Parvovirus Infection, Malaria, and Anemia in the Tropics—a New Hidden Enemy?

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(See the article by Wildig et al., on pages 146–53.)

Anemia takes an exacting toll on the lives of individuals, particularly children living in tropical areas where malaria is endemic. In such areas, there is general agreement that the major causes of anemia are malaria, iron deficiency, hookworm infection, and the hemoglobinopathies, especially sickle-cell disease. In general, anemia is caused by factors that decrease hemoglobin production and those that lead to increased blood loss. In this respect, iron deficiency represents a major cause of decreased hemoglobin production, whereas worm infection (via fecal blood loss), hemoglobinopathies, and malaria (mainly via hemolysis) relate to blood loss.

Parvovirus B19 (B19) infection in humans is unique in that it can specifically and abruptly lead to a transitory cessation of erythropoiesis [1]. Parvovirus has specificity for red blood cell precursors and can totally suppress erythropoiesis for ∼3–7 days. The bone marrow of patients with B19 infection reveals an absence of maturing erythroid precursors, together with the presence of giant pronormoblasts that are pathognomonic for the cytopathic effect of the virus. Reticulocyte counts in volunteers exposed to B19 infection decrease to zero [2]. B19 infection leads to rapid viral replication that continues for ∼9 days, after which it is brought under control by the production of specific IgM; on day ∼16, the bone marrow begins to recover. The lowest hemoglobin level would therefore be detected relatively soon after this; in healthy individuals, the subsequent decrease in hemoglobin level is seldom >2 g/dL, because of the long lifespan of erythrocytes, relative to the duration of limitation of red blood cell production. However, in hemolytic situations (e.g., sickle-cell disease and hereditary spherocytosis), anemic crises have long been recognized in which the combination of a severe hemolytic condition and parvovirus-induced cessation of red blood cell production can lead to a precipitous decrease in hemoglobin levels [3].

It was for these reasons that we argued in 1990 that, although these cases of aplastic crisis had been recorded and associated with inherited hemolytic disorders, there was no reason why similar episodes could not occur in cases of acquired hemolytic conditions [4]. Malaria appeared to be a strong candidate to cause such crises, mainly because of its dramatic hemolytic potential and because of the observation of remarkably low hemoglobin concentrations in areas of the world where malaria is endemic. We found limited evidence to support this hypothesis in an uncontrolled study in Niger in Africa and, like other researchers, found that the acquisition of B19 infection in tropical, rather than temperate, regions was a common occurrence in young children at an age when severe malarial anemia is at its worst [4]. By the end of the second year of life in this African population, >90% of the children studied had evidence of past B19 infection, as was evidenced by a positive B19 IgG result. However, supportive evidence for parvovirus infection contributing to anemia in children in the tropics has been limited. In some areas, it has not been identified at all [5, 6]. This is perhaps because B19 infections tend to occur in outbreaks over relatively brief periods [7]. Moreover, an aplastic crisis is usually a unique event for a patient and results in long-lasting protective immunity, making the frequency of such crises relatively uncommon.

In a case-control study performed in Papua New Guinea and reported in this issue of the Journal of Infectious Diseases, Wildig et al. [8] examined archival blood samples of 169 children 6 months–5 years old with severe anemia (hemoglobin level, ≤50 g/L), collected over the course of 6 years, and compared them with an equal number of samples from control subjects matched for age, sex, and time for B19 IgM and DNA, using nested polymerase
chain reaction (PCR). What they found was that B19 infections played a significant role in the development of severe anemia in this area of malarial endemicity. B19 infection had, until that time, been largely undetected. They also found that parvovirus infection occurred in the very young, with 60% of children <2 years old already positive for B19 infection and 90% positive by the time they were 6 years old. However much Wildig et al. were able to emphasize that parvovirus infection was yet another contributor to the many other common causes of anemia—such as iron deficiency and hookworm infection—they were unable to detect a combined deleterious effect of malaria and parvovirus infection acting in concert. Each of these factors (malaria and B19) contributed independently, so that the effect was additive, rather than leading in combination to severe anemia.

These findings highlight the importance of this hitherto-unseen enemy as a leading contributor to anemia in the tropics. Parvovirus infection might be the proverbial “last straw” that pushes the already anemic child to even lower hemoglobin levels—which, in terms of their findings, can occur in the absence of hemolysis caused by malaria or other factors. As these authors rightly indicate, the development of a B19 vaccine may well be a highly effective public-health intervention to reduce the severity of anemia in these regions.

References