INVITED COMMENTARY

Rethinking the Ironclad Approach to Iron Deficiency Anemia

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The latest National Family Health Survey (NFHS-5, 2019-2021) reported an alarming increase in the prevalence of anemia in children (67.1%, an 8.5% increase from the figure reported in NFHS-4) aged 6-59 months [1]. A caveat of the survey was a possible overestimation of anemia due to the use of capillary blood samples and cutoffs derived from Western populations [2]. Secondly, the anemia was presumed to be nutritional and secondary to iron deficiency (ID) without performing any investigation for the etiology [2]. Four of the six basic interventions of the Anemia Mukt Bharat strategy of the Indian Government address iron deficiency anemia (IDA): prophylactic iron-folic acid supplementation, deworming, delayed cord clamping in newborns and other behavior changes, and fortification of foods with iron/folic acid [3]. The Comprehensive National Nutrition Survey which used venous blood sampling demonstrated a lower prevalence of anemia in children in comparison to the NFHS-5 data [4]. The anemia could be attributed to ID (indicated by low serum ferritin) in 32%, 17%, and 22% of toddlers, primary school children, and adolescents, respectively [4]. The survey reiterated the need for health professionals as well as policymakers to be cognizant of other causes of anemia in children and adolescents.

With increasing access to a complete blood count reported by a coulter counter, most physicians managing children with anemia interpret the red blood cell indices before starting treatment. Mean corpuscular volume (MCV) is a vital investigation in the algorithmic approach to the diagnosis of anemia. ID is an important, yet not the sole cause of anemia with a low MCV. In children with microcytic anemia with no clinical evidence to suggest an alternative diagnosis, it is reasonable to start iron therapy considering ID as the most common diagnosis. However, follow-up to document improvement in hemoglobin, and investigating for alternative causes if there is a poor response to oral iron is vital. With a carrier rate of 3-4% for beta-thalassemia in the country and higher rates for the HbE variant in the eastern states, hemoglobinopathy is an important differential for microcytic anemia. Identification of children who are heterozygous carriers and counseling their parents can be a powerful tool to prevent the birth of children with a severe thalassemia phenotype. In children with mild microcytic anemia (Hb $\geq$ 9 g/dL); a preserved red cell distribution width, normal red blood cell count, and the presence of target cells on the smear must alert the physician to obtain a high-performance liquid chromatography for hemoglobinopathy.

Bhatia et al reported their observations on 550 children with microcytic anemia in whom 60 (11%) were refractory to oral iron therapy [5]. The authors presented an approach to such children with the combination of serum ferritin and serum hepcidin [5]. Serum hepcidin, a peptide produced in the liver can be imagined as the policeman who controls the presence of iron in the body [6]. Hence, an excess or deficiency of hepcidin translates into reduced iron or iron overload, respectively. Low ferritin and low hepcidin suggest typical ID [5]. Such children require assessment for compliance and intolerance. Traditionally, oral iron has always been preferred for treating ID. The administration of parenteral iron has been restricted to patients with malabsorption, in pregnancy, and anemia of chronic disease. With the advent of safer formulations such as ferric carboxymaltose, it may be time to consider a more liberal use in ID, as compliance to three months or more of regular oral iron therapy is easier said than done [7]. The combination of low ferritin and high hepcidin may be attributed to anemia of chronic disease [5]. Celiac disease is an important consideration, particularly when the child has gastrointestinal symptoms or short stature. Normal to elevated ferritin with low hepcidin should alert the physician to hemoglobinopathy [5]. Normal or low normal ferritin with an inappropriately high hepcidin level suggests an iron refractory iron deficiency anemia due to the TMPRSS6 gene mutation [5].

In the current issue of the journal, Singh et al from New Delhi describe a study performed in children with severe ID [8]. Serum hepcidin was measured at different time points of treatment with oral iron. There was a significant

rise in serum hepcidin after one day of treatment, a pattern that was sustained at 2 weeks too. Serum hepcidin shares the limitation of serum ferritin in being affected by inflammation. Therefore, the authors excluded patients who had an elevated C-reactive protein. The study illustrates the utility of serum hepcidin in being a very early marker of successful iron therapy (preceding reticulocyte count that increases by the third day of therapy). In the discussion, the authors also highlight the potential role of hepcidin in recognizing patients who may require parenteral iron over oral iron [8].

The study reminds us to think beyond the current paradigm of the management of ID in children. One cannot undermine the importance of diagnosing and treating ID, both at the individual and community level. The traditional approach that is commonly followed is obtaining a complete blood count (CBC) in a child with a clinical suspicion of nutritional anemia and giving a therapeutic trial of oral iron therapy when the CBC shows anemia with a low MCV and high red cell distribution width. Thinking beyond regular ID is an equally important exercise, especially for the 10% of children who do not respond in the first 2-3 weeks of oral iron therapy. The judicious addition of investigations such as serum ferritin and hepcidin to the management of ID, at least in children with atypical clinical features or a meager response to oral iron can help in establishing an alternate diagnosis. Additionally, the tests can guide the selection of candidates for parenteral iron therapy. The national policymakers have rightly taken several initiatives to combat nutritional anemia. It may also be time to augment the approach to other diseases that cause anemia. Chiefly, there is a need for screening populations such as adolescents and pregnant women for carrier status of thalassemia and sickle cell anemia, and offering them premarital and antenatal counseling.

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