Effects of induced arginase enzyme on arginine availability for nitric oxide production in children with severe malaria.

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INTRODUCTION:

Malaria is still one of the major leading causes of morbidity and mortality in developing countries regardless of the use of effective antimalarial drugs. Immunological response as a result of malaria acquisition contributes much to pathogenesis of malaria. Recent studies have indicated that malaria infection is associated with low plasma arginine levels with subsequent low NO production and endothelial dysfunction. NO is important for normal endothelial function which is impaired during malaria infection. The causes of hypoargininemia with low NO production in malaria are not well understood. Arginase, an enzyme responsible for metabolism of arginine to ornithine, competes with NOS for its substrate arginine. Ornithine is a precursor for polyamine biosynthesis and other anabolic pathways. The contribution of arginase to the development of low plasma arginine levels has not been studied in children. OBJECTIVES:

The aim of this study was to assess the role of plasma Arginase in the observe dhypo argininemia in children with malaria.

METHODS:

Across-section prospective, observational study was done in Dar es Salaam, Tanzania. Children aged 6 months to 9 years were recruited from Mwananyamala, Amana, and Mikocheni hospitals after obtaining informed consent. Participants were grouped into severe malaria (SM), uncomplicated malaria (UM), and healthy controls (HC) using WHO criteria. Blood samples were taken from participants and analyzed for plasma arginine, plasma arginase activity, and cell-free hemoglobin. PBMCs were separated from anticoagulated blood for determination of mRNA for arginase1, arginase2, and NOS2.

RESULTS:

Eighty (80) SM, 80UM, and48HCwere recruited. Plasma arginine levels were significantly lower in malaria groups compared to healthy controls ($p<0.0001$). The mean values were 58.8±3.9μmol/L in SM, 54.8±3.3μmol/L in UM,and94.58±4.2 μmol/L in HC. Plasma arginase activity was higher in children with malaria, but it was not statistically significantly higher ($p=0.75$). The mean values were 0.273±0.034μmol/ml/hour in SM, 0.252±0.030μmol/ml/hour in UM, and 0.200±0.0566μmol/ml/hour in HC. There was no correlation between plasma arginase activity and plasma arginine levels in SM group (Pearson r=-0.001).Cell free Hb levels were higher in the SM and UM groups ($p=0.02$), but it did not correlate with plasma arginase activity($r=-0.09$). There was a marked increase in arginase 1mRNAin PBMCs7 from SM and UM compared to HC group. The median values were9.31and4.51fold increase in SM and UM groups, respectively ($p=0.008$ and 0.02, respectively). mRNA values for arginase2 were slightly higher in the HC group, but this was not significantly higher than that of the other groups($p=0.89$). NOS2 mRNA was lower in PBMC of malaria patients (SMand UM) compared to HC($p=0.0001$foreachcomparison).

DISCUSSION, CONCLUSION, AND RECOMMENDATIONS:

Plasma arginine levels were low in children with malaria compared to previously reported findings. Hypoargininemia and plasma arginase activity do not significantly correlate with one another. Elevated arginaseIm RNA levels in PBMC patients with malaria, suggests that arginase 1 could also be induced in other mononuclear phagocytes, including fixed macrophages. These arginase1-bearing cells may in part be responsible for hypoargininemia. Induction of mononuclear phagocyte arginase1anddiminished NOS2mRNA and NO production bymononuclear phagocytes conforms to the phenotype of "alternative macrophage activation." Hypoargininemia and alternative macrophage activation correlate with clinical malaria and may be markers of malaria disease severity. Assessment of arginase activity in PBMCs (and purified mononuclear phagocytes) during malaria infection is warranted to fully establish therole of alternative lyactived monocytes-macrophagesin the hypoarginaemia observed during the malaria infection.