

CORRECTED PROOF

Cerebrospinal Fluid Pterins, Pterin-Dependent Neurotransmitters, and Mortality in Pediatric Cerebral Malaria

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Abstract

Background

Cerebral malaria (CM) pathogenesis remains incompletely understood. Having shown low systemic levels of tetrahydrobiopterin (BH₄), an enzymatic cofactor for neurotransmitter synthesis, we hypothesized that BH₄ and BH₄-dependent neurotransmitters would likewise be low in cerebrospinal fluid (CSF) in CM.

Methods

We prospectively enrolled Tanzanian children with CM and children with nonmalaria central nervous system conditions (NMCs). We measured CSF levels of BH₄, neopterin, and BH₄-dependent neurotransmitter metabolites, 3-O-methyldopa, homovanillic acid, and 5-hydroxyindoleacetate, and we derived age-adjusted z-scores using published reference ranges.

Results

Cerebrospinal fluid BH₄ was elevated in CM (n = 49) compared with NMC (n = 51) (z-score 0.75 vs -0.08; P < .001). Neopterin was increased in CM (z-score 4.05 vs 0.09; P < .001), and a cutoff at the upper limit of normal (60 nmol/L) was 100% sensitive for CM. Neurotransmitter metabolite levels were overall preserved. A higher CSF BH₄/BH₂ ratio was associated with increased odds of survival (odds ratio, 2.94; 95% confidence interval, 1.03–8.33; P = .043).

Conclusion

Despite low systemic BH₄, CSF BH₄ was elevated and associated with increased odds of survival in CM. Coma in malaria is not explained by deficiency of BH₄-dependent neurotransmitters. Elevated CSF neopterin was 100% sensitive for CM diagnosis and warrants further assessment of its clinical utility for ruling out CM in malaria-endemic areas.

Keywords: [cerebral malaria](#), [neopterin](#), [neurotransmitter](#), [P](#)
[alciparum](#), [tetrahydrobiopterin](#)

Topic:

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