EDITORIAL

Malaria: Morbidity, Mortality and its Associated Complications

IA Ibanga[1], CR Nwokocha[2]

Severe malaria is a leading cause of childhood mortality and morbidity especially in sub-Saharan Africa (1, 2,). In 2008, 247 million cases of malaria were estimated worldwide, resulting in 881 000 deaths (1). The financial cost to tackle malaria is staggering. It was estimated that expenditure to tackle malaria globally in 2009 and 2010 are USD 5.335 billion and 6.180 billion, respectively, and include direct costs for diagnosis, treatment and prevention (1).

Malaria is caused by *Plasmodium* species. Only four namely *P falciparum, P ovale, P vivax* and *P malariae* among the 100 known *Plasmodia* species infect man. *P falciparum* malaria manifests as a spectrum ranging from asymptomatic infection through mild, severe and fatal disease. Complications involve multi-organ dysregulation-nervous, respiratory, renal and haemopoietic systems. Metabolic acidosis and hypoglycaemia are common underlying systemic complications. It may present with a number of syndromes including severe anaemia, respiratory complications and acidosis, renal failure, pulmonary oedema, hepatic dysfunction, cerebral malaria and coma.

Uncomplicated malaria is an acute febrile illness characterised by fever, chills and headaches particularly in immune individuals in endemic areas. High morbidity and mortality are seen in common and uncommon complications of severe disease. Cerebral Malaria (CM) is life threatening and is the most studied complication. It is a syndrome of decreased consciousness not attributed to other causes of encephalopathy in patients with *P falciparum* parasitaemia. The onset is dramatic rapidly becoming fatal; when patients survive, recovery is usually complete. The incidence of long-term sequelae is low. Neurological sequelae include cranial nerve abnormalities, ataxia, hemiplegia, speech disturbances, behavioural disturbances and epilepsy (3). Cerebral malaria occurs in individuals who have not acquired *P falciparum* specific immunity thus the burden is suffered by children and travellers to endemic areas.

Pulmonary oedema is non-cardiogenic and may progress to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). It complicates *P falciparum* malaria and has been described in *P vivax, P ovale* and *P malariae*. It is more common in adults such as pregnant women and non-immune individuals than in children. There have been increases in incidence in both sub-Saharan Africa and the industrialised countries especially in returning travellers. Patients present with acute onset dyspnoea that can rapidly progress to respiratory failure. It has a high mortality and is a com-mon cause of admissions to intensive care units (ICU). Increased alveolar capillary permeability resulting in intravascular fluid loss into the lungs appears to be the key pathologic mechanism.

Acute tubular necrosis leading to established renal failure is reported to be rare in African children but may occur in non-immune adults. Acute renal failure is usually oliguric (< 400 ml/day) or anuria (< 50 ml/day). Lesser degrees of dysfunction with raised serum creatinine and urea may occur. These changes predominantly reflect reduction in circulatory fluid volume leading to pre-renal impairment. Other factors include metabolic acidosis associated with high lactate levels, cyto-adherence, intravascular coagulation and intravascular haemolysis which may reduce circulatory volume and reduced oxygen carrying capacity (4). The pathogenesis of anaemia in malarial is complex and it involves loss of infected and uninfected red cells, a degree of marrow suppression alongside several other causes of anaemia in the tropics of which iron deficiency is important. Thrombocytopaenia is common though not associated with bleeding while disseminated intravascular coagulopathy is rare. Other findings include hypoglycaemia, acute pancreatitis and for the unborn child, increased risk of intrauterine growth retardation, low birthweight, spontaneous abortion and stillbirth.

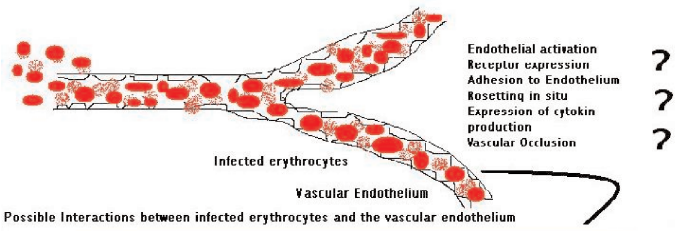
Many aspects of molecular biology, immunology and epidemiology that govern the pathogenesis of the parasite are still unclear and as such insights into the pathogenesis are vital to understanding the disease (5). Investigations into malarial pathogenesis have implicated host and parasite pathways in the disease severity and outcome.

The mechanism of pathogenesis is incompletely understood; several host-parasite interactions are involved. Proteins on the surface or apical organelles of merozoites mediate invasion of the erythrocytes by merozoites, the merozoite surface protein include merozoite surface protein-1 (MSP-1), MSP-2, PfHSP-1, MSP-3, MESP, AMA-1 (6). These merozoite surface protein diversity can be used as a tool for enumerating multiple concurrent infections and clinical patterns. Antibodies that recognise the proteins can block erythrocyte invasion and cyto-adherence and thus induce protective

[1]Department of Haematology, University of Calabar Teaching Hospital Calabar, Nigeria, [2]Department of Basic Medical Sciences, The University of the West Indies, Kingston 7, Jamaica.

Correspondence: Dr CR Nwokocha, Department of Basic Medical Sciences, The University of the West Indies, Kingston 7, Jamaica, West Indies. E-mail: chukwuemeka.nwokocha@uwimona.edu.jm

immunity. In this issue, Ojurongbe *et al* (4) analysed the parasite population polymorphism and genotype by nested-PCR of merozoite surface protein 2 (MSP2) blocks 3. They reported that the field isolates are highly diverse in respect of MSP2 and multiplicity of infection was neither age nor parasite density dependent in the study population.



Possible Interactions between infected erythrocytes and the vascular endothelium

The hypothesis that tends to explain the mechanisms of malaria pathogenesis include adherence of erythrocytes infected with *Plasmodium falciparum* to microvascular endothelial cells and (sequestration) is considered to play an important role in parasite virulence and pathogenesis (5, 7), [Figure]. Adhesion of IEs to host endothelial receptors is mediated by members of a large diverse protein family called *P falciparum* erythrocyte membrane protein 1 (PfEMP1), Intercellular adhesion molecule (ICAM-1), Vascular cell adhesion molecule (VCAM-1), E-selectin expressed on endothelial cells (EC) and host proteins such as CD36 (7). The associated rossetting of uninfected cells to infected cells leads to vascular blockade and circulatory shock which is a major cause of morbidity and mortality. In this issue of the Journal a study by Nwokocha *et al* (5) on altered vascular reactivity induced by malaria parasites demonstrated that vascular effects of malaria parasites are mediated, at least in part, *via* endothelium-dependent mechanism(s). This could in part contribute to the various end-organ damage and other cardiovascular dysfunctions associated with malaria infection.

Cytokine hypothesis describes the role of tissue factors in the induction of pro-inflammatory cytokines, these inflammatory cytokines include TFN- alpha, IL-1, IL-2, IL-6, IFN-gamma, P-selectin, CD40 and promote initial rolling and tethering interactions between circulating leucocytes to endothelial cells. Tissue factor (TF) is expressed in the endothelium of parasitized patients and induces the initiation of coagulation cascade. A procoagulant state characterized by thrombocytopaenia, haemostatic alteration and microparticle production occur, however, overt clinical signs of coagulation such as bleeding or thrombi are not seen.

The tissue factor model differs from the two previous hypotheses in that it highlights the fundamental importance of sequestration-associated activation of EC to trigger the blood coagulation cascade on one hand while indicating the role of RBCs and activated platelets in amplifying the response through formation of multi-molecular blood coagulation complexes. In other words TF is needed but is not sufficient alone (as in the case of sequestration) to produce disease without an amplification step to sustain the coagulation-inflammation cycle. The TFM places TF as the interface between sequestration, endothelial cell activation, blood coagulation and inflammation.

Although thrombosis and haemorrhage are rare in *P falciparum* infection, microvascular lesions are underlying cellular events in this disease. Considering the role of coagulation factors, TF and membrane proteins/receptors in the regulation of inflammation and the pathogenesis of complications of malaria development of new therapies and vaccines that target them coupled with public health education and enlightenment may be the way forward in the reduction of morbidity and mortality in malaria.

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