Role of malaria exposure on renin-angiotensin aldosterone system polymorphisms and hypertension

Quite contrary to malaria, the burden of hypertension is rapidly increasing in the tropical world and their inverse disease burden trend observed in India suggests a potential inter-relationship. This inverse trend is scientifically explainable with existing evidence. Many investigators have suggested that antecedent malaria exposure predisposes individuals to hypertension risk. One such evolutionary adaptation hypothesized and studied, although scarcely, is the occurrence of severe malaria protective polymorphisms in the human Renin Angiotensin Aldosterone System (RAAS) that involves the two functionally pivotal enzymes, ACE and ACE2, the actions of which are crucial for maintaining the blood pressure homeostasis. We tested this hypothesis by exploring the association between malaria and hypertension risk via RAAS mutations using Mendelian randomization on the basis of the sickle-cell trait (HbAS).

A literature review outlining the basis of the malaria-hypertension hypothesis and Mendelian randomization was conducted. Two independent association studies were performed, using HbAS as a marker for presence of severe malaria (SM) pressure and using SM cases using a case-control design. In vitro Plasmodium falciparum assay was also conducted to explore the anti-Plasmodium activity of ang II.

The susceptibility (HbAA) to SM was found to be 94% in the studied states of India. With the use of HbAS as a surrogate marker, DD genotype of ACE was found to be statistically significantly and positively associated (p value <0.05) with the individuals with SM pressure and survival advantage (SMPSA). In case-control study, RAAS polymorphisms (ID genotype of ACE) was found to be in statistically significant negative association with SM (OR 0.45; 95% CI 0.24-0.86)). Ang II was found to have an inhibitory role at 10-6 M (in Pf invasion) and at 10-9 M and 10-7 M as IC50 on ring and schizont growth of Pf, respectively.

Malaria exposure has a role on RAAS polymorphism specifically on DD and ID genotype of ACE. Ang II has inhibitory effects on Plasmodium falciparum with unknown mechanism of action. Hence, it can be concluded that such polymorphisms in RAAS may protect from SM and therefore get positively selected under SM pressure but also aggravate the risk of hypertension. Future work should focus on confirming the findings using alternative study designs such as a population-based study by avoiding suggested limitations in which components of RAAS polymorphisms, levels and activities of ACE and ACE2 including blood pressure can be examined and selection tests must be applied to confirm whether these polymorphisms are under malaria pressure.