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Commentary

Liver injury in uncomplicated malaria: an overlooked phenomenon

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Liver dysfunction is recognised as a common feature of severe malaria, however, the pathophysiology by which liver injury occurs is unclear. Compared to other aspects of clinical malaria, little focus has been placed on liver function abnormalities (LFAs) in uncomplicated infections, most likely precipitated by the lack of clinically symptomatic liver dysfunction [1]. At present, monitoring of malaria-associated liver injury is heterogeneous, with measurement of biochemical liver function tests (LFTs) being the primary determinate for liver injury [1]. In these studies, elevated enzyme levels are most often associated with antimalarial drug-induced liver toxicity, with little consideration given to the potential contribution of parasite-induced liver injury. The temporal pattern of liver abnormalities over the course of an infection is also unclear [1–3].

The study reported by Reuling et al. in *EBioMedicine* presents a novel approach to characterise liver injury in uncomplicated falciparum malaria [3]. This was achieved by investigating longitudinal associations between routine clinical LFTs, parasite density, and haematological and immunological parameters in patients with naturally acquired falciparum malaria ($n = 217$) and Controlled Human Malaria Infection (CHMI) volunteers ($n = 187$). A strength of the study was the innovative inclusion of longitudinal CHMI data, enabling the characterisation of liver injury specific to uncomplicated falciparum infection whilst controlling for influencing variables. Comparison of this data to that from patients with naturally acquired infections allowed the authors to define the contributions of parasite density, route of infection, and antimalarial drug administration on LFA prevalence and severity in uncomplicated disease. Consistent with previous longitudinal studies of naturally acquired malaria [1], LFAs were characterised by elevations in bilirubin, alanine aminotransferase (ALT) and aspartate transaminase (AST) concentrations, all which peaked shortly after the start of antimalarial therapy and resolved within three to six weeks. These findings also correlate with clinical studies reporting safety data for artemisinin combination therapies (ACT) where, despite a lack of clinical symptoms, 20 to 60% of participants had elevated LFTs at time of recruitment which resolved within 1 to 3 weeks after drug administration [2,4,5]. However, in contrast to previous publications, the authors extended their evaluation of liver injury by additionally investigating the dynamics of inflammatory cytokine responses and oxidative stress markers as predictors for LFAs. This comprehensive approach resulted in positive associations being identified between parasite burden ($r = 0.33$, $p < 0.001$) and inflammatory parameters, including cumulative inflammatory markers ($r = 0.65$, $p = 0.008$) and oxidative stress markers ($r = -0.63$, $p = 0.001$).

The significance of the described association between LFAs and malaria-induced injury bodes well for clinical investigations for drug development. Whilst a clear association between antimalarial drug administration and elevated liver enzymes is recognised, particularly with ACT regimens, the mechanics behind the described liver-injury is not yet elucidated. As such, it is crucial that we have a greater understanding of the underlying pathology of malaria parasites on the liver during uncomplicated infections, to ensure that the clinical development pathway of efficacious antimalarial drugs is not compromised. At present, the assumption is that reported toxicity associated with ACT use is due to accumulation of heme and reactive oxidants in the liver [1,2,6,7]. Despite Reuling et al. reporting that type of antimalarial therapy did not influence the prevalence of LFAs in the CHMI model, cases of naturally acquired malaria show a positive correlation between increased reporting of LFAs and ACT use [1,2,5]. However, it has been proposed that the increased prevalence of LFAs after ACT may be a consequence of the rapid parasiticidal activity of the artemisinin compound, leading to increased clearance of parasites by the reticuloendothelial system and increased release of relative oxygen species [2]. This is consistent with the reported patterns of bilirubin concentrations associated with haemolysis, where elevations occurred within the first days after treatment, did not amplify after administration of consecutive drug doses, and rapidly resolved after the clearance of parasitaemia [1,3]. Monitoring of bilirubin concentrations during drug therapy may therefore prove to be a useful parameter for differentiating malaria-associated changes from drug-induced toxicity, where a more delayed liver injury meeting Hy's Law would be expected [3].

This study highlights the need to have a better understanding of influencing variables of LFAs during uncomplicated malaria infection, given the significant impact these may have on patient care, treatment selection, and the potential success of candidate therapies through the drug development pipeline. In comparison to previous studies, a strength of the research presented by Reuling et al. was their ability to investigate the influence of low parasite densities on liver pathology using the CHMI model. This provided a unique ability to define the dynamics and basis of liver injury, given that confounding

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effects could be mitigated in the controlled research environment. Furthermore, intensive longitudinal sampling, complimented by a comprehensive assessment of potentially influencing variables, enabled the authors to conclude that LFAs are a common feature of uncomplicated malaria infection, with the pathophysiological basis attributed to a pro-inflammatory response associated with oxidative stress resulting in transient liver injury. Ultimately, the authors provide evidence that suggest clinical studies assessing antimalarial safety should take into account the temporal relationship between elevated LFTs, malaria infection, parasite density and antimalarial therapy. This is particularly relevant in the assessment of novel antimalarial compounds in the drug-development pipeline, where liver safety outcomes play a significant role in the future success of the drug for future clinical use. Additional, well-controlled temporal studies in uncomplicated disease are required to consolidate the reported findings, and further investigate the precise parasite mechanics that contribute to liver injuring during uncomplicated malaria infections.

Declaration

The author declares no conflict of interest.

References

[1] Woodford J, Shanks GD, Griffin P, Chalon S, McCarthy JS. The dynamics of liver function test abnormalities after malaria infection: a retrospective observational study. Am J Trop Med Hyg 2018;98(4):1113–9.
[2] Silva-Pinto A, Ruas R, Almeida F, Duro R, Silva A, Abreu C, et al. Artemether-lumefantrine and liver enzyme abnormalities in non-severe plasmodium falciparum malaria in returned travellers: a retrospective comparative study with quinine-doxycycline in a Portuguese centre. Malar J 2017;16(1):43.
[3] Reuling IJ, de Jong GM, Yap XZ, Asghar M, Walk J, van de Schans LA, et al. Liver injury in uncomplicated malaria is an overlooked phenomenon: an observational study. EBioMedicine 2018. https://doi.org/10.1016/j.ebiom.2018.09.018. [Epub ahead of print].
[4] Laman M, Moore BR, Benjamin JM, Yadi G, Bona C, Warrel J, et al. Artemisinin-naphthoquine versus artemether-lumefantrine for uncomplicated malaria in Papua New Guinean children: an open-label randomized trial. PLoS Med 2014;11(12):e1001773.
[5] Tangpukdee N, Thanachartwet V, Krudsood S, Luplertlop N, Pornpininworakij K, Chalermrut K, et al. Minor liver profile dysfunctions in plasmodium vivax, P. malariae and P. ovale patients and normalization after treatment. Korean J Parasitol 2006;44(4):295–302.
[6] Dey S, Mazumder S, Siddiqui AA, Iqbal MS, Banerjee C, Sarkar S, et al. Association of heme oxygenase 1 with the restoration of liver function after damage in murine malaria by Plasmodium yoelii. Infect Immun 2014;82(8):3113–26.
[7] Dey S, Bindu S, Goyal M, Pal C, Alam A, Iqbal MS, et al. Impact of intravascular hemolysis in malaria on liver dysfunction: involvement of hepatic free heme overload, NF-kappaB activation, and neutrophil infiltration. J Biol Chem 2012;287(32):26630–46.