ejpmr, 2018,5(12), 109-113

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

CEREBRAL MALARIA IN TROPICAL SUB-SAHARAN AFRICA; A SENTINEL DISEASE FOR EPILEPTIC SEIZURES: "A FOCUSED REVIEW"

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Article Received on 11/10/2018 **Article Revised on 31/10/2018** **Article Accepted on 21/11/2018**

ABSTRACT

The World Health Organization estimated that more than 83% of *Plasmodium falciparum* malaria occurs in sub-Saharan Africa. Malaria in its cerebral form known as Cerebral Malaria (CM), may lead to acute or long-term neurological complications. Generally, neurological sequelae are rare in adults recovering from cerebral malaria, accounting for less than 1%, compared with children in whom neurological residual abnormalities are more common, with approximately 12% still having sequelae such as hemiplegia, cortical blindness, aphasia and cerebellar ataxia. These features often resolve in over 50% of the children, but about 25% will be left with major residual neurological deficits. Furthermore, sequelae such as epilepsy have been reported and may only become evident later during the adolescent age. Among all cases of severe malaria caused by plasmodium falciparum, Cerebral Malaria (CM) stands as the most severe neurological presentation of acute plasmodium falciparum infection. It causes diffuse encephalopathy associated with seizures in at least 80%, and status epilepticus, in more than 30% of cases. Although survivors of CM make a full recovery, neurological sequelae such as epilepsy occur in 3-31%. Cerebral malaria is histopathologically characterized by swelling of small blood vessels such as cerebral capillaries and venules with both parasitized and non- parasitized red blood cells. There may be impairment in the structural and physiological dysfunction of the blood-brain barrier. Furthermore, There is histological evidence of cerebral edema, with petechial haemorrhages. Durck's granuloma may also be seen due to accumulation of glial cells surrounding hemorrhagic foci. This review tends to discuss the mechanisms involved in the neuropathology caused by CM, focusing on epilepsy.

KEYWORDS: Cerebral Malaria, epileptic seizures, Sentinel disease, Tropical Sub-Saharan Africa.

INTRODUCTION

According to World Health Organization's (WHO) criteria[1], severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction and/or high parasite burden; this high parasitemia can be a risk factor for death from *Plasmodium falciparum* malaria.[1] Clinical features of severe malaria include cerebral malaria (CM) with impaired consciousness , prostration and multiple convulsions.[1-3] CM induces acute or chronic neurological damage, affecting several central nervous system regions responsible for neurological functions which may result in epilepsy. Detection of post malaria lesions that result in epilepsy require the use of structural genomics, which uses computational techniques to analyze and characterize the function of protein structures and the implications of their variants. For example, it was recently discovered that Exp-1 is a new malarial glutathione-s-transferase that metabolizes hematin and is inhibited by Artesunate. This predicts accurately the effect of protein coding mutations *in vivo* and *in vitro*; the morbidity and mortality of mutations in disease-causing genes; and the frequency distribution of human coding polymorphisms.[4-10] This observation opens a new therapeutic window against malaria since Artesunate is the best current malarial drug. The actual mechanisms involved in the nervous system alterations that result in epileptic seizures are yet to be unraveled. Nevertheless, several proinflammatory mediators have been implicated in the etiopathogenesis of post malaria epilepsy syndromes.

Role of Inflammatory cytokines: It has been suggest that, glycosylphosphatidylinositol released on ruptured merozoite induces cytokine cascade from macrophage-monocyte series, that stat with release of pro-inflammatory cytokines such as IL-I and TNF alpha which then in turn induces IL-6, and IL-8. These cytokines are not only implicated in the phathogenesis of inflammatory changes in cerebral malaria, but are also associated with severity of the disease. For instance, elevation of serum level of TNF alpha in patients with falciparum malaria is highly associated with disease severity, including coma, hypoglycemia, hyperparasitaemia and death.[11,12] Additionally, TNF may also induce coma by stimulating the production of nitric oxide (NO) which interferes with synaptic

transmission.[13] High circulating levels of NO are associated with severity, mortality and frequency of neurological sequelae in severe malaria.[12]

Role of inflammatory adhesion molecules: Another possible mechanism of cerebral lesion that may eventually lead to epilepsy in cerebral malaria, is cytokine adherence otherwise known as cytoadhesion. Cytoadhesion is an inflammatory process that is mediated by a parasite derived protein called Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP-1). Elevation of core temperature induced by cytokines enhances expression of PfEMP-1 on the surface of RBC as 'knobs', acting as points of attachment to the vascular endothelium.[14,15] This process is thought to play a significant role in reducing micro vascular blood flow, which in turn is partly responsible for cerebral dysfunction.[16] Furthermore, sequestered parasites may produce toxins, especially during schizont rupture that disrupts brain metabolism.[17] The endothelial receptor for parasites expressing these proteins, has been identified as endothelial protein C receptor (EPCR).[18,19] The PfEMP1 subtypes containing domain cassettes (DCs) 8 (group B/A hybrid) and 13 (group A) are shown to mediate adherence of P. falciparum -infected erythrocytes to brain endothelial cells.[18,20] These observations suggest that DC8 and DC13 PfEMP1 variants play a key role in cytoadhesion of P. falciparum -infected erythrocytes to various endothelial cells.[21-24]

Role of Genetics

Recent multi-scale evidence including clinical, molecular and population genetics data suggests that,, scientific advancements offer the potential to define an individual's risk of developing epilepsy sequel to acute neuronal insult such as Cerebral malaria based on their genetic make-up. Therefore, the increasingly widespread availability and applicability of molecular genetic tools provide the medical community with an ample opportunity to uncover and understand the heritable component of complex diseases such as cerebral malaria. In the past twenty years, significant efforts have been made in identifying the genetics of epilepsy. There have been many discoveries of the importance of genetic mutations, understanding the complexities of genotype–phenotype relationships, genetic heterogeneity and pleiotropy.[25-27] Moreover, the dramatically reduced cost of genetic testing, the availability and cost effective nature of whole exome or whole genome sequencing at the clinical interface mean that genetics is rapidly becoming part of routine investigation in evaluation of epilepsy.

Furthermore, finding a specific genetic diagnosis avoids unnecessary testing with repeated blood tests, Magnetic Resonance Imagings (MRI) and invasive biopsies. Additionally, a genetic diagnosis may provide useful prognostic information regarding the natural history of the disorder as large case series accumulate like Dravet syndrome and PCDH19-related epilepsy. Infarct, the empowerment derived by specific diagnosis, understanding the disorder and contributing to solve it cannot in any way be overemphasized.[28-30]

A part from the above mentioned benefits of genetic evaluation, there is a growing number of genetic diagnoses in which specific alterations in management are indicated. This may include the choice of conventional antiepileptic agents or the use of an alternative treatment. For example, in Dravet syndrome, which is the result of mutations in SCN1A, there is growing evidence that early therapy improves outcome especially when recognized in adult life.[31-35] Sodium channel blockers such as lamotrigine and carbamazepine should be avoided, whereas valproic acid, topiramate, clobazam, and stiripentol appear to be beneficial.[32,33]

Neuropathological changes: Seizures in CM are common and inflammatory products such as quinolinic acid contribute to the neuropathology, considering that this metabolite from the kynurenine pathway is a N-methyl-D-aspartate agonist that causes neuroinflammation, convulsions, and cell death.[36-38] As far back as the year 2000, Dobbie *et al*[39] reported that quinolinic acid provokes seizures in animals, possibly, altering the neurotransmission excitatory and triggering long-term deleterious effects. While in 2003, Sokol *et al*[40] demonstrated irreversible neuron damage after long-term seizure activity, followed by gliosis and focal atrophy, resulting in more seizures and brain damage. Epilepsy seizures occur in approximately 10% of pediatric cases and may be occasioned by focal or global hypoxia or ischemia.[41,42] Structural brain damage and the presence of Durck's malarial granuloma may contribute to the epileptogenesis mechanisms[43]; however, other factors should also be considered, like genetic propensity.[44] Some studies have shown that, severe brain injury occurs after CM and 25% of pediatric cases result in epilepsy.[45-47] In animals with CM[48], an inflammatory cytokine profile has been associated with CNS dysfunction similar to what is found in human CM. In the course of experimental CM induced by *Plasmodium berghei* (strain ANKA), leukocyte migration into the brain, as well as the production of TNF-α and chemokines (CCL2, CCL3, CCL5 and CXCL9) preceded neurological changes, suggesting that the inflammatory changes may be involved in the neurological impairment.[49] Other studies have reported correlations between neurological dysfunctions and glutamate levels and their contribution to the neuropathological changes.[50] Glutamate is the principal excitatory neurotransmitter in the mammalian CNS, participating in several neurological functions under physiological conditions.[51] Therefore, large amounts of glutamate release trigger neurotoxicity and neuronal cell death, being involved in neuropathological disorders.[52]

Clinical application

Brain is one of the most complex biological organs in the human body. However, as with all living tissues brain remain susceptible to myriad of medical disorders, some of which are related to chronic neurological diseases such as epilepsy. Ideally, diseases affecting any part of the human body should exhibit a unique pathology to allow clinicians to distinguish particular conditions and give a reliable diagnosis and treatment. However, in reality, many chronic neurological diseases share similar symptoms and features and the task of diagnosis is often challenging. Appropriate approaches aimed at detecting pathogenic processes are part of the measurable characteristics for brain disorders that are needed to evaluate monitor and follow disease progression.

In view of the above mention evidence of role of molecular biology in evaluation of post-malaria epilepsy, scientist advocated that, genetic assays should be part of everyday clinical diagnosis of epilepsy. In some genetically related neurological diseases, specific therapeutic decisions can now be made based on genetic findings, and this scenario of precision therapy is likely to play a significant role in overall management of chronic epilepsy syndromes.

CONCLUSION

Malaria is a parasitic disease that can affect the CNS, altering its functions. Neurological changes described in the course of experimental or human CM are mainly a consequence of brain hyperinflammation, vascular obstruction, reduced cerebral blood flow, and disruption of the BBB associated with high levels of cerebral vasoconstriction, thrombus, ring hemorrhage, ruptured capillaries, and cerebral blood vessels filled with infected erythrocytes, with consequent axonal damage and demyelination. Additionally, neurologic alterations have been observed as motor deficits, seizures and epilepsy.

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