International Scholars Journals

African Journal of Malaria and Tropical Diseases ISSN 4123-0981 Vol. 9 (1), pp. 001-004, December, 2021. Available online at www.internationalscholarsjournals.com © International Scholars Journals

Mini Review

Possible Reasons Why Malaria-Endemic Regions are Less Susceptible to Covid-19

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Accepted 03, December, 2021

Malaria remains one of the most common parasitic infections in the tropical regions across the globe, specifically in sub-Saharan Africa while maintaining an epidemiological and holoendemic status quo [1]. This infection known to be caused by single-celled eukaryotes of the plasmodium genus proliferate through the bites of infected anopheles' mosquitoes and introducing the parasite led to its proliferation within the vertebrate tissues most especially, the liver organ before entering the bloodstream to poison the erythrocytes. Interestingly, this parasitic disease shares some similar symptoms with the lethal infectious coronavirus disease 2019 (COVID-19). Currently, one-third of the world is battling either Malaria or COVID-19 with both illnesses having high morbidity and mortality rate.

Keywords: Malaria, COVID -19, Malaria endemic regions, Africa, Parasitic diseases, Immunity, Renin-angiotensin-aldosterone system (RAAS).

INTRODUCTION

Curiously, the majority of African countries, particularly Malaria-endemic regions have accounted a low number of cases of COVID-19 deaths relative to other non-endemic areas and the rest of the continents [2]. However, out of scientific curiosity, a question arises; is there a correlation between tenacious management of Malaria victims with antiplasmodial drugs and increased immunity against other viral infections particular of Ebola and COVID-19?

Epidemiologically, evaluating the exact statistics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) incidents is quite difficult because of the various challenges that are altering the monitoring procedure all over the world ranging from clinical efficiency to setback in case notification [3]. Regardless, according to world health organization (WHO) quantification report as at 1 October 2021, the current number of confirmed cases and death is 234,763,219 and 4,801,067 respectively while having a continental distribution as follows: 59,096,742 confirmed cases and 1,225,381 death in Europe, 53,275,799 cases and 1,081,556 death in North America, 75,951,895 cases and 1,124,000 death in Asia, 37,814,021 cases and 1,155,297 death in South America, 230,858 cases and 2,944 death in Oceania, 8,393,183 cases and 211,874 death in Africa [4]. Generally, the majority of African countries exposure to various prophylaxis and antiplasmodial drugs used in the treatment of malaria recorded low cases of the deadly viral infection, while those African countries that are less affected by malaria such as South African, Algeria, and Egypt accounted for a significant increase in the number of COVID-19 cases and death. Nevertheless, malaria still poses a serious health concern around the world and menacing African regions where it has taken more lives. Considering the most recent World Malaria Report published on 30 November 2020, over 229 million cases and over 409,000 deaths have shaken the globe. Whereas 6 African countries summed up approximately half of all the malaria mortality – the Democratic Republic of the Congo 11%, United Republic of Tanzania 5%, Burkina

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Faso 4%, Niger 4%, Mozambique 4%, and Nigeria 23% with children under 5 years of age and pregnant women being the most endangered category affected by malaria [5]. Considering the emergence of COVID-19, one would expect that the Malaria-endemic regions in Africa will witness extremely severe cases of this disease owing to multifactorial reasons -- the two diseases share similar symptoms presentation which includes fever, general body weakness, difficulty in breathing, acute headache, and loss of appetite.

This can cause a misdiagnosis of Malaria for COVID-19 and vice versa, especially in communities where there are limited diagnostic resources and has to rely heavily on self-diagnosis using symptoms. In addition, the symptom of Malaria prevail 10-15 days after a sporozoite enters the host cells, multiple organ failure and respiratory distress are common in severe cases and this is similar to those seen in coronavirus patients [6]. Furthermore, before the outbreak of COVID-19, African regions have been ravaged with poor healthcare resources and limited trained workers to manage the overly increasing malaria cases. The emanation of COVID-19 led to a sudden shift of focus from Malaria, this may cause delayed access to Malaria treatment and a possible increase in mortality rate [7]. However, despite all this perturbation and forecast, the tropics and subtropics malaria-ridden regions have recorded the lowest cases of COVID-19 outbreak. As of 1st October, 2021, an estimated 234,763,219 cases and 4,801,067 deaths have been recorded respectively [4]. Out of this, only 8,391,451 and 211,853 infections and mortality have been confirmed in Africa representing about 4% of confirmed deaths worldwide [8]. A further observation into these figures showed that some African countries that recorded the lowest COVID-19 cases and deaths such as Nigeria (2,721 deaths), the Democratic Republic of Congo (1,084 deaths), Uganda (3,156 deaths) Mozambique (1,917 deaths), and Niger (201 deaths) are responsible for more than half of global Malaria outbreaks and mortality [5]. Meanwhile, the five African countries with the highest number of COVID-19 cases and deaths; South Africa (87,626 deaths), Tunisia (24,890 deaths), Egypt (17,331 deaths), Morocco (14,276 deaths), and Algeria (5,812 deaths) have fewer cases of Malaria majorly caused by cross-border migration while countries like Tunisia, Morocco and Algeria have been certified as malaria-free by World Health Organization [8]. These figures all pointed to a key question, is there an inverse relationship in the pathophysiology of malaria and COVID-19? In this article, we look at factors that may be attributable to the low prevalence of COVID-19 cases in these Malaria-endemic regions.

The possible immunomodulatory effect of chloroquine (CQ) and hydroxychloroquine (HCQ) in the management of COVID-19 may be a factor to be considered. CQ and HCQ have been used tremendously in management of Malaria before the outbreak of resistance in the Malaria-endemic region. Due to its similar pathological symptoms with SARS-CoV-2 infection, several studies were carried out during the initial SARS outbreak to confirm its antiviral activity [9, 10, 11]. In a study by Vincent et.al., the prophylactic and therapeutic activity of CQ was evaluated in the management of SARS-CoV-2. It was observed that in vitro introduction of CQ 24 hours before viral infection and immediately after infection significantly reduced the viral count by 100% on a dose-dependent of 0.1 - 10μM [10]. Another study showed that CQ may interfere with the activation of T-cells due to its high pH, thereby preventing antigen presentation and cytokine release [12]. Since the outbreak of COVID-19 at the end of 2019, numerous trials were performed to also test the in vitro and in vivo efficacy of CQ and HCQ. The in vitro studies showed that it can potentially inhibit the endosomal acidification and glycosylation of angiotensin converting enzymes 2 (ACE2) receptors, thus, preventing continued viral invasion of the host cells [13]. The key point to take note in CQ and HCQ usage in coronavirus management include but are not limited to; the stages/severity of the disease, efficacy, and safety. It should however be noted that chloroquine and its derivatives have been withdrawn due to itscardiotoxic effect and replaced with artemisinin and its derivatives which have no known effect on COVID-19 or is yet to be investigated.

LITERATURE REVIEW

Another factor to be considered is the role of immunity as a result of constant malaria infection. Over the years, malaria populated countries have constantly protected themselves from Plasmodium species which consequently produce a significant combination of T helper type 1 (Th1) and T helper type 2 (Th2) cells which promotes the cell-mediated immune responses that are required by the human cells to fight against intracellular viral infections and other pathogens [6]. The pathogenesis of SARS-CoV-2 victim beings as a mild symptom such as fever, difficulty in breathing, cough, and fatigue to utmost respiratory failure. As replication occurs, the virus moves across the airways while binding to epithelial cells of the respiratory tract. This expeditious replication of SARS-CoV-2 in the lungs evokes an excessive immune response (Cytokine storm) that causes the death of the patients. Thus, interferons which are well-recognized cytokines for their antiviral effects inhibit the viral multiplication which reduces the severity of the disease and also improves recovery [14]. A recent study conducted on 375 patients who were subjected to diagnosis COVID-19 using severe acute respiratory syndrome coronavirus -2 nucleic acid, toxoplasma immunoglobulin M (IgM), and immunoglobulin G (IgG) antibody detection, stool examination, and quantitative interferon-gamma measurement show that there is a correlation between the lower number and severity of COVID-19 cases and areas that have been infected with malaria due to function of interferons [15].

In concluding this write up, one will not fail to also look into the role of angiotensin II receptor in Plasmodium falciparum and SARS-CoV-2. The Renin-Angiotensin-Aldosterone System (RAAS) is a complex cascade of coordinated hormonal systems involved in the regulation of blood pressure, body fluids, electrolyte levels, vascular tone, cardiovascular and renal health, thus, it is a rate-determining step in systemic blood pressure balance [16]. The system consists of angiotensinogen, angiotensin-converting enzyme, and its homolog, angiotensin-converting enzyme 2 (ACE2) and angiotensin II (Ang II) type 1 and type 2 (AT1, AT2).

In the past, greater attention was given to the RAAS system on its role in systemic blood regulation and

cardiovascular functionality. However, there is an emerging interest to understand its etiological role in the lung, especially in COVID-19 pathology. Studies have explicated that RAAS plays a critical role in the pathogenesis of several lung diseases through one of its homologs ACE2, which is overly expressed in the entire alveolar cells of the lungs, endothelial cells of organs including the heart, kidneys, blood vessels, and gastrointestinal tracts [17, 18]. In addition to the vasoprotective activity, the ACE2 enzyme serves as the receptor site for SARS-COV-2 entry into the body system thus [19], serving as a double edge. A depletion in ACE2 enzyme can lead to the upregulation of the ACE1 substrate, Ang II, in the pulmonary cells, which may contribute to increased neutrophils accumulation and vascular porosity thereby causing acute respiratory distress syndrome (ARDS) and/or ventilator-induced lung injury (VILI) [20].

DISCUSSION

An early report has linked Ang II to the impairment of the erythrocytic cycle of Plasmodium gallinaceum, an avian malaria parasite. Ang II is said to reduce the uptake of sporozoites, a motile-spore-like parasite cell that marks the entry of the parasite into the host cell. This will disrupt the parasite membrane and life cycle stages thereby reducing the in vitro parasite growth. Subsequent studies afterward have validated the antiplasmodial effect of Ang II in malaria infection. The protective effect of Ang II on malaria has been attributed to two genetic polymorphisms on the ACE1 and ACE2 enzymes. This is characterized by the deletion/insertion (D/I) polymorphism on intron 16 of ACE1. This D allele of ACE1 I/D polymorphism ultimately determines the concentration of circulating and tissue-bound ACE1 enzyme, thereby causing an increase in Ang II concentration and a reduced expression of ACE2. Also, the ACE2 polymorphism (C1173T) reduces the receptor site of ACE2 in the presence of the T allele while increasing Ang II. The downregulation of the ACE2 expression by the two genetic variants may confer a protective effect against COVID-19 since an abundance of ACE2 receptors is needed for the viral entry into the host cells [21].

CONCLUSION

In contrast to the antiplasmodial activity of Ang II, the high level of Ang II generated by the genetic polymorphisms is also associated with an increase in systemic blood pressure leading to arterial hypertension. Studies have shown that people of African and South Asian descent have a high occurrence of hypertension than their Hispanic counterparts [29, 30]. Therefore, the role of Ang II, ACE1 and ACE2 polymorphisms on hypertension and malaria could inform further on the low cases of COVID-19 outbreak recorded in malaria-endemic regions in Africa. However, the current data is not enough to validate this hypothesis. Further genetic studies are required to unravel this interconnectedness.

REFERENCE

1. Chinwe S. Alaribe and Akolade R. Oladipupo, (2021) Suppressive, curative, and prophylactic potentials of an antimalarial polyherbal mixture and its individual componets in plasmodium berghei-infected mice. J of ephacology. 15: 114105.
2. Lipsitch M, Swedlow D, Finelli L, (2020) Defining the epidemiology of COVID-19 studies needed. N Engl J Med. 382: 1194-96.
3. hallenger JD, Gonçalves BP, Bradley J, (2019) How delayed and non adherent treatment contribute to onward transmission of malaria: a modelling study. Bmj Glob Health. 4: 1856.
4. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R, (2003) Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 3: 722–7.
5. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et. al. (2005) Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2:69.
6. Dyall J, Gross R, Kindrachuk J, Johnson RF, Olinger GG, Hensley LE, et al. (2017) Middle east respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. Drugs. 77: 1935–66.
7. Accapezzato D, Visco V, Francavilla V, Molette C, Donato T, Paroli M, et al. (2005). Chloroquine enhances human CD8 + T cell responses against soluble antigens in vivo. J Exp Med. 202: 817–28.
8. Adachi K, Ichinose T, Takizawa N, Watanabe K, Kitazato K, Kobayashi N, et al. (2007). Inhibition of betanodavirus infection by inhibitors of endosomal acidification. Arch Virol. 152: 2217-24
9. Lokken K, Stull-Lane A, Poels K, Tsolis R, (2018). Malaria parasite-mediated alteration of macrophage function and increased iron availability predispose to disseminated nontyphoidal Salmonella infection. Infect Immun. 86:301-18.
10. Ena F, Mohamed N, Nahed E, Howayada S, Nahla E, et al. (2021). Role of interferon gamma in SARS-CoV-2- positive patients with parasitic infection.
11. Santos R, Sampaio W, Alzamora A, Motta-Santos D, Alenina N,Bader M, et al. (2018) The ACE2/Angiotensin-(1-7)/MAS1 axis of the Renin-angiotensin system: Focus on angiotensin system- (1-7). Physiol Rev. 98; 505-53.
12. Metzger R, Franke FE, Bohle RM, Alhenc-Gelas F, Danilov SM. (2011) Heterogeneous distribution of angiotensin I-converting enzyme (CD143) in the human and rat vascular systems: vessel, organ and species specificity. Microvasc Res. 81:206-15.
13. Wiener RS, Cao YX, Hinds A, Ramirez MI, Williams M, (2007) Angiotensin converting enzyme 2 is primarily epithelial and is developmentally regulated in the mouse lung. J Cell Biochem. 101:1278–91.
14. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 579: 270–3.
15. Wosten-van Asperen RM, Lutter, Specht PA, Moll GN, Van Woensel JB, van der Loos CM, et al. (2009) Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. J Pathol. 225: 618–27.
16. Zhang R, Pan Y, Fanelli V, Wu S, Luo AA, Islam D, et al. 2015. Mechanical stress and the induction of lung fibrosis via the midkine signaling pathway. Am J Respir Crit Care Med. 192: 315-23.
17. Maciel C, de Oliveira Junior VX, Fázio MA, Nacif-Pimenta R, Miranda A, Pimenta PF, et al. (2008) Anti-plasmodium activity of angiotensin II and related synthetic peptides. plos one. 3:3296.
18. Dhangadamajhi G, Mohapatra BN, Kar SK, and Ranjit M, (2010) Gene polymorphisms in angiotensin I

converting enzyme (ACE I/D) and angiotensin II converting enzyme (ACE2 C–>T) protect against cerebral malaria in Indian adults. Infect Genet Evol. 10; 337-41.
19. Saab YB, Gard PR and Overall ADJ, (2008) The distribution of the ACE II genotype: a novel finding. IGentical rech: 89: 259-67.
20. Silva LS, Silva-Filho JL, Caruso-Neves C, Pinheiro AAS, (2006) New concepts in malaria pathogenesis: the role of the renin-angiotensin system. Front Cell Infect Microbiol. 5: 103.

21. Gallego-Delgado J, Baravian C, Edagha I, Ty MC, Ruiz-Ortega M, Xu W, et al. (2015). Angiotensin II moderately decreases plasmodium infection and experimental cerebral malaria in mice. plos one. 10: e0138191.