Malaria: a moderate to fatal disease

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Abstract

Malaria is a major public health threat among the population across the world especially tropical and sub-tropical regions. It is caused by the infection of Plasmodium spp. present in the mid gut of female Anopheles mosquitoes. Approximately, only 1% of malaria infections are fatal but more than 0.4 million people die per year, predominantly young children. It is therefore important to consider why a subset of infected people develops severe syndromes and some of them die and what separates these cases from the rest that recovers. Below, in our understanding of malaria pathogenesis, we discuss advances made over the past decade, concentrating on the fatal human disease caused by the parasite Plasmodium falciparum.

Keywords: malaria, pathogenesis, Plasmodium, cerebral malaria

Introduction

Malaria has great impact as a disease caused by Plasmodium spp. in human population. Genetic variability among the human population was also found to be protecting some people in the case of sickle cell anemia [1]. Plasmodium spp. have been found to be the major killers in Asia, Africa and Europe for thousands of years while in America, prevalence of malaria was only a few centuries ago due to slave trade [2]. Malaria parasites were discovered from the patients suffering from malaria by Alphonse Laveran in 1880. In 1897, Ronald Ross and William MacCallum discovered the various stages of sexual cycle and transmission cycle of malarial parasites. Thereafter, several scientists demonstrated the transmission of malarial parasites by female Anopheles mosquitoes to human beings [3]. Anopheles mosquitoes are the definitive host of malarial parasites where sexual life cycle occurs while humans are the intermediate host where asexual life cycle, maturation and pathogenesis occur [4]. In 1939, malaria eradication program was initiated particularly in Europe after the discoveries of quinine and dichlorodiphenyltrichloroethane (DDT) [5]. Thereafter, worldwide malaria eradication program was started by World Health Assembly in 1955 and ended in 1969, resulting in drastic reduction of the number of cases in southern Europe and subtropical areas of Asia. In the early 20th century, cases of malaria again raised that peaked at ~2 million deaths per year. Therefore, a second effort was initiated for malaria eradication in 2006, resulting in reduction of mortality rate by more than half with respect to the mortality rate in early 2000s [6]. Further, development of vaccine (RTS,S; trade name Mosquirix) against malarial parasites supported mankind protection against malaria but there is evidence of a risk of rebound because vaccine doesn’t provide sustained protection [7]. Despite these progresses, increasing resistance in the parasite against antimalarial compounds as well as
insecticides again pushed back and it would require more research to find out new antimalarial drugs to cope up with this highly adaptable parasites.

The causes of malaria in humans are documented by five species of human malaria parasites and three zoonotic species. Most fatal cases occur in children under 5 years of age, mostly caused by *Plasmodium falciparum*. *P. falciparum* infection mortality also occurs in pregnant women. *P. vivax* is common in sub-Saharan Africa, causing significant morbidity, whereas *P. ovale* and *P. malariae* are less widespread and rarely cause severe illness. *P. knowlesi* primarily infects long tailed macaques in Southeast Asia, but people living near the primate host may become infected and develop severe diseases with high parasitemia [8]. Several other species that infect non-human primates have been identified that infect humans, and some have caused isolated pockets of human infection, including *P. cynomolgi* in western Cambodia and *P. brasilianum* in remote Venezuelan Amazon [9, 10].

Given the importance of these other malaria species, in this article we focus on *P. falciparum* infection pathogenesis, which remains predominantly the greatest killer, accounting for 95 percent of all malaria deaths. Every year about 200 million infections are caused by *P. falciparum* worldwide. Most of these diseases do not result in severe illness. *P. falciparum* malaria, however, still causes approximately 430,000 deaths per year, representing 0.2% of all clinical episodes. *P. falciparum* specifically infect humans and transmitted by female anopheles mosquitoes. Sporozoites initially infected with liver cells by the mosquito, where they multiply over a 7-day asymptomatic replication cycle. Invasive merozoites are eventually released from hepatocytes and these infect red blood cells, where the parasites are subjected to repeated growth, replication, egress, and invasion. During the maturation of infected red blood cells (iRBCs), the parasite expresses ligands on the surface of the iRBC that give the iRBC the ability to adhere to the vasculature endothelium and thus sequester capillaries and postcapillary venules. Thought to be an adaptation to prevent the spleen from removing mature iRBCs, this feature is a key virulence determinant that distinguishes *P. falciparum* from other plasmodia that infects humans and other animals that either lack or have this capacity to a much lesser degree. A key issue that recent advances have brought us closer to resolving is the mechanistic link between parasite sequestration and disease.

**Cerebral malaria**

Malarial infection by *P. falciparum* leads to severe anemia and respiratory distress during cerebral malaria [11]. Respiratory distress is very common in case of malaria but acuteness of respiratory distress depends on patho-physiological conditions of the patients [12]. The exact cerebral malaria pathogenesis mechanisms remain uncertain till date but the sequestration of infected RBCs in capillaries and post-capillary venules is known in the case of *P. falciparum* infection. Doubts about cases of sequestration-free cerebral malaria were addressed through elegant postmortem studies leads to correlate between the degree of sequestration and the degree of cerebral symptoms [13]. Retinopathological symptoms are also observed...
in case of cerebral malaria but adults show lesser frequency than children. Magnetic resonance imaging technique improved further advancement in our understanding of cerebral malaria [14-16].

**Acute injury in kidney**

*Plasmodium falciparum* malaria affects the kidney severely and cause acute renal injury. Kidney failure is very frequent in severe condition of malaria leads to the requirement of kidney transplantation along with dialysis [17]. Kidney association is very less in case of children with severe malaria in comparison to adults. Recently, a clinical trial in 62 randomly selected malaria patients, paracetamol has been shown to enhance the recovery of creatinine compared to placebo, possibly due to oxidative damage caused by free hemoglobin release [18].

**Infection in lungs**

In *P. falciparum* malaria, two specific clinical syndromes are identified in the lung: acute respiratory distress and pulmonary edema [12]. Pneumonia is well known to be caused by several bacteria, viruses and also due to vitamin deficiency. Pulmonary edema has a well-established connection to fluid overload, which can result from the administration of excessive intravenous fluid, congestion resulting from cardiac failure or fluid retention in renal failure, and may be exacerbated by increased vascular permeability [19]. Acute respiratory distress syndrome is a clinical term for a hypoxic condition which develops through a variety of etiologies that lead to alveolar damage to the diffuse inflammation of the lung. Acute respiratory distress syndrome and pulmonary edema are uncommon in children in comparison to adults but there is an increased chance of capillary leakage that leads to pulmonary edema in children with cerebral malaria [20].

**Spleen**

The spleen plays a major role in the selection and clearance of senescent or abnormal RBCs as well as removal of antigens and inclusion bodies [21]. It is a key component of malaria immunology that facilitates the antigen presenting cells to lymphocytes. Removal of infected RBCs by spleen is important for the prevention of severe disease, while removing uninfected RBCs is a key contributor to anemia [22].

Anemia is very common complication in case of malaria infection in all ages but it has significant impact on mortality and morbidity in pregnant women and children [23]. There are several factors that lead to severe anemic condition in malaria. Destruction of infected RBCs by the malaria parasite during schizogony, removal of infected as well as uninfected RBCs by spleen and immune cell mediated hemolysis are the major causes of severe anemia with malaria infection and provide more risk of bacterial and viral infections [24, 25]. Highly active splenic clearance results in the effective removal of immature infected RBCs prior to sequestration is protective mechanism against cerebral malaria but it leads to anemia due to excess removal of uninfected RBCs along with infected RBCs. The restoration and recovery
of normal hemoglobin levels requires effective hemoglobin synthesis in most children having anemia who don’t receive transfusions. Iron supplementation to infected person may become harmful because it can support microbial growth [26]. Hepcidin is an iron metabolism regulator. Hepcidin inhibits the transport of iron by binding to the ferroportin iron export channel protein present on the membrane of gut enterocytes and reticuloendothelial cells [26]. Hence, hepcidin level can be used as a biomarker for the requirement of iron supplementation during anemia [27].

Other causative agents of severe malaria

Several reports are available that ensures the association of bacteremia with severe malaria such as Salmonella infection to the patients suffering from severe malaria [28-30]. Sickle cell trait protects against malaria but there is an increased risk of bacteremia associated with the person having sickle cell trait [31]. It is supposed to be that malaria increases the gut permeability leads to facilitation of translocation of gut microbes to the blood vascular system but the reason behind nontyphoidal Salmonella (NTS) infection in particular during malaria is still unknown [32]. Malaria has also been shown to inhibit the mobilization of granulocytes from bone marrow and oxidative burst of neutrophil through induction of heme oxygenase, a process which impairs the clearance of NTS [33]. Due to the strong association of NTS bacteremia with severe malaria, it is recommended to administer specific antibiotic that that have antimalarial as well as anti-NTS until the confirmation of absence of NTS through blood culture report [28, 34].

Summary

Given the importance of all other malaria species, in this article we focus on *P. falciparum* infection pathogenesis, which remains predominantly the greatest killer, accounting for 95 percent of all malaria deaths. Every year about 200 million infections are caused by *P. falciparum* worldwide. Most of these diseases do not result in severe illness. *P. falciparum* malaria, however, still causes approximately 430,000 deaths per year, representing 0.2% of all clinical episodes.

Conflict of interest

Authors declare no conflict of interest.

References


