Correspondence

Procalcitonin Levels in Severe Plasmodium falciparum Malaria: Predictor of Outcome or Reflection of Pathomechanisms?

To the Editor—In a recent paper, Chiwakata et al. [1] demonstrated a striking relationship between procalcitonin (PCT) levels and outcome in severe Plasmodium falciparum malaria. However, the authors did not discuss the possible role of PCT in the pathogenesis of severe P. falciparum malaria. In addition to being a marker of severity, PCT levels also might reflect pathomechanisms responsible for lethal complications. A similar observation has been made for plasma thrombomodulin levels, which are extremely elevated in fatal malaria cases and seem to reflect neutrophil-mediated endothelial damage [2].

The possible role of PCT in malarial pathology might be found by also looking at the calcitonin gene–related peptide (CGRP), which is an alternative splicing product derived from the same calcitonin gene transcript. In sepsis and septic shock, elevated serum levels of PCT and CGRP [3] correlate with severity and outcome. Both peptides reduce endotoxin-induced tumor necrosis factor–α (TNF-α) production by cells in human whole blood [4]. Reduced ex vivo TNF-α production capacity is seen before therapy, and a rapid recovery of TNF-α production capacity predicts rapid clearance of malarial parasites and clinical cure [5]. On the other hand, factors that inhibit TNF-α production may be associated with high parasitemia [6].

In addition, the serum levels of PCT correlate with those of granulocyte colony-stimulating factor in P. falciparum malaria [7]. Such a link also exists for CGRP, which enhances adhesion of neutrophils to the vascular endothelium [8]. Interaction between neutrophils and endothelial cells probably contributes to endothelial damage and organ failure in patients with P. falciparum malaria [2]. Thus, PCT might be involved in the pathogenesis of severe malaria.

Christoph J. Hemmer and Emil C. Reisinger
Department of Internal Medicine, Tropical Medicine, and Infectious Diseases, University of Rostock Medical School, Rostock, Germany

References

Reply

To the Editor—The functional role of procalcitonin (PCT) has not been identified, but there is an obvious specificity for severe systemic inflammations due to bacterial, fungal, and parasitic infections. Since elevated tumor necrosis factor–α (TNF-α) levels occur ~4 h before PCT elevations [1], a counterregulatory role may be hypothesized. Interactions between TNF-α and PCT could be demonstrated [2], but the 24% inhibition of TNF-α production in whole blood by PCT appears to be low for a significant role in vivo.

Calcitonin gene–related peptide (CGRP) is a vasoactive peptide that probably is restricted to vascular nerve endings [3] and that also appears to direct enhanced neutrophil adhesion to human umbilical vein endothelial cells [4]. However, PCT and CGRP seem to be linked phylogenetically but are separate with respect to function and compartment of expression. To our knowledge, there is no evidence of a functional coregulation or interaction of both gene products.

A correlation between granulocyte colony-stimulating factor and PCT in certain situations also does not justify the assumption of functional dependencies. A direct hint to the functional role of PCT was given, however, by demonstration of reduced sepsis-induced mortality after administration of anti-PCT antibodies in a hamster model [5].

In conclusion, hypotheses regarding a functional role of PCT that are based on correlations between different factors in the complex system of severe inflammatory reaction seem to be rather speculative. Current knowledge allows acceptance of PCT as a useful surrogate marker of disease severity, but its pathogenetic role must be investigated further and confirmed by direct experimental evidence.