No Man Is an Island: Multiple Pathologies in Patients with Malaria

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(See the article by Berkley et al on pages 336–43)

When John Donne stated, “No man is an island,” he could have been meditating on microbes and their interactions. Some agents provoke expression of a second infectious disease by disrupting immune mechanisms; of these, human immunodeficiency virus (HIV)/AIDS is the most well-known, predisposing to tuberculosis (Mycobacterium tuberculosis and Mycobacterium avium), cryptococcosis, cryptosporidiosis, and other opportunistic infections. The association between the 1918–1919 influenza pandemic and severe bacterial pneumonia as a cause of death was recently confirmed by a study of autopsy samples to involve viral-bacterial copathogenesis [1]. Over the past 2 decades, evidence has emerged confirming that HIV infection and malaria interact, with malaria increasing HIV disease progression and transmission and vice versa; this deleterious effect is most marked during pregnancy [2].

In this issue of Clinical Infectious Diseases, Berkley et al. [3] use closely linked analytic approaches to assess the possible biological association of severe childhood malaria with, independently, HIV infection, invasive bacterial infection (IBI; mainly bacteremia), and malnutrition. Their first step was an estimation of the malaria-attributable fraction of severely ill children, as determined using a logistic model dependent on parasite prevalence and densities in the patients and community control subjects [4, 5]. HIV infection, IBI, and malnutrition status in the malaria-attributable fraction group of patients was assessed according to different levels of parasitemia.

The authors screened 3362 children aged >2 months who presented during 1998–2002 with presumed severe malaria at admission to the Kilifi District Hospital in coastal Kenya. Of the 3068 children studied, 67% had parasitemia, and 23% had parasite counts of >50,000 parasites/mL, equivalent to ~1% parasitemia. Although 12% of the parasitemic children with malaria syndrome were HIV positive, compared with 17% of the nonparasitic children (also with malaria syndrome) and 1.7% of asymptomatic children in the community, patients with malaria who were HIV positive had a significantly higher parasite density than did those who were HIV negative. In addition, HIV positivity was associated with a higher probability of a diagnosis of severe and fatal malaria. Malnutrition was present in 25% of the parasiticemic patients (with malaria syndrome) and 37% of the nonparasiticemic patients (with malaria syndrome), and the parasite densities were lower in children who were malnourished. This is counterintuitive and bears fuller explanation. Although malnourished patients without parasitemia had a ~20% case-fatality rate, severely ill patients with malaria who had malnutrition and high parasite loads had a significantly higher case-fatality rate (~14%) than did normally nourished children with severe malaria (~7%).

It is striking that 10% of all patients admitted with presumptive severe malaria had IBI, mainly consisting of bacteremia; 18% of the parasite-negative, symptomatic patients had IBI, compared with 6% of the patients with confirmed malaria. As with the other conditions, the higher the parasite load, the higher the case-fatality rates for patients with concurrent bacteremia.

It is not surprising that this retrospective study found that increasing parasite levels were associated with a higher chance of the disease being attributable to malaria. Using the malaria-attributable fraction approach, the authors showed that ~50% of children with a parasite load <500 parasites/μL had severe malaria; likewise, only ~70% of children with parasite loads of 500–4999 parasites/μL and 85% of those with parasite loads of 5000–49,000 parasites/μL had severe malaria. Children with
the highest parasite loads had a greater chance that they would also have HIV infection, IBI, or malnutrition and die with these multiple pathologies.

What is the cause of the nonmalaria disease fraction? What are the implications for front-line clinicians and laboratory and public health workers? Clearly, there is a need for improved diagnosis (or diagnoses) in each patient, especially for those who have treatable infectious diseases associated with fever, most often called “malaria” in areas of endemicity. Readers must not interpret these results as indicating that patients who have low parasite loads and mild or severe illness can go without antimalarial treatment; parasite loads can be increasing at the time of testing, and patients—particularly children, pregnant women, and nonimmune travelers—become critically ill quickly. Where this study occurred—in one of the most renowned malaria research centers—the authors routinely treat severely ill febrile patients with antimalarial drugs and antibiotics at admission. Improvement of laboratory capabilities for performance of high-standard basic parasitological, bacteriological, and, under certain conditions, HIV examinations must receive priority in malaria control and elimination initiatives and in maternal-child health programs. The PATH Diagnostics Technology Initiative (http://path.org/diagnostic-technologies.php), which is supported by the Bill & Melinda Gates Foundation, has established a very innovative program to define the basic laboratory needs and solutions for point-of-service rapid diagnosis in low-income countries. One innovation is a “lab on a card” based on a microfluid system to identify specific infections.

Malaria itself has many manifestations, several of which are life-threatening and can occur in the same patient [6, 7]: cerebral malaria, anemia, and hypoglycemia require a minimum laboratory capability for performing a rapid diagnostic test or microscopic examination of blood specimens for malaria parasites, determination of hematocrit or hemoglobin concentration, determination of blood sugar level, and performance of other blood chemistry examinations [8]. Two major challenges for developers of rapid diagnostic tests for malaria are quantification of the parasite load and distinguishing of parasite species.

The strongest associations of severe malaria, comorbidities, and case-fatality rates were found in patients who had the highest parasitemia loads, indicating a biological predisposition. Acute malaria is known to impair T cell functions [9, 10]. Many genes that protect their carriers from and predispose them to severe infectious diseases have been described elsewhere [11]. To understand more fully the microbial interactions, genetic, immunological, and environmental determinants of malaria and other infectious diseases need further study. In addition, there are interactions between treatments for HIV/AIDS and malaria [12].

Each year, hundreds of millions of patients experience febrile episodes caused by “malaria.” This diagnosis is given to 50% of outpatients and inpatients in many countries where malaria is endemic, most of which lack precise diagnostic capabilities [13]; many of these patients may have multiple pathologies. The bell tolls loudest for the 1–2 million African children who die each year of falciparum malaria. Fortunately, much is being done to understand, diagnose, and manage these complex conditions and their interactions, but there is much left to do.

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References