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SICKLE CELL DISEASE: CAUSES, EFFECTS AND TREATMENT

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ABSTRACT

Sickle cell disease is a genetically inherited hematological (blood) disorder that results from a mutation in the beta globin gene that is responsible for the development of hemoglobin. Hemoglobin is the protein that delivers oxygen to the red blood cells throughout the body. In the disease, a mutated variant of normal hemoglobin generates an abnormal structure of the cells, leading to the development of symptoms. Sickle cell anemia and beta thalassemia are two common types of sickle diseases that are discussed in this review. The symptoms, complications, and therapies are also highlighted in the context of the path physiology of the disease.

KEY-WORDS: Sickle Cell, Treatment, Causes, Disease, Effects

SICKLE CELL DISEASE: AN OVERVIEW

Sickle cell disease is a genetically inherited blood disorder and it is characterized by an abnormal structure or production of hemoglobin. Hemoglobin is the protein in red blood cells that transports oxygen to cells throughout the body (National Institutes of Health, 2014). The disease results from a mutation in the beta globin gene causing a class of sickle diseases, such as sickle cell anemia and beta thalassemia (Thein, 2008). Together, they are often referred to as the beta hemoglobinopathies and present a range in disease severity (Thein, 2008). Beta globin is a protein that produces hemoglobin and the gene mutation in both diseases produces abnormal variants of hemoglobin in the blood. This results in either a predominance of abnormal hemoglobin molecules in red blood cells or an absence of normal hemoglobin, and thus, normal red blood cells (Edwards et al., 2005). There are a number of available therapies that manage sickle cell disease and the only curative treatment is hematopoietic cell transplantation.

PATHOPHYSIOLOGY OF SICKLE CELL DISEASE

The National Institutes of Health reports that sickle cell disease is the most common inherited blood disorder in the United States and it affects 70,000 to 80,000 Americans (National Institutes of Health, 2014). It is estimated to occur in 1 in 500 African Americans and 1 in 1,000 to 1,400 Hispanic Americans (National Institutes of Health, 2014). The disease affects 30 million people worldwide and it is most common among people who have ancestors from Africa, Mediterranean countries, the Arabian Peninsula, India, parts of South America, Central America and the Caribbean (Khoury, Musallam, Mroueh, & Abboud, 2011; National Institutes of Health, 2014). As it is an inherited disease, the sickle gene is presumed to have a genetic advantage in which it protects from the development of malaria infection (Stuart & Nagel, 2004). There are many types of sickle diseases, such as sickle cell anemia and beta thalassemia. Sickle cell anemia is considered the most commonly occurring type of sickle cell disease (National Institutes of Health, 2014). In sickle cell anemia, hemoglobin S replaces both beta-globin and the sixth amino acid is changed from glutamic acid to valine (National Institutes of Health, 2014; Rees & Gibson, 2011). Sickle cell trait is not considered a disease and it is found in approximately 1 in 10 African Americans (Edwards et al., 2005). When both parents have the sickle cell trait, there is a one in four chance with each pregnancy that the child will have sickle cell anemia (Edwards, et al., 2005). Today, many health organizations offer newborn screenings that can determine if a child has either the disease or trait (National Institutes of Health, 2014).

The development of the disease occurs due to the polymerization of deoxygenated hemoglobin S (Chirico & Pialoux, 2012). The polymer formation modifies the normal red blood cell disc shape into a rigid, irregular-shaped, unstable cell and causes intravascular hemolysis, or rupture of the cells, to release hemoglobin into the plasma of the blood (Chirico & Pialoux, 2012). The repeated polymerization leads to sticky blood cells (blood cell adhesion), obstruction of blood vessels (vasocclusion), and restriction of blood supply to tissues and organs in the body (ischemia) (Chirico & Pialoux, 2012). Additionally, the endothelium and leukocyte, or white blood cells, are also found to play a role in disease mechanisms.

Studies have found a connection between the endothelium, a thin layer of cells that line the interior surface of blood vessels, and sickled red blood cells (Stuart & Nagel, 2004). The red blood cell receptors that are associated with cell adhesion are present in increased numbers on sickled immature red blood cells and mature sickle cells compared to normal red blood cells (Stuart & Nagel, 2004). This finding demonstrates a structure-function abnormal activity that leads to coagulation on cell surfaces, leading to anemia (Stuart & Nagel, 2004). Like cell adhesion, leukocytes have an impact in disease activity. White blood cells are found to be at an increased baseline in sickle cell disease, which serves as an independent risk factor for pulmonary and cardiac complications (Stuart & Nagel, 2004). The size of the white blood cell, its rigidity, and adhesive characteristics are implicated in microvascular blood flow, vascular inflammation, and vasocclusion (Stuart & Nagel, 2004).

CLINICAL SYMPTOMS OF SICKLE CELL DISEASE

The clinical manifestation of sickle cell disease can lead to inflammatory responses and may result in acute chest syndrome, pulmonary hypertension, and stroke (Chirico & Pialoux, 2012). People with sickle cell disease may also encounter several physical complications, such as delayed growth, fatigue, headaches, and cerebral vascular

damage (Edwards et al., 2005). Acute chest syndrome is considered the second most common cause of hospital admissions and a leading cause of death in patients with sickle cell disease (Khoury, Musallam, Mroueh, & Abboud, 2011). It involves the presence of a pulmonary infiltrate on a chest X-ray and the symptoms may include chest pain, a temperature of more than 38.5 degrees Celsius (101.3 degrees Fahrenheit), tachypnea (rapid breathing), wheezing or cough ((Khoury, Musallam, Mroueh, & Abboud, 2011). The symptoms at clinical presentation vary with age as wheezing, cough, and fever are common in children 10 years or younger (Khoury, Musallam, Mroueh, & Abboud, 2011). Pain in the arms and legs and shortness of breath are more commonly presented in adults with the disease (Khoury, Musallam, Mroueh, & Abboud, 2011). It is believed that there are three mechanisms involved in acute lung injuries, which include infection, fat embolization (clotting) from bone marrow, and sequestration of sickled red blood cells (Khoury, Musallam, Mroueh, & Abboud, 2011). People with sickle cell disease have an increased risk for developing infections, particularly pneumonia. Treatment for acute chest syndrome is primarily supportive and includes supplemental oxygen to keep the saturation above 92% (Khoury, Musallam, Mroueh, & Abboud, 2011). Pain is considered the most frequent complication associated with the disease and acute chest syndrome stimulates this crisis (Edwards et al., 2005; Khoury, Musallam, Mroueh, & Abboud, 2011). Repeated episodes of acute chest syndrome predispose patients to chronic pulmonary disease, such as pulmonary hypertension (Stuart & Nagel, 2004). The occurrence of asthma is also associated with the increased incidence of acute chest syndrome, which is considered a comorbid condition found in people with sickle cell disease (Khoury, Musallam, Mroueh, & Abboud, 2011).

BETA THALASSEMIA

Beta thalassemia is a common genetic blood disease that reduces hemoglobin production (National Institutes of Health, 2014). The hemoglobin gene mutation results in an unusually low level of beta-globin (National Institutes of Health, 2014). There are different levels of thalassemia based on the number of copies of beta thalassemia alleles or different copies of the same gene (Thein, 2008). The variety in alleles impacts the deficit in beta globin production, which, in turn, impacts disease severity (Thein, 2008). Carriers, for example, who have inherited a single copy of the beta thalassemia allele are clinically asymptomatic and may demonstrate mild anemia (Thein, 2008). Unlike a globin imbalance that is found in sickle cell anemia, variants of beta chains are broken down and result in ineffective red blood cell production in beta thalassemia (Thein, 2008). Physical complications involve cardiac and bone disease, bilirubin metabolism, and iron metabolism. Such symptoms may include jaundice and a predisposition to gallstones (Thein, 2008).

TREATMENT FOR SICKLE CELL DISEASE

Several complications may emerge from sickle cell disease, whether it is in sickle cell anemia or in beta thalassemia. The purpose of therapies for sickle cell disease is to prevent and treat complications (Inati, Chabtini, Mounayar, & Taher, 2009). The treatment of sickle cell disease is best achieved by decreasing the amount of hemoglobin S through the prevention of its production (Inati, Chabtini, Mounayar, & Taher, 2009). People with severe sickle cell disease are treated with three validated therapies: hydroxyurea, transfusion and chelation therapy, and a hematopoietic or stem cell transplant (Inati, Chabtini, Mounayar, & Taher, 2009). Hydroxyurea has been shown to be an effective form of treatment for children and adults with the disease. It has been demonstrated to reduce pain and acute chest syndromes, and it decreases the frequency of hospitalizations and the need for

transfusions. This therapy has also been found to play a role in stroke prevention (Inati, Chabtini, Mounayar, & Taher, 2009). At a molecular level, hydroxyurea reduces the adhesion of sickle red cells to endothelial cells. It also modulates endothelial cell activation and nitric oxide generation (Inati, Chabtini, Mounayar, & Taher, 2009). Nitric oxide has been found to affect acute and chronic complications of sickle cell disease (Stuart & Nagel, 2004). Nitric oxide, on a normal functioning level, induces relaxation of smooth muscle and dilation of blood vessels. In sickle cell disease, the bioavailability of nitric oxide is impaired, resulting in an imbalance between endothelial production and consumption (Stuart & Nagel, 2004). The lungs are most affected by a reduction of nitric oxide and tend to constrict, which predisposes an individual to acute chest syndrome (Stuart & Nagel, 2004). No adverse effects have been thus far reported on the usage of hydroxyurea and any toxicity is typically reversible (Inati, Chabtini, Mounayar, & Taher, 2009).

Transfusion therapy is currently considered a standard of care treatment for primary and secondary stroke prevention in children with sickle cell disease (Inati, Chabtini, Mounayar, & Taher, 2009). It is used for short and long term management, preventing a first stroke in high-risk children as well as preventing against a recurrent stroke (Inati, Chabtini, Mounayar, & Taher, 2009). Transfusions are also used for chronic and severe pain or in cases when patients with acute chest syndrome do not respond to hydroxyurea (Inati, Chabtini, Mounayar, & Taher, 2009). Chelation therapy is used for patients who experience iron overload. Iron overload is a serious and inevitable outcome from receiving regular transfusion therapy (Inati, Chabtini, Mounayar, & Taher, 2009). Unless treated, iron overload may result in severe organ damage and other life threatening complications and this treatment mediates this by removing excess metals from the body (Inati, Chabtini, Mounayar, & Taher, 2009).

While hydroxyurea, tranfusions, and chelation therapy aim to prevent and treat complications, they do not cure sickle cell disease (Inati, Chabtini, Mounayar, & Taher, 2009). The currently available curative treatment is a stem cell transplant. A transplant is indicated in those patients who experience complications, such as recurrent severe pain, acute chest syndrome, and stroke (Inati, Chabtini, Mounayar, & Taher, 2009). Only one-third of affected children meet the criteria for a stem cell transplant as it is an aggressive and serious procedure (Inati, Chabtini, Mounayar, & Taher, 2009). The goal of a stem cell transplant is to replace the host's marrow with normal cells, resulting in a new immune system (Stuart & Nagel, 2004). Studies on stem cell transplant as a curative option for patients with severe sickle cell disease are demonstrating mean overall survival and event-free survival rates between 95 and 85% (Inati, Chabtini, Mounayar, & Taher, 2009). Significant advancements have been made for pediatric patients who have beta thalassemia and were treated with a stem cell transplant. Over the last three decades, disease-free survival rates have exceeded 80% in patients who received transplants from biologically compatible family donors (Mehta & Faulkner, 2013).

Sickle cell disease is a genetically inherited blood disorder that is primarily diagnosed in people who have ancestors from Africa, Mediterranean countries, the Arabian Peninsula, India, parts of South America, Central America and the Caribbean (Khoury, Musallam, Mroueh, & Abboud, 2011; National Institutes of Health, 2014). The disease results by a mutation in the gene that creates beta globin, which is the protein that is responsible for producing hemoglobin. Hemoglobin is the protein in red blood cells that transports oxygen to the body's organs and tissues. When the mutation occurs, a hemoglobin variant is produced, resulting in a structural and functional change in the red blood cells. Several physical complications emerge in both children and adults who have the disease. These may include, but not limited to, pain, acute chest syndrome, cerebral and vascular damage (Edwards et al., 2005).

There are three primary therapies for managing and/or treating the disease. These include the drug, hydroxyurea, transfusion and chelation therapy, and hematopoietic cell transplantation (Inati, Chabtini, Mounayar, & Taher, 2009). More research is underway in the development of additional treatment options, such as gene therapy and clinical trials are exploring this possibility.

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