PLASMODIUM FALCIPARUM MALARIA TRANSMISSION EFFECTS ON NATURAL KILLER CELL FUNCTION IN THE ETIOLOGY OF ENDEMIC BURKITT LYMPHOMA IN CHILDREN FROM WESTERN KENYA

ABSTRACT

The exact etiological mechanism underlying endemic Burkitt lymphoma (eBL) remains unknown. Past studies show T and B cells are immuno-deregulated in children from malaria holoendemic regions. However, no study has examined the effect of *P. falciparum* transmissions on Natural Killer (NK) cell, which shape T and B immune responses. NK cells are critical in immunosurveillance, elimination of cancerous cells and controlling EBV viremia. This is by production of anti-viral cytokines like Interferon gamma (IFN-γ), cytotoxic degranulation molecules (CD107a and Granzyme B, GrB), and expression of pro-apoptotic markers e.g. programmed death-1, (PD-1). This study investigated how malaria impacts on NK cell function in eBL etiology. Thus 42 children aged 3½ years from areas with diverse malaria transmission and eBL incidence, (Kisumu n=16, malaria holoendemic region of high eBL incidence), Nandi, n=16, malaria hypoendemic region, low EBL incidence) and eBL n=10, (cancer children at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) were enrolled. To investigate differences in Epstein Barr Virus (EBV) antigen specific NK cell frequencies, peripheral blood mononuclear cells were stimulated with Epstein Barr Nuclear Antigen 1 (EBNA1). The frequencies of EBNA1 and MSP1 specific cells were evaluated by flow cytometry. Merozoite surface protein 1 (MSP1) was a control antigen for malaria exposure. To correlate viremia with NK cell activity, EBV burden was determined by qPCR. Results show that Kisumu children had high parasitemia ($p=0.0180$) and viral load ($p=0.0006$) compared to Nandi. Moreover, Kisumu children presented with low EBNA1 specific IFN-γ NK response ($p=0.0262$) but high MSP-1-specific IFN-γ NK cell response ($p=0.0174$), EBNA1 PD-1 ($p=0.0130$) and CD107a ($p=0.0293$) specific responses. However, there was no significant difference in the frequencies of GrB specific cells among the three study groups in response to either EBNA1 ($p=0.9150$) or MSP-1 stimulation ($p=0.8911$). It was observed that high viral loads led to low NK EBNA1 specific GrB response in Nandi children ($p=0.0490$, $r^2=0.3390$) while there was no association between EBV viral load and EBNA1 specific IFN-γ and CD107a NK cell across the study groups ($p > 0.5$). High viral burden was weakly associated with high EBNA1 specific PD-1 expression ($p=0.05$, $r^2=0.02$) in Kisumu children. This shows that *P. falciparum* transmission affects EBV viral burden and NK cell function. Thus a relationship exists between holoendemic malaria and NK cell function in the presence of high EBV burden. Therefore, malaria perturbation of EBV specific NK, T and B cells could have synergistic effect in eBL etiology.

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