Malaria-induced Coagulopathy: Complexities and Treatment Challenges in Intracranial Hemorrhage

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Syeda Mahrukh Fatima Zaidi[1] and Faizan ur Rehman[1]

Background

Coagulopathy also plays a significant role in the development of intracranial hemorrhage.[1] These bleeds can have serious implications for neurological function and overall health. The most common types include subdural hematomas, epidural hematomas, intraparenchymal hemorrhages, and subarachnoid hemorrhages. Various factors and conditions can contribute to coagulopathy, including both inherited bleeding disorders, such as hemophilia or von Willebrand disease, as well as acquired conditions like liver disease, malaria-induced coagulopathy, or medication-induced coagulopathies.[2,3]

Malaria-induced coagulopathy, though rare, can disrupt the body's normal clotting mechanism, leading to abnormal bleeding, including intracranial hemorrhage.[3] The complex interactions between the parasite, the immune system response, and the coagulation cascade contribute to the development of coagulopathy and subsequent intracranial bleeding. The exact mechanisms underlying the development of intracranial bleeding in these cases are not yet fully understood, but it is believed to involve a combination of factors, such as endothelial dysfunction, platelet dysfunction, and microvascular sequestration of infected erythrocytes. The recurrence of intracranial bleeding poses an additional challenge, as it indicates a more severe and refractory form of malaria-induced coagulopathy, requiring urgent and aggressive treatment interventions.

Main Text

Plasmodium falciparum malaria is an uncommon kind of malaria that can cause severe brain injury. In the developing world, malaria is among the leading causes of sickness and impermanence. The 2020 Malaria Report by the World Health Organization claims that *P. falciparum* is responsible for more than 90% of all malaria-related deaths worldwide, killing over 400,000 people annually.[4] Female Anopheles mosquitoes transmit *P. falciparum*. Once transmitted, the parasite develops inside the liver. The erythrocyte cycle, which comes after the hepatic phase and is in charge of the disease's clinical manifestation, is what happens next. Brain damage from malaria can result. An explanation for the cerebral symptoms of malaria involves the obstruction of brain capillaries caused by the sequestration of infected red blood cells (IRBCs) and enlarged endothelium.[5]

The pathophysiology of cerebral malaria's effects on neuronal health is unknown but autopsy studies have provided some insight. It most likely stands in for the illness's most severe symptom. The main cause of the development of brain damage in cerebral malaria is thought to be the sequestration of IRBCs in the cerebral microvasculature. Sequestration of IRBCs in the cerebral microvasculature is regarded to be the main contributor to brain injury in cerebral malaria. IRBCs can adhere to vascular endothelium through the intercellular adhesion molecule-1 (ICAM-1), which is expedited by the *P. falciparum* erythrocyte membrane protein-1 (PfEMP) on the surface of the IRBCs. This adhesion can lead to the formation of rosettes, which are clusters of IRBCs and non-infected RBCs. The sequestration of IRBCs in the brain, both in the form of rosettes and individual IRBCs, can cause a perfusion deficit and a decrease in the supply of brain substrates (glucose and oxygen). This can lead to both acute and long-term effects of cerebral malaria. Additionally, the parasite antigen produced during the schizogony stage can activate a cytokine, which can further contribute to the damage caused by cerebral malaria.[6] *P. falciparum* infection is characterized by low platelet counts, low levels of anticoagulants, formation of activated thrombin and pro-coagulant microparticles, systemic endothelial activation, and patchy endothelium damage.[7] This strongly implies that the coagulation system is

[1]Department of Surgery, Dr. R K Pfau Civil Hospital, Karachi, Pakistan

Corresponding author:
Syeda Mahrukh Fatima Zaidi, Department of Surgery, Dr. R K Pfau Civil Hospital, Karachi, Pakistan.
E-mail: mahrukhfatima2010@live.com

deregulated. Most children with CM exhibit clinically significant hemorrhages in the microvessels of the eye, which corresponds to the presence of multiple microthrombi and hemorrhages in the brain's small blood vessels in deceased children.[8] Activated partial thromboplastin time and prothrombin time, two common functional markers of coagulation, are typically only minimally abnormal. However, severe clinical symptoms of coagulopathy are uncommon. This raises the question of whether coagulation factor changes contribute to pathogenesis or whether they are only a side effect of other Inherent pathogenic processes that appear in a small number of people with severe disease.

Although severe thrombotic or hemorrhagic events are rare in CM, their presence shows that *P. falciparum* infection and coagulation clearly interact. Adults with CM, rarely present with overt bleeding. However, in children, its occurrence is in 5% of cases, typically coming from the gastrointestinal system.[9] Although uncommon, reports of spontaneous massive cerebral hemorrhage as a clinical symptom of the complicated syndrome exist. The types of bleeding that have been recorded include SAH, subdural, intracerebral, and even extradural hemorrhage.[10] Verma et al. described a complex case involving a 38-year-old male who presented with brain hemorrhage secondary to suspected malarial coagulopathy.[11] The treatment process was significantly challenging due to rapid neurological decline, anisocoria, low platelet count, and the development of hydrocephalus. Despite aggressive interventions such as hematoma evacuation, antimalarial therapy, platelet transfusions, tracheostomy, and external ventricular drain placement, the patient's neurological recovery remained limited, highlighting the difficulty in managing such a complex and multifactorial condition.

This sheds light on the complicated and complex interaction between the clotting and inflammatory pathways, which are both activated following damage and are likely amplified by the existence of malarial infection. It also emphasizes the difficulties experienced by the treating doctors and the medical complexity supported by deregulated homeostasis and increased pace of secondary damage.

Conclusion

In conclusion, the management of intracranial hemorrhage associated with malaria-induced coagulopathy presents significant challenges due to complex interactions between the parasite, immune response, and coagulation system. Further research is needed for better understanding and improved treatment strategies. A comprehensive approach is crucial to address the multifactorial nature of these conditions.

Authors' Contribution

The conceptualization was done by SMFZ and FUR. The literature and drafting of the manuscript were conducted by SMFZ AND FUR. The editing and supervision were performed by SMFZ. All authors have read and agreed to the final version of the manuscript.

Availability of Data and Materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Statement of Ethics

No experiments were conducted by the author for this Commentary. Hence, ethical approval was not required.

Declaration of Conflicting Interests

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ORCID iD

Syeda Mahrukh Fatima Zaidi https://orcid.org/0009-0004-1723-4097

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