JURNAL KESEHATAN LINGKUNGAN
JURNAL DAN APLIKASI TEKNIK KESEHATAN LINGKUNGAN

ISSN 1829-9407 (Print)
ISSN 2581-0898 (Online)

Volume 22, No. 2, July 2025 ; Page: 273-282; DOI: https://doi.org/10.31964/jkl.v21i2.1038

IMMUNOPATHOLOGICAL MECHANISMS OF BRAIN DAMAGE IN CEREBRAL MALARIA: A LITERATURE REVIEW ON IMMUNOLOGICAL PATHWAYS AND NEUROINFLAMMATORY BIOMARKERS

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Article Info

Article history:

Received June 18, 2025
Revised June 18, 2025
Accepted July 28, 2025

Keywords:

Cerebral Malaria
Immunopathology
Brain Damage
Neuroinflammatory Biomarkers
Blood-Brain Barrier

ABSTRACT

Immunopathological Mechanisms of Brain Damage in Cerebral Malaria: A Literature Review on Immunological Pathways and Neuroinflammatory Biomarkers. *Cerebral malaria, a complication of Plasmodium falciparum infection, affects the central nervous system and has the potential to cause brain damage. Reviewing its immunopathological mechanisms is crucial for developing more effective diagnostic and therapeutic strategies. This study aims to investigate the immunopathological mechanisms of brain damage in cerebral malaria by synthesizing recent literature through a narrative literature review approach. A total of 29 articles from the Scopus database were screened, with 23 meeting the inclusion and exclusion criteria. Thematic analysis identified five key sub-themes: (1) immune system activation and endothelial dysfunction; (2) the role of neutrophils and macrophages in neurological pathogenesis; (3) implicated molecular pathways and gene expression; (4) neuropathological findings in experimental models; and (5) clinical implications and therapeutic advancements. The findings indicate that immune overactivation, the release of pro-inflammatory cytokines, and dysregulated gene expression are core mechanisms underlying blood-brain barrier (BBB) disturbances and neural tissue damage. A profound understanding of these mechanisms is essential for designing more effective therapeutic interventions to mitigate the long-term neurological sequelae of cerebral malaria.*

INTRODUCTION

Malaria, a disease caused by *Plasmodium* parasites, remains one of the major infectious diseases posing a global public health problem, particularly in tropical and subtropical regions. In 2023, the World Health Organization (WHO) reported more than **240 million malaria cases worldwide**, with approximately **597,000 deaths annually**. The increase in these figures has been attributed to several factors, including resistance to antimalarial drugs and insecticides, climate change, and disruptions in health services during the pandemic [(1)].
Cerebral malaria is caused by *Plasmodium falciparum*. This condition affects the central nervous system and brain, leading to clinical manifestations such as high fever, impaired consciousness, seizures, and coma [(2–3)]. Cerebral malaria may also result in severe complications and long-term neurological sequelae, including cognitive and motor impairments, and can be fatal if not treated promptly [(4–6)]. One study demonstrated the

occurrence of global hypoxia and cerebral edema, accompanied by increased cerebrospinal fluid protein levels and decreased brain activity velocity in adult patients [7].

Although antimalarial treatment with artesunate and other antiparasitic drugs is effective in reducing parasite burden, it does not prevent brain injury [8]. One contributing factor is the excessive immunological response of the host to the infection [9]. Activation of immune responses in cerebral malaria triggers the release of proinflammatory cytokines, including TNF-α, IL-8, and IFN-β. Excessive cytokine release can damage the blood–brain barrier (BBB), leading to cerebral edema and neurodegeneration [9]. In addition, parasitic heme within endothelial cells stimulates molecular pathways such as STING1 activation, increasing the production of type I interferons and the chemokine CXCL10, thereby promoting neuroinflammation and microvascular dysfunction [10].

The adhesion of infected red blood cells (iRBCs) to the cerebral vascular endothelium contributes to reduced cerebral blood flow and expansion of hypoxic areas, further compromising the integrity of the blood–brain barrier [11]. Pathological experiments using animal models and three-dimensional human cell cultures have demonstrated immune cell infiltration, neuronal degeneration, and microcirculatory dysfunction in cerebral malaria infections [13].

Previous studies have largely focused on isolated aspects, such as cytokines, specific immune cell populations, or molecular models. Comprehensive reviews integrating all immunopathological pathways remain limited. Therefore, this review aims to address this gap in the literature by providing an integrated overview of the immunopathological mechanisms underlying brain injury in patients with cerebral malaria. This review is expected to provide a strong scientific basis for the development of clinical and therapeutic strategies to minimize the neurological impact of cerebral malaria on the global population.

MATERIALS AND RESEARCH METHODS

This literature review employed a narrative literature review approach aimed at synthesizing recent research findings on the pathophysiological mechanisms, molecular pathways, and the roles of immune cells in brain injury associated with cerebral malaria.

The preparation of this review was conducted in four stages.

In the first stage, the research questions and scope of the review were formulated based on the clinical manifestations of cerebral malaria related to brain health.

The second stage involved a systematic search for scientific articles using Publish or Perish (PoP) version 8.17 with the Scopus database. The primary keyword used in the article title search was “cerebral malaria”, while additional keywords included neuroinflammation, cytokine, TNF, IL-6, IL-1, and immune response. The publication period was limited to 2021–2025, and the literature search was conducted in June 2025.

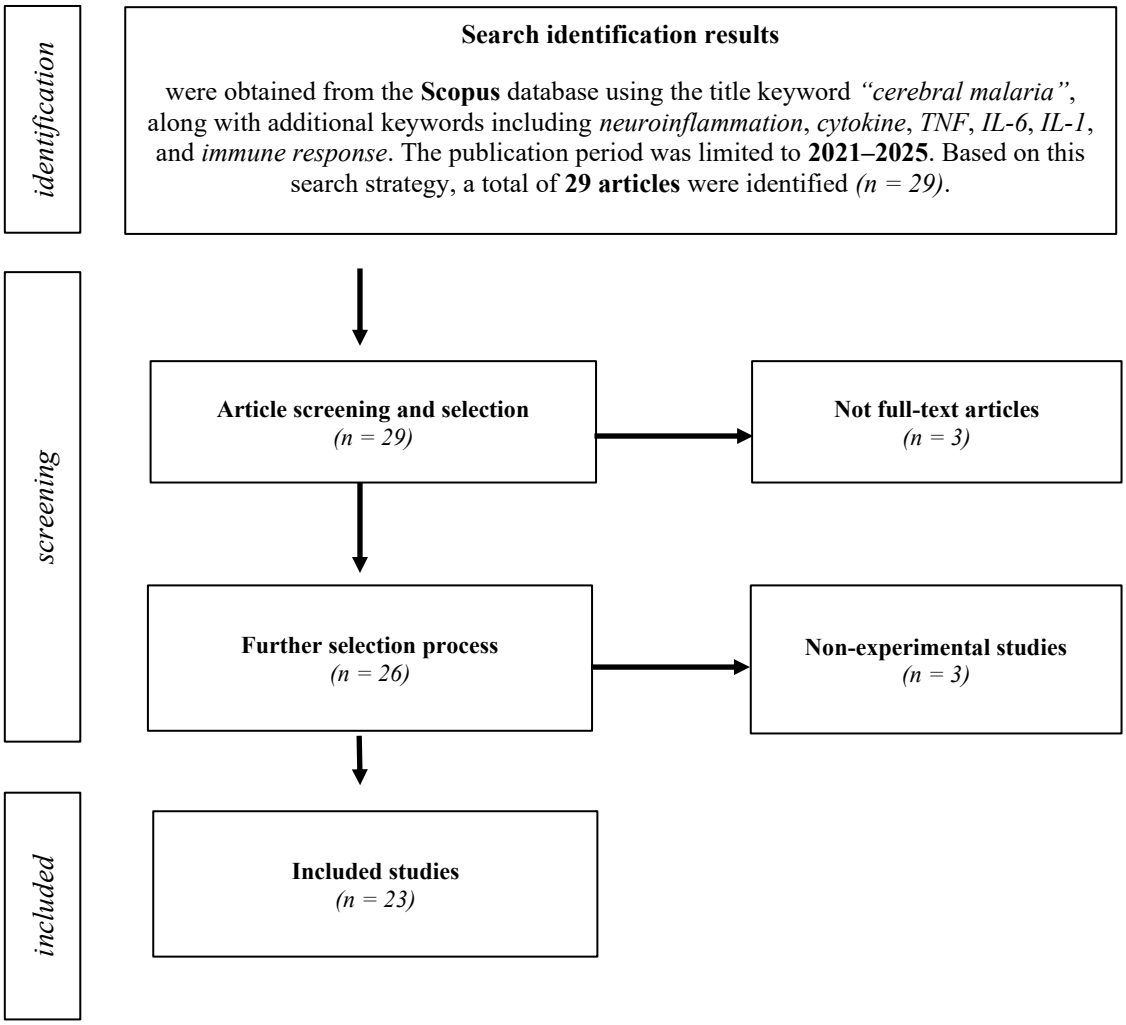
The third stage consisted of article selection based on the following inclusion criteria: articles published in English, issued between 2021 and 2025, available in full-text format, employing experimental or observational study designs, and focusing on biological, molecular, or neurological aspects of cerebral malaria. Of the 29 articles initially identified, 23 articles met the inclusion criteria, while 6 articles were excluded (3 articles were not available in full text, and 3 articles were epidemiological survey studies). The selection process was conducted by two independent reviewers to ensure reliability.

The fourth stage involved data extraction and analysis. Data extraction was performed using Microsoft Excel, reviewing key elements including article title, year of publication, research objectives, theoretical framework, methodology, participant or animal model characteristics, main findings, as well as study conclusions and recommendations.

Data analysis was conducted using a thematic analysis approach. The results yielded five main sub-themes: 1) activation of the immune system and cerebral endothelial dysfunction; 2) the roles of neutrophils and macrophages in neurological pathogenesis; 3) molecular

pathways and gene expression involved in malaria-induced brain injury; neuropathological finding; 4) s from experimental models; and 5) clinical implications and future directions for research and therapeutic development.

The analyzed articles comprised experimental animal studies, in vitro studies, and observational studies in humans. The article selection process is illustrated in the following flowchart.



RESEARCH RESULTS AND DISCUSSION

Immune System Activation and Cerebral Endothelial Dysfunction

Plasmodium falciparum infection triggers hyperactivation of the immune system, which plays a critical role in disrupting cerebral endothelial integrity through molecular pathways involving STING1 (Stimulator of Interferon Genes), IL-8, and interferons (IFNs), as well as through the infiltration of immune cells migrating across a weakened blood–brain barrier (BBB). This condition induces neuroinflammation that leads to cerebral edema, local hypoxia, and neuronal degeneration[6,10,11,14–18].

Uncontrolled immune activation, particularly via the STING1 molecular pathway, results in the release of type I interferons and other proinflammatory cytokines, causing endothelial cell polarity disruption and damage[10]. This process increases endothelial permeability and promotes the adhesion of infected erythrocytes (iRBCs) to the cerebral vascular surface[14,17]. Erythrocyte adhesion is mediated by the upregulation of vascular adhesion molecules such as ICAM-1 and VCAM-1, which occur as a direct response to inflammatory

signaling. These findings indicate that vascular inflammation and endothelial activation represent critical points in the transition from uncomplicated malaria to cerebral malaria[17,18].

Perivascular macrophages surrounding cerebral blood vessels function as immune checkpoints. During malaria infection, these cells undergo intense activation and contribute to amplifying inflammatory responses[19,20]. The release of cytokines such as TNF-α and IL-6 from these macrophages further compromises endothelial integrity and triggers the recruitment of neutrophils and lymphocytes to infected areas, thereby increasing immunological stress on the central nervous system[15,19,21].

From the perspective of inflammatory biomarkers, elevated plasma levels of interleukin-8 (IL-8) in malaria-infected individuals correlate with the clinical severity of cerebral malaria. IL-8 is recognized as a potent chemokine that recruits neutrophils and contributes to the formation of a damaging inflammatory milieu. High IL-8 levels are associated with an increased risk of neurological impairment, indicating that systemic inflammatory components may serve as early indicators of brain injury[6].

Hyperactive immune system activation plays a pivotal role in compromising the integrity of the blood–brain barrier in cerebral malaria. This mechanism facilitates the infiltration of immune cells and proinflammatory cytokines, exacerbating neuroinflammation and leading to cerebral edema, local hypoxia, and neuronal degeneration. Damage to cerebral endothelial structures, increased BBB permeability, and immune cell recruitment impose substantial immunological stress on the central nervous system. These findings suggest that cerebral malaria is not solely caused by the presence of malaria parasites, but also by complex and uncontrolled immune dysregulation that aggravates brain injury[22].

The observed elevation of IL-8 levels highlights the potential of this biomarker as an early predictive tool for assessing the risk of brain damage associated with cerebral malaria.

Role of Immune Cells (Neutrophils and Macrophages) in Neurological Pathogenesis

Macrophages and neutrophils are central players in the escalation of cerebral inflammation and are not merely secondary effects of systemic infection. Regulating the activity of these two cell types may be key to reducing long-term neurological morbidity in patients with cerebral malaria[20,23].

One of the most significant aspects of cerebral malaria pathogenesis is the destructive role of immune cells, particularly neutrophils and macrophages. When activated uncontrollably, these cells become primary agents of brain tissue damage. Their infiltration and hyperactivation in perivascular brain regions contribute to neuroinflammation, tissue injury, and impaired neural function[17,20,23].

Perivascular macrophages normally help maintain immune homeostasis within the central nervous system. However, during cerebral malaria infection, they undergo excessive activation characterized by massive production of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6. These cytokines increase BBB permeability and promote adhesion of infected erythrocytes to endothelial walls, thereby exacerbating microvascular obstruction and local hypoxia[15,19–21,24].

Furthermore, macrophage activity induces the recruitment of additional immune cells, particularly neutrophils, which exert destructive effects on brain tissue. Neutrophils migrating into the brain release neutrophil extracellular traps (NETs), consisting of chromatin fibers coated with proteolytic enzymes such as elastase and myeloperoxidase. Although NETs function to trap and kill pathogens, they also damage vascular endothelium and neuronal cell membranes, thereby intensifying local inflammation[6].

The synergistic interaction between macrophages and neutrophils establishes a pathological cycle: macrophages release recruitment signals, neutrophils migrate and release NETs, which further damage endothelial cells and neurons, prompting macrophages to produce even more inflammatory cytokines. This inflammatory feedback loop is a major explanation for

the occurrence of cerebral edema, seizures, and coma in patients with cerebral malaria[6,19,20].

Upregulation of cellular adhesion molecules such as ICAM-1 and VCAM-1 reinforces leukocyte adhesion to cerebral vascular walls. This process not only slows blood flow but also creates hypoxic zones that promote secondary inflammatory activation in the brain parenchyma. Such histopathological features have been consistently observed in murine models that mimic human cerebral malaria[14,17].

These findings underscore the importance of targeting not only the parasite in cerebral malaria therapy but also modulating immune responses, particularly macrophage and neutrophil activity[12,19,25,26]. Immunoselective therapeutic approaches hold promise as adjunct strategies to reduce neurological damage in severe malaria[27].

Macrophages and neutrophils play critical roles in brain damage during cerebral malaria. Their excessive activation leads to the release of various proinflammatory molecules and tissue-destructive enzymes, resulting in BBB leakage, capillary obstruction, and neural tissue injury. Macrophages serve as the primary source of cytokines that recruit neutrophils to the brain, where neutrophils release NETs that kill parasites but also damage endothelial and neural cells. Recurrent interactions between these cells create an inflammatory cycle that exacerbates cerebral edema, seizures, and coma[28].

Molecular Pathways and Gene Expression Involved in Malaria-Induced Brain Damage

Plasmodium falciparum infection in cerebral malaria causes not only structural damage due to microvascular obstruction and localized inflammatory responses, but also induces molecular dysregulation affecting gene expression in brain and immune cells. These molecular pathways play crucial roles in mediating inflammation, apoptosis, oxidative stress, and neurodegeneration, thereby aggravating neural tissue damage[6,15,24].

Genes such as *CXCL10*, *ICAM-1*, and *TNF-α* are significantly upregulated in animal models and patients with cerebral malaria[10,24]. Activation of STING1 in endothelial cells triggers type I interferon production and induces downregulation of tight junction proteins, resulting in BBB leakage. This STING1 activation represents part of the immune response to parasitic foreign DNA and serves as a key molecular signal driving inflammatory gene expression cascades[10].

Malaria infection also induces alterations in proapoptotic gene expression that contribute to neuronal cell death. These changes are particularly evident in the hippocampus and cerebral cortex of murine cerebral malaria models—regions closely associated with memory and cognitive function. Dysregulation of gene expression worsens neurological outcomes and explains why many cerebral malaria survivors experience cognitive impairment even after recovery from acute infection[15,18]. Reduced expression of neuroprotective genes has also been reported, further supporting the presence of infection-induced neurodegenerative processes[21].

Understanding these molecular pathways opens opportunities for the development of targeted molecular therapies. In addition, specific gene expression profiles may serve as molecular biomarkers for predicting the risk of cerebral complications in malaria patients[6,16,27,29,30].

Cerebral malaria in children exhibits more aggressive clinical and immunopathological patterns than in adults, with a higher risk of long-term neurological complications. A key finding is elevated plasma IL-8 levels in pediatric patients, which are associated with neutrophil recruitment and cerebral endothelial damage[6]. This intense inflammatory response is reinforced by the activation of specific molecular biomarkers related to cytokine and vascular adhesion pathways, as identified in immunological and serological studies[29,31]. In addition to cytokines, genetic factors such as IgG3 hinge-region length have been implicated in individual susceptibility to cerebral complications through their roles in parasite neutralization and complement activation[32].

In clinical immunology contexts, pediatric cerebral malaria is also influenced by viral coinfections, such as cytomegalovirus (CMV) reactivation, which exacerbates neurological outcomes by amplifying inflammatory pathways and disrupting immune regulation[18]. These findings emphasize the importance of a multidimensional approach to cerebral malaria analysis, considering not only parasitemia but also individual immune profiles and secondary infections. Accordingly, prevention and treatment strategies for pediatric cerebral malaria should extend beyond parasite elimination to include immune biomarker monitoring, selective anti-inflammatory therapy, and viral coinfection screening as part of integrated clinical management[33].

Plasmodium falciparum infection in cerebral malaria causes cerebral vascular obstruction, genetic regulatory disturbances, and immune system dysregulation, leading to progressive neural damage. Multiple genes involved in inflammation, cellular injury, and neuroprotection are affected in regions critical for memory and cognitive function[34]. In children, cerebral malaria presents with greater severity than in adults, characterized by higher IL-8 levels and more pronounced endothelial damage[35].

Neuropathological Findings from Experimental Models

Experimental models play a pivotal role in elucidating the complex pathophysiology of cerebral malaria and supporting the development of mechanism-based therapies. Understanding cerebral malaria pathophysiology has been greatly advanced through the use of experimental models, particularly animal models such as mice and in vitro models based on human cerebral endothelial cell cultures. These models have been widely employed to characterize inflammatory processes, vasculopathy, and neural tissue damage during *Plasmodium falciparum* infection, as well as to evaluate therapeutic interventions. Experimental models hold strategic value in cerebral malaria research, both for elucidating pathological mechanisms and for guiding the development of more selective and effective molecular and immunological therapies.

Several studies included in this review utilized mice infected with *Plasmodium berghei* ANKA, a widely recognized standard animal model for cerebral malaria[10,12,13,15,19,20,23,25,26]. Histopathological examination revealed macrophage and T-cell infiltration around cerebral capillaries, accompanied by BBB disruption, cerebral edema, and microcirculatory impairment. Neuronal damage was evident in the hippocampus and cortex, including cellular degeneration, nuclear fragmentation, and microglial activation. These findings indicate that brain damage in cerebral malaria results from a combination of vascular obstruction and neuroinflammatory responses[20,25]. Additional studies in BALB/c mice demonstrated that immunomodulatory treatments suppressing macrophage activity reduced tissue damage, further confirming the direct role of immune cells in cerebral pathology[23,25].

Beyond animal models, three-dimensional human brain endothelial culture models have provided valuable insights. Using microvasculature systems, human brain tissues inoculated with *P. falciparum* exhibited adhesion of infected erythrocytes to endothelial walls, accompanied by loss of tight junction protein expression[24].

Overall, findings from these models consistently demonstrate neuropathological patterns including immune cell infiltration in perivascular regions, neuronal degeneration and microglial activation, increased BBB permeability, and impaired cerebral microcirculation due to adhesion of infected blood cells[19,21,24,26,30].

Clinical Implications and Recommendations for Future Research

Evidence from the reviewed literature confirms that cerebral malaria is not merely an acute manifestation of *Plasmodium falciparum* infection, but a complex neurological syndrome involving immune system activation, BBB disruption, gene expression dysregulation, and direct brain tissue damage. The clinical consequences are extensive, ranging from acute neurological symptoms such as seizures and coma to long-term cognitive impairment that

severely affects survivors' quality of life, particularly among children in endemic regions[6,18,31,32].

Clinically, cerebral malaria management remains focused on parasite elimination using antimalarial therapies such as artesunate. However, evidence from animal models and molecular studies indicates that parasite control alone is insufficient to prevent brain damage. Although parasitemia can be reduced with artesunate, inflammation persists and continues to damage tissue unless accompanied by therapies that suppress immune overactivation[15].

IL-8 shows promise as a predictive biomarker for early detection of neurological complication risk[6]. Therapeutically, the development of selective immunomodulatory strategies—such as inhibition of the STING1 pathway or specific proinflammatory cytokines like TNF-α—may reduce endothelial and neuronal damage without compromising parasite clearance. This approach enables a more balanced strategy between pathogen control and neuroprotection[12,25].

Additionally, human 3D microvasculature models demonstrate significant potential for testing novel interventions in more physiologically relevant human microenvironments. These models represent ideal platforms for evaluating drug candidates or combination therapies and should be further developed for translational research[24].

Future research should also prioritize long-term studies on post-infection cognitive outcomes in cerebral malaria survivors. Many children who survive the acute phase exhibit learning difficulties, memory impairment, and behavioral problems. Longitudinal studies are required to quantify these impacts and identify early neuroprotective or rehabilitative interventions[18].

Integrating molecular immunology approaches with biomarker monitoring systems holds the potential to shift cerebral malaria management paradigms from reactive to preventive strategies.

CONCLUSIONS AND RECOMMENDATIONS

Cerebral malaria is a severe neurological complication caused by *Plasmodium falciparum* infection, characterized by excessive immune activation and blood–brain barrier (BBB) disruption. Its pathogenic mechanisms involve proinflammatory cytokines, adhesion of infected erythrocytes, and regulation of inflammatory gene expression, leading to both structural and functional brain damage. Children exhibit higher susceptibility due to a more reactive immune profile and an increased risk of long-term effects on neural development.

Longitudinal studies on cognitive function in pediatric survivors from endemic regions are essential for designing early rehabilitative interventions. Biomarker-based approaches and selective immunological interventions may enhance clinical responses to cerebral malaria while minimizing long-term neurological consequences.

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