Introduction

An emerging paradigm in the pathophysiology of sickle cell disease is the strong link between hemolysis-related nitric oxide system dysfunction and risks for pulmonary hypertension, leg ulcers, priapism, and death. In sickle cell disease hemolysis is the consequence of hemoglobin S (Hb S) polymerization, which causes red cell rigidity and sickling. Mechanical injury to the membrane of these rigid, Hb S polymer-containing red cells shortens their intravascular survival. The strongest factor determining Hb S polymerization both in solution and within red cells is Hb S concentration. Because iron deficiency lowers the Hb concentration (MCHC) within erythrocytes, Lincoln et al. hypothesized in 1973 that inducing iron depletion could be beneficial in sickle cell disease. More recently, and with the same rationale, Koduri suggested that iron restriction could be explored as a therapeutic strategy in selected patients with sickle cell disease. There is a report of a sickle cell patient in whom the 51Cr red cell survival was longer (T1/2: 15.9 days) during a period of iron deficiency than that (T1/2: 5.2 days) measured after its correction. Alpha-thalassemia, which lowers the MCHC (though not to the degree seen with iron deficiency), also improves 51Cr red cell survival in SCD. The problem, however, is that severe iron deficiency also suppresses erythropoiesis and so the net effect of iron restriction could be worsening anemia despite its beneficial effect on hemolysis. It would be interesting, therefore, to know whether induction of iron restriction in sickle cell disease proceeds through an intermediate stage in which its hemolysis-lowering effect is equal to or greater than its inhibitory effect on erythropoiesis. If so, one would expect decreased hemolysis without additional anemia during this putative intermediate stage of iron deficiency.
restriction in sickle cell disease have shown that low MCHC and lower reticulocyte counts can occur without further decreases in the hemoglobin level. This suggests that such an intermediate iron deficiency stage may in fact develop in these patients. We report here a patient with sickle cell disease and severe iron deficiency anemia whose laboratory findings also indicated a marked reduction of hemolysis. In this patient, serial laboratory parameters during iron therapy demonstrated that correction of the iron deficiency component of her anemia could take place without significant worsening of the hemolytic rate.

**Case summary**

A 47 year-old woman with homozygous sickle-cell disease was seen in our clinic with severe and long-standing iron deficiency from of heavy menstrual flow associated with uterine fibroids. Her stools for occult blood and endoscopic examination of the gastrointestinal tract were negative. Two years earlier iron deficiency had to be corrected with intravenous iron and red cell transfusion because severe nausea and vomiting precluded the use of standard oral iron preparations even at low doses. She declined gynecologic surgery. This time, to avoid parenteral iron and transfusions, she was prescribed prenatal vitamin tablets (Cal-Nate™, Ethex Corporation, St. Louis, MO, USA), which contain 27 mg of carbonyl iron, one twice daily. With this gradual, low dose iron supplementation there were no problems with gastrointestinal intolerance or treatment adherence. Table 1 shows the patient's laboratory values at (a) baseline, before iron treatment, (b) an early stage of iron treatment during which anemia improved without an excessive increase in the hemolytic rate (LDH and reticulocytes were used as surrogates for hemolysis), and (c) iron repletion, in which hemolysis increased markedly but with only a modest additional improvement of the anemia.

<table>
<thead>
<tr>
<th>Table 1. Sequential laboratory results in sickle cell anemia patient during iron deficiency (baseline) and during iron treatment</th>
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<tbody>
<tr>
<td><strong>Parameter</strong></td>
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<td>----------------</td>
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<tr>
<td>Hemoglobin (g/dl)</td>
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<tr>
<td>Hematocrit (%)</td>
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<tr>
<td>RBCs (x10⁶/µl)</td>
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<td>RDW (%)</td>
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<td>MCV (fl)</td>
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<td>MCH (pg)</td>
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<td>MCHC (%)</td>
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<tr>
<td>Reticulocytes (%)</td>
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<td>Retics. abs. (x10⁶/µl)</td>
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<td>Ferritin (ng/ml)</td>
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<td>WBC (x10⁶/µl)</td>
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<td>Platelet count (x10⁵/µl)</td>
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<td>Total Bilirubin (mg/dl)</td>
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<td>LDH (IU/L)</td>
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<td>AST (mU/ml)</td>
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<td>ALT (mU/ml)</td>
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<td>Creatinine (mg/dl)</td>
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**Discussion**

Our experience with this single case report suggests that a state of partial iron deficiency can develop in sickle cell disease and that it could be beneficial by reducing the hemolytic rate without making the anemia substantially worse. We believe that this was possible because modest reductions in the MCHC (30.1-31.7%), see Table 1) during partial iron deficiency reduced intracellular polymerization and hemolysis to a greater extent than its inhibition of erythropoiesis. Direct red cell survival measurements were not carried out, but the following parameters were used as surrogates to define the degree of hemolysis: relative and absolute reticulocyte counts, and serum levels of LDH, AST and bilirubin. The potential benefit of limited iron deficiency suggested by our case is also supported by published reports of spontaneous and induced iron restriction in sickle cell anemia.

This sickle cell patient's serial hematologic and hemolytic parameters, measured during slow iron repletion, also allowed characterization of the partial iron deficiency stage as a potential therapeutic "window". An MCHC lower than 32% but higher than 30% (Table 1 and Figure 1) appeared to keep hemolysis at a relatively low rate: the patient's hemoglobin levels ranged from 6.6 to 6.8 g/dl (and the RBC counts from 3.4 to 3.7 x10⁶/µl) despite the moderate iron deficiency state. The changes in RBC counts were particularly interesting, since, with continued iron supplementation, they actually decreased by 16% (2.99 x10⁶/µl) below those seen at the baseline, severe iron deficiency state (3.28 x10⁶/µl).

Severely affected adult sickle cell disease patients who are unresponsive of hydroxyurea or transfusion therapy could be candidates for careful studies of iron restriction, which, at least in non-iron overloaded patients, is easily...
Ret%: percent reticulocytes, LDH: serum lactic dehydrogenase cell count, MCHC: mean corpuscular hemoglobin concentration, to the baseline (day 0) values. Hb: blood Hb level, RBC: red blood
iron-deficient sickle cell anemia patient. All data points are relative
Figure 1. Changes in laboratory parameters during iron treatment in
animals, and in humans it increases NO production even in
apart from its inhibitory effect on hemolysis: iron deficiency
may have a direct, vaso-protective effect in sickle cell patients,
achievable by phlebotomy. An RBC count rise above
40% (over non-iron deficiency values), as seen in our patient,
may turn out be a useful predictor of the partial iron deficiency
state, in which hemolysis decreases without substantial
morrow suppression.

However, iron deficiency, while generally a more benign
disorder than sickle cell disease at least in adults, can be
associated with rare but serious problems such as cerebral
sinovenous thrombosis. On the other hand, iron deficiency
may have a direct, vaso-protective effect in sickle cell patients,
part from its inhibitory effect on hemolysis: iron deficiency
anemia up-regulates vascular nitric oxide synthase in animals,
and in humans it increases NO production even in
the absence of anemia.

Resumo
Uma mulher com anemia falciforme homozigote para a Hb S evoluí com anemia ferropriva grave devido a sangramento uterino prolongado. A dosagem de dehidrogenase lática era normal e a contagem de reticulócitos estava levemente aumentada. Isto sugere que concentrações baixas de hemoglobina, que resulta de anemia ferropriva, também diminuem a polimeração de Hb S e reduz a taxa de hemólise. O complemento de ferro levou, primeiramente, a uma concentração substancialmente maior de hemoglobina com apenas um aumento mínimo na taxa hemolítica e subsequentemente a um aumento leve adicional na concentração da hemoglobina e um aumento notável na taxa hemolítica. As mudanças hematológicas observadas nesta paciente e aquelas em outras pacientes com anemia falciforme e também deficientes de ferro relatadas na literatura sugerem que pode ser interessante considerar a indução de deficiência de

Palavras-chave: Anemia falciforme; hemólise; anemia ferropriva.

References

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