Iron Overload in Rare Anaemias

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The development of iron overload and its consequences is a problem commonly ascribed to transfusion-dependent thalassaemia major, sickle cell disease, and myelodysplastic syndromes. The problem of iron overload needs also to be considered in the setting of transfusion-dependent rare anaemias, in which iron accumulation occurs both hepatically and extrahepatically.

The rare anaemias may be categorized as: 1) production anaemias (eg, pure red cell aplasia, Fanconi anaemia, Diamond-Blackfan anaemia, inherited sideroblastic anaemias, acquired aplastic anaemia, and myelofibrosis); 2) haemolytic anaemias (eg, pyruvate kinase deficiency, erythropoietic protoporphyria, and chronic autoimmune haemolytic anaemia); and 3) dyserythropoietic anaemias (eg, congenital dyserythropoietic anaemia [CDA] types I and II).

Diamond-Blackfan anaemia, a production anaemia, is a disorder of ribosome biogenesis. It presents clinically as a pure red blood cell aplasia of childhood attributable to an intrinsic defect in erythropoietic progenitors. Mutations of the *RPS19* gene have been reported in more than 25% of cases, and mutations of genes encoding other ribosomal proteins have also been implicated. Although anaemia is corrected by steroid treatment in the majority of cases, nonresponders need chronic transfusions or stem cell transplantation. Cardiac magnetic resonance imaging has shown that approximately 75% of multitransfused patients have cardiac iron accumulation, exceeding the rate in patients with thalassaemia major.

Pyruvate kinase deficiency, a haemolytic anaemia, is highly variable, and affected individuals can become iron overloaded even without transfusions. Elevated serum ferritin levels are seen in half or more of nontransfused patients; liver fibrosis and siderosis are also reported. Serum ferritin elevations appear to be independent of age, gender, and haemolysis; splenectomy and HLA-A3 positive status are risk factors. Cardiac iron loading occurs in about 20% of multitransfused patients.
CDA type I, a dyserythropoietic anaemia, is seen in Western Europe, the Middle East, India, and Japan. It is characterized by macrocytic anaemia with erythroblast internuclear bridging in the marrow. Splenomegaly, hyperbilirubinaemia, and gallstones are common. Affected infants may be transfusion-dependent through 4 months of age; by adulthood, serum ferritin levels are typically 600 to 1500 µg/L due to increased absorption. CDA type II is seen in Southern Italy, Northwest Europe, North Africa, and Italy, and results in a variable anaemia with haemoglobin levels between 8 g/dL and 11 g/dL and anisocytosis with or without poikilocytosis. Approximately 10% of affected individuals are transfusion-dependent during infancy and early childhood. By age 50 years, approximately 40% of patients have serum ferritin levels greater than 1000 µg/L.

Given the significant rate of iron overload in patients with rare anaemias, it is important to assess the response to chelation therapy. More specifically, it is important to assess the impact of the underlying cause of anaemia on the response of total iron excretion, serum ferritin levels, and labile plasma iron levels to chelation therapy.

A study published in the *European Journal of Hepatology* demonstrated no systematic differences in dose-dependent iron excretion response to deferasirox chelation therapy across the rare anaemia diagnoses. The relationship between serum ferritin and liver iron concentration (LIC) in chelated patients also was similar across the rare anaemias, with ferritin proving to be an appropriate surrogate marker for LIC. In a substudy of EPIC that evaluated 57 patients with transfusion-dependent rare anaemias, there were no systematic differences between production and haemolytic anaemias in terms of labile plasma iron response to deferasirox. Ferritin response also was similar in production and haemolytic anaemias. Although the ferritin response was initially better in production anaemias, by 1 year there was no difference.

Aplastic anaemia, a type of production anaemia, is a heterogeneous group of diseases characterized by pancytopenia, hypocellular bone marrow, and bone marrow failure. Management includes allogeneic bone marrow transplant, immunosuppressive therapy, and supportive care (ie, transfusions, infection control, and iron chelation therapy). Iron overload secondary to transfusion correlates with increased cardiac dysfunction, hepatic dysfunction, and
death. In regularly transfused individuals with aplastic anaemia, prevention requires chelation therapy when serum ferritin exceeds 1000 µg/L.

Interestingly, a haematologic response to deferasirox chelation therapy has been observed in patients with aplastic anaemia and was subsequently studied in 116 transfusion-dependent patients with aplastic anaemia enrolled in the EPIC study. Nearly 50% had a partial haematologic response, including 22% of those with severe aplastic anaemia. Improvement in haematologic parameters in response to deferasirox and deferoxamine has been noted previously in other conditions, such as myelodysplastic syndromes. A number of mechanisms of action have been proposed, including an anti-proliferative or anti-oxidant effect, functional improvement in the bone marrow microenvironment, or inhibition of nuclear factor-kB.

Future studies need to better define the mechanisms of extrahepatic iron distribution in the rare anaemias, as well as to better define which forms of anaemia are likely to show haematologic response to chelation therapy.

**Suggested Readings**


