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Physiopathology of Malaria-Associated Acute Respiratory Distress Syndrome

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Abstract

Malaria is a major global health problem, affecting mainly tropical and subtropical areas. In Brazil, in most cases, it was caused by *Plasmodium vivax* and *Plasmodium falciparum*, respectively. Malaria can lead to severe complications like severe anemia, placental malaria, cerebral malaria and others. When associated with lung, severe malaria can cause Acute Respiratory Distress Syndrome (ARDS). The main problems of this syndrome are the presence of inflammatory infiltrate, hemorrhages and edema. It is not known what starts the development of malaria-associated ARDS, but it could be related to adhesion molecules expressed by the parasite on the surface of the erythrocyte membrane, or with the inflammatory responses of the host. However, latest researches show new mechanisms involving neutrophils are the key to the establishment of this syndrome.

Keywords: Malaria; *Plasmodium* ; ARDS; Cytokines; Physiopathology

Introduction

Malaria is an infectious disease caused by a protozoan of the genus Plasmodium. It is considered a public health problem, exposing many populations around the world at risk, especially those who live in tropical and subtropical areas. Present in 91 countries considered endemic areas, 212 million cases were registered in the world, causing around 430 thousand of deaths, in 2015 [1].

In Brazil, 139.518 autochthonous cases were registered in 2015, especially caused by *Plasmodium vivax* infection, responsible for 84% of the cases and *Plasmodium falciparum* for 16% of the cases [2,3].

The most serious complications observed in malaria are metabolic acidosis, severe anemia, hemorrhages, placental malaria, Cerebral Malaria (CM) [4-7] and pulmonary complications that can lead to Acute Respiratory Distress Syndrome (ARDS) [8].

Unfortunately, there are not many epidemiological data on MA-ARDS [6]. It occurs mainly in adults with a rapid and poor prognosis, and may have a lethality rate of 20% -80%, even with antimalarial treatment [9]. Symptoms range from mild respiratory complications such as cough and dyspnea to evolution in ARDS [6,9].

In Malaria-Associated ARDS (MA-ARDS), the majority of reported cases are in low transmission area or non-immune travelers [10]. ARDS has, as main characteristics, the acute inflammation and injury of the alveolar endothelium and the pulmonary parenchyma, which consequently, causes dysfunctions and increased permeability of the pulmonary alveolar-capillary barrier and, therefore, edema's formation [4]. Decreased gas exchange and increased inflammatory mediators in the lungs result in respiratory failure in critically ill patients, leading to death [4,10,11].

The alveolar-capillary membrane is the separation between air and blood in the lungs, formed by pneumocytes in the wall of the alveolus, endothelial cells in the capillaries, and the interstitium [9]. The pulmonary endothelium is a semipermeable cell barrier that stays between the vascular compartment and the interstice being formed by a monolayer of Endothelial Cells (EC) which covers the blood vessel [12,13].

The full complexity of the MA-ARDS study in humans increases the need to understand the physiopathology of the disease [9]. It is known that it takes more time to conclude studies in humans, besides ethical impediments. On the other hand, the murine models help to understand the numerous complications of the pathogenesis, such as pulmonary findings, the immune response, especially neutrophils involvement and degrees of hypoxemia, are similar to those observed in humans [9,14,15].

Life Cycle

Protozoan of the genus *Plasmodium sp.* are heteroxenes parasites living part of their life cycle in female mosquitoes of the genus Anopheles sp. and part in vertebrate host where they invade different cell types (Figure 1) [1,16,17].

The asexual phase of the erythrocytic cycle corresponds to the period of clinical manifestations of the disease (Figure 1C). Inside the erythrocyte, the merozoite changes into young trophozoite and, as it matures, it becomes a schizont. The schizont originates new merozoites which will be released due to erythrocytes rupture. Hemolysis also releases metabolites of the parasite into the circulation that ultimately activate the host's immune response causing morphological and functional disorders [16,17]. Patients infected by *P. falciparum* (tertian fever) and *P. vivax* (quartan fever) run fever each 48 h and 72 h, respectively, the time of maturation of schizonts and rupture of erythrocytes [17].

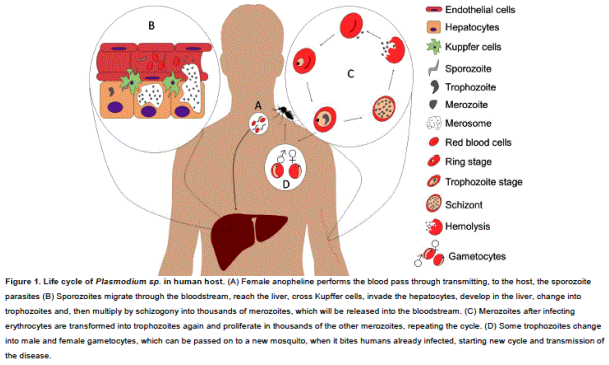

Figure 1. Life cycle of *Plasmodium sp.* in human host. (A) Female anopheline performs the blood pass through transmitting, to the host, the sporozoite parasites (B) Sporozoites migrate through the bloodstream, reach the liver, cross Kupffer cells, invade the hepatocytes, develop in the liver, change into trophozoites and, then multiply by schizogony into thousands of merozoites, which will be released into the bloodstream. (C) Merozoites after infecting erythrocytes are transformed into trophozoites again and proliferate in thousands of the other merozoites, repeating the cycle. (D) Some trophozoites change into male and female gametocytes, which can be passed on to a new mosquito, when it bites humans already infected, starting new cycle and transmission of the disease.

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Pathology and Symptomatology

The incubation period varies according to the species of *Plasmodium*. However, the initial phase of the disease is characterized by malaise, fatigue, myalgia, headache and fever [1].

Clinical manifestations are mainly due to the destruction of infected red blood cell (iRBC), release of toxins and [14], exacerbated immune response, anemia and, in specific cases, the sequestration of the parasite caused by the adhesion of erythrocytes containing a membrane protein expressed by the parasite [18] or capillary lesion due to the accumulation of immunocomplexes [17].

Severe Malaria

Most severe cases are related to *P. falciparum* (Table 1) associated with high mortality, while severe disease could be caused by all species [19-22]. In humans, they are associated to many complications mainly influenced by individual factors such as age, exposure and their immune status, occurring mainly in children, pregnant women and those primary infected due to immunological factors, and also by the species and virulence of Plasmodium. Complexities of the parasite may cause damage to host tissue CM, placental malaria and indirectly cause other problems such as acute renal injury and ARDS [4,5].

Criteria		References
Loss of consciousness	Glasgow Coma Score<11 [22]	-
Jaundice	Bilirubin in serum >3 mg/dL [33]	0,3-1,9 mg/dL
Renal failure	Serum creatinine >3 mg/dL [19,22]	0,7-1,5 mg/dL
Hypoglycemia	Glucose in plasma <40 mg/dL [33]	80-100 mg/dL
Severe anemia due to malaria	◦Hemoglobin <5 g/dL [22]	12-16 g/dL
	◦Hematocrit <15% [22]	35-45%
Shock	Systolic blood pressure <80 mmHg [22]	100-139 mmHg
Acidosis	Deficit of bicarbonate ions or excess lactic acid manifested by respiratory distress [33]	-
Pulmonary edema	Based on the degree of hypoxemia [18] ◦ Mild 200 mmHg <PaO_2 / FiO_2 ≤ 300 mmHg ◦ Moderate – 100 mmHg <PaO_2 / FiO_2 ≤ 200 mmHg ◦ Severe - PaO2 / FiO_2 ≤ 100 mmHg	PaO2/FiO_2 ≥ 300 mmHg
Adapted: [19,22]		

Table 1: Criteria of severe malaria by *Plasmodium falciparum* in adults.

Malaria-Associate Acute Respiratory Distress Syndrome (MA-ARDS)

Symptoms related to MA-ARDS are like those of ARDS by other diseases, with the addition of the malaria symptoms described above. It is common to start with less severe complications such as cough and dyspnea progressing until the formation of pulmonary edema [6,23].

The mechanisms of MA-ARDS are still not well established, research demonstrates the importance of $CD8^+$ T cells in murine MA-ARDS, and the action of leukocytes integrins on pathogenesis [24,25].

However, there are two main strands that seek to clarify this pathogenesis. One is focused on the inflammatory response of the host associated with the dysfunction of the cells of the pulmonary microvasculature [26,27] and the other one is related to the adhesion of the iRBC to the EC of pulmonary endothelium for the pathogenesis the disease [5,28].

In the lung tissue, the exudative phase is the starting point of the syndrome, where damage to the endothelial barrier occurs, due to EC necrosis, resulting in edema that spills out into alveoli, causing the formation of a hyaline membrane in the alveolar wall [14]. In histological sections from MA-ARDS patients show abundant leukocytes, mainly macrophages in the tissue or alveolar spaces and lower number of lymphocytes and neutrophils (Figure 2) [9,6]. The fibroproliferative phase occurs later on and is associated with fibroblast cells proliferation and collagen deposition [9,14].

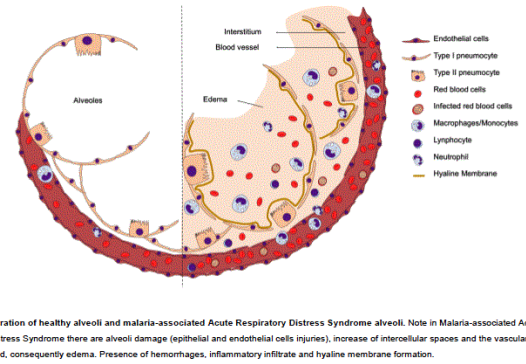

Figure 2. Illustration of healthy alveoli and malaria-associated Acute Respiratory Distress Syndrome alveoli. Note in Malaria-associated Acute Respiratory Distress Syndrome there are alveoli damage (epithelial and endothelial cells injuries), increase of intercellular spaces and the vascular permeability and, consequently edema. Presence of hemorrhages, inflammatory infiltrate and hyaline membrane formation.

Figure 2: Illustration of healthy alveoli and Malaria-associated Acute Respiratory Distress Syndrome alceoly. Note: In Malaria-associated Acute Respiratory Distress Syndrome there are alveoli damage (epithelial and endothelial cells injuries), increase of intercellular spaces and the vascular permeability and, consequently edema. Presence of hemorrages, inflammatory infiltrate and hyaline membrane formation.

During the erythrocyte cycle (Figure 1C), the parasite metabolizes hemoglobin to form a compound of the heme toxic group, hemozoin (malaria pigment), which induces the release and activation of proinflammatory factors (Table 2) like chemokines (interferon-ɣ (INF-ɣ), CXC-ChemokineLigand-10 (CXCL10), CC-Chemokine Ligand2 (CCL2), Keratinocyte-Derived Chemokine (CXCL1)), Cytokines (interleukin-1 beta (IL-1β), Tumoral Necrosis Factor (TNF), Interleukin (IL)-6, IL-8, IL-10, transforming growth factor–beta (TGF-β) and other inflammatory mediators such as heme oxygenase–1 (HO-1) [6,29-31].

Chemokines	Materials	Methods mRNA
CXCL10	Lung tissue [26]	mRNA expression
CXCL1	Lung tissue [31]	mRNA expression
INF-ɣ	Lung tissue and serum [26,28]	Cytometric bead array and mRNA expression
Cytokines		
IL-1β	Lung tissue [26,34]	mRNA expression
IL-6	Lung tissue and bronchoalveolar lavage [26,34]	mRNA expression
IL-10	Lung tissue, bronchoalveolar lavage and serum [26,28]	Cytometric bead array and mRNA expression
TNF	Lung tissue, bronchoalveolar lavage and serum [23,26,28]	Cytometric bead array and mRNA expression
Cells markers		
Neutrophils (Ncf-2)	Lung tissue [31,32]	mRNA expression

Macrophages (MCP-1)	Lung tissue, bronchoalveolar lavage. [26,31,34]	mRNA expression

Table 2: Chemokines, cytokines and proinflammatory mediators in malaria-associated Acute Respiratory Distress Syndrome in murine models.

In *P. falciparum* infection, iRBC have the peculiarity of adhering the cells of the endothelial microvasculature of several organs, due expression of protein named *P. falciparum* Erythrocyte Membrane Protein 1 (PfEMP1) [32]. This family of proteins mediate adhesion with non-infected erythrocytes and iRBC forming structures named rosettes, also promoting the adhesion in several receptors such as the CD36, Intercellular Adhesion Molecule-1 (ICAM-1), Vascular Adhesion Molecule-1 (VCAM-1), Chondroitin Sulfate A (CSA) [5] and Endothelial Protein C Receptor (EPCR) [33] present in endothelial from the microvasculature of some different tissues, such as, cerebral, pulmonary and placental. This adhesion allows the parasite complete its life cycle without being eliminated by hemocathesis, thus increasing the severity of disease [5]. However, in MA-ARDS it is not very clear which adhesion molecule is responsible for the interaction of iRBC with pulmonary vascular endothelium [11,24,31].

Recent researches indicate that the formation of Neutrophil Extracellular Traps (NETs) may be related to the severity of the disease in MA-ARDS as well as to other complications of malaria [34,35]. Inside the blood vessel, NETs protect the endothelial barrier from inflammatory factors, at the same time, activate of complement system, affects the hemostasis, formatting a disseminated intravascular coagulation and causing hemorrhages and thrombi formations and, consequently, ischemia [35-37]. In addition, tests *in vivo* and *in vitro* performed by Sercundes et al., using murine models, show that the treatment to inhibit the NETs formations had a significant improvement in the MA-ARDS pathology [34].

Conclusion

Even after decades of research, the pathology of malaria-associated acute respiratory distress syndrome has not been well understood and, there is no standard protocol of treatment. Although the trigger of the syndrome is not clear, it is known that both parasite sequestration and inflammatory responses of the host are extremely important to understand the pathogenesis and, consequently, the increased pulmonary vascular permeability. Many studies still need to be performed to comprehend the mechanisms of malaria-associated ARDS and, therefore, to reach an early diagnosis and more effective treatment, in order to reduce the morbidity and especially the mortality caused by this disease.

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