophages. Parasitized RBC's develop protrusion on their surfaces called as 'knobs'.[33] These knobs express parasite-derived proteins termed PfEMP1 (*P. falciparum* derived epithelial membrane protein 1). These proteins are encoded by the *var* gene.[34] Each parasite encodes 60 different *var* genes and switching between them permits the parasite to evade host defense mechanisms. PfEMP1 mediates attachment of the RBC's to the receptors on the capillary and venular endothelium. The parasitized RBC's thus become sticky and adheres to the microvasculature eventually blocking them. Various receptors for PfEMP1 binding have been identified of which Intracellular adhesion molecule-1 (ICAM-1) is more important in the brain, chondroitin sulfate B in the placenta and CD 36 in most other organs. CD36 binding also plays a role in the non-opsonic phagocytosis of the infected RBC's. Another novel receptor described recently by Turner et al. is the endothelial protein C receptor (EPCR), which is expressed on the endothelial cells and leucocytes.[35] The protein C-EPCR pathway has anti-inflammatory activity in leucocytes and protects the endothelial cells. EPCR binding of parasitized RBC's is associated with severe malaria.