WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 1, 12-19. Review Article ISSN 2277– 7105

PATHOPSIOLOGY OF CEREBRAL MALARIA

Nur Laili Rahmatin*

Magister of Pharmacy, University of Surabaya, East Java, Indonesia.

Article Received on
26 September 2021,

Revised on 16 Nov. 2021,
Accepted on 06 Dec. 2021,

DOI: 10.20959/wjpr20221-22556

***Corresponding Author**
Nur Laili Rahmatin
Magister of Pharmacy,
University of Surabaya, East
Java, Indonesia.

ABSTRACT

Malaria is a common protozoan infection that is responsible for worldwide mortality and economic burden on the society. One of the most common central nervous system diseases in tropical countries is cerebral malaria (CM). Plasmodium falciparum (Pf) caused Cerebral Malaria may be lethal. Many pathophysiological hypotheses underlying cerebral malaria have been revealed. But what has developed until now is the mechanical, permeability and humoral hypothesis. In this review article, emphasized how pathogenesis of the disease is effected by the parasite and host responses including blood brain barrier (BBB) disruption, endothelial cell activation and the role nitric oxide and neuroinflammation. In these hypotheses the aspects involved are expressed and many are still not understood. Understanding this will help in the treatment of cerebral malaria.

KEYWORDS: Malaria, Plasmodium, Cerebral Malaria, Pathogenesis, Cytoadherence.

INTRODUCTION

Malaria is a major public health problem in the developing world owing to its high rates of morbidity and mortality. Of all the malarial parasites that infect humans, *Plasmodium falciparum* is most commonly associated with neurological complications, which manifest as agitation, psychosis, seizures, impaired consciousness and coma (cerebral malaria).[1] Cerebral malaria is an injection of parasites caused by malaria in the brain. this is one form of malignant malaria with high mortality. Plasmodium falciparum as the main cause. This disease is characterized by decreased awareness, symptoms and signs other neurologists, and symptoms of tropical malaria in general. Malaria remains one of the most prevalent infectious diseases in the world. The World Health Organization (WHO) reports that 50% of the world's population living in 109 countries are still at risk of malaria. Approximately 1% of *P.*

falciparum infections results in Cerebral Malaria with 90% of these cases in children in sub-Saharan Africa. In adults in South-East Asia, Cerebral Malaris accounts for 50% of the malaria deaths, as they not only suffer from encephalitis but also have multiple organ failure.[1] Several processes have been implicated in Cerebral Malaria pathogenesis, including microvascular obstruction by *P. falciparum*-parasitized red blood cell, excessive proinflammatory cytokine production microvascular thrombosis, loss of endothelial barrier function and endothelial dysregulation.[2] The way these pathological mechanisms are linked and how they are by host and parasite factors remains to be elucidated. In addition, the reason why circulating cytokins, caogulation factors, or PRBC specifically target only the brain in African children, and the brain as well as other organs in Southeast asian adults, are still unclear.[3] Other studies too linking the role of inflammation and cytoadheren as the etiology of the occurrence of cerebral malaria.[1] The exact diagnosis of cerebral malaria is post-mortem where brain hemorrhage and lesions will be found in the brain with accumulation of erythrocytes in microvascular cells.[1] In this paper we will discuss some of the latest research on falciparum malaria and pathogenesis to see cerebral malaria to see future developments in improving neurological damage clinical improvement in cerebral malaria.

Etiology

The five Plasmodium species that infect humans are: P. falciparum, P. vivax, P. ovale, P. malariae, P. knowlesi. The causes of cerebral malaria are mainly P. falciparum, while P.vivax and P. knowlesi can also be, but although rarely.[4]

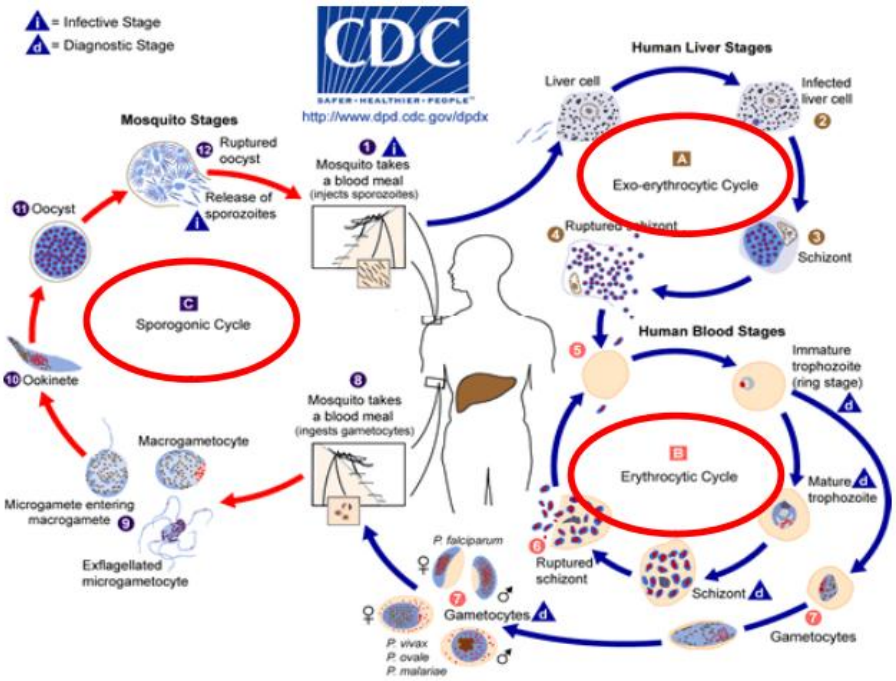
Malaria Parasite

Cycle in Human

Infection of the malaria parasite begins when a female Anopheles mosquito bites a human and releases sporozoite into a blood vessel. Sporozoites will live and enter the heart. Part of Plasmodium will be damaged by the immune system, others will survive. In the liver parenchyma cells, asexual development (intrahepatic schizogony) begins, called the pre-erythrocyte or echoerythrocytic stage. After that the parasites enter the circulation to infect the erythrocytes and damage the erythrocytes so that the merozoites are released inside circulation, this is called the erythrocytic stage. Then the parasite changes to sizont, and if ruptured sizonts will produce 6-36 merozoits and ready to infect other erythrocytes.

Cycle in Anopheles

In the blood, some parasites will form microgamethocytes and macrogamethocytes, if they are mosquitoes sucking sick human blood will occur the sexual cycle in the body of the mosquito. Multiplication of parasites in mosquitoes is known as a cycle sporogenic. When inside the microgamet mosquito's stomach macrogamets produce zygotes to produce zygotes. More zygotes moves into an ookinet that pierces the mosquito's stomach wall and will eventually form an oocyst that will grow, break, and removing sporozoites that migrate to the mosquito's salivary gland and are ready to infect humans[5] (*see picture 1*)(CDC,2016).



Picture 1: Cycle of Pllasmodium falciparum.

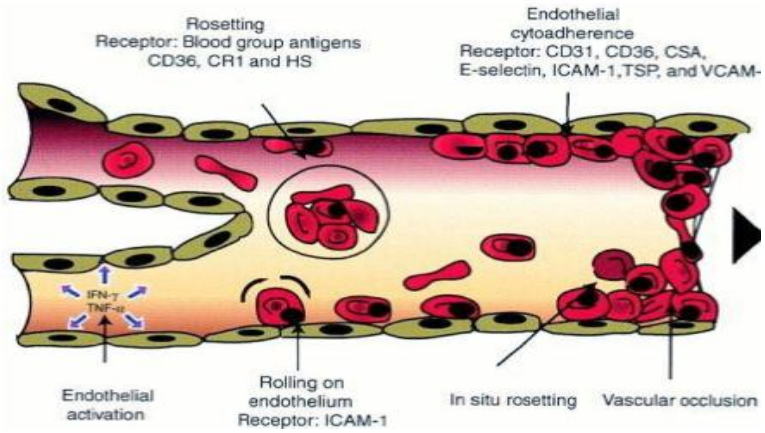
Cerebral Malaria

Cerebral malaria occurs as a complication of severe malaria caused by Plasmodium falciparum. Cerebral malaria is one of the manifestations of severe malaria characterized by behavioral disorders, disorders consciousness, convulsions, coma, and other neurological disorders.[5] The commonly accepted clinical definition of Human Cerebral Malaria is the neurological syndrome with patients in unrousable coma. Seizures, retinopathy and brainstem alterations due to elevated intracranial pressure and brain swelling are also clinical features frequently observed during Human Cerebral Malaria to meet the Cerebral Malaria definition, P. falciparum infection has to be confirmed and other causes of encephalitis (of viral or bacterial origins) to excluded. However, in field settings with limited resources, only easily

diagnosed or obvious infectious diseases with brain involvement are investigated. Many viral, bacterial and parasitic infections can alter Plasmodium infections or pathologies and the reverse is also true.[6]

Patoghenesis

Erythrocytes added by P. falciparum will improve the sequestration process, which is the spread of parasitic erythrocytes to the capillary vessels of organs in the body. Erythrocytes containing young parasites (ring shape) circulate in peripheral blood but mature parasitic erythrocytes are localized to the organ blood vessels. On the surface of the erythrocyte that is easily injured will make a knob containing various P. falciparum antigens.[1] Cytokines (TNF, IL-6 and others) are made by macrophages, monocytes, and lymphocytes cells will cause receptors to express capillary endothelium. At the time of the knob binding to capillary endothelial cell receptors there is a cytoadherence process. The result happened capillary obstruction that causes tissue ischemia. The occurrence of this blockage is supported by the formation of "rosette", which is a cluster of red blood cells that have parasites with other red blood cells.[6] (*see picture 2*).

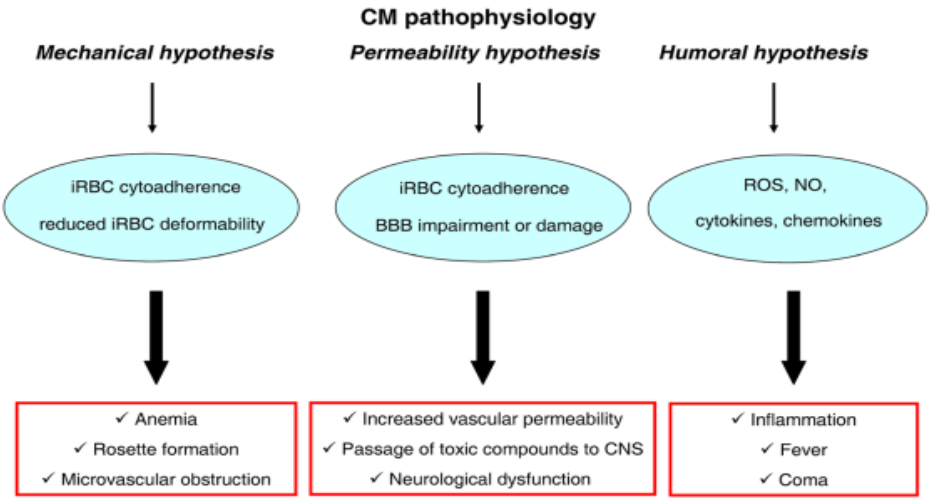


Picture 2: *Cytoadherence* and *resetting.*

Pathopsiology of Cerebral Malaria

The pathophysiological mechanism underlying cerebral malaria is not fully understood. Some recent clear theories on cerebral malaria, namely the mechanical, permeability, and humoral hypothesis (*see picture 3). i*) Mechanical hypothesis related to infected red blood cells (iRBC) cytoadherence and decrease deformability, causes anemia, rosette formation and microvascular obstruction; ii) The permeability hypothesis is based on a blood brain barrier (BBB) disturbance and an increase in permeability vascular, followed by toxic compounds

that reach the brain parenchyma and cause neurological disorders; iii) The humoral hypothesis focuses on increasing the production of pro-inflammatory molecules, including cytokines and chemokines, and other dissolved factors such as reactive oxygen species (ROS), which are responsible for inflammation, fever and coma during cerebral malaria.[7,11]

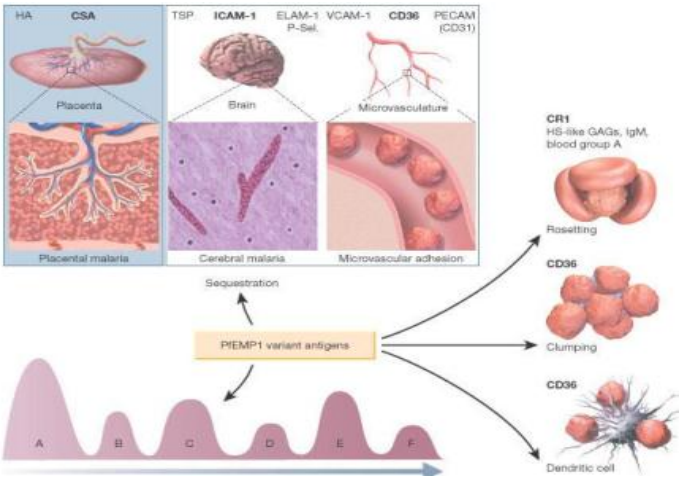


Picture 3: Pathopsiology Hypotesis of Cerebral Malaria.

Mechanical Hypotesis

Cytoadherence

Infected erythrocytes will experience attachment to uninfected erythrocytes (forms a rosette) and also attaches to other infected erythrocytes (autoagglutination). Besides the cytoadherence process which results in obstruction capillaries, this blockage is also supported by the formation of rosette.[5] P.falciparum infection is a membrane knob called PfEMP-1 is found on the erythrocyte surface which mediates the attachment of erythrocytes on capillary and venule endothelial receptors, called cytoadherence.[2] Vascular endothelial cell receptors that bind to (*see picture 4*) PfEMP-1 are CD-36, Intercellular adhesion molecular-1 (ICAM-1), Vascular cell adhesion molecul-1 (VCAM-1), PECAM-1, ELAM-1, thrombospondine and Chondroitin sulfate. Of several capillary and venule endothelial receptor proteins identified, ICAM-1 is considered the most important role in the pathogenesis of cerebral malaria.[7]



Picture 4: Vascular endothelial cell rece.

Permebealitas Hypotesis

Blood Brain Barrier (BBB) Disorders

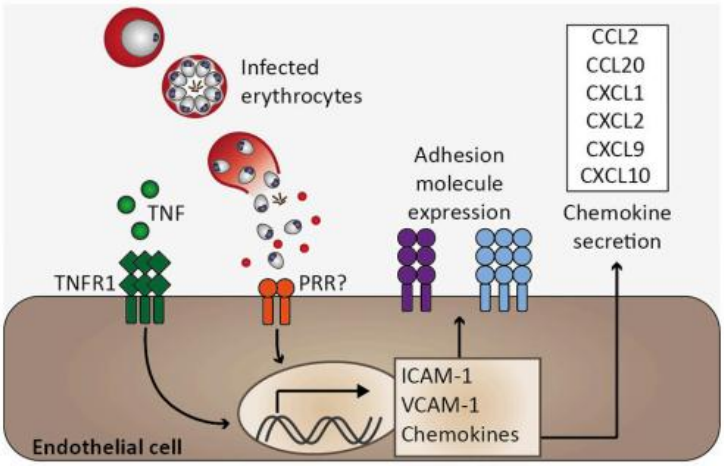
One structure that is important in protecting the nervous system of the brain is the blood brain barrier (BBB) or blood brain barrier. BBB constituent component: capillary endothelial cells, perisit, foot processes of astrocytes and basal membranes and neurons that make up neurovascular units.[8] Brain endothelial cells differ from endothelial cells found in other organs; they have intracellular tight and adherens junctions which impede passive paracellular diffusion of small and large molecules and prevent infiltration of blood borne cells into brain parenchyma.[9] During infection, pathogens invade endothelial cells and modulates vascular permeability. Endothelial cells are semiprofessional antigen presenting cells, triggering T cell costimulation and activation of specific immune cells. This results in the release of inflammatory mediators and damage to cells infected by effectors such as CD8 + T cells which play a major role in cerebral malaria.[7] This barrier disorder can cause pathology through edema and inflammation. During infection, barrier disorders can be caused by the release of active mediators, the interaction of microbial components with endothelial cell receptors (immunoglobulin; Toll-like receptor, TLR), and interactions with pathogens and leukocytes which can be followed by activation of the transmigration pathway. During malaria infection parasitic antigens transfer to endothelial cells.

Humoral Hypotesis

This hypothesis shows that host factors such as leukocyte-derived cytokines and chemokines can enter the brain parenchyma after increasing BBB permeability, which causes symptoms of cerebral malaria such as fever and coma.[7]

Cytokines and Chemocin

Cytokines are produced in response to microbes and parasites. The result is an increase in TNF α, IFN γ, IL-1, IL-3, and IL-6.14 TNF α responsible for the emergence of clinical manifestations cerebral malaria, including increased vascular permeability, impaired glucose metabolism (glucose transport, gluconeogenesis at liver, and glycolysis), and sequestration. TNF α and IL-1 can increase tissue factor expression in endothelial cells and mononuclear cells. A characteristicm feature of Plasmodium infection is endothelial activation, which is likely induced by elevated serum tumor necrosis factor (TNF) levels. Binding of TNF to its receptor (TNFR1) induces transcription of adhesion molecules, including ICAM-1 and VCAM-1 and chemokine secretion. (*see picture 5*). Furthermore, it will start the thrombin activation pathway, which is the molecule that plays a role in the inflammatory cascade and coagulation process.[5]



Picture 5: Endothelial activation and chemokine secretion.

***NITRIC OXIDE* (NO)**

The role of NO in the pathogenesis of cerebral malaria is still controversial. But in several studies it was said that NO is a key factor for TNF in the pathogenesis of cerebral malaria. NO plays a role in host's body defense, maintain vascular status, and also as effector of TNF. Cytokines will increase NO synthesis in brain endothelial cells and result in an increase in NO production. Increased NO activity can change the rate of blood flow and reduce glutamate uptake, resulting in toxicity to brain tissue.[9,10] NO can move and penetrate the blood brain barrier, diffuse into brain tissue, and will interact with neurotrasmiter, and this plays an important role in the mechanism of coma in cerebral malaria.[9,10]

CONCLUSION

Cerebral malaria is the heaviest complication of malaria. The species that can cause cerebral malaria is P. falciparum. The mechanism of the pathogenesis of cerebral malaria is not known with certainty but there are several theories that might explain the incidence of malaria cerebral. Several hypotheses of cerebral malaria have been described. Pathogenesis commonly used is the occurrence of sequestration or spread of infected erythrocytes so that it can clog arteries blood in the brain, this causes clinical symptoms in the form of a decreaseawareness, behavior disorders, seizures, and death.

REFFERENCES

1. Storm J, Craig AG, Hansen DS, Walter T. Pathogenesis of cerebral malaria inflammation and cytoadherence MALARIA, 2014; 4: 1–8.
2. Paulo, Medicine T. World Journal of Translational Medicine, 2014; 3: 9–17. doi:10.5528 /wjtm.v3.i1.9
3. Sahu PK, Satpathi S, Behera PK, Mishra SK, Stumhofer JS. Pathogenesis of cerebral malaria : new diagnostic tools, biomarkers, and therapeutic approaches, 2015; 5: 1–13. doi:10.3389/fcimb.2015.00075.
4. World Health Organization. World *Malaria*. Report *2014*; Switzerland; WHO, *2015*.
5. *CDC*. *Malaria* Central Deseas and Control Prevention; Malaria severe, *2016.*
6. Dunst J, Kamena F, Matuschewski K. Cytokines and Chemokines in Cerebral Malaria Pathogenesis, 2017; 7. doi:10.3389/fcimb.2017.00324
7. Polimeni M, Prato M. Host matrix metalloproteinases in cerebral malaria : new kids on the block against blood – brain barrier integrity ? Fluids Barriers CNS, 2014; 11: 1–24. doi:10.1186/2045-8118-11-1.
8. Bellet D, Chabra R, van Doom R, et al. The Blood Brain Barrier (BBB). Springer-Verlag Berlin. 2014.
9. Hora R, Kapoor P, Thind KK, Mishra PC. Cerebral malaria – clinical manifestations and pathogenesis, 2016. doi:10.1007/s11011-015-9787-5 doi:10.3389/fcimb.2014.00100.
10. Health I, Malaria RB. Severe Malaria, 2014; 19: 7–131. doi:10.1111/tmi.12313.
11. Movila A, Sohet F, Girgis NM, Gundra UM. Experimental Cerebral MalariaPathogenesis Hemodynamics at the Blood Brain Barrier, 2014; 10. doi:10.1371/journal.ppat.1004528.