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Oral 1821- 2 - Decreased systemic tetrahydrobiopterin bioavailability and increased oxidized biopterins in children with cerebral malaria

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Background: Falciparum malaria causes over 600,000deaths worldwide each year. Despite advances in anti-parasitic drug therapies, 10–20% of children treated for severe malaria die. We have previously documented that NO protects against development of severe malaria, and that NO levels are low in malaria patients. Tetrahydrobiopterin (BH4) is an enzyme co-factor required for NO synthase that converts L-arginine to NO. Low or absent BH4 results in superoxide (instead of NO) pro-duction by NOS, with a consequent increase in “oxidative stress.”

Hypothesis: Systemic levels of BH4are decreased in children with cerebral malaria, contributing to low NO bioavailability and increased severity of malaria.

Objective: Determine systemic levels of BH4 in children with malaria.

Methods: In an observational study in Tanzania, we measured urine levels of biopterin in its various redox states [fully reduced biopterin (BH4), and the oxidized metabolites dihydrobiopterin (BH2) and biopterin (B0)] in children with un-complicated malaria (UM, n=55), cerebral malaria

(CM, n=46),as well as control children with non-malaria central nervous system conditions (NMC, n=48) and healthy control children(HC, n=111). Urine was collected into dithioerythritol and diethylene triamine penta-acetic acid (DETAPAC). Pterins were measured by high-performance liquid chromatography using sequential electrochemical and fluorescence detection.

Results: Urine BH4concentrations [μmol/mmol creatinine; median (IQR)] in CM were significantly lower compared to those in children in each of the other three groups. Oxidized biopterin were increased, and the BH4:BH2ratio was markedly reduced in CM. Blood mononuclear cell guanosine triphosphatecyclohydrolase I mRNA was not low in any of the groups compared to the HC children. In a multivariate logistic regression model, each unit decrease in urine BH4was independently as-sociated with a 3.85 (95% CI: 1.89–7.69) fold increase in oddsof CM ($p<0.001$).

Conclusions: Low systemic BH4levels and increased oxidized biopterins likely contribute to the low NO bioavailability observed in cerebral malaria. Adjunctive interventions to increase BH4 may reduce occurrence of severe falciparum malaria in children.

Keywords: Malaria; Tetrahydrobiopterin; BH4; Nitric oxide.