2 distinct clusters (#3 and #11) highly enriched for SF mutations and RAEB/AML-LBC phenotypes with significantly lower bone marrow blast counts, together with known clusters characterized by the presence of t(8;21), inv(16), t(15;17), and CEBPA mutations.9,10 Interestingly, whole exome sequencing of 14 cases with SF mutations within the 2 clusters revealed mutations in 3 genes implicated in RNA splicing. Among the 2 clusters, #11 was characterized by an erythroid signature with higher erythroblast percentages and differentially expressed or hypomethylated genes involved in erythroid development, whereas cluster #3 was significantly enriched for NRAS/KRAS mutations and poor overall survivals compared with other patients.

Although the conclusions need to be validated further in independent studies with more comprehensive detection of SF mutations, not just hot-spot mutations, the present study points to an intriguing possibility that SF mutations could override the conventional separation between AML and MDS and help to define novel biological subtypes of myeloid malignancies for better understanding and management of AML/MDS. However, the biological basis for the SF-mutated AML is still unclear, as is the reason why the 2 SF-mutated clusters are identified only through combined GEP and DMP analysis. Finally, and more importantly, the impact of the SF-mutated AML or the novel clusters identified through GEP/DMP profiling on the choice of therapies and patients’ outcomes should be clarified before these subtypes are found to be relevant to clinical practice.

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Comment on Atkinson et al, page 3211

The iron fist: malaria and hepcidin

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In this issue of Blood, Atkinson and colleagues document dynamic fluctuations in plasma concentrations of hepcidin, the master regulator of iron homeostasis, in African children during malaria transmission season and further show that low hepcidin levels and iron deficiency are more prevalent at the end of the malaria season, implying that iron therapy may be most beneficial at this time.1

Our understanding of iron homeostasis in humans has made huge strides in the last decade, and Atkinson and colleagues have now brought the new knowledge to bear on the troubling clinical problem of iron deficiency in malaria.1 Iron deficiency with or without anemia commonly accompanies malaria, especially in cases with a high parasite burden, and is too often seen in African children. More than 250 million episodes of febrile illness due to malaria occur each year in sub-Saharan Africa. Although iron supplements are known to promote their development, young children have been denied this benefit because of the fear that an elevated iron concentration could increase their susceptibility to malaria and other infectious diseases.2,3 Recent studies on iron homeostasis have shown us that iron absorption and recycling are tightly regulated by plasma hepcidin levels which are themselves affected by infection, inflammation, and iron loading, as well as by iron deficiency and ineffective erythropoiesis.4,5 High levels of hepcidin suppress iron absorption whereas low hepcidin levels have the contrary effect. It has been found, moreover, that hepcidin levels rise following infection by malaria parasites, which makes it unlikely that iron supplements would afford any significant benefit in treatment of iron deficiency in malaria at the point in the infectious disease cycle.6,7 So far, so good, but these discoveries raise new and deeper questions, and until now there has been no data on fluctuations of hepcidin levels and iron status in any sizeable cohort of children during the malaria season. It is in this context that the findings of the present study, showing that plasma iron concentration and hepcidin levels in children in 2 different parts of Africa vary with time through the malaria season, should be seen. That hepcidin levels are low and prevalence of iron deficiency is high at the end of the malaria season suggests that iron therapy will be most beneficial for these children when administered during this time window, so as to minimize the adverse effects of iron on malaria victims, while delivering at the same time optimal correction of iron deficiency through increased iron absorption, by reason of the low hepcidin levels.

The work of Atkinson et al represents a start toward taming both the “iron fist” and the complex problem of disentangling the many factors contributing to the regulation of hepcidin levels in malaria-endemic areas of Africa. These factors include such imponderables as nutritional deficiencies, the exact role of iron in malaria pathogenesis, and the role of parasites and inflammation themselves on iron regulation, recycling, and bioavailability. Thus, many questions remain. The authors have restricted
the analyses to subjects with paired observations from the start and the end of the malaria season, and so we do not know how the parameters that they have measured vary during the 6-month interim. Do the hepcidin and iron levels in the individual fluctuate or follow a smooth course? What are the relative contributions to changes in hepcidin levels of infection, inflammation, iron status, and ineffective erythropoiesis? This is not to carp, for the report gives us a valuable and much-needed place to start to attack a refractory problem, with significant implications in a global health context.

What then are these implications? One is that, at the population level, multiple factors working independently and/or together likely have a bearing on hepcidin levels in African children, notably time relative to the malaria season. In the broader context, this study has health, health care, and economic implications for countries, clinicians, and public health workers seeking to combat the coexisting problems of malaria and iron deficiency for our world’s children.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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