Hyperhemolysis Syndrome in Patients With Sickle Cell Disease

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Sickle cell disease is a genetic disease commonly affecting people of African, Indian, and Mediterranean descent. Patients with this chronic disease often require lifelong red blood cell transfusions. Formation of alloantibodies and autoantibodies are well-known complications that can arise with multiple transfusions. Another rare, but serious complication associated with transfusion is hyperhemolysis syndrome. The acquisition of new and/or rare alloantibodies can make it more difficult to find compatible blood products for patients with sickle cell disease. Genotyping and national donor registries are useful tools for finding appropriate blood products for these patients. This review will describe the clinical and laboratory findings of sickle cell disease, including hyperhemolysis syndrome. The challenges associated with locating compatible blood for patients with various red blood cell antibodies will be reviewed.

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Sickle cell disease (SCD) affects more than 250 million people globally, primarily those of sub-Saharan African, South and Central American, Arabic, Indian, and Mediterranean descent.1 A genetic disease, the most common mutation is the substitution of valine for glutamic acid in the structure of the β-chain hemoglobin molecule.1 The resulting hemoglobin is hemoglobin S (HgbS). This mutation results in red blood cells (RBCs) forming characteristic “sickle” shapes at low oxygenation levels. Red blood cell sickling can lead to chronic blood vessel occlusion, ischemia, and immune dysfunction. Additionally, the abnormal RBCs are prematurely removed from circulation, resulting in hemolytic anemia. Sickle cell disease has an autosomal recessive inheritance pattern requiring mutation in both copies of the β-chain hemoglobin gene for clinical disease.

The diagnosis of SCD is relatively simple. There are chemical and solubility tests that identify HbS. These tests are presumptive and require confirmatory testing for SCD. Definitive diagnosis of SCD can be determined by multiple techniques, including electrophoresis, using standard alkaline gel, isoelectric focusing, capillary electrophoresis, or high-performance liquid chromatography.2

The clinical features of SCD can be divided into vaso-occlusive, infectious, and anemic symptoms. Vaso-occlusion can result in osteonecrosis, skin ulcers, organ failure, acute chest syndrome, and cerebrovascular accidents. The “sickling” of red blood cells results in their shortened life span in the circulation and characteristic anemia. As sickled RBCs circulate through the spleen, they cause splenic injury due to their inability to pass through the sinusoids. Splenic sequestration can be life-threatening because it can lead to hypovolemia. In addition, the spleen is an important immunologic organ, helping to fight infections with encapsulated organisms such as Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis. Viruses can cause significant illness in patients with SCD. For example, parvovirus B-19, a common childhood virus responsible for Fifth disease, causes a rash, the classic “slapped-cheek” appearance, and high fevers. It can suppress bone marrow production by destroying the RBC precursor cells in the bone marrow, resulting in a pure red cell aplastic anemia and crisis.3,4 Sickle cell disease results in hemolytic anemia, and patients may exhibit signs and symptoms common to hemolytic anemia, including tachycardia, dyspnea, weakness, fatigue, and end-organ damage.2

Treatments for SCD are aimed at support and crisis prevention. For acute, non–life-threatening vaso-occlusive episodes, first-line treatment includes hydration, applying heat, antibiotics, anti-inflammatory agents, and opioids, which are useful in controlling pain and improving oxygen delivery to tissues.4,5 Hydroxyurea, a crisis-prevention mainstay treatment, is a ribonucleotide reductase inhibitor that has multiple effects in SCD. It increases hemoglobin F concentrations, which decreases HgbS concentration and prevents HgbS polymerization, which in turn decreases RBC sickling and hemolysis.1,5 Additional effects include inhibiting white blood cell and platelet production, which may ameliorate occlusive episodes. Blood transfusion therapy, including exchange and simple transfusion, are indicated for stroke, severe acute chest syndrome, splenic sequestration, and symptomatic anemia.4,6 Depending on the clinical circumstances, blood transfusion therapy may be supportive, preventative, or both. The purpose of transfusion therapy is to increase oxygen delivery to tissues and decrease HgbS concentration. Curative therapies include hematopoietic stem cell transplantation and gene therapy.
One of the complications associated with multiple transfusions is the formation of new and/or rare alloantibodies. In the United States, this may in part be due to the discrepancy in blood group frequencies between minority patients with SCD and predominantly white blood donors. Other alloantibody formation factors include sex, number and timing of blood transfusions, age, pregnancy, recipient’s diagnosis and treatment, and genetic factors related to the antigenic response. Additional complications with chronic transfusions include iron overload, bloodborne infections, transfusion-related lung injury, transfusion-associated circulatory overload, transfusion-associated graft-versus-host disease, and hemolytic transfusion reactions (acute and delayed). Transfusion reactions, especially hemolytic reactions, can be clinically significant.

HYPERHEMOLYSIS SYNDROME

Hyperhemolysis syndrome (HS) is characterized by the development of severe anemia with posttransfusion hemoglobin levels that are lower than pretransfusion levels. In addition to an increased prevalence in hemoglobinopathies, such as SCD, HS has also been reported in patients with other conditions, such as thalassemia, myelofibrosis, anemia of chronic disorders, and lymphoma. HS rarely recurs. The clinical presentation of HS usually includes fever, jaundice, and pain. Laboratory results demonstrate elevated bilirubin and lactate dehydrogenase concentrations, with a decrease in absolute reticulocyte count. The direct antiglobulin test result is negative in many cases, and new alloantibodies may or may not be present. Hyperhemolysis syndrome can be subdivided into acute and delayed forms based on length of time from transfusion to clinical symptoms and the potential formation of alloantibodies. Acute HS occurs within 7 days of transfusion without alloantibody formation, whereas the delayed form occurs later than 7 days and alloantibody formation often occurs. HS rarely recurs. The pathophysiology of HS has not been completely elucidated. Multiple mechanisms have been proposed, including ‘bystander hemolysis,’ increased hemolysis by activated macrophages, increased RBC exposure of phosphatidyserine, and suppression of erythropoiesis. Bystander hemolysis occurs when both native and donor red blood cells are hemolyzed, possibly through complement activation. Hemoglobin levels in HS may be decreased as a result of increased destruction of RBCs by activated macrophages. Phosphatidyserine, when expressed on the red blood cell surface, results in increased clearance from circulation. Because of the consumptive effect of HS, it is likely that multiple mechanisms play a role.

TREATMENT

Current treatment recommendations for hemodynamically stable patients with HS include avoiding further transfusions to prevent worsening hemolysis. For situations requiring transfusion, intravenous immunoglobulin G and corticosteroid coverage may be considered. In severe cases, additional immunoglobulin G treatment may be needed, with the understanding that it carries a risk of renal toxicity and thromboembolic events. Rituximab can be an effective therapy because of the rapid recovery of reticulocyte count. Erythropoietin has been studied as a potential treatment, with the idea of overcoming erythropoiesis suppression; however, more studies are needed to demonstrate efficacy. Similarly, eculizumab, a C5 convertase inhibitor, has been used as a treatment for hyperhemolysis in patients with SCD. Eculizumab inhibits the complement cascade, facilitating RBC membrane integrity preservation. Therapeutic plasma exchange has been successful in the treatment of severe hemolysis and proposed to be useful in episodes of severe hyperhemolysis. Hemoglobin-based oxygen carrier substitutes, such as cross-linked tetramer hemoglobin and conjugated tetramer hemoglobin, may be beneficial as oxygen carriers and for their potential to reduce free HgbS, an oxidizer and proinflammatory agent. These agents are not routinely used. They require further study because there are currently no hemoglobin-based oxygen carrier substitutes that have been approved by the US Food and Drug Administration. In the United States, approximately 1 person per 70 people who receive transfusions develops antibodies to RBC antigens. For patients requiring chronic transfusions, alloimmunization is higher (20%–30%). Alloimmunization to RBC antigens is relatively common, and the likelihood of additional antibody responses is also relatively high. A current theory regarding alloimmunization involves heme oxygenase, which converts heme into iron, bilirubin, and carbon monoxide. Heme oxygenase has anti-inflammatory and immunosuppressive effects. In SCD patients, heme oxygenase levels are lower at baseline, resulting in incomplete clearance of heme by monocytes, which promotes a proinflammatory state and increases alloimmunization.

Genotyping, which is polymerase chain reaction amplification of blood group antigen polymorphisms, predicts the phenotype for antigens in the RHCE, KEL, FY, DO, LW, CO, SC, LU, DI, JK, and MNS systems, as well as for HgbS. Genotyping has numerous advantages, including not being affected by immunoglobulin coating of the RBCs, by the presence of recently transfused RBCs, or by any form of polyanagglutination. High-throughput genotyping methods can be applied to both patients and blood donors, resulting in the possibility of providing genotype-matched, rather than just ABO/RhD-matched or crossmatch-compatible, RBCs. This approach has the great advantage of potentially avoiding almost all alloimmunization. The addition of rare or new alloantibody formation to a hemolytic transfusion reaction, such as HS, can increase the complexity of treatment and may require specialized blood products. The American Rare Donor Program is a cooperative program of the American Association of Blood Banks and the American Red Cross. It was formed in 1998 when their rare donor databases merged. A 2014 review by Flickinger reveals that the database has expanded to approximately 59 000 active rare donors, with approximately 1800 rare blood units shipped per year for transfusion in the United States. When patients develop rare or multiple alloantibodies, molecular techniques, such as genotyping, may be required.

CONCLUSIONS

Hyperhemolysis syndrome is a potentially fatal transfusion complication, especially in patients with SCD. Multiple mechanisms, including “bystander hemolysis,” increased macrophage-mediated hemolysis, and increased red blood cell exposure of phosphatidyserine, with subsequent hemolysis and suppression of erythropoiesis, may play a
role in HS. Transfusion should be avoided if possible in HS, and even transfusion with genotype-matched red blood cells is not without risk. When transfusion is necessary, corticosteroids and immunoglobulin G should be initiated. Newer molecular methods and rare donor registries are useful in procuring compatible units for SCD patients who have been alloimmunized. Future studies may demonstrate the benefits of hemoglobin-based oxygen carrier substitutes in HS.

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