Anemia and infection: a complex relationship

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We read with great interest the article published in this issue of the *Revista Brasileira de Hematologia e Hemoterapia* (*Journal of Hematology and Hemotherapy*),[1] as the relationship between anemia and infection is a complex one.

Preliminarily, we must distinguish acute from chronic infection. When it comes to chronic infection, associated anemia is part of a more general chapter of the association between anemia and chronic conditions. Supposedly there is a common pathophysiological basis for the occurrence of anemia and several chronic diseases, whether infectious, inflammatory or neoplastic. Although the anemia related to malignancy may also have this common basis, it is clear that there are other mechanisms by which anemia occurs. Such is the case of leukemia that, by definition, originates in the bone marrow, gradually leading to anemia both because of the progressive occupation of the tissue that produces the red blood cells and due to their normal senescence. The degree of anemia and the speed in the drop of hemoglobin concentrations depend on the different subtypes of leukemia. A similar mechanism can also be invoked in other neoplasms that secondarily involve the bone marrow. Of course there may be other mechanisms that contribute to the onset of anemia, such as blood loss, nutritional deficiencies, side effects of medications and elevations of certain cytokines that are responsible, in most cases of chronic diseases, for the association with anemia. In advanced renal failure, although other mechanisms are at work, the main reason for severe anemia is a deficiency in the production of erythropoietin by the damaged kidney tissue. The management of the hematopoietic factor, generally involving intravenous iron, raises the level of hemoglobin, even without changes in other aspects of patient care.

Let us see what is the current understanding for the most frequent cases in which anemia is associated with chronic infections or inflammatory diseases.[2-4] In these cases anemia is linked to reticuloendothelial siderosis, and is usually mild or moderate. It is characterized by decreased serum iron with a decrease in the total iron binding capacity and percentage of transferrin saturation. Serum ferritin may be normal or increased. The differences in the laboratory tests for iron deficiency anemia are that, in the latter, the transferrin binding capacity rises, the ferritin is low and marrow iron is missing.

Although other mechanisms may be operating concurrently, depending on the underlying disease, the main one is impairment in the release of iron by the reticuloendothelial system. This happens, briefly, due to the increased concentration of hepcidin, a regulatory hormone produced by liver cells that rises with inflammation. Hepcidin induces the degradation of ferroportin, responsible for the transmembrane transfer of iron to plasma transferrin.[3,4]

When anemia exists in acute infections, it is due to several factors. Clearly, in a patient with malaria the main reason for anemia is the destruction of red blood cells by the parasite. In parvovirosis, on the other hand, anemia is secondary to the inhibition of medullary erythropoiesis caused by this virus. In a patient, usually a child without previous contact with the virus, the degree of anemia will depend on whether the child has a concomitant hemolytic anemia or is healthy. In the latter case, the anemia may go unnoticed because the drop in hemoglobin is very slow, there is a rapid recovery of erythropoiesis in one to two weeks and the average life span of red blood cells may reach 100-120 days. However, in a child with congenital or acquired hemolytic anemia, the clinical picture can become dramatic, requiring transfusions of red blood cells. Although there is anasimilar degree of recovery of erythrocyte production, the survival of red blood cells is severely shortened, for example, to less than 20 days in sickle cell anemia. Many other acute infections, either viral or bacterial, can cause anemia through other mechanisms, such as mild idiopathic hemolysis and marrow inhibition. But in general this type of infection is more severe. Simple upper respiratory infections leading to anemia are quite unusual, even in patients with concomitant hemolytic disease.

Now let us comment on the article published in this issue of the journal.[1] Its objective was to examine a possible association between subclinical infection and anemia in children aged 6 months to 5 years in the state of Paraíba. This age group, in particular infants, are

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particularly prone to have iron deficiency in Brazil.[5-7] The study was part of a wider investigation that sought to estimate the prevalence of iron deficiency anemia in the state, apparently as yet unpublished, because the authors did not include a corresponding reference. The population sampling of the primary study was random and followed appropriate methodological criteria. However, as stated by the authors, "children included in this study were only those who presented data on the values of C-reactive protein and hemoglobin". It is very unlikely, however, that this would give sampling bias, because the inclusion rate was 92% (1117/1211) of children originally randomized.

The authors defined that a child would be anemic if its hemoglobin concentration was below 11 g/dL, regardless of age. Although this definition is common in many studies, based on recommendations of the World Health Organization[8,9] to make results of prevalence comparable in many regions, it overestimates the prevalence of iron deficiency anemia in infants (under two-year-old children), known to have reference values for hemoglobin below that cutoff point.[10] For the same reason, the prevalence of microcytic and hypochromic anemia in infants is overestimated because the mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) are physiologically lower in this age group. The recommended cutoff points, 70 fL and 23 pg, are lower than those in adults, 80 fL and 26 pg, respectively.[10]

In the study the authors reported a prevalence of 36.3% of anemic children. We can estimate that, according to the above stated, the rate is probably lower than that. In comparison with other populations, however, the reported level, as the authors correctly state, puts anemia in Paraíba, as in other northeastern Brazilian states (Pernambuco and Piauí as cited by the authors) as "a moderate public health problem according to criteria of the World Health Organization."[9] It is very interesting that other authors had found an prevalence of anemia (36.4%) in Paraíba similar to a study performed 15 years earlier.[11] The prevalence of anemia in several states in Brazil, reported in a recent review, is generally higher than that, often reaching figures above 50%.[5]

As expected, the study "found that older children had higher mean hemoglobin levels (p-value < 0.001)". This finding reflects both the actual higher prevalence of iron deficiency anemia in younger children and, as mentioned above, the use of the same reference values for different age groups.

The authors' definition for probable subclinical infections was a C-reactive protein (CRP) value above 6 mg/L. This cutoff point is the one generally used when the latex agglutination method is used. However, it is lower than the one used when immunoturbidimetric methods are used (8-10 mg/L). This could, perhaps, overestimate the prevalence of subclinical infections in the population as a whole (11.3%), but does not change the fact that certain groups had, on average, higher or lower values than others. Subclinical infection was supposed in the study, because the authors explicitly state that "chronic clinically-detectable infections (tuberculosis, pneumonia, colds, etc.) and symptoms possibly related to infections such as fever and diarrhea were used as exclusion criteria." Therefore, this study falls within the category of those that look for a possible association between mild or subclinical acute infection and anemia.

Table 3 of the paper shows a significant association (p-value = 0.037) between anemia (Hb < 11 g/dL) and infection (CRP ≥ 6 mg/L), considering both as categorical variables. In Table 4, the association is also reported to be significant (p-value = 0.005), here considering hemoglobin as a continuous variable. Means of hemoglobin were compared between groups with and without infection, defined by the value of CRP above or below the cutoff point.

To reach this conclusion, however, would require the authors to have taken into account that it is possible that, in fact, the association found might reflect an underlying association not revealed by univariate analysis: that younger children have higher probability of presenting higher CRP values, exactly because they are more prone to have acute, apparent or subclinical, infections. The authors should have tested this hypothesis by checking, for example, if the average age of children with elevated CRP differed significantly from that of children with CRP levels below the reference values. Or, more elegantly, using a multivariate logistic regression model to check whether CRP values above the cutoff point (y=1, if yes; y=0, if not) were still associated with low levels of hemoglobin concentration after adjusting for the child's age.[12]

From what was stated above, we feel that, very likely, the association reported in the study is not real, but it is similar to the famous epidemiological situation described by many authors: there would be an association between coffee consumption and lung cancer but what underlies this association is that smokers drink more coffee than non-smokers. In fact, smoking is associated with a higher incidence of lung cancer. It is interesting to note that a modest association between coffee consumption and lung cancer, after controlling for the effect of smoking, was demonstrated in a recent meta-analysis, but the authors urge caution in interpreting the results.[13]

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