EBioMedicine 40 (2019) 29–30

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Malaria, immunity and mental disorders: A plausible relationship?

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Malaria is the most common and dangerous parasitic disease, being responsible every year for nearly half a million deaths, and an estimated 219 million clinical cases, globally [1]. The devastating short-term effects that an acute malarial infection can have on any given individual have been historically well characterized, and there are also abundant data on the subacute and chronic sequelae derived from severe malarial episodes, which are understandable in the context of the sudden and profound insult that such an aggressive infection may have in the central nervous system and other key organs [2]. However, much scarcer information exists regarding other more subtle or prolonged deleterious effects of malarial infection and disease on well-being, beyond its acute phase, particularly in regard to common mental disorders (CMD) and neuro-psychiatric health.

In this recent article of *EBioMedicine* [3] Rachel Jenkins and colleagues explore the three-way relationship between malaria, mental disorders and immunity in a representative sample of adults randomly selected from the Kombewa Health and Demographic Surveillance system running in Kisumu, a highly malaria-endemic county located in Western Kenya [4]. To do so, authors applied a myriad of validated structured questionnaires designed to assess mental health and collected blood samples of the studied individuals to confirm malaria parasitaemia and test for common markers of immune function (CD4/CD3 ratio, CD4 counts, IL-1β, IL-6, IL-8, and IL-10, TNF-β, TNF-α). Although no associations were found between malaria and psychotic symptoms, their results confirm a statistically significant association between malaria and CMD (OR 1.7, $p = 0.014$), a heterogeneous group of distress states which typically manifest with anxiety, depressive and unexplained somatic symptoms. Their results also hint at the potential mediating role that the cytokine TNF-α may play in this association.

The association between mental health and non-communicable diseases has been widely studied [5], with evidence of inflammation significantly contributing to the pathogenesis of major psychiatric disorders (including depression [6] or schizophrenia [7], among others), and the inflammasome -a multiprotein oligomer responsible for the activation of inflammatory responses- proposed as a central mediator [8]. Conversely, the association between mental health and communicable diseases has been historically neglected and thus largely unexplored, perhaps with the exception of some chronic infections such as HIV [9]. Findings reported in this study are of public health relevance, as they propose for the first time a solid association between malaria infection and CMD, while venturing a hypothetical cytokine pathway for such an association. The association between TNF-α and depression has been previously described and may be explained by its influence in the hypothalamo-pituitary-adrenocortical axis, neuronal serotonin transporters and in the indoleamine 2,3-dioxygenase pathway [10]. Additionally, TNF-α may play a dual role in both the pathogenesis of and protection against malaria, although the actual implication of this cytokine in the course of disease has not been fully understood [11]. In fact, anti-TNF therapies have been tested as adjuvant therapies in severe malaria but have shown no effect in its prognosis [12].

In spite of its large sample size ($n = 1158$) and high consent rates (97.2% for the interviews, 91.4% for the blood samples), factors for which authors are to be praised, this study has important limitations that need to be highlighted. First, it is possible that some of the conclusions derive from chance findings, due to the multiple comparisons conducted. Second, concomitant conditions such as anemia or HIV, both highly prevalent in the area, could have acted as confounders of the association, and would need to be determined in future studies. Third, a more comprehensive approach to understanding the immune response is needed, including both the cellular and humoral components, and with a longitudinal design. Finally, malaria infections may lead to a wide spectrum of clinical symptomatology, ranging from pure asymptomatic carriage of parasites, to life-threatening disease [13]. Thus, one should avoid talking of malaria as a single clinical entity. It is probable that adults in this highly-endemic malarious setting have acquired a significant amount of immunity and tolerance to the infection, allowing them to carry malaria parasites without clinical expression, something that undermines some of the author's hypotheses regarding the causal relationship. Understanding the role of such asymptomatic infections, as opposed to those with overt clinical symptoms (and its different clinical phenotypes), and how they may differentially expose the individual to the risk of developing mental illness is necessary and would require more precisely designed studies.

This study raises many questions and opens highly relevant gateways that need to be further substantiated with additional research. The first critical issue is that for these findings to unequivocally support the author's conclusions, they need to be replicated in other malaria-

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.11.064.
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https://doi.org/10.1016/j.ebiom.2019.01.008

endemic areas, possibly with distinct transmission and epidemiological conditions (*i.e.* involving other malaria species and other intensity of transmission scenarios). A wider use of the mental health screening tools used here should therefore be encouraged, not only for the purposes of replication, but also to more widely ascertain mental health problems at the population level of low-income settings, an area unfortunately so far neglected [14]. Second, due to its cross-sectional nature, and although authors venture some hypotheses on how malaria could lead to depression or *vice versa,* inference on directional causality is impossible. To further understand causal relations, prospective epidemiological studies following cohorts of population at risk of acquiring malaria should be established, and repeatedly evaluated to record both their malaria infection status and the incidence of newly acquired mental health problems. Additionally, by selectively inducing some of the conditions under consideration, or activating some of the inflammatory pathways proposed, research with animal models could experimentally confirm some of these findings. Other areas warranting further research include the impact of malaria elimination campaigns on the mental health of both adults and children in endemic areas; and possible target areas for preventive or therapeutic interventions to avoid incident mental health problems in malaria endemic areas.

Authors' contribution

RV wrote the first draft of the manuscript, together with QB. RV and QB critically revised the manuscript. Both authors approved the final manuscript.

Conflict of interests

The authors declare no conflicts of interest.

Acknowledgements

ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya (http://cerca.cat/en/suma/). CISM is supported by the Government of Mozambique and the Spanish Agency for International Development (AECID).

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