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SICKLE CELL DISEASE: BACKGROUND AND MANAGEMENT

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Abstract:

Introduction: *Sickle cell disease is considered to be one of the commonest hereditary diseases around the world with being highly prevalent in the regions of sub-Saharan Africa, Mediterranean, Middle East, and Southeast Asia. Sickle cell disease is known to be a chronic hematological disease that leads to severe hemolysis, and is characterized by hemoglobin particles that tend to polymerize within the RBCs and cause the RBC to become in a crescent, sickle shape, which will cause hemolysis along with vasoocclusive events in different organs.*

Aim of the work: *we tried to understand the pathogenesis, impact, diagnosis, and management of sickle cell disease in this study.*

Methodology: *we conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from January 1950 to March 2018. The following search terms were used: sickle cell anemia, hemoglobinopathy, genetics of sickle cell, complications of sickle cell, management of sickle cell disease*

Conclusion: *It is important to develop therapeutic options that reduce the risk of complications of sickle cell disease. Despite all advances in treatment, sickle cell disease remains to be an important serious disease that is associated with severe morbidity and mortality, and poor quality of life. More research and clinical trials should be conducted on this disease to develop advanced treatment options that will further improve quality of life and decrease mortality and complications.*

Keywords: *sickle cell disease, hemoglobinopathies, Middle-east hematological disorders*

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INTRODUCTION:

Sickle cell disease is considered to be one of the commonest hereditary diseases around the world with being highly prevalent in the regions of sub-Saharan Africa, Mediterranean, Middle East, and Southeast Asia. Sickle cell disease is known to be a chronic hematological disease that leads to severe hemolysis, and is characterized by hemoglobin particles that tend to polymerize within the RBCs and cause the RBC to become in a crescent, sickle shape, which will cause hemolysis along with vasoocclusive events in different organs. Sickle cell disease is an autosomal recessive disease that occurs in both homozygous and heterozygous individuals. In individuals who are homozygous we call the disease sickle cell anemia. Other subtypes of sickle cell disease include sickle beta plus thalassemia, sickle beta zero thalassemia (which is the most similar to sickle cell anemia regarding severity), hemoglobin SO Arab disease, hemoglobin SC disease, hemoglobin SD Punjab, along with other subtypes that differ among each other by clinical picture and severity[1].

METHODOLOGY:

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE, from January 1950 to March 2018. The following search terms were used: sickle cell anemia, hemoglobinopathy, genetics of sickle cell, complications of sickle cell, management of sickle cell disease

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

History

Sickle cell disease was first described by Dr. Horton in the year 1874. Then, in the year 1910, a more discrete definition was introduced by Herrick, after the shape of abnormal RBCs was noticed in a patient who carried the disease. Later, in the year 1927, Hahn and Gillespie monitored RBCs' sickling and correlated it with the absence of high oxygen tension. Linus Pauling et al then were able to prove that sickle cell patients had hemoglobin that was distinguished from normal hemoglobin which is present in normal individuals. They achieved this using the techniques of protein electrophoresis. The cause of these abnormalities in hemoglobin was later discovered by Venon Ingram and J. A. Hunt in the year 1956 when the sequenced hemoglobin molecules in sickled cells and were able to discover the presence of substitution of valine for glutamate on the sixth position of the gene responsible for the sickle beta-hemoglobin. This change in the gene was discovered in 1977 to be due to changes in the sixth codon from GAG to GTG within the beta-globin gene. Several more studies have been conducted on the pathophysiological mechanisms of sickle cell disease to lead to more understanding of the disease and become able to provide improved amd more advanced modalities of treatment [2].

Sickle Cell Mutation Origin

The genetic mutation responsible for the development of sickle cell disease is thought to have originated from Asia and Africa. In fact, researchers believe that the disease is a result of the natural mutation of the gene of beta-hemoglobin that affected gametes and was later transferred to later generations. To further understand this, researchers were able to characterize 4 haplotypes (originating from Africa) and 1 haplotype (originating from Asia) using the techniques of restriction fragment length polymorphism analysis. These 4 African haplotypes are Benin, Senegal, Cameroon, and Bantu [3]. The most severe subtype of sickle cell disease is considered to be the Bantu subtype, while, on the other hand, the Asian subtype (known as Arab-Indian sickle disease) is considered to be the mildest sickle cell disease [4].

Sickle cell disease can also be found in other regions around the world like Europe and the United States. This is believed to be a result of migration and marriage. Some studies have suggested that sickle disease has higher prevalence in sub-Saharan Africa because of its beneficial effects against infections with *Plasmodium falciparum.* In fact, sickle cell trait can provide protection to individuals against infection with *Plasmodium falciparum*. Thus, this gene has been able to continue and survive through generation in areas where malaria is highly prevalent. This whole mechanism is usually called balanced polymorphism [5].

Genetics

Studies conducted by Pauling et al have concluded that sickle cell disease is a result of molecular defects in hemoglobin. It is known to be transmitted through generations by an autosomal recessive manner. Ingram et al. were able to prove that the mutation causing sickle cell disease as a result of substation of glutamine to valine on the sixth position of the beta globin gene. When the cloning of human hemoglobin genes was achieved, many years later, the sequence of the DNA involved in the mutation became known, with characterization of hemoglobin gene clusters

[6].
In humans, hemoglobin consists of a molecule in a tetrameric shape, which in turn is consisted of two polypeptide subunit identical pairs. These subunits are coded by different genes in the human genome. Chromosomes 16 and 11 have the alpha globin and beta globin genes, respectively. Another type of globin, known as F, is found dominant in fetal life. One less common subtype of globin is alpha 2, which is present in less than 2.5% hemoglobin molecules in normal adults [7].

In patients who have the sickle cell gene, the clinical picture of the disease will start to manifest when hemoglobin switches from the F type to the alpha type (at about six months of age). Therefore, one of the common treatment modalities is the stimulation of F hemoglobin production in adults with sickle cell disease. This modality was approved by the FDA, which led to hydroxyurea use in sickle cell patients [8].

The most common and severe phenotype of sickle cell disease results from the presence of a homozygous state of the sickle mutation. Other less possible phenotypes result from different interactions between mutated and normal beta globin genes. For example, a sickled beta gene may interact with another thalassemic beta gene leading to a sickle disease whose severity will vary according to the thalassemia severity [9].

Pathophysiology
The first and most clear change that results in sickle disease is the change in the shape of the red blood cell to form polymers of intracellular hemoglobin which will directly influence the plasma membrane of red cells. This will eventually lead to the exposure of glycolipids and epitopes out of the cell. All these previous modifications in the expression and morphology of the hemoglobin will lead sickled red cells to adhere to the endothelium of the vessels. Many studies have been conducted to study this adhesion on a molecular level, due to its importance in the clinical picture and vaso-occlusive events in patients with sickle disease. These studies produced important results that led to the development of potential therapeutic agents that will target these adhesion pathways to decrease the rates of vaso-occlusive [10,11].

The development of sickle mouse models has led to significant improvements in our knowledge of sickle disease. Models are produced with controlling globin chains, MCHC, and hemoglobin types. However, scientists have not been able to produce mouse models that show severe clinical manifestations that are similar to those observed in humans. Still, these models provide significant benefits in the research on sickle disease [12].

Sickle mouse models have shown the involvement of inflammation and inflammatory reactions in the pathophysiological pathway of sickle cell disease. These inflammatory reactions are thought to be stimulated by the abnormal shape of red blood cells along with the constant presence of hemolysis. Moreover, sickle cells usually develop dehydration which can also trigger inflammatory reactions. All these reactions and abnormalities will aid the development of a negative charge on glycolipids which will cause the activation of the coagulation cascade. This activation will cause thrombin and tissue factor to be generated leading to more inflammatory reactions. In addition, the constant presence of hemolysis leads to the presence of high levels of hemoglobin which is plasma-free. This hemoglobin has the ability of scavenging NO and damaging the endothelium. In addition, iron present in the heme molecule will be released following the lysis of red cells, causing oxidative stress which will further enhance inflammation [13].

Another crucial mechanism in the development of vaso-occlusive events in the leukocytic adhesion phenomenon. The importance of this mechanism comes from the potential use of it as a target of new therapies. Moreover, the presence and amount of leukocytic adhesion have been found to be correlated with several poor outcomes including acute chest syndrome, strokes, and higher mortality [14].

Management
Diagnosis
It is usually simple to establish a diagnosis of sickle cell disease. This simplicity comes from the dominant presence of hemoglobin in blood, which can be easily examined. The most widely used technique used in the diagnosis of sickle cell disease is electrophoresis that separates diseased hemoglobin molecules from normal hemoglobin molecules. This technique uses isoelectric focusing, high performance liquid chromatography, standard alkaline gel, or capillary electrophoresis [15].

On the other hand, chemical tests and other solubility tests which are generally used to detect hemoglobin S are not recommended to use when confirming a diagnosis of sickle disease. This is because their relatively high liability to errors [15].

Finally, some more advanced modalities of treatment

have been being developed to diagnose sickle cell disease more rapidly and accurately. These include the use of DNA and antibodies in detecting the disease [16].

Blood transfusion and iron chelation

The first step in the management of acute sickle attacks, chronic sickle cell disease, and sickle disease complications, is transfusion of red blood cells. This transfusion is effective as it leads to anemia correction, decline in hemoglobin S concentrations, suppression of the syntheses of hemoglobin S, and significant reduction in hemolysis. All these results of transfusion will lead to immediate improvement of the clinical picture. Transfusion can be administrated simply or exchanged with the patient's blood, which is usually needed in cases where the concentration of hemoglobin is high, or when the clinical manifestations are severe and require immediate correction of the hemoglobin S concentrations. In addition, people who present with sickle disease complicated by neurological symptoms also require exchange transfusion to prevent increased viscosity of the blood [17].

Generally, sickle cell patients have a relatively higher risk of alloimmunization following blood transfusion. This could be explained by the mutual origins between patients and donors. This issue is usually overcome in regions where, for example, most donors originate from Europe leading to significant reduction of alloimmunization risk [18].

Another complication of blood transfusion is iron overload, which will definitely occur following chronic multiple transfusions. However, the mechanisms by which iron overload causes hemosiderosis seem to differ from those in patients with thalassemia. The main difference between the two diseases is the difference in target organs [19].

The high prevalence of iron overload among sickle cell patients makes iron chelation essential in any sickle cell patient who routinely receives blood transfusions. This is achieved by several methods including the parenteral administration of desferrioxamine or the oral intake of deferasirox [19].

Induction of Hb F

Several studies have been conducted on hemoglobin F, with increasing evidence that supports its use in patients with sickle cell disease to decrease the severity of clinical manifestations. This was first noticed in patients who originated from India and Saudi Arabia, and showed mild clinical picture of sickle disease, along with the presence of higher concentrations of hemoglobin F in their blood [20]

Later, it was established that hemoglobin F acted as a prognostic factor that reduced the risk of complications like pain attacks, acute chest syndrome and mortality. Several hypotheses have been made to explain the mechanism in which hemoglobin F improves sickle cell clinical picture. One of these mechanisms is the possible interference of hemoglobin F with the polymerization process that deoxygenated hemoglobin undergoes. These proposed mechanisms paved the way for the use of hemoglobin F production for the pharmacological treatment of sickle cell disease [21].

Hydroxyurea

Hydroxyurea was developed as a pharmacological agent that stimulated the induction and production of hemoglobin F in patients with sickle cell disease. Moreover, hydroxyurea works in inhibition of ribonucleotide reductase and this mechanism is beneficial for myeloproliferative disorders treatment. Hydroxyurea is tolerated orally and used simply. The use of hydroxyurea was tested in several trials in human adults with sickle disease. It has been found to lead to significant decline in pain attacks, acute chest syndrome, and vaso-occlusive events, along with less need for blood transfusion and exchange. Moreover, the use of hydroxyurea led to less hospitalization in patients with severe sickle disease. After nine years of treatment with hydroxyurea, sickle cell patients showed significantly improved survival. Several other studies were also conducted to study the efficacy of hydroxyurea in children with sickle cell disease [22].

More recent laboratory studies have concluded that hydroxyurea also acts by in-vivo generating NO, which will cause NO/cGMP activation along with upregulation of the gene expression of gamma globin in patients who have sickle cell disease. Patients with sickle cell disease can benefit from other mechanisms also. As an example, hydroxyurea was also seen to be associated with a decline in soluble VCAM-1 expression. In addition, its activity in myelosuppression aids in decreasing the count of circulating white cells and thus the rate of leukocytic adhesion to the walls of vessels. This will further benefit patients by decreasing rates of vaso-occlusive events [23].

Other mechanisms by which hydroxyurea works are still not clear and require further studies and research to be established and proven.

Bone marrow transplantation

One of the therapeutic approaches in the treatment of sickle cell disease is replacing the whole diseased bone marrow, which is in fact the source where dysfunctional sickled cells emerge, with a normal bone marrow that can produce normal red cells. This approach can provide definitive treatment of the disease. However, it has been considered too invasive for a patient who does not have a malignancy. Moreover, it is associated with a relatively high mortality rates that can reach 20% [24].

Recent advances in therapeutic immunosuppression along with supportive care both led to improved survival following bone marrow transplant, and it was thus used in patients with beta-thalassemia and led to significantly improved survival rates. These improvements changed the general thoughts about these therapeutic approaches and led to the conduction of several trials to study bone marrow transplant in children with sickle cell disease. These trials were conducted in several regions of the world and showed an improved survival that reached more than 90% [25].

Despite this efficacy and improved safety of bone marrow in treating sickle cell disease, finding a matched donor remains a huge limitation that limits the availability of this treatment to less than 15% of sickle cell patients [25].

Recently, several trials have been conducted to assess the transplantation of cord blood in sickle cell disease treatment. The main aim of this treatment is to provide a more available treatment than bone marrow transplantation[26].

Up till now, the number of bone marrow transplantation operations in adults with sickle disease has been very low. This is due to higher concerns in adults than children regarding morbidity and mortality following the procedure. On the other hand, nonmyeloablative bone marrow transplant has been used in attempts for decreasing the mortality following the transplantation. However, this was associated with a higher risk of graft rejection [25].

Despite all disadvantages and limitations, bone marrow transplantation remains to be the only treatment modality that provides definitive treatment for patients with sickle disease.

Management of Complications

Acute clinical complications

Patients with sickle disease can suffer from a large number of complications, which can be attributed to the complexity of the disease's pathophysiology. These complications can include infections, infarctions, vaso-occlusive events anemia, and other possible complications. Developed countries have relatively low mortality for sickle children with acute complications, but higher mortality for sickle adults, as those can suffer from chronic multi-organs failure. Moreover, strokes and acute chest syndromes are considered serious with higher mortality rates [27].

The most important clinical manifestation of sickle disease is the development of acute pain. This could potentially reflect the presence of vaso-occlusion along with impairments in the supply of oxygen. It can also be a result of an infarction-reperfusion injury. in infants and children, dactylitis may occur leading to painful bones in several regions of the body. During these pain attacks, opioids are administrated along with NSAIDs to relief the pain [27].

Bacterial infections:

These infections are considered serious and cause more severe diseases than the general population due to the presence of significant damage to the spleen, which develops in all sickle patients as a result of intraparenchymal occlusion. This asplenia make sickle patients, since childhood, vulnerable to infections and severe complications including meningitis, sepsis, and pneumonia [28].

Encapsulated organisms are more common in these patients due to the damaged liver. These organisms include *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Therefore, the Pneumococcal conjugate vaccine has been recommended for all sickle cell patients and led to a significant decline in the rates of pneumococcus infections in this population. however, there are still concerns regarding the emergent of new strains of the bacteria that are resistant to the vaccine[29].

Other than vaccination, young children with sickle cell are recommended to receive penicillin prophylactically and should be educated to immediately seek medical advice whenever they develop fever or any systemic symptoms. In these cases, immediate blood culture is warranted [28].

Acute chest syndrome:

It is defined by the development of new infiltration into the lung, with the presence of fever, increase respiratory rate, severe pain, cough, or wheezing. Acute chest syndrome is considered one of the most common causes of death among young adults with sickle cell disease.

Management of a patient with acute chest syndrome should include the immediate initiation of antibiotics that cover mycoplasma, pneumococcus, and chlamydia. It is also important to provide oxygen therapy and blood transfusion. Immediate exchange transfusion should be performed in cases with worsening oxygen saturation [30].

Other complications:

Progressive anemia in sickle patients could be a result of several mechanisms like transient red cell aplasia, acute splenic sequestration crisis, or hemolysis. Strokes can also occur in sickle cell patients and are more common in children, leading to neurological dysfunctions and infarctions. If strokes occur in adults, a cerebral hemorrhage is more common to occur [31].

Chronic organ complications

Our understanding of chronic damage that occurs to body organs in sickle disease is relatively low. It is thought that mechanisms involving infarctions, vaso-occlusive events, and hemolysis will all contribute to the development of a long-term damage to the body organs and lead to multi-organs failure later in life, worsening quality of life, and increased mortality. In fact, when a sickle patient reaches the third decade of life, organs failure becomes one of the main causes of death [32].

In a large retrospective cohort on sickle adults, about half the deaths were attributed to either pulmonary or cardiac causes. Moreover, adults with sickle cell disease have higher rates of developing pulmonary hypertension and diastolic heart disease, which are both correlated with increased mortality. Anemia and hemolysis have both been thought to be causing these consequences, but these hypotheses still lack evidence to support it [31].

Currently, several interventions are present to decrease the risk of developing these long-term complications. These interventions include hydroxycarbamide, bosentan, riociguat, and chronic blood transfusion. However, none of these interventions has been able to prove efficacy in decreasing the risks of developing a chronic organs failure [33].

CONCLUSION:

Sickle disease is a common and serious hematological disease that is affecting an increasing number of individuals. It is transmitted in an autosomal recessive manner and is known to have a wide variety of clinical manifestations and late complications. Complications can be severe and lead to significant increases in morbidity and mortality. Previous clinical trials have demonstrated high efficacy and improvement of symptoms when using hydroxyurea and blood transfusions. Other more recent interventions aim at larger improvement in clinical picture, and further decreasing the rate of developing vaso-occlusive events and related complications. It is also important to develop therapeutic options that reduce the risk of developing multi-organs failure. Despite all advances in treatment, sickle cell disease remains to be an important serious disease that is associated with severe morbidity and mortality, and poor quality of life. More research and clinical trials should be conducted on this disease to develop advanced treatment options that will further improve quality of life and decrease mortality and complications.

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