Neurocognitive Complications of Cerebral Malaria: A Literature Review and Recommendations for Improving Outcomes

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Abstract- Malaria is a major cause of morbidity and mortality amongst infants and children less than 5 years of age, and current research suggest that cerebral malaria-a manifestation of severe malaria is associated with long-term neurodevelopmental sequelae in some survivors. The long term neurocognitive complications of cerebral malaria is currently under reported, with little or no established policy platforms to follow up survivors who suffer from its debilitating consequences. The resultant effect of this unmet public health need, is an increased odds of victims growing up with disabling neurocognitive manifestations, which may lead to future economic and societal burdens a region of the world already plunged by poverty and deprivation. In this paper, we present recommendations that could mitigate the long term neurocognitive decline reported in some CM survivors. We advocate the use of preventive strategies of disease- primordial, primary, secondary and tertiary preventions to address this unmet public health need.

Index Terms- Cerebral Malaria, Plasmodium Falciparum, Pathogenesis, Pathology, Neurocognitive complications, Outcomes, Prevention, Sub-Saharan Africa

I. Malaria Pathogenesis and Epidemiology

The World Health Organization's media center describes Malaria as a life-threatening disease caused by parasites transmitted to people through the bites of infected female Anopheles mosquitoes [1]. According to the latest World malaria Report of 2017, the global tally of malaria in 2016 was 216 million cases and 445,000 deaths [2]. Most of the cases in 2016 were in the WHO African Region (90%), followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%) [2]. The degree of endemicity varies between countries and even between different areas in the same country [3]. Malaria is a protozoan disease transmitted by the female Anopheles mosquito [4]. Most cases are caused by either *Plasmodium falciparum* or *Plasmodium vivax*, but human infections can also be caused by *Plasmodium ovale*, *Plasmodium malariae*, and, in parts of southeast Asia, the monkey malaria Plasmodium knowlesi [4]. Almost all deaths are caused by falciparum malaria [4]. Research has revealed that malaria is a major cause of morbidity and mortality amongst infants and children less than 5 years of age. Malaria was more prevalent throughout the globe, but has been widely eradicated from the USA, Canada, Europe and Russia [4]. However, malaria still remains a major public health problem in Sub Sahara Africa and South East Asia. Uncomplicated malaria presents mainly with fever, prostration, vomiting and lethargy. In some cases however, malaria can often become complicated; especially that caused by Plasmodium falciparum. Complicated malaria often presents as cerebral malaria, severe anemia, acidosis and hypoglycemia, pulmonary edema, acute kidney injury, jaundice, and interaction with other infections [4]. This paper will be focusing on the detrimental neurocognitive disabilities resulting from a complication of malaria, cerebral malaria.

II. Cerebral Malaria

Cerebral malaria is a medical emergency demanding urgent clinical assessment and treatment [5]. The World Health Organization (WHO) defines CM as an otherwise unexplained coma in a patient with malarial parasitemia. Worldwide, CM occurs primarily in African children and Asian adults, with the vast majority (greater than 90%) of cases occurring in children 5 years old or younger in sub-Saharan Africa [6]. The pathophysiology of the disease is complex and involves infected erythrocyte sequestration, cerebral inflammation, and breakdown of the blood brain barrier (BBB) [6]. Brain imaging may show neuropathology around the caudate and putamen [5]. Mortality is high [5] and some surviving patients have an increased risk of neurological and cognitive deficits, behavioural difficulties and epilepsy, making cerebral malaria a leading cause of childhood neurodisability in the malaria transmission area [7]. Despite several international campaigns targeted at eradicating malaria as a disease in itself, little or no efforts are being channelled towards addressing the debilitating effects of a catastrophic complication of severe malaria-cerebral malaria. The resultant effect of the current malaria eradication approach may have future economic and societal implications in terms of missed school days, suboptimal cognitive and economic function, and a diminished workforce. Despite decades of research, cerebral malaria still remains one of the most serious complications of

Plasmodium infection and is a significant burden in Sub-Saharan Africa, where, despite effective antiparasitic treatment, survivors develop long-term neurological sequelae [8]. Even though there is still a lot unknown about the pathogenesis of cerebral malaria, the *American Journal of Pathology* has been pivotal in presenting original research from both human and experimental models [8]. Information stemming from their work has thrown more insight into the pathogenesis of the vascular damage that occurs in this devastating disease [8].

III. Cerebral Malaria Pathogenesis

The pathogenesis of cerebral malaria is due to damaged vascular endothelium by parasite sequestration, inflammatory cytokine production and vascular leakage, which result in brain hypoxia, as indicated by increased lactate and alanine concentrations [5]. The way these pathological mechanisms are linked and how they are influenced by host and parasite factors remains to be elucidated. In addition, the reasons why circulating cytokines, coagulation factors, or parasitized red blood cells specifically target only the brain in African children, and the brain as well as other organs in Southeast Asian adults, are still unclear [9]. The levels of the biomarkers' histidine-rich protein II, angiopoietin-Tie-2 system and plasma osteoprotegrin serve as diagnostic and prognostic markers [5].

The BBB is a selectively permeable structure responsible for regulating ion and nutrient transport into the brain. It serves as a key interface between the central nervous system and the blood, restricting the free flow of physiological molecules between the bloodstream and parenchyma [8]. The BBB is composed of specialized endothelial cells (ECs) that line cerebral blood vessels [8]. The BBB is a highly complex structure, consisting of many cell types and possessing multiple functions [8]. Disruptions of the integrity of the BBB can lead to the passage of potentially harmful substances into the brain, which may subsequently cause disease [8]. Vascular compromise with major disruptions to the BBB has been implicated in the pathogenesis of Cerebral Malaria [6].

Globally, of all the population at risk of acquiring falciparum malaria, children ages 5 years or younger are at a greater risk of developing severe malaria, in the form of cerebral malaria [10]. This population is associated with a staggering 90% of CM-related fatalities [10]. CM that occurs in young children, also termed pediatric CM, is characterized by impaired consciousness, severe anemia, hypoglycemia, fever, and neurological sequelae [10]. Cerebral malaria is considered a leading cause of neurodisability in Sub-Saharan Africa among children and about 25% of survivors have long-term neurological and cognitive deficits or epilepsy [11]. Their development was reported to be associated with protracted seizures, deep and prolonged coma [11].

The burden of the long lasting effects of cerebral malaria on survivors is adjudged to be under estimated, as a framework to guide global health practitioners in preventing the neurocognitive complications of the disease as well as, adequate follow up of survivors is currently not in place. Following apparent recovery from a diagnosis of CM, a lack of information or misinformation may not motivate caregivers to follow up with clinicians should they notice a change from baseline in the behaviours of their wards after the period of convalescence. Some of the mood and behavioural residual effects of cerebral malaria such as unexplained anxiety, attention deficits, hypersensitivity, and hyperactivity may be regarded as typical childhood behaviour by caregivers who are often uninformed about the potential of the disease to cause these neurocognitive changes. In more profound circumstances where CM survivors experience epileptic feats and learning disabilities, cultural and societal norms may preclude the need to seek further medical management. Therefore, survivors may not benefit from timely interventions, which could predispose them to lifelong disabilities. Consequently, a frame work to improve the long term neurocognitive outcomes in CM survivors is imperative, to empower practitioners in providing the support needed to this patient population which may enhance their chances towards the attainment of their fullest potentials.

IV. Literature findings

We did a systematic PubMed search between June and July of 2017, using keywords and reviewed several studies from the past 15 years on the neurocognitive outcomes of CM that documented at least a 6 month follow up of CM survivors.

A study by C. John et al, reveals that cerebral malaria is associated with an increased frequency of cognitive impairment 6 months after the initial malaria episode [12]. A follow up study by C. John et al to determine the long term effect of cerebral malaria on the cognitive function of the affected children, revealed that 1 in 4 survivors suffered impairments more than 6 months after the original episode of cerebral malaria [12]. Another review by Kihara *et al* on post malarial cognitive impairment concluded that a significant proportion of children with cerebral malaria and severe falciparum malaria are at risk of subsequent cognitive impairment [13]. This impairment in cognitive abilities was seen in all cognitive spheres; language, attention, memory, visuospatial skills and executive functions [14,15]. A strong indicator of academic performance is an assessment of the cognitive ability of an individual and P. Bangirana et al. in their study of 62 Ugandan children cerebral malaria survivors concluded that working memory, visual spatial skills, and learning combined together, stood out as the best combination to predict this performance [16]. A study by M. Boivin et al carried out with an objective to assess the developmental outcomes in children with retinopathy positive cerebral malaria, concluded that children with retinopathy positive cerebral malaria had a higher odds of language delays using local standardized test scores compared with controls [17]. The conclusion by Boivin et al [17] corresponds to the result of a similar study conducted by J. Carter et al which also concluded that children who had suffered from cerebral malaria had greater odds of developing language impairment, compared with matched controls [18]. A prospective cohort study done by G. Birbeck et al to establish whether retinopathy positive cerebral malaria was a risk factor for epilepsy or other neurodisabilities, concluded that cerebral malaria survivors had greater odds of developing both epilepsy and new neurodisabilities [19]. D. Postels et al, in trying to ascertain if there was any difference in neurocognitive outcomes between retinopathy positive and retinopathy negative cerebral malaria survivors, concluded that both groups had equal odds of developing adverse neurologic

outcomes, which was higher than the control group [20]. S. Christensen et al conducted a meta-analysis to quantitatively assess the association between CM and the development of long-term neurologic impairment, and concluded that CM was associated with an increased risk of epilepsy, Intelligent Quotient impairment, neurodisabilities and behavioral disorders [21]. The conclusions drawn from these studies indicate the need to channel public health resources towards addressing this current unmet need in areas of the globe affected by the malaria epidemic. The current global fight against malaria should therefore employ a holistic cost effective approach towards addressing the complications of malaria, including cerebral malaria. More needs to be done to tackle this public health scourge especially in Sub Saharan Africa where resources are already limited, in order to limit the long lasting effects of neurocognitive compromise in CM survivors. A change in current management strategies could start with an all-inclusive policy adjustment and prioritization. Global organizations currently involved in spearheading the fight against malaria should adopt an encompassing strategy to also address the silent catastrophes of the neurodevelopmental complications of cerebral malaria, so as to give CM survivors a fair chance at conquering the odds against them.

V. Discussion

Cerebral malaria is the most severe neurological complication of infection with Plasmodium falciparum [22]. With >575,000 cases annually, children in Sub-Saharan Africa are the most affected [22]. Surviving patients have an increased risk of neurological and cognitive deficits, behavioral difficulties, and epilepsy making cerebral malaria a leading cause of childhood neurodisability in the region [22]. The pathogenesis of neurocognitive sequelae is poorly understood: coma develops through multiple mechanisms and there may be several mechanisms of brain injury [22]. Understanding these mechanisms is important to develop appropriate neuroprotective interventions [22] to mitigate against the long lasting neurocognitive consequences of CM. This is a public health problem afflicting people in a region of the world plunged by poverty, depravity and unsustainable health policies. Efforts to address and manage this under reported global health problem should be promoted. Effective stakeholder analysis should be done in order to encourage the buy-ins of all policy and decision makers in the regions of the world affected. CM survivors currently suffering neurocognitive complications of the disease including epilepsy should be given the opportunity to live to their full potentials in society. In order to tackle this public health unmet need, we employ the preventive strategies of disease and suggest strategies that could be adopted for global impact.

Primordial Prevention

The aim of Primordial prevention is to avoid the emergence and establishment of the social, economic and cultural patterns of living that are known to contribute to an elevated risk of disease [23]. Primordial prevention consists of actions to minimize future hazards to health and hence inhibits the establishment of factors which are known to increase the risk of disease [24]. It addresses broad health determinants rather than preventing personal exposure to risk factors, which is the goal of primary prevention [24]. Primordial prevention can be employed at the level of the government or policy makers, to curb the factors which predispose to the development of neurodevelopmental complications from CM. This may be achieved by:

Championing Focused Research

More emphasis should be placed on the conduct of focused pre-clinical and clinical research. Several studies have indicated that many children afflicted with cerebral malaria go on to achieve full neurological recovery 6 months to 1 year after the initial insult. However, many studies have also reported a fraction of CM survivors developing disabling neurologic complications including epilepsy, several years after the episode of CM. Unfortunately, the long term effects of impairments resulting from CM are poorly characterized, and their importance to the overall burden of malaria are rarely discussed [25]. The fundamental question that needs to be asked is why do some CM survivors recover completely from the neuronal insult; while others go on to develop long term neuro disabilities? Are there unidentified environmental or genetic factors that play a role in this divergent outcome? Are there other predisposing factors for long term neurocognitive complications other than the severity or duration of coma? Could prior nutritional status, baseline health conditions or other co-morbidities be contributing factors to this subtle menace? Focused research aimed at answering some of these questions may throw more light on the complexities leading to the neurocognitive complications experienced by some CM survivors. In addition to campaigns aimed at combating the global malarial burden, efforts should also be targeted at research with the aim of revealing vulnerability indices of this under reported public health burden.

Policy Prioritization

Directly stemming from the above point is policy prioritization by local institutions and government entities. With current global attention focused on the eradication of malaria in endemic regions, little efforts if any is being channeled towards addressing the complications, survivors of severe malaria experience. A big cause of this neglect of this affected cohort is a dearth of policy that targets this group of CM survivors. With current government policies facilitating the distribution of insecticide treated bed nets and the provision of effective anti-malaria therapies to combat falciparum malaria, there is need for diversification of existing policies to capture the complications associated with severe malaria. Raising awareness on the long lasting neurocognitive complications associated with CM should be prioritized by public health agencies. The few long term follow up studies of childhood survivors of CM have reported impairments in 3-31% of children [26-29], with a weighted mean of 10.9% [30]. Malaria is still considered the number one cause of morbidity and mortality in Sub Sahara Africa. While the current anti-malaria international and local campaigns are laudable, efforts to address the complications resulting from the disease should also be championed. CM has the potential of depriving a subset of survivors from attaining their full economic and cognitive potentials. Policies favoring long term follow up of survivors and reporting of cases should be instituted. International organizations and governmental agencies currently

involved in spearheading campaigns against malaria eradication should also channel resources towards focused research and the management of CM survivors suffering long term neurocognitive disabilities.

Primary Prevention

Primary prevention seeks to prevent the onset of specific diseases via risk reduction by altering behaviors or exposures that can lead to disease or by enhancing resistance to the effects of exposure to a disease agent [24]. Primary prevention efforts should be aimed at targeting susceptible CM survivors in order to prevent or reduce the incidence of neurocognitive complications resulting from the disease. Primary prevention is a step lower than primordial prevention, as it employs strategies that are closer to the target population. Primary prevention efforts are more hands on, and require a buy in from all stake holders, which should include the health care providers, as well as the patients. Primary prevention efforts may include:

Establish guidelines for follow up of CM survivors

Several published literature indicate that many CM survivors experience a full recovery 6 months after the initial insult. However, studies that do provide information about the CM survivors who do not make full neurological recovery hardly indicate established follow up patterns for this cohort of survivors. There should be structured follow up guidelines for all CM survivors. Physicians, nurses and other health care workers involved with the management of patients should be educated on the long term neurocognitive complications of CM. Well established follow up schedules should be instituted, so that survivors who are more at risk of the long term neurological complications can be identified on time, with appropriate management strategies employed. CM survivors should be followed beyond the 6 month mark, which is what is currently reported in some regions, while some other regions have no established follow up regimens. The few long term follow up studies of childhood survivors of CM have reported impairments in 3-31% of children [26-29]. Only one report has offered a comprehensive analysis of long term impairments associated with CM [31], but followed up a selected group of children (n=452) for 18 months only. Their findings suggest that a broad range of developmental deficits may persist after recovery. Follow up guidelines should include timed comprehensive neurocognitive evaluations, to identify at-risk CM survivors prone to developing long term neurological and developmental sequelae. Regular follow up of CM survivors may detect early those more prone to developing neurocognitive complications, and instituting appropriate follow-up measures to limit disability.

Physician/ Health worker education:

Physicians and health workers in poor resource countries with a huge burden of malaria and its consequences need to be educated on the debilitating consequences CM survivors may experience. This awareness is imperative, as a key step to improving outcomes in these survivors, is trained health personnel equipped with the tools and knowledge of identifying at risk patients, and referring them for proper follow up services.

Secondary and Tertiary Preventions

Secondary prevention includes procedures that detect and treat pathological changes and thereby control disease progression [24]. Screening procedures are often the first step, leading to early interventions that are more cost effective than intervening once symptoms appear [24]. Once the disease has developed and has been treated in its acute clinical phase, tertiary prevention seeks to soften the impact caused by the disease on the patient's function, longevity, and quality-of-life [24]. For reversible conditions, tertiary prevention will reduce the population prevalence, whereas for incurable conditions it may increase the prevalence if it prolongs survival [24]. However, if the condition is not reversible, tertiary prevention minimizes the effects of disability and disease by surveillance and maintenance activities aimed at preventing complications and deterioration [32]. Tertiary prevention focuses on rehabilitation to help people attain and retain an optimal level of functioning regardless of their disabling condition [32]. The objective is to return an affected individual to a useful place in society, maximize remaining capacity or both [32]. Secondary and tertiary preventions target both asymptomatic and symptomatic CM survivors to reduce the prevalence of neurodevelopmental complications, or mitigate the complications resulting from disability. These prevention strategies should target the families and caregivers who provide support for this patient population, as well as provide resources to manage neurodisabilities from CM sequelae. Such strategies should include:

Caregiver education

Caregiver education should also be prioritized as part of efforts towards combating this public health scourge. Caregivers involved in the care of CM survivors, more often than not, may be the first to observe any changes from baseline in the neurodevelopmental presentation of their wards. In Sub Sahara Africa where the levels of literacy do not match that of industrialized nations, tightly held cultural and religious beliefs may preclude the need to seek medical care in the early phases of observable neurocognitive impairments. Survivors of CM who suffer neurocognitive insults including epilepsy following a bout of CM, may be regarded as being possessed by witchcrafts or other evil spirits. These strongly held beliefs may lead to consultations with exorcists and other cultural norms, rather than with medical personnel. Unfortunately, the lag time between the onset of neurocognitive decline and the institution of any form of therapies may play a role in the clinical outcomes of CM survivors. Therefore, health education campaigns should also be targeted at caregivers on recognizing the neurocognitive complications of CM and seeking medical help in a timely manner, should they arise. All stakeholders, including local community leaders and especially caregivers should be educated on recognizing the symptoms associated with cognitive impairments resulting from CM, and advised to promptly seek medical expertise in such situations.

Family support and Advocacy

Families of CM survivors should be provided with the support that they need in order to easily access services to mitigate neurodisabilities resulting from the disease. This would involve the coordinated efforts of advocacy support groups, as well as local indigenous partners. Families need to be made

aware of accessible services and be motivated to access them. They need to know that it is the priority of global and local partners in ensuring that CM survivors achieve their societal potentials, in the most uncompromising way. This support is imperative, because other than educating these families of the neurodisabilities CM can cause, caregivers need to be informed of the services that they may employ for their wards, in order to increase their chances of living disability free lives.

Provision of early intervention services

Early intervention strategies should be implemented for CM survivors identified as "at-risk" of long term neurocognitive complications. Global and local partners should ascribe budgetary relevance to this strategy, as part of targeted efforts at reducing the neurocognitive complications of CM. Early intervention service providers ranging from speech and language pathologists, physical therapists, occupational therapists, psychologists, audiologists, vision therapists and developmental therapists should be employed in addressing the challenges that survivors of CM face, in order to give them an opportunity to integrate fully into society. At the core of this solution, is providing caregivers and families with the resources and advocacy that they need to limit disabilities, and improve the quality of life for CM survivors.

VI. Conclusion

Cerebral malaria is a medical emergency demanding urgent clinical assessment and treatment [5]. Mortality is high [5] and some surviving patients have an increased risk of neurological and cognitive deficits, behavioural difficulties and epilepsy, making cerebral malaria a leading cause of childhood neurodisability in the malaria transmission area [7]. Current international and local efforts targeted at eradicating malaria, rarely address the long term neurocognitive complications that survivors of CM experience, which may predispose this cohort to unsuccessfully achieving their full economic and societal potentials. This is a public health problem that should be approached in a holistic manner in order to meet this unmet need. A change in current global health strategies is warranted in tackling this problem.

Author Contributions

All authors reviewed and agreed upon the relevance of the topic to current public health initiatives. All authors contributed significantly to the manuscript and approve of it in its final format.

Disclosures

The authors have no potential conflicts of interest to disclose.

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