The Cytokine Balance in Severe Malarial Anemia

To the Editor—Othoro et al. [1] report a high ratio of tumor necrosis factor (TNF) to interleukin (IL)–10 in Kenyan children with malarial anemia. In this respect, their finding confirms our studies of Ghanaian children with severe malarial anemia (SA) [2, 3]. However, the high TNF/IL-10 ratio seen in the anemic compared with the nonanemic malaria patients in the Kenyans was chiefly due to the higher TNF levels in the former group, whereas no significant difference was seen in IL-10 levels between the 2 patient groups. In contrast, our data from three independent studies clearly identify low IL-10 levels in SA as the key difference between these and nonanemic patients.

Although the net result is a high TNF/IL-10 ratio in both groups, the difference between the Kenyan study and our studies in Ghana is of interest for several reasons. First, it points to the importance of comparing studies from areas of different endemicity that may affect the immune response to infection. Second, it illustrates the need for coordination and standardization of such studies to allow comparison of findings, and third, both studies suggest an immunologic dysfunction as a central element in the pathogenesis of malarial anemia, motivating investigation of the mechanism behind it.

The Kenyan study was conducted in an area of perennial, high-intensity transmission of malaria parasites. In such an epidemiologic setting, cerebral malaria (CM), another serious complication of Plasmodium falciparum malaria, is rarely seen [4], and CM patients were not included in the Kenyan study. In contrast, CM is a common complication in our study area, where transmission is seasonal and less intense. This difference in clinical presentation is assumed to involve endemicity-dependent differences in the immune response to infection [5]. However, there is no hard evidence to support this assumption, and determination of whether it is really so requires the availability of comparable data.

The Kenyan study included children with both moderate (hemoglobin <8 g/dL) and severe (hemoglobin <5 g/dL) anemia. This is unfortunate, because moderately anemic children did not show the pronounced IL-10 defect seen in the SA patients in our studies. Thus it is difficult to determine whether the difference between the studies reflects dissimilar endemicity of the study areas or is simply due to different case definitions, possibly confounded by differences in methodology.

It is important to compare carefully matched and clinically well-defined patient categories when pursuing mechanisms of putative pathogenic significance. Persons with mild malaria seen at primary-care health facilities constitute a highly heterogeneous group that may include children with asymptomatic parasitemia who have fever due to other causes and others who were treated early enough to prevent complications. Children who are sufficiently ill from malaria to be admitted as inpatients, but who are free from the complication(s) under study, may constitute a more useful control group. That fact that these...
children do not develop complications indicates that they raise an adequate immune response to prevent complications. In any case, consensus on case definitions and study design will facilitate the interpretation of data obtained in different studies.

In the same Journal of Infectious Diseases issue as the study by Othoro et al. [1], McGuire et al. [6] reported an association between SA and allelic variation in the TNF promoter gene. The functional significance of their finding remains unclear, but the authors suggest that malarial anemia is the consequence of chronic, low-grade TNF production. Our recent findings support this hypothesis (unpublished data). In 2 independent studies, we found that levels of both TNF and its receptors depend significantly on parasitemia in inpatients with uncomplicated Plasmodium falciparum malaria. In contrast, neither CM nor SA patients showed such a relationship. Rather, levels of all of these markers tended to be high in CM and low in SA, largely independent of parasitemia. This pattern was not seen for a range of other cytokines. Our findings of low IL-10 levels and impaired TNF response suggest for the first time the intriguing possibility that SA, like CM, is a consequence of dysregulation of immunologic inflammation. This has now been supported in the study by Othoro et al. [1]. The different patterns of immunologic dysregulation in CM and SA indicate that an appropriate immune response to malarial infection requires a delicate balance between the beneficial and detrimental effects of inflammation, whereas the loss of this balance in either direction can have dire consequences. What may cause such an immunologic loss of balance constitutes a fascinating topic for further investigation.

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Reply

To the Editor—Kurtzhals et al. [1] call attention to the importance of conducting investigations in different disease-endemic areas by standardized protocols. They rightly point out that there is no hard evidence to show that endemicity-dependent immunologic disparities contribute to differences seen in the clinical presentation of severe malaria in areas with various transmission pressures. This issue clearly deserves further investigation.

With reference to their comment on the tumor necrosis factor (TNF)-α and interleukin (IL)-10 levels in our study groups, we would like to clarify that, at the level of the individual patient, anemic patients had higher levels of TNF than of IL-10, while patients with mild disease had higher IL-10 than TNF [2]. Therefore, the IL-10/TNF ratio was calculated for each patient separately and not by using mean cytokine values. With reference to the differences between the moderately anemic and severely anemic patients, we point out in our paper that there were no statistically significant differences in the IL-10/TNF ratio between the moderately anemic and severely anemic patients. In subjects with severe anemia, there was a trend toward lower levels of both IL-10 and TNF compared with those in moderately anemic patients, but this difference was not statistically significant. Although one can speculate that some of the differences between our study [2] and that of Kurtzhal et al. [3] may be due to endemicity-based immunologic differences, other factors, including differences in study design, intensity of parasite exposure, and genetic background of the study population, must be considered.

In summary, despite differences in methodologies, transmission pressures, and study populations, both studies arrived at similar conclusions. Future studies with comparable case definitions, study design, and standardized protocols applied in different disease-endemic settings will undoubtedly lead to unraveling the pathogenic basis of cerebral malaria and severe malarial anemia.

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