EFFECT OF AGE AND MALARIA INFECTION ON EPSTEIN - BARR VIRAL REACTIVATION IN CHILDREN

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Burkitt lymphoma (BL) remains one of the most common pediatric cancers in sub-Saharan Africa. The two critical co-factors in the etiology of BL are EBV infection and repeated *Plasmodium falciparum* (Pf) malaria infections. Elevated levels of antibodies to EBV lytic antigens in BL patients suggest that lytic reactivation of EBV precedes tumorigenesis. Malaria induced reactivation of EBV has been reported in earlier studies based on presence of EBV DNA in plasma of children with acute malaria and subsequent clearance following treatment [1] but other studies argued with improved malaria control, effects of malaria on EBV viral load in whole blood was no longer evident [2]. In evaluating past studies, it was clear that no single study evaluated EBV in both mucosal (e.g. saliva) and systemic (cell-associated in PBMC and cell-free in plasma) compartments. In addition, because immunity to malaria disease occurs following repeated infections, age also needs to be considered. To address this question, we enrolled children ages 2-10 years from a malaria-endemic high-risk region of Western Kenya with acute uncomplicated malaria [blood smear (BS) positive for Pf] and as a comparison age-and sex-matched control children without evidence of fever or malaria (RDT-, BS-). We collected saliva and blood samples (separated into plasma and PBMC) and measured EBV viral load. We first tested all samples for Pf infection by Q-PCR. Consistent with clinical results, all children with acute malaria had confirmed high levels of Pf parasitemia. Interestingly, 57% of the children that were RDT-BS- for Pf were found to have detectable Pf DNA by Q-PCR indicative of a submicroscopic infection. Levels of Pf were 5 logs less than in the acute malaria group. As a consequence, we evaluated this group separately as an "asymptomatic Pf infection" group. When we evaluated EBV load in the saliva, we found that there was no difference in the frequency of EBV shedders (59% acute, 58% asymptomatic, and 49% healthy controls), mean viral load in those individuals shedding or age effect on viral load. In contrast, when we evaluated EBV load in PBMC, the highest EBV load was found in children <5 years with acute malaria compared to all other groups. EBV DNA was also frequently detected in the plasma of all 3 groups (35% acute, 32% asymptomatic, 30% healthy controls) with the children <5 years in the asymptomatic group having the highest viral load. Our results suggest that malaria does not affect control of EBV in the mucosal compartment. Rather, the effects of acute malaria on the viral load set-point in PBMC was age dependent and occurs primarily in younger children where immunological control of malaria has not yet developed. On the other hand, asymptomatic parasitemia increased the cell-free viral load in children under 5 years old. The paradox in these results is that the incidence of BL is highest in children between the ages of 6 and 8 years suggesting that repeated malaria infections set the stage for BL but an acute malaria infection is likely not the final precipitating event.

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