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KIDNEY COMPLICATION OF SEVERE MALARIA

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Abstract

Malaria is an infectious protozoan parasitic disease transmitted by Anopheles spp mosquito. As a disease entity, malaria is still a major global health problem due to its morbidity and mortality that endangered millions of individuals inhabitants in tropical region. Kidney derangement is moderately frequent in severe malaria caused by the species *P. falciparum* and also *P. malariae*, but seldom this condition has also been reported in malaria due to *P. vivax*. Severe or complicated malaria can occur due to delay or failure of treatment. Making correct and early diagnosis is a prerequisite for successful treatment. Actually, a series of events that begins with the entry of blood protozoa into the host which then causes hemodynamic disturbances and loss of normal capillary capacity. Hemodynamic dysfunction, immune response and with addition from the consequences of severe malaria complications in other organs (*e.g.,* liver) leading to worsening of kidney function in severe malaria.. This paper cover the main aspects of kidney involvement in malaria and important findings of the most recent research addressing this issue.

Keywords: severity, complication, glomerulonephritis, acute, capillary, hemodynamic

Introduction

Malaria is a global blood protozoan based parasitic infection (*Plasmodium* spp) transmitted by specific mosquitos, Anopheles spp. Its existence in the environment is related to the continuity of their breeding place and the guarantee of the existence of food sources.[1,2] Epidemiologically, malaria related morbidity and mortality are still high, especially among children and women living in endemic areas.[3] It affects +200 million people globably, with estimated number of mortality due to malaria and its complication reaching in up to 303,000 children annually. Although the low prevalence in tropical under-developed countries is common, maybe due to budget constraints [4] that caused underreported or undetected cases, but unfortunately for travelers or other visitors that came from low transmission regions to visit endemic regions, they are very prone to malaria and its impediment; especially if they have returned to their area of origin/hometown where malaria may not be a type of disease that is commonly found locally [3,6].

Without early diagnosis and proper adequate antimalarial treatment, what was originally just a simple malaria can then progress to severe or complicated malaria in immune-naive people, *e.g.*, children, by way of cytoadherence- an infected erythrocyte cellular architecture, conferring cytoadhesive properties to the infected erythrocytes [7,8]. Severe malaria able to cause noteworthy and simultant multiorgan dysfunction, *e.g.*, kidney derangement [8]. Acute kidney injury (AKI) is the most prevalent form of malaria related kidney complication [9].

Common pathophysiological pathways include impaired microcirculation [10], due to sequestration of parasitized erythrocytes, systemic inflammatory responses, and in the end trigger endothelial activation [9].

The pathogenesis of AKI in severe malaria is not clearly revealed but suggested mechanisms include acute tubular necrosis (ATN) due to (1) encumbrance in renal microvasculature and its local circulation, (2) intra-renal infection-triggered proinflammatory effects, and (3) full blown metabolic disturbances [11]. Doctors must carefully consider the potency of malarial infection in AKI patient if the patient had a pilgrimage history to endemic region; in this scenario an early clinical recognition and treatment are mandatory to prevent disease worsening and eventually improving outcomes [12]. This article will describe severe malaria-induced AKI in order to improve a better understanding of this infection's consequences on the kidneys.

Malaria Pathogenesis

The infection starts when the infective stage named sporozoites are inserted by the aid of Infectious Anopheles mosquito in susceptible individual [13,14]. After going through some periods of transformative cycle until the appearance of the schizonts in peripheral blood and foolowed by numbers of merozoites attack erythrocytes. The infected erythrocytes lost its deformability property that leads to the cell wall rupture, named hemolysis [15]. The mean incubation time is estimated, from the time the parasite enters the host until clear clinical symptoms appeared, for a period of 12 days for malaria *falciparum*, 14 days for malaria *vivax* and last but not least 30 days for malaria *malariae*.

Malaria itself, regardless of the causative species, is clinically divided into acute, fulminant or chronic, chronologically [16]. In general, infected individuals present with certain duration of intermittent fever, chills, headache, asthenia, anorexia, myalgia-arthralgia, nausea and vomiting [17]. According to Bria *et al* [17], the previous symptoms combined with patients' history of malaria as a non symptom-related factor contribute most to correct malaria diagnosis. Diagnosis made microscopically by discovering intracellular parasite inside erythrocytes in stained thin blood films using Giemsa's while the thick blood smear is only to show the result is positive or negative [18,19].

The acute condition is occasionally caused by *P. vivax*, *P. ovale* and to some extent less frequent, by *P. Malariae* [18]. Patients regularly suffer from obvious paroxysm fever, with intervals ranging from 1 to 4 days, and usually always accompanied with *frigidus*/chills, sweating, anemia, hepatomegaly and splenomegaly. Fulminant malaria is clasically believed caused by *P. Falciparum* [20], eventhough malaria caused by *Plasmodium vivax* was long considered to have a low mortality, but recent reports from certain geographical regions suggest that severe and complicated vivax malaria may be more frequent than previously known [21].

A number of symptoms are often found in clinical conditions of severe malaria, including: anemia, acute kidney injury, disseminated intravascular coagulation, respiratory failure, adynamia, severe diarrhea, prominent jaundice, hydroelectrolite disturbances, shock and ends in coma [20-22]. For someone who has actually recovered from malaria, a state of reactivation can occur in malaria *ovale* and malaria *vivax*. Reactivation occured due to

remaining hypnozoites the liver and manifest with reappearance of: high fever, anemia, hepato-splenomegaly and malnutrition [23,24]. The chronic malaria is usually caused by *P. Malariae*, which is the most frequently related in glomerulonephritis *et causa* malaria [25], but the species *P. vivax*, notwithstanding being appraised as a "benign" organism, causing in insignificant mortality percentages, to some extent has also been involved in severe condition [21]. Kidney involvement and its derangements in *P. vivax* infections are relateded with the patient's age, microvasculature-hemodynamic derangement and if the condition worsens, then it can have caused fatal respiratory failure [20-22,25].

Histopathology of Affected Kidney: Involvement in severe malaria

Clinically, indications of kidney derangement in severe malaria are numerous, with the most often condition meet are as follows: moderate to severe proteinuria, microalbuminuria and urinary casts, proclaimed in >50% of patients [18]. Actually, the condition of nephrotic syndrome has also been delineated in malaria *falciparum*, but luckily it is seldom to happen [27]. In falciparum malaria, renal tubular disease actually exhibited by a well-established entity , the condition identified as hemoglobinuric nephrosis ("blackwater fever"); the happening of remarkable glomerular derangement is inconspicuous and is very likely to be missed by doctors for two reasons: (1) the kidney derangement signs and symptoms masked by the more severe symptoms that are more prominent, (2) cases like this are rarely encountered (for example in imported malaria conditions due to traveling to endemic areas).

Rather than the parasite burden itself, the delayed complications malaria-induced dysregulated immune responses that combined with the direct parasite-its products related tissue impairment can lead to a series of events as a consequence of the chronicity of the disease; without realizing it because the symptoms are not always clear, it can be irreversible and deteriorating [8,9,21, 29]. Furthermore, the complete elimination of this protozoan parasites inside the host probably difficult due to the existence of liver stage, and the remaining often lead to incomplete recovery from the disease as silent complications that can still persist for a long time. After completed treatment with artemisinin derivatives, a number of asexual parasites set off inactive (dormant) for a short periode of time within their infected erythrocytes[30]. Reactivation of dormant parasites can occur immediately after anti-malarial regimen concentrations decline [31].

In complicated malaria due to *P. falciparum*, actually it is a multiple-organ disease characterized by successive failure of vital organs with diverse conditions including sudden cerebral malaria, fatal severe anaemia, lactic-acidosis, hypoglycaemia, acute renal failure and massive pulmonary edema [32]. In the context of renal impairment due to malaria, the severity and progression of the disease course clearly show signs of clinical deterioration that tend to be fatal and potentially lethal.

Histopathologically, microscopic analysis of diseased kidney tissue in severe malaria revealed signs of: (1) glomerulonephritis, (2) acute tubular necrosis and (3) acute interstitial nephritis. It is also attainable for the patient to develop gradual chronic kidney disease due to malaria, chiefly in those individuals living in endemic areas which experience repetitive episodes of malaria [18]. Plasmodium antigens have already been noticed in the glomeruli, pointing a straight consequences of this blood protozoan in the functional units of the kidney,

which can provoke sequence of inflammatory process that advancing to distinctive patterns of glomerulonephritis [32].

According to the result of post-mortem histopathology examination regarding specimens of renal tissue assembled from lethal cases of severe falciparum malaria (n=63) revealed that in many patients, actually several conditions of severe disease happened be in conformity almost at the same time, accentuating the characteristic of multi-organ involvement in severe malaria disease. Eventhough that the complications were unassociated to each other and were scattered independently among each patients, but still, unfortunately regardless of the severity of the condition of the affected organs, but all conditions lead to the fatality of patients who are not successfully treated, as soon as possible [32].

Qualitative observation of pathological apperances in the kidney tissues of patients who died due to severe malaria conducted with specific focus to the section of glomerular capillaries region, basement membranes areas, peritubular capillaries and blood vessels [32]. Representative picture of histopathology of glomeruli in the kidneys of the *P. falciparum* malaria patients compared with the normal/control can be seen in comprehensive report conducted by Wichapoon *et al* [33].

Within these specific kidney micro vasculature, close observation of the attributes and severity of kidney injury are carefully observed. Previously mentioned condition usually marked with histology changes regarding diseased kidney structure as follows:

(1) the signs of presence or absence of intravascular sequestered parasitized red blood cells (PRBC),

(2) number and type of non erythrocte blood cells, *e.g.*, leukocytes, fibrin thrombus and also platelets found on the spot,

(3) Endothelial cells were examined carefully for the possibility of cell hypertrophy and or cell bulging, pseudopodia formation, changes in organelle shape and intercellular bridges, with also sign of vacuolation,

(4) signs of glomerular basement membrane solidifying and the existence of any electron dense deposits inside the glomerular capillaries lumen, which correlate to immune complex deposition, either in the area of peripheral capillary loops or nearby mesangium,

(5) The shape and appearance of glomerular epithelial cell foot processes was carefully examined to determine whether foot process fusion (effacement) was seen, which may indicate proteinuria.

(6) Last but not least, the presence or absence of intra cappilaries malarial haemorrhages was evaluated within the perivascular spaces and interstitium,

(7) Sequestration index (in percent) counted by compared themagnitude of asequestration in to the peripheral blood parasitaemia,

All of these changes lead to major circulatory disturbances in the renal microvasculature, which can be fatal if not treated immediately, and the consequences are listed below.

Impediments in renal microvasculature and its local circulation

Erythrocytic stage of plasmodium parasite gives direct consequences to the host's infected red blood cells. These changes include loss of the normal discoid shape, loss of deformability properties due to escalated rigidity of the membrane, increased cell wall permeability due to a wide array of ionic and other species, and expanded its adhesiveness, mostly to microvasculature endothelial surfaces. At that location, blood cells approximate the size of the microvasculature themselves; and sophisticated interactions among blood cells, plasma molecules, and the endothelium constantly ensue. The size of the microvasculature, speed of fluid intra-luminal, and unique rheological properties of blood all of these three play a role in influencing the shear stress and also increased the possibilities of adhesiveness PRBC [35]. One that must be remembered that abnormalities exclusively occur intra-luminal of mucrovasculature [36].

The sequence of events took part gradually but perhaps rapidly, starting with sequestration of parasitized erythrocytes [37], rosetting [38] and aggregation of parasitic particles in the kidney [39]. This aggregation causing series of events that lead to endothelial activation [36, 40] and microvascular flow hindrance [36], and in the end impairment and even total impenetrable of renal blood flow causing local tissue hypoxia, especially in non-immune adults [41,42]. Disturbance that initially occurs locally and may be only partial in the beginning but can then spread rapidly to encompass the entire anatomy of the kidney as the disease progresses to worse [22,27-29].

Particular ensigns of malaria infection is the condition of intravascular hemolysis, primarily of PRBCs, which followed by the liberation of cell-free heme systematically, as well as both damaged host and parasite-derived molecules that surely stimulate further inflammatory reactions [26]. Once released from cells and from hemeproteins, free heme generates series of oxidative damage and inflammation, thus enacting as a prototypic damage-associated molecular pattern [43].

To some extent, intravascular hemolysis actually occurs in all type of malaria (falciparum, vivax, malariae or ovale) but the most proclaimed causing considerable hemolysis happens only in *falciparum* malaria, as an outcome of the excessive densities of the malaria parasite in the blood (hyper-parasitemia); customarily occurring with this type of parasite species [44]. The distinct virulence of *P. falciparum* is also appertaining to the expression of malaria proteins on the superficial aspect of PRBC, a condition which authorize their adhesion to the endothelium section of microvasculature, through attaching to the receptors of endothelial lining (*e.g.*, ICAM-1, EPCR) [45].

As the red pulp of spleen is actually very effective in destroying rheologically impaired and less deformable erythrocytes, but unfortunately the developing malaria parasite has developed mechanisms that changes the host cell in certain ways to run away splenic clearance [46]. Sequestered pRBCs able to avoid splenic clearance by cytoadhering to the vascular endothelium and sequestering in capillary beds of organs that are less dangerous than the spleen, bestowing to elevated number of parasite count, block any microvasculature being entered through rosetting, bring about permanent tissue hypoxia, and actuate vascular

endothelial cells, a condition that precedes glycocalyx degradation and microvascular dysfunction, permanently [36].

Endothelial activation is believable a focus of pathological reaction for the permanent loss of microvasculature function, causing in disablement of its barrier affair that contributed to the dysregulation of blood movement intravasculature and triggers coagulation cascades with the emanation of proinflammatory cytokines, further magnifying the host inflammatory reaction [32,33,35,36].

Endothelial activation contributes significantly to the pathogenesis of severe malaria, specifically through upregulating cell adhesion molecules (CAMs) that mediate cytoadherence of PRBC in certain microvasculature, contributing to the happening of acute tissue hypoperfusion that triggers ischemia locally (which initially occurs only locally in certain areas of the affected kidney but can quickly expand massively) and cause metabolic acidosis, as well as permanent blood-brain barrier dysfunction [40, 47].

More comprehensive clinical research is needed in order to build a detailed understanding of the clinical worsening of the disease, it can provide insight for medical personnel elsewhere in treating difficult cases like this.

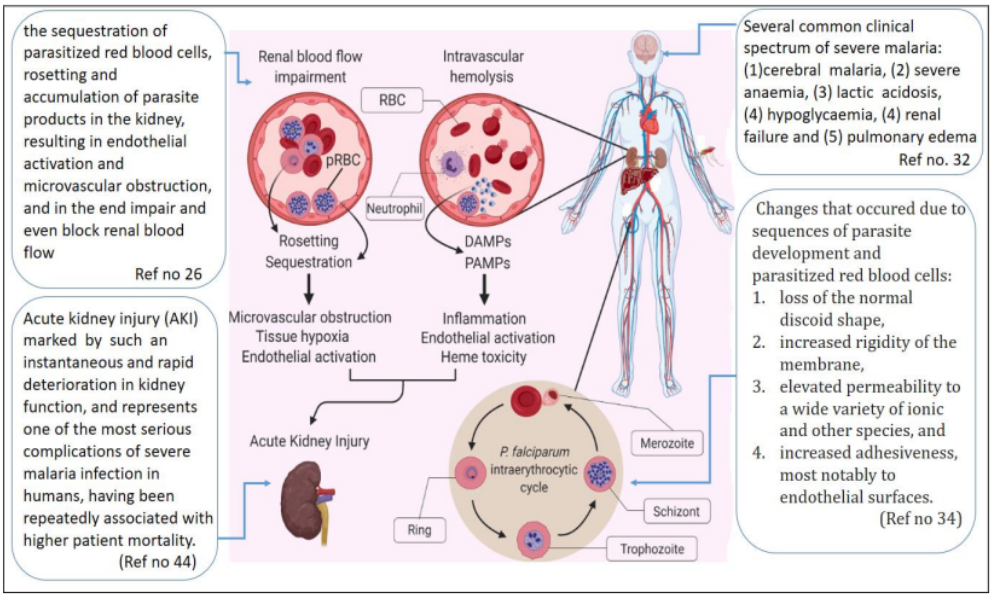

Fig 1. Response of the host to malaria-specific virulence factor and in turn, the awakening of the host's systemic inflammatory response with focus on its effect in the formation of malaria-related acute kidney injury (AKI). [26, with modification].

The interdependent occurrence of the unique hallmarks of pathology clearly characterized by several life-threatening symptoms, including PRBC sequestration, microvasculature deteriorated, endothelial activation, massive intravascular hemolysis and hemodynamic

uncertainty, crowning in the exacerbation of an active systemic inflammatory reaction on the kidneys, might constitute the uppermost mechanism of developing AKI (Figure 1).

infection-triggered proinflammatory reactions within the kidney

Understanding the contribution of the host's inflammatory reaction against malarial parasite and the extent to which it significantly affect the disease progression/worsening, could help in several ways, *e.g.*, (1) developing early identification tools to prevent specific disease progression, (2) by identifying specific chain of inflammatory response and the exact part of the host's affected the most, (3) to the production of new immunomodulatory therapies which crucially reduces malaria-related mortality.

In individuals living in malaria-endemic areas, initial parasitaemia baseline for the onset of clinical symptoms actually fluctuate with transmission intensity. Since theoretically, inflammatory responses to this hemo-protozoan infection contribute significantly to the clinical manifestation of malaria, it is important to evaluate the inflammatory cytokine responses in individuals suffer from active malaria, especially children, based on the areas with different transmission [48].

As one of the vulnerable groups, young children differs in their immune response compared with adults [49], and these differences likely contribute to the increased susceptibility of children to severe malaria [50,51] and to their postponement development of immunity against this blood protozoan parasite [52]. Elevated levels of pro-inflammatory cytokines and chemokines in the peripheral blood during acute infection [53,54] contribute to parasitaemia [55], but are also responsible for much of the immunopathology seen during clear and visible symptomatic malaria [56] and also in condition of asymptomatic malaria [57] and its differing and fluctuating, based on the intensity of malaria transmission [58]. Clinical immunity to malaria may revolve upon the ability to balance these pro- and anti-inflammatory responses [59], possibly through mechanisms of immunologic tolerance and this provide an alternative strategy of acquired immunity to malaria [60].

The process of malaria related AKI in fevered African youngster are presumably multi-factorial in origin. According to the study conducted by Hawkes *et al* [61] among Sub-Saharan African children who suffer from malaria, there was indication of more notabled endothelial activation with boosted in sVCAM-1, sICAM-1 and higher IL-8 levels.

Several condition that can be found in malaria related AKI are as follow:

1. Definite jaundice perhaps be an early clinical sign of hemolysis and clinicians must be observed this situation carefully for its progression, because this can be an early indication AKI in malaria. Hemolysis is common condition found in falciparum malaria, because as an obligate intra-erythrocyte parasite, this organism can have caused its infected host's cells to disrupt its function and even causing cell lysis. This results in the discharge of free heme- a precursor to hemoglobin, which has long been known as a potent nephrotoxic substance [62]. Beside intravascular hemolysis, jaundice can also occur due to the condition of disseminated intravascular coagulation, and, rarely, 'malarial hepatitis' [63].

2. Delayed capillary refill, an often neglected clinical sign of diminished tissue perfusion, which can quickly progress to shock (if not immediately detected and treated) [64]. This situation may strongly indicate pre-renal causes of AKI in malaria patients, especially children who are susceptible to massive perfusion changes to the peripheral tissues. According to Evans *et al* [64], A prolonged (> 2 seconds) capillary refill time (pCRT) was identified as an independent prognostic indicator of death along with acidosis, coma and respiratory distress in patient with severe and complicated malaria.

3. Host biomarkers also supply clinicians with supplementary mechanistic intuitions. For example, Cystatin C is a well-known functional biomarker of AKI in pediatric populations. Overall, 19.4% of the participants had a positive cystatin C test in Hawkes *et al* study [61]. Unfortunately, the relationship between severe AKI and mortality in severe malaria, independent of the disease progression and severity, suggesting alternative pathways may be chipping in to escalated mortality in vulnerable children with severe malaria and AKI.

4. Endothelial activation seems to be a relatively frequent pathway leading to AKI in severe malaria. Increased endothelial activation in malaria-associated AKI may reflect straight offense to the glomerular endothelium due to specific properties of *P. falciparum* cytoadherence. However, as severe malaria is a multi-system disease, we cannot rule out endothelial activation in other organ systems contributing to enhanced systemic endothelial activation in the context of severe malaria-associated AKI.

5. Elevated circulating levels of cell surface molecules namely soluble intercellular adhesion molecule-1 (sICAM-1) [65], soluble vascular cell molecule-1 (sVCAM-1) [65], soluble fms-like tyrosine kinase 1 (sFlt-1) [61], and Angiopoietin-2 (Angpt-2) [66] levels. These results, eventhough as a non-specific marker of disease, are congruent with severity or progression that happens in critical illness [67]. Angpt-2 levels have been implicated severe malaria. A polymorphism (rs2920656C > T) located close by the ANGPT2 gene linked with a functional reduction in Angpt-2 formation is correlated with lessened risk of the possibility of evolving a sub-phenotype of AKI elucidated centered on the level of sTNFR1, Angpt-2, and Angpt-1. Changes in sTNFR1, Angpt-1, and also Angpt-2 level were whole apparent in severe malaria-associated AKI. Prospective researches are needed in order to examine the potency of polymorphisms in the ANGPT2 gene that perhaps modified the chance of AKI severity and also healing in relation to severe malaria.

6. severe AKI was also characterized by immune activation with specific elevations in sTNFR1, sTREM-1, CHI3L1, and IL-8 [61]. In malaria, a higher immune activation index (IAI) was associated with several diseases, including severe AKI [69-71]. These findings are consistent with at least three condition: (1) markers of immune activation as biomarkers of AKI and also disease severity, (2) to risk-stratify patients at risk of mortality in outpatient settings, and (3) for prognostic enrichment of patients with sepsis [41]. additional data also supports CHI3L1 and sTREM-1 as biomarkers of AKI, disease severity and progression, and even mortality in severe malaria. Additional longitudinal researches are entailed urgently in order to examine the practicality of these biomarkers in context of AKI duration, severity, and even

perhaps kidney healing. particularly when this condition took place in a remote resource limited settings. detection of such biomarkers is still expensive and limited in the context of research and still cannot be applied clinically; This is an obstacle as well as a challenge for researchers and clinicians to make it happen. In terms of the development of specific and unique biomarkers which is considered a pathgnomonic marker for severe malaria, *e.g.*, their identification, validation and even optimalization, are still in the early period. Some candidate biomarkers appear to be promising for making prognosis, but further studies are still needed to establish their prognostic importance.

The direct causes of kidney dysfunction remain incompletely understood until nowadays. Optimal treatment involves making a correct and early diagnosis followed by effective antimalarial treatment with appropriate regiment. In case of kidney derangement, sufficient and optimal renal replacement therapy which conducted as sson as possible seems to reduces mortality in AKI. Unfortunately, in places where malaria is not common to happen, delayed diagnosis is still always a prblem which puts the patient in danger of mortality. Until nowadays, there is no robust prognostic risk model or biomarker that can predict malaria related AKI due to malaria or the requirement for renal replacement therapy in order to tackle AKI. All patients with malaria should be considered at risk and in danger of developing AKI. To improve the outcomes of the patients, early diagnosis and suitable patient management is critical.

Conclusion

Kidney malfunction is still one of the leading fatal complication in severe malaria. Management of malaria-associated kidney disease comprises appropriate antimalarial regiment, besides all supportive procedures that AKI requires (hydroelectrolytic disorder amendment, fluid balanced management and if necessary performing dialysis. Technologically, the coming of new technologies would also be helpful in strengthening the molecular process regarding identification, validation and optimalization of clinical biomarkers, but from the point of economy value and interest, affordable alternative assay systems urgently need to be developed for translation in the clinical context of malaria.

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