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State of art

Management of iron overload in hemoglobinopathies

Traitement de la surcharge en fer des hémoglobinopathies

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Abstract

Hemoglobinopathies, thalassemia and sickle cell disease are among the most frequent monogenic diseases in the world. Transfusion has improved dramatically their prognosis, but provokes iron overload, which induces multiple organ damages. Iron overload is related to accumulation of iron released from hemolysis and transfused red cell, but also, in thalassemic patients, secondary to ineffective erythropoiesis, which increases intestinal iron absorption via decreased hepcidin production. Transfusion-related cardiac iron overload remains a main cause of death in thalassemia in well-resourced countries, and is responsible for severe hepatic damages in sickle cell disease. Regular monitoring by Magnetic Resonance Imaging (MRI) using myocardial T2* (ms) and Liver Iron Content (LIC) (mg of iron/g dry weight) are now standards of care in chronically transfused patients. Serum ferritin level measurements and record of the total number of transfused erythrocyte concentrates are also helpful tools. Three iron chelators are currently available, deferoxamine, which must be injected subcutaneously or intravenously, and two oral chelators, deferiprone and deferasirox. We will review the main characteristics of these drugs and their indications.

Keywords: Iron overload; Thalassemia; Sickle cell disease; Deferoxamine; Deferiprone; Deferasirox

Résumé

Les hémoglobinopathies, les syndromes thalassémiques et drépanocytaires, sont parmi les maladies monogéniques les plus fréquentes au monde. Leur pronostic a été profondément amélioré par la transfusion sanguine, mais celle-ci entraîne une surcharge en fer responsable de l'atteinte de différents organes. Le fer provient de l'hémolyse des globules rouges du patient et de ceux transfusés, et, chez les patients thalassémiques, d'une hyperabsorption intestinale secondaire à l'érythropoïèse inefficace avec diminution de la production d'hepcidine. La surcharge en fer cardiaque est aujourd'hui la principale cause de décès des patients thalassémiques vivant dans des pays développés ; les patients drépanocytaires souffrent surtout des conséquences hépatiques de cette surcharge. Les techniques d'IRM de mesure du temps T2* au niveau du coeur et de la concentration en fer au niveau du foie sont les outils diagnostiques de référence de la surcharge en fer. Les contrôles de la ferritinémie sérique et le nombre de concentrés érythrocytaires transfusés peuvent aussi être utilisés. Trois chélateurs, la deferoxamine, qui doit être injectée par voie sous-cutanée ou intraveineuse, et deux chélateurs oraux, la deferiprone et le deferasirox, sont disponibles aujourd'hui. Nous présenterons leurs principales caractéristiques et indications.

Mots clés : Surcharge en fer ; Thalassémie ; Drépanocytose ; Deferoxamine ; Deferiprone ; Deferasirox

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Hemoglobinopathies, thalassemia and Sickle Cell Disease (SCD) are among the most frequent monogenic diseases in the word [1]. Their prognosis depends not only on the causative genetic mutation, which have highly variable clinical and hematological expressions but also on the affordability of medical care, and above all transfusion and iron chelation. Here we will present keys issues in iron chelation in patients with hemoglobinopathies living in France.

1. Epidemiological data

A register of thalassemia published in 2010 has identified 378 patients living in France [2].

There is no register of patients with SCD. The systematic neonatal screening program, generalized in 2000 in France, identifies a major sickle cell syndrome in around 400 newborns every year. The current estimation is that around 20,000 patients, children and adults, are living in France.

2. Transfusional needs

Thalassemia is caused by mutations affecting the production of globin chains (α and β chains for α and β thalassemia respectively). Severity of anemia depends of the degree of imbalance between α and β chains production, which is associated with accumulation of free globin chains, generation of reactive oxygen species, membrane damages, apoptosis, and ineffective erythropoiesis. Clinically, some patients have a major thalassemic syndrome (their disease is called Transfusion-Dependent Thalassemia, previously called Cooley's anemia), and require monthly transfusions to maintain permanently hemoglobin (Hb) level > 9–10 g/dL, threshold demonstrated to allow normal growth and activity. Other patients have less severe anemia (their disease is called thalassemia intermedia, or Non-Transfusion-Dependent Thalassemia). Recent surveys have demonstrated that long-term severe complications, such as pulmonary hypertension, thromboembolic events, hematopoietic extramedullary tumors have a high frequency in NTDT patients, and that regular transfusions decrease their risk of occurrence. Recently, therefore, NTDT patients may be prescribed regular transfusion programs [3].

Transfusion needs are very different in patients with SCD. Polymerization of HbS induces occlusion in microcirculation by sickled red cells, and chronic hemolytic anemia. Median baseline Hb level is around 8 g/dL. Erythropoiesis is in most cases very active in SCD patients, and increased reticulocyte production alleviates anemia. Transfusions may be required in emergency, to correct a sudden drop in Hb level (in case of infection, pain, Parvovirus B_{19} infection, or splenic sequestration). Transfusion may also aim to bring new deformable red cell, either in emergency (in case of stroke, acute chest syndrome. . .) or in patients with cerebral vasculopathy to prevent a first episode or a recurrence of stroke [4].

3. Origins of iron overload in hemoglobinopathies

Iron accumulates from 3 different origins in patients with hemoglobinopathies, with different rates according to the disease and the treatments:

1. hemolysis releases iron-bound Hb which is taken up by macrophages. Iron necessary for Hb synthesis is normally carried by transferrin to bone marrow to produce new red cells. However, when hemolysis is very high, the transferrin capacity to bind iron is also overwhelmed, and Non Transferrin Bound Iron (NTBI) appears and accumulates toxically in parenchyma particularly the heart and endocrine tissue. It has been shown that NTBI form enters the myocytes through the voltage-dependent L-type calcium channels and the hepatocytes via soluble carrier SLC39A14, also called ZIP14 [5];
2. in diseases characterized by inefficient erythropoiesis, whether inherited such as thalassemia or acquired such as myelodysplactic syndromes, iron is not well consumed through erythropoiesis. In addition, hepcidin production is suppressed and iron absorption is increased [6,7]. This mechanism explains why NTDT patients may have significant iron overload while they have not been transfused;
3. one milliliter of packed red blood cells brings 1.08 mg of iron. Iron derived from transfused red blood cells initially accumulates in macrophages, but later accumulates in the liver. One year of regular transfusion for a thalassemic patient weighing 60 kg brings 9 g of iron. In SCD patients undergoing chronic transfusion regimen, in whom transfusion does not aim to increase Hb level but to decrease HbS percentage, exchange transfusion is preferable to simple transfusion, because it decreases the global amount of iron [8]. To note, automated procedure, i.e. erythrocytapheresis, needs higher number of erythrocyte concentrates than manual exchange transfusion to control HbS.

Cardiac iron overload is the leading cause of death in patients with thalassemia who require chronic transfusion [9]. Main targets for iron overload are also the liver, endocrine glands, notably the pancreas with therefore risks of cirrhosis, diabetes, hypothyroidism, hypoparathyroidism, and infertility [10]. The relationship between excess iron and mortality in SCD is more difficult to analyze, because patients with transfusion-related iron overload are also those who have greater disease severity requiring chronic transfusion [11]. The heart is relatively spared and iron deposits mostly in the liver [12,13]. In a study of 141 patients with SCD who died in adulthood, at a mean age of 36 ± 11 years, Darbari et al. found that 16 (11.4%) had cirrhosis and 10 (7.1%) iron overload; seven of 16 (43.8%) patients with cirrhosis had iron overload compared with 3 of the 125 without cirrhosis (2.4%) ($P < 0.001$) [14].

4. Monitoring iron overload

Serum ferritin measurement is the most used tool worldwide to assess the importance of iron burden, but it is not specific, as