Review Article.

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A Critical Interpretation on Sickle Cell Anaemia: A Genetic Disorder A Brief Review Study

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ABSTRACT

HbS is a homozygous type of Sickle Cell Anaemia (HbSS). This is the product of a single point substitution of β-globin chain valine for glutamine 6. This limits the solubility of the red cells, which in turn leads to the polymerization and vaso-occlusion of the vasculature. The gene for β-globin is found in the short arm of chromosome 11. The combination of two β-globin mutant subunits forms haemoglobin S (HbS). Under low-oxygen conditions, the absence of polar amino acid at the six-point position of the β-globin chain promotes non-covalent hemoglobin polymerization, which distorts the composition of red blood cells in the sickle and decreases their elasticity. Low oxygen tension in sickle cell disease promotes the sickling of red blood cells and frequent episodes of sickling weaken the cell membrane and reduces the elasticity of the cell. When normal oxygen voltage is restored, these cells fail to return to normal form. As a result, these compact blood cells cannot deform as they travel through small capillaries, leading to occlusion of the arteries and Ischemia. The underlying condition anaemia is caused by hemolysis, the breakdown of the red cells within the spleen.

KEYWORDS: Sickle cell anaemia, pathophysiology, Genetics, etc

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INTRODUCTION

A life-long blood condition characterized by red blood cells that adopt an irregular, stiff, sickle form is sickle - cell disease or sickle cell anemia. Sickling reduces the flexibility of the cells which results in the possibility of multiple complications. In the hemoglobin gene, the sickling happens because of a mutation[1]. Sickle cell disease, which typically occurs in infancy, occurs most often in people from areas of the tropical and subtropical regions where malaria, as the infestation of plasmodium malaria is prevented by the sidelines of the cells it infects. Sickle cell anemia is a group of diseases known as sickle cell disease. Anemia from sickle cells is a red blood cells genetic condition that does not supply oxygen in the body to healthy red blood cells. The blood vessels normally have flexible, circular red blood cells traveling quickly. Red blood is formed as sickles or crescent lunes in sickle cell anemia. Solid, adhesive cells can be locked into tiny blood vessels that can delay or hinder blood and oxygen from passing into areas of the body.

AIMS AND OBJECTIVES

Detail and descriptive study of Sickle cell anemia.

MATERIAL AND METHOD

Sickle cell anemia material have been obtained from various publications, current text books, reputed authoritative blogs, authoritative literature, manuscripts, etc.

CONCEPTUAL STUDY

HISTORY OF SICKLE CELL ANAEMIA

The origin of the condition was traced back to 1670 in a single Ghanaian family[2,3]. Linus Pauling and colleagues were the first to prove, in 1949, that sickle cell disease is caused by an abnormality in the hemoglobin molecule. This was the first time a genetic disorder had been related to a mutation in a single protein, a landmark in the development of molecular biology, and it has been published in their article, Sickle Cell Anemia, a Molecular Disease.

CLASSIFICATION OF SICKLE CELL ANAEMIA

The most prevalent type of sickle cell anemia is the inheritance of homozygous HbS. The next most common form of sickle cell anemia is the co-inheritance of HbS and HbC—referred to as HbSC, which is most prevalent in Western Africa, especially Burkina Fasso and Mali, and in coastal countries such as Ghana, Benin and Western Nigeria[4, 5, 6]. Co-inheritance of β thalassemia results in a sickle β thalassemia genotype (HbS/βo or HbS/β+), based on the genetic lesion of the thalassemia portion, the clinical manifestation can be mild or as extreme as the homozygous sickle cell

anemia (HbS/HbS) [7].HbS/βo-thalassemia patients have a more serious path of disease compared to homozygous SS patients, while HbS/β+-thalassemia-dependent offspring of β-globin mutation are associated with variable phenotypes of moderate to severe Sickle Cell disorder phenotypes[8, 9].

PATHOPHYSIOLOGY

The sickle cell anaemia pathophysiology. Red blood cells that produce HbS or HbS in conjunction with other irregular β-alleles when subjected to deoxygenated environments undergo polymerization and become rigid[10.] RBC rigid are vulnerable to hemolysis and can affect blood supply and endothelial wall integrity due to increased density[11, 12, 13].

During deoxygenation; stable haemoglobin is rearranged into a different conformation, allowing the binding of carbon dioxide molecules that return to normal when released[14]. In the other side, HbS continues to polymerize into hard insoluble strands and which are gel-like compounds comprising Hb crystals. Intravascular hemolysis results in free haemoglobin in the serum during acute sickling, while RBC gains Na+, Ca2+ with resulting depletion of K+[15,16,17]. Erythrocyte lyses result in an increase in extracellular haemoglobin, thereby increasing affinity and binding to available nitric oxide or nitric oxide precursors, thereby reducing its levels and thus leading to vasoconstriction[18.]

GENETICS OF SICKLE CELL ANAEMIA

A single difference in the amino acid allows fibers to form haemoglobin protein. Geographic regions of the sickle cell genome, as indicated by restriction studies of endo nucleases. Cameroon, Senegal, Benin and Saudi-Asian are referred to as these variations. Their clinical importance derives from the fact that some of them, such as Senegal and Saudi-Asian varieties, are associated with higher HbF levels, and appear to be milder[19]. The polymerization issues are small in people heterozygous for HbS since the typical allele is capable of generating over 50 percent of the hemoglobin. Sickle cell disorder occurs when glutamic acid, the seventh amino acid (if we count the original methionine), is substituted with valine in order to modify its structure and function[20]. The gene defect is a recognized single nucleotide (A to T) mutation of the p-globin gene that results in valine substitution of glutamate at position 6. In contrast to normal adult HbA, haemoglobin S with this mutation is referred to as HbS.

The genetic defect is due to a single nucleotide mutation, from a mutation of a GAG to a GTG codon. This is typically a mild mutation that causes no obvious effects on the haemoglobin initial, tertiary, or quaternary structure. Between the E and F helices, the deoxy form of haemoglobin reveals a hydrophobic patch on the protein. At position 6 of the beta chain in haemoglobin, hydrophobic valine residues may be associated with the hydrophobic patch, allowing haemoglobin S molecules to accumulate and form fibrous precipitates[21].

INHERITANCE OF SICKLE CELL ANAEMIA

Sickle cell anaemia is inherited by the parent in the same way as blood colour, hair color and texture, skin color and other physical features. A person's level of haemoglobin in red blood cells relies on what hemoglobin genes are derived by his or her ancestors.

CLINICAL SIGNS

Protein signs ranging from acute generalized pain to early onset stroke, leg ulcers and risk of premature death due to multi-organ failure are characterized by sickle cell anaemia[22]. As a consequence of the effect of HbF, clinical features do not begin until the middle to second part of the first year of postnatal life, where this has mainly transferred to adult haemoglobin.

VASO-OCCLUSIVE PAIN

Pain is the cardinal aspect of sickle cell anaemia and

is characteristically erratic, episodic in nature, described as one of the most exaggerating types of pain involving human beings. Pressure is triggered by inflammation of the nociceptive nerve fibers caused by microvascular occlusion. Some symptoms like-

(i) Ischaemia
(ii) oedema
(iii) discomfort
(iv) necrosis
(v) organ damage[23]

One of the cardinal characteristics in the first year of existence is 'hand-foot syndrome' due to vaso-occlusion of post-capillary vasculature resulting in tissue oedema and extremity pain[24], [25].

ANAEMIA

The most frequent symptom of sickle cell anaemia is symptomatic anaemia, generally more prevalent of sickle cell anaemia, which commonly has the lowest amount of haemoglobin common in double heterozygous states. However, the rate of drop from the person steady-state haemoglobin level can cause symptoms of hypoxia or shock-like conditions[26,27.]

ACUTE APLASTIC CRISIS

Parvovirus B19[28] is the most frequent cause of acquired bone marrow dysfunction in sickle cell anaemia and other haemolytic disorders. There is a small reduction in hematocrit in children with HbAA who are typically unaffected, but there is a substantial decrease in haemoglobin concentration in sickle cell anaemia as the lifespan of RBC is shortened to about 10–20 days. [29,30].

SPLENIC REQUISITIONING CRISIS

The spleen's key function is to eliminate defective red blood cells, including sickled red blood cells (sRBCs), resulting in further hemolysis[31]. The supply of blood into the spleen slows down oxygen stress and strengthens the polymerization of HbS. More hypoxia occurs with RBC polymerization and entrapment of affected blood cells as a feature of the narrow capillaries in the splenic vascular bed. This leads to a period of hypoxia, RBC polymerization, and insufficient blood flow that causes the spleento swell, and can occur spontaneously inside the vascular bed in the blood stream, leading to shock and circulatory failure for unexplained reasons.[32].

PSYCHOSOCIAL EFFECT

For patients and families, sickle cell anaemia has a major psychosocial impact[33]. This mainly derives from the effects of pain and symptoms on their personal lives, and society's attitudes towards them. Cultural effects are highly important to these issues because of beliefs and customs.[34,35].

GROWTH AND DEVELOPMENT

Children with sickle cell disease have observable growth retardation by 2 years of age that affects weight rather than height and may not have a significant gender disparity in Platt et al.,[36]. By maturity, normal height is reached, but weight remains smaller than that of the controls. There is also delayed skeletal maturation. [37].

NEUROLOGICAL COMPLICATIONS

Transient ischaemic attacks, brain infarction, cerebral haemorrhage, strokes, unexplained paralysis, spinal cord infarction or compression, central nervous system inflammation, vestibular dysfunction, and auditory hearing loss are the neurological complications found in 25 percent of patients with sickle cell disease[38.]

HEPATOBELIARY COMPLICATIONS

Centrilobular parenchymal atrophy, bile pigment, periportal fibrosis, haemosiderosis, and cirrhosis are seen by histological analysis of the liver..[39]

OCULAR COMPLICATIONS

Anterior chamber ischaemia, conjunctival vessel tortuosity, retina artery occlusion, proliferative retinopathy, and retinal detachment and haemorrhage can be ophthalmologic problems[40]. For patients with sickle cell disease, regular retinal testing is part of routine healthcare management.

BONE COMPLICATIONS

The product of extended hematopoietic marrow causing spreading of medullary space, thinning of trabeculae and cortices, and osteoporosis is the recurrent tower skull, bossing of the forehead, and fish mouth deformity of the vertebrae[41]. The first symptom of sickle cell disease is always the aggravating discomfort of bone infarction in 'hand-foot syndrome' that develops about the age of 12 years[42,43]. Arthritic pain, swelling, and effusion can be related to periarticular infarction or gouty arthritis.

DERMATOLOGIC COMPLICATIONS

Leg ulcers occur starting in the teenage years in patients with sickle cell disease. Near the lateral or medial malleoli, they usually arise and can become recurrent and crippling. It is possible that their pathogenesis is related to tissue necrosis. It primarily happens in males, those with more extreme anaemia, and those with lower levels of HbF. Cleansing, debridement, and topical antibiotics continue with the treatment of leg ulcers. Leg edema slows ulcer healing and can be treated with elastic wraps or raising of the leg.

CARDIAC COMPLICATIONS

Chronic sickle cell disease anaemia is offset by high cardiac production, which, often in young children, results in chronic enlargement of the chamber and cardiomegaly. Although a patient with sickle cells has limited capacity for exercise, congestive heart disease is unusual and limitations of motion are rarely required. Age-dependent cardiac reserve loss44 raises the risk of heart failure in adult patients during fluid overload, transfusion, reduced oxygen carrying capacity or hypertension.[45].

DIAGNOSIS OF SICKLE CELL ANAEMIA

The falling blood count (FBC) in HbSS shows haemoglobin levels with a high reticulocyte count in the region of 6-8g/dl. Hb levels tend to be higher than other types of sickle cell disease. By incorporating sodium meta bisulfite, the sickling of red blood cells on a blood film may be caused. It is also possible to show the existence of sickle haemoglobin with the' sickle solubility test.' In a reduction solution (such as sodium dithionite), a mixture of hemoglobin's (HbS) gives a turbid appearance, while regular Hb gives a smooth solution.

TREATMENT AND MANAGEMENT

Comprehensive sickle cell anaemia treatment is being managed in the United Kingdom by expert haemoglobinopathy teams[46]. These teams have an important role to play in supplying patients and their families with information on anaemia of the sickle cells and in directing therapies for illnesses, psychological entry, social and health service.

SUPPORTIVE MAINTENANCE

Since sickness, exposure to cold or dehydration, often exacerbates pain, diligent treatment in these episodes ensures that the underlying illnesses are supplied with all the medicines.In avoiding conditions such as acute chest syndrome, basic instruments such as reward spirometry may be important. Longer-term avoidance of infection varies regionally, but can include vaccine services and prophylaxis of penicillin[47, 48,49,50,51].

OXYGEN

Patient with SS disease have lowered arterial oxygen saturation in the steady state and this may fall further during acute illness, especially the acute chest syndrome, under these conditions, high levels of inspired oxygen can only be beneficial[52].

BLOOD TRANSFUSION

Transfusions are provided to correct acute extreme anaemia when the haemoglobin falls considerably below the baseline of the person, and the resultant deficiency in the supply of oxygen to body tissues will otherwise spread more deoxygenated Hb sickling. Examples include red cell aplasia caused by infection with Parvovirus B19, acute splenic

sequestration, or crisis hyperhaemolysis[53].

BONE MARROW TRANSPLANTATION

The only current cure for sickle cell anaemia is Bone marrow transplantation, and it is one of the newest treatment options available. The findings reveal an event-free survival rate of about 91% and a mortality rate of less than 5%. BMT brings major threats, such as the new leukocyte-producing bone marrow that targets host tissue cells known as Graft-versus-host-disease[54]. The infected tissues include the skin, kidneys, gastrointestinal tract and eyes, and symptoms include fatigue, weight loss, and jaundice[55]. If the donor and recipient are not linked or there is a discrepancy of HLA forms, the chance of developing Graft-versus-host-disease is greater; techniques for diligent post-transplant immunosuppression may minimize the risk of Graft-versus-host-disease.

DISCUSSION AND CONCLUSION

This stems from the single-point substitution at position 6 of the β- globin chain of glutamine with valine. This lowers red cell solubility, which in turn contributes to vasculature polymerisation and vaso-occlusion. The lack of polar amino acid at position six of the β-globin chain, under low oxygen conditions, facilitates non-covalent haemoglobin polymerization, which distorts red blood cells into a sickle form and reduces their elasticity. Proper and appropriate counselling should be provided to the planned couple prior to marriage and genetic counseling for haemoglobin and education should be included in the curriculum of pupils.

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