



SICKLE CELL ANEMIA AN UPDATED REVIEW

Hematology

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ABSTRACT

This paper evaluations Sickle cell anemia. Sickle cell anemia is a homozygous shape of HbS (HbSS). This result from single factor substitute of glutamine with the aid of valine at role 6 of β -globin chain. This reduces solubility of the red cells which in flip leads to polymerization and vaso-occlusion in the vasculature. The β -globin gene is determined on the short arm of chromosome eleven the affiliation of two mutant β -globin subunits types haemoglobin S (HbS). Under low - oxygen conditions, the absence of a polar amino acid at function of six of the β -globin chain promotes the non - covalent polymerization of hemoglobin, which distorts red blood cells into a sickle structure and decreases their elasticity. In sickle cell disease, low oxygen anxiety promotes red blood cell sickling and repeated episodes of sickling injury the cell membrane and decreases the cell's elasticity. These cells fail to return to ordinary form when ordinary oxygen anxiety is restored. As a consequence, these inflexible blood cells are unable to deform as they omit thru slim capillaries, leading to vessel occlusion and Ischemia. The authentic anemia of the sickness is induced via haemolysis, the destruction of the red cells internal the spleen. Those struggling from this sickness are existing with persistent anemia which these with everyday adult hemoglobin genotype will now not live on due to the fact of the misshape of the cells main to destruction of the cells at the spleen.

KEYWORDS

Sickle cell disease (SCD), Sickle cell anemia, pathophysiology, Genetics of Sickle cell anemia, Crisis and Treatment.

INTRODUCTION

Sickle cell anemia is a homozygous state induced by means of a mutation in the β -globin gene. This hemolytic anemia is characterized via vaso-occlusive disease, enormous acute and chronic organ injury and a decreased lifespan. Patients with this disorder are dwelling longer, new treatments are turning into accessible for adults as nicely as children, and early detection does matter. Almost each and every nation in the United States displays the blood of all newborns for SCD. For example, hemoglobinopathies, in which the sickle gene is inherited from at least one parent. These genetic issues are characterised through the manufacturing of HbS, anemia, and acute and continual tissue harm secondary to the blockage of blood flow produced with the aid of abnormally shaped red blood cells.

Sickle cell anemia sufferers have frequently HbS (more than 70% of hemoglobin) in their purple cells. It has been recommended that HbS presents safety towards falciparum malaria. Sickle - cell disorder or sickle cell anemia (or depanocytosis) is a existence -long blood disorder characterized by way of purple blood cells that anticipate an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and effects in a danger of various complications. The sickling happens due to the fact of a mutation in the hemoglobin gene. Life expectancy of 42 and forty-eight years for adult males and females, respectively [1]. Since the first description of the irregular sickle-shaped red blood cells (RBC) greater than a hundred years ago, our grasp of the sickness has developed tremendously. Recent advances in the field, extra so inside the remaining three decades, have led to the alleviation of signs for limitless patients, mainly in high-income countries. In 1984, Platt et al. first mentioned the use of hydroxyurea in growing the tiers of HbF. [2]

ETIOLOGY

Hemoglobin (Hb) is a principal protein inside the purple blood cell (RBC). It is made up of 4 globin chains, two of which are derived from alpha-globin (locus on chromosome 16) and two from beta-globin (locus on chromosome 11). There are many subtypes of Hb. The most frequent ones that are discovered in adults besides hemoglobinopathies are listed here:

HbA1- contains two chains of the alpha-globin and two chains of the beta-globin (a2b2) - This constitutes 95% of the person hemoglobin.

HbA2- involves two chains of the alpha-globin and two chains of the delta-globin (a2d2) - This constitutes less than 4% of the person hemoglobin.

HbF- includes two chains of the alpha-globin and two chains of the

gamma-globin (a2g2) - This Hb is more prevalent in the fetus (due to excessive oxygen binding affinity that helps in extracting oxygen from maternal circulation).

The sickle cell mutation happens when negatively charged glutamine is changed through a impartial valine at the sixth position of the beta-globin chain. The mutation is transmitted by means of Mendelian genetics and is inherited in an autosomal co-dominant fashion.[3]

A homozygous mutation leads to the severest structure of SCD, i.e., SCA- additionally known as HBSS disease. A heterozygous inheritance leads to HbAS. Patients with HbAS are no longer regarded inside the spectrum of SCD as most of them by no means existing with traditional signs of SCA. They would possibly solely be detected at some point of screening procedures conducted for the duration of childbirth, blood donation, etc.

Several different compound heterozygote exist the place a single replica of the mutated beta-globin gene is co-inherited with a single reproduction of some other mutated gene. The 2nd most frequent variant of SCD is the HbSC disease, the place the sickle cell gene is co inherited with a single reproduction of the mutated hemoglobin C gene. HbC is shaped when glutamine is replaced by means of lysine at the sixth function on the beta-globin chain. HbSC disorder accounts for 30% of sufferers in the United States.

EPIDEMIOLOGY

The epidemiological records on SCD is scarce. It is nicely regarded that SCD and HbAS are greater well-known in sub-Saharan Africa, the place the service of HbAS is afforded natural safety in opposition to extreme Plasmodium falciparum malaria. It is estimated that ~230,000 adolescents have been born with SCA, and extra than 3.5 million neonates had been born with HbAS in sub-Saharan Africa in 2010. an estimated 75% of the SCD associated births take location in sub-Saharan Africa. West Africa is domestic to the biggest populace of men and women with HbSC disease.[4]

The United States (US) Center for Disease Control (CDC) estimates that about 100,000 Americans have SCD. The CDC additionally estimates that 1 in thirteen children born to African-American mother and father have sickle cell trait, and 1 in 365 African-Americans have SCD. The average ratio of Hispanic-Americans with Sickle cell disease is 1 in 15,200. Children and adolescents make up to 40% of all the SCD sufferers in the US. The incidence varies by means of kingdom and geographical concentration of ethnicities. Besides, the migration inside the USA and immigration from overseas international

locations alter the prevalence of SCD and HbAS. This is authentic for quite a few international locations the place sufferers with SCD and SCA are living. Genetic studies in Brazil have additionally tied the beginning of such sufferers to the slave alternate originating from West Africa (Mina Coastland Angola).[5]

With the enhancement in science and ease of global migration, the incidence of SCA is predicted to upward push in the future. It is estimated that the annual range of newborns with SCA will exceed 400,000 through the year 2050.

PATHOPHYSIOLOGY

SCA is characterised via two fundamental components: Hemolysis and vaso-occlusive crises (VOC). The defect in the beta-globins gene makes the sickle hemoglobin (HbS) molecule inclined to convert into rigid, elongated polymers in a deoxygenated state. The sickling system is cyclical initially, where sickle erythrocytes oscillate between the normal biconcave form and the extraordinary crescent form (acquired underneath low oxygen pressure). However, there comes a time when the trade will become irreversible, and the sickle erythrocytes gather a everlasting sickle form growing the risk for hemolysis and VOC. All versions of SCD share the equal path physiology main to polymerization of the HbS component.[4]

Multiple elements inherent to sickle erythrocyte like low affinity of HbS to oxygen, physiologically excessive 2,3-diphosphoglycerate, and extended sphingokinase-1 recreation lead to deoxygenation, which promotes polymerization of HbS. In addition to this, excessive attention of HbS, unusual endeavor of Gados channel main to dehydration, and repeated injury to purple blood cell (RBC) membrane additionally extend the threat of polymerization of HbS.

Oxidative stress contributes to hemolysis with the aid of auto-oxidation of HbS, main to harm of the erythrocyte cell membrane. The expanded expression of xanthine dehydrogenase, xanthine oxidase, and reduced expression of NADPH oxidase make bigger the oxidative stress inside sickle RBC. A hemolyzed mobile releases free hemoglobin (scavenges nitrous oxide) and arginase 1 (competes for L-arginine) that forestall the motion and formation of nitrous oxide and make a contribution to oxidative stress and vascular redesigning (arginase-1 converts arginine to ornithine).[4]

Besides the polymerization of the HbS and intravascular hemolysis, numerous different elements additionally make a contribution to vaso-occlusion. The sickle RBC (expresses countless adhesion molecules on the surface), free heme and Hb, reactive oxygen species, and endothelium engage with every different and with neutrophils and platelets to promote vaso-occlusion and thrombosis.

CLINICAL FEATURES

Acute crises are brought on by means of recurrent obstruction of the micro circulation by means of intravascular sickling. Aside from the painful crisis, sickling takes its toll on the physique in different ways. Through the years, the cumulative injury from vascular occlusion can lead to organ and tissue failure. Other complications may consist of an enlarged heart, modern loss of pulmonary or renal function, stroke, arthritis, liver damage, and different complications. There is significant activation of coagulation with consequent expand in fibrinolysis during both the sickle phone disaster and in the consistent state. There is version in the severity of SCD. Many patients are moderately nicely and have surprisingly few complications. However, 5% to 10% of sufferers account for 40% to 50% of hospital visits.

Chronic Hemolytic Anemia

Patients go through from lifelong hemolysis, however most sufferers have moderate anemia. Hemolysis is normally extravascular, however sickled crimson cells being automatically fragile can purpose intravascular hemolysis also. Chronic hemolytic anemia motives expanded tiers of unconjugated (indirect) bilirubin, which predisposes to improvement of pigmented bilirubin gallstones. Cholelithiasis may lead to cholecystitis.

CRISES

Any new syndrome or episode that develops hastily in sickle cell anemia is termed crises. The Protracted path of sickle cell anemia is often exacerbated through a range of crises. Four types of crises are encountered. These are:

1. Sickling disaster (vaso-occlusive/pain/painful/infective crisis) The most frequent and the hallmark of sickle cell sickness is vaso-occlusive crisis. Blockage of Microcirculation via sickled pink cells reasons hypoxic damage and infarction. Clinically it presents with acute, extreme ache in the affected vicinity (severe abdominal, thoracic, muscle or bone pain).

This kind of crises may also be precipitated by using fever, contamination and dehydration (conditions which favor sickling) or may additionally be except any predisposing cause. It regularly includes bones, lungs, liver and spleen.

- Bone: In children, bone involvement might also resemble acute osteomyelitis. They show up as the hand-foot syndrome, dactylitis of the bones of the palms or toes or both.
- Lung: It gives with fever, cough, chest ache and pulmonary infiltrate which is acknowledged as acute chest syndrome (dangerous). These are once in a while initiated by way of a easy lung infection.
- Spleen: Acute belly ache lasting for 4-5 days, may additionally be the supplying symptom caused by infarcts of belly viscera due to vaso-occlusive crises lasting 4-5 days. Recurrent splenic infarction leads to entire involution of spleen with impaired or absent splenic function (autosplenectomy).

Hyper hemolytic crisis

This is uncommon kind and affords with marked extend in hemolysis with a surprising decreasing of hemoglobin and reticulocytosis.

Aplastic crisis

A transient cessation of bone marrow erythropoiesis can also strengthen due to an acute contamination of erythroid progenitor cells by using parvovirus B19. Reticulocytes disappear from the peripheral blood causing a surprising and fast worsening of anemia. Recovery starts offevolved inside 5 to 10 days.

Sequestration crisis

Usually happens in teens with chronically enlarged however everyday functioning spleen. Sudden trapping of blood in spleen or liver reasons speedy growth of the organ with resultant drop in hematocrit and hypovolemic shock.

Other crises encountered hardly ever are hypoplastic disaster and megaloblastic disaster (due to inadequate folate).

Infections

Children with sickle cell anemia are prone to acute infections with encapsulated organisms. Common infections are pneumonia due to pneumococcus, meningitis due to S. pneumonia and osteomyelitis due to Salmonella. Increased susceptibility to infections is because of:

1. Hypo-function of spleen

- In children, it is due to congestion and negative blood flow.
- In adults, it is due to a couple of infarcts and resultant auto splenectomy.

2. Defects in the choice complement pathway

This defect impairs opsonization of encapsulated microorganism such as pneumococci and Haemophilus influenzae. Septicemia and meningitis are the most frequent motives of dying in children. Increased frequency of osteomyelitis

LABORATORY DIAGNOSIS SICKLE CELL ANEMIA

Peripheral Blood

- Hemoglobin: It is lowered and typically in the vary of 5-10 gm/dL.
- Hematocrit (PCV) : Decreased and generally in the vary of 18 to 30%.
- Reticulocytosis: Increased reticulocyte count number and generally in the vary of 5 to 20% is observed.
- Higher reticulocyte matter is discovered when hemolysis is of extreme degree.
- ESR: Low due to the fact sickle cells do no longer structure rouleaux.
- Peripheral smear

RBCs:

- Red blood cells are normocytic normochromic to mildly hypochromic.
- There is average to extreme degree of anisopoikilocytosis.

- The attribute cell which is viewed in the smear is the sickle cell. These show up as long, curved cells with pointed ends. Smear might also additionally exhibit goal cells (due to red cell dehydration) and ovalocytes. Number of sickle cells is variable.
- There is polychromatophilia due to reticulocytotic.
- Few RBCs exhibit Howell- Jolly our bodies (small nuclear remnants), which is due to hypofunction of spleen ensuing from auto splenectomy.
- Few nucleated RBCs are additionally observed.

WBCs: Total rely is mildly elevated with shift to left as in most different hemolytic anemias.

Platelets: Platelet count number is mildly increased.

Bone Marrow

- Cellularity: Bone marrow is hypercellular.
- Erythropoiesis: The bone marrow hypercellularity is due to the fact of a compensatory normoblastic erythroid hyperplasia. However, persistent hemolysis can end result in secondary folate deficiency and bone marrow might also exhibit megaloblastic kind of hyperplasia.
- Bone marrow hyperplasia expands the marrow inflicting desorption of bone and secondary new bone formation. In extreme cases, these adjustments end result in outstanding cheek bones and skull bone which resemble a crew-cut in roentgenograms.
- Myelopoiesis: Within everyday limits.
- Megakaryopoiesis: Within everyday limits.
- Iron stores: These are normally increased.

TREATMENT

Bone marrow transplant gives the solely workable therapy for sickle cell anemia. However, finding a donor is difficult and the procedure has serious dangers related with it, together with death. Conventional administration of sickle cell anemia is primarily supportive. It is necessary to discover infections early and deal with them with antibiotics, as these infections may trigger painful and aplastic crises. General supportive care includes day by day oral folate supplementation, antibiotic prophylaxis in childhood, Pneumovax, Haemophilus influenzae vaccine, meningococcal vaccine, each year flu shot, a every year eye examination, instantaneous cure of infections, and avoidance of dehydration. Treatment of ache crises consists of hydration, adequate analgesia, and ample oxygenation. Exchange transfusions may also play a confined function in treatment, however possible reasons for their use encompass prevention of stroke recurrence, acute chest syndrome, in practice for elective surgery, refractory priapism, refractory ache crises, and splenic sequestration crises.[6]

Experimental remedy methods include

- Gene therapy. Gene remedy entails inserting a normal gene into the bone marrow of sufferers with sickle cell anemia to produce regular hemoglobin. Another approach is to try to flip off the faulty gene whilst reactivating another gene accountable for the manufacturing of Hb F.
- Butyric acid. Butyric acid is typically used as a meals additive but it might also extend the quantity of Hb F in the blood.
- Clotrimazole. This over-the-counter antifungal medication helps prevent a loss of water from red blood cells, which might also limit the range of sickle cells that form.
- Nitric oxide. Abnormal characteristic of the cells lining blood vessels may additionally make contributions to the issues of SCD. Disruption in the synthesis of nitric oxide, an important regulator of blood vessel relaxation, contributes to these abnormalities. Treatment with nitric oxide may additionally prevent sickle cells from clumping together.
- Nicosan. This is a natural remedy in early trials in the United States. Nicosan has been used to forestall sickle crises in Nigeria, West Africa.

CONCLUSION

Sickle cell anaemia is a homozygous structure of HbS(HbSS). This end result from single factor replacement of glutamine by means of valine at function 6 of β - globin chain. This reduces solubility of the red cells which in turn leads to polymerisation and vaso-occlusion in the vasculature. The affiliation of two mutant β -globin subunits types haemoglobin S (HbS). Under low - oxygen conditions, the absence of a polar amino acid at position of six of the β - globin chain promotes the non - covalent polymerization of haemoglobin, which distorts red

blood cells into a sickle form and decreases their elasticity. As a consequence, these inflexible blood cells are unable to deform as they pass by via narrow capillaries, main to vessel occlusion and Ischemia. Proper and sufficient counseling have to be given to intending couple earlier than marriage and hemoglobin genetic counseling and schooling should be blanketed in the curriculum of scholars and students from major faculty to tertiary training tiers to avert the pains and the disaster related with the burden of sickle cell anaemia and the sources to take adequate care of them.

REFERENCES

1. Platt OS, Brambilla DJ, Rosse WF; Mortality in Sickle Cell Disease. Life Expectancy and Risk Factors for Early Death. *N. Engl J Med*, 1994; 330(23): 1639-1644
2. Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B, Nathan DG. Hydroxyurea enhances fetal hemoglobinproduction in sickle cell anemia. *J Clin Invest*. 1984 Aug;74(2):652-6.
3. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. *Am J Hematol*. 2012 Aug;87(8):795-803.
4. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, Smith WR, Panepinto JA, Weatherall DJ, Costa FF, Vichinsky EP. Sickle cell disease. *Nat Rev Dis Primers*. 2018 Mar 15;4:18010.
5. Naoum PC. Sickle cell disease: from the beginning until it was recognized as a public health disease. *Rev Bras Hematol Hemoter*. 2011;33(1):7-9.
6. Turgeon ML. Hemoglobinopathies and Thalassemias. In: *Clinical hematology: theory and procedures*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. p. 216-217.