POSSIBLE MECHANISM FOR HYPERRHENYLALANINEMIA IN CHILDREN WITH FALCIPARUM MALARIA IN DAR ES SALAAM

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ABSTRACT

Introduction: Patients with falciparum malaria develop reversible hyperphenylalaninemia (HPA) (Lopansri, et al. Infect Immun 74:3355, 2006). HPA is relevant to cerebral malaria since brain aromatic amino acid metabolism is critical for synthesis of biogenic amine neurotransmitters. Phe levels are controlled by substrate-level regulation of Phe hydroxylase (PAH), an enzyme activated by elevated plasma Phe and inhibited by elevated intracellular tetrahydrobiopterin (BH4; PAH's obligatory cofactor). This substrate regulation of PAH tightly controls plasma Phe levels. HPA could result from BH4 deficiency or increased pterin synthesis with elevated intracellular BH4 and inhibition of PAH.

Methods: I prospectively measured urine pterin metabolites and plasma Phe in 62 healthy controls (HC) and 47 with uncomplicated malaria (UM) (6 months to 6 years old) from outpatient clinics at Amana and Mwananyamala district hospitals in Dar es Salaam, Tanzania. Blood samples were immediately processed, and plasma was frozen for measurements of amino acids by ion exchange chromatography. Urine was collected directly into pterin stabilizers, frozen, and later analyzed for biopterin and neopterin metabolites by HPLC using both fluorescence and electrochemical detection. Urine pterin levels were normalized to urine creatinine concentration.

Results: Children with UM had significant HPA (plasma Phe > 80 uM, $p<0.0001$). The Phe:tyrosine ratio (a sensitive measure of Phe regulation; normal ~1.0;) was elevated (^1.3) more often in UM (43 of 47) ($p<0.0001$; ; UM vs. HC). Likewise, urine BH4 was significantly higher in UM ($p = 0.017$; UM v^. HC). Other urine pterin metabolites (dihydrobiopterin, biopterin, and neopterin), and total biopterins were also significantly higher in UM vj'. HC participants.

Discussion/conclusions: Thus, UM is associated with elevated pterin synthesis. This is likely due to inflammatory cytokine-stimulated increases in expression of GTP cyclohydrolase, the rate-limiting enzyme for BH4 de novo synthesis, with consequent production of neopterins and biopterins (including BH4). Allosteric inhibition of hepatocyte PAH by rising BH4 concentration follows, leading to disrupted Phe homeostasis. Plasma Phe levels rise as the liver is unable to catabolize the increased Phe flux from accelerated protein turnover in malaria infection. Hence, increased intracellular BH4 likely contributes to HPA observed in UM.