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STATUS OF SERUM FERRITIN LEVEL IN SUBJECTS WITH SICKLE CELL ANEMIA: A REVIEW ARTICLE

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ABSTRACT Hereditary abnormalities in the structure of hemoglobin cause sickle cell disease. Valine, instead of glutamine, is at position 6 of the beta-globin chain in the aberrant hemoglobin. The majority of people with sickle cell disease (SCD) suffer from sickle cell anemia, a hemolytic anemia that may cause organ damage, pain crises, and transfusions throughout health. The serum ferritin level is a crucial indicator of the iron balance in sickle cell disease patients in steady state. This research aims to synthesize existing knowledge on sickle cell anemia and serum ferritin by reviewing the relevant literature.

KEYWORDS : Sickle Cell Anemia, pathophysiology of sickle cell anemia and Serum Ferritin level.

INTRODUCTION:

Sickle Cell anemia (SCA):

Sickle cell disorders are caused by a mutation in the β-globin gene that shifts the sixth amino acid from glutamic acid to valine. When deoxygenated, HbS $(\alpha_2\beta_2^{6\ Glu\rightarrow Val})$ polymerizes reversibly to produce a viscous network of fibrous polymers. This stiffens the RBC membrane, increases viscosity, and causes dehydration via potassium leakage and calcium influx(Jameson J. Larry et al., 2018). Sickle cell disease, also known as sickle cell anemia or drepanocytosis, is a chronic blood illness defined by the presence of red blood cells that adopt an unnatural, inflexible, sickle form. Sickling reduces the pliability of the cells, leading to a susceptibility to diverse problems (Ifeanyi et al., 2015). These irregularities cause unforeseeable occurrences of microvascular Vaso occlusion and early destruction of red blood cells (hemolytic anemia) in the liver and spleen. The inflexible adhering cells also obstruct narrow capillaries and venules, resulting in tissue ischemia, sudden discomfort, and progressive end-organ harm. The veno-occlusive component often has a predominant influence on the clinical progression. Notable symptoms include bouts of reduced blood flow causing pain (known as painful crises) and reduced blood flow or complete tissue death in many organs such as the spleen, central nervous system, bones, joints, liver, kidneys, and lungs(J. Larry Jameson, 2010; Jameson J. Larry et al., 2018).

History:

Dr. Africanus Horton originally described a condition similar to SCA in his book The Disease of Tropical Climates and its treatment (1872)(Ankit Mangla et al., 2023). Nevertheless, it was only in 1910 when Dr. James B. Herrick and Dr. Ernest Irons observed the presence of 'sickle-shaped' red blood cells in a dentistry student named Walter Clement Noel from Grenada(Rees et al., 2010). In 1949, Dr. James V Neel and Col. E. A. Beet independently provided findings on the inheritance patterns seen in individuals with Sickle Cell Disease (SCD). Dr. Linus Pauling elucidated the molecular composition of sickle hemoglobin (HbS) in his publication titled 'Sickle Cell Anemia Hemoglobin' during the same year. In 1956, Ingram Vernon used a fingerprinting approach to elucidate the substitution of negatively charged glutamine with neutral valine, therefore confirming the veracity of Linus Pauling's discoveries(Eaton, 2003).

More than 100 years have passed since the first report of the uneven sickle-shaped red blood cells (RBC). In that time, we have learned a huge amount about the disease. Recent progress in the area, especially in the last thirty years, has helped a huge number of people, mostly in countries with high incomes. If you want to know how to raise the amounts of HbF, Platt et al. were the first to report on it in 1984(Platt et al., 1984). Since then, new medicines like voxelotor, crinzalizumab, L-glutamine, and most recently gene therapy have made it possible to treat sickle cell to a whole new level (Ankit Mangla et al., 2023).

Etiology:

The RBC protein hemoglobin (Hb) is important. It has four globin chains, two from alpha-globin (chromosome 16) and two from beta-globin (chromosome 11). There are various Hb subtypes. These are the most prevalent in people without hemoglobinopathies(Ankit Mangla et al., 2023):

1. HbA_1—95% of adult hemoglobin—has two alpha- and two beta-globin chains (a_2b_2).
2. HbA_2- has two alpha- and two delta-globin chains (a_2d_2), less than 4% of adult hemoglobin.
3. HbF- This Hb is more common in the fetus owing to its high oxygen binding affinity that helps draw oxygen from maternal circulation.

Epidemiology:

HbS distribution worldwide reflects two factors: carriers' survival advantage in malaria-endemic areas and subsequent migration. The discovery of four African haplotypes (Senegal, Benin, Bantu, and Cameroon) and one Asian haplotype (Arab-India) supports the hypothesis that the HbS mutation has occurred and been amplified locally on multiple occasions(Rees et al., 2010).

Epidemiological information regarding SCD is scant. The higher prevalence of SCD and HbAS in sub-Saharan Africa, where the carrier of HbAS naturally protects against severe Plasmodium falciparum malaria, is well known. In sub-Saharan Africa in 2010, an estimated 230,000 infants were born with SCA, and over 3.5 million neonates were born with HbAS. Sub-Saharan Africa is the site of approximately 75% of childbirths attributed to SCD. The most individuals afflicted with HbSC disease reside in West Africa(Kato et al., 2018).

The Centers for Disease Control and Prevention (CDC) of the United States (US) estimates that around 100,000 Americans have SCD. Additionally, the CDC estimates that 1 in 365 African-Americans and 1 in 13 infants born to African-American parents have sickle cell trait or SCD, respectively. One in 16,300 is the estimated prevalence of SCD among Hispanic Americans. The proportion of children and adolescents with SCD in the United States can reach 40%. The incidence differs according to the geographical preponderance of ethnicities and the state. Additionally, both domestic and international migration have an impact on the prevalence of SCD and HbAS. This is the case in a number of nations where SCD and SCA patients reside. In Brazil, genetic research has also linked the slave trade from West Africa (specifically, Mina Coast and Angola) to the ancestry of these patients(Naoum, 2011).

Mortality and morbidity rates also differ significantly between high-income and low-income nations. Intensive screening procedures and the implementation of vaccination guidelines for children with SCD

have significantly decreased the mortality rate of children with SCD aged 0 to 4 years (a 68% decline from 1999 to 2002 compared to 1983 to 1986). Conversely, between fifty and ninety percent of infants born with SCD in sub-Saharan Africa will perish before their fifth birthday. Life expectancy has increased in high-income countries as a result of enhanced healthcare provisions and targeted provider training. In contrast, matched non-SCD cohorts are ahead by decades in terms of quality-adjusted life expectancy (67 years as opposed to 54 years for projected life expectancy) and 33 years for life expectancy(Lubeck et al., 2019).

Pathophysiology:
Hemolysis and vaso-occlusive crises (VOC) are the two critical features that define sickle cell anemia. Sickle hemoglobin (HbS) molecules converted into rigid, elongated polymers in a deoxygenated state are susceptible to this consequence of the beta-globin gene defect. Initially, sickle erythrocytes exhibit a cyclical pattern in which they alternate between the characteristic biconcave shape and the aberrant crescent shape, which is specific to conditions of low oxygen pressure. Eventually, however, the transformation becomes permanent and the sickle erythrocytes acquire a permanent sickle shape, which elevates the likelihood of hemolysis and VOC. All variants of SCD are characterized by the polymerization of the HbS component due to the same pathophysiology (Kato et al., 2018).

Sickle cell anemia is distinguished by two primary features: Hemolysis and vaso-occlusive crisis (VOC). The mutation in the beta-globin gene renders the sickle hemoglobin (HbS) molecule prone to transforming into inflexible, elongated polymers when it lacks oxygen. The sickling process is initially cyclical, with sickle erythrocytes alternating between the normal biconcave form and the aberrant crescent shape, which is obtained under low oxygen pressure. Nevertheless, there is a point at which the transformation becomes permanent and the sickle-shaped red blood cells undergo a process known as hemolysis, which increases the likelihood of vaso-occlusive crises (VOC). All forms of SCD have the same underlying mechanism that causes the HbS component to form polymers(Kato et al., 2018; Naoum, 2011; Oyiro Peter et al., 2018; Platt et al., 1984).

Diagnosis:
Sickle cell disorders are suspected based on the presence of hemolytic anemia, abnormal red blood cell shape, and recurring bouts of ischemia discomfort. The diagnosis is validated by the use of hemoglobin electrophoresis, mass spectroscopy, and sickling testing(Jameson J. Larry et al., 2018).

The diagnosis is often made during infancy, however some individuals, particularly those with compound heterozygous conditions, may not exhibit symptoms until the start of puberty, pregnancy, or early adulthood. Performing genotyping on family members and possible parenting partners is essential for the purpose of genetic counseling. Comprehensive information on the individual's early history is crucial in determining the prognosis and determining the need of aggressive or experimental treatments. Factors linked to higher morbidity and worse survival rates include experiencing more than three hospitalizations per year due to crises, having persistent neutrophilia, a history of splenic sequestration or hand-foot syndrome, and experiencing second bouts of acute chest syndrome.

Individuals who have already had cerebrovascular accidents are more susceptible to recurrent episodes and need partial exchange transfusion. Additionally, they require meticulous monitoring via the use of Doppler carotid flow measurements. Individuals with severe or recurrent occurrences of acute chest syndrome may need ongoing transfusion assistance, particularly by partial exchange transfusion if feasible(J. Larry Jameson, 2010; Jameson J. Larry et al., 2018).

Complications in Patients with Sickle cell anemia:
Iron Overload:
Iron (Fe) accumulation is a prevalent issue in patients with SCA as a result of frequent blood transfusions and persistent destruction of red blood cells. Every packed red blood cell unit includes a quantity of iron ranging from 200 to 250 milligrams.

The heart, lungs, and endocrine glands are most impacted by an excess of iron (Remacha et al., 2013). Hepatic cirrhosis resulting from excessive iron accumulation is a significant contributor to mortality in individuals with sickle cell anemia (SCA). Studies conducted on individuals with thalassemia have shown a clear correlation between the overall accumulation of iron in the body and both survival rates and occurrences of cardiac events (G M Brittenham et al., 1994).

Avascular Necrosis (AVN) of Joints:
Avascular necrosis (AVN) of the femoral head is a prevalent factor leading to long-lasting discomfort and impairment in individuals with sickle cell anemia (SCA). While the hip joint is often afflicted, it is important to note that other joints may also be impacted. Avascular necrosis (AVN) often develops in the distal region of the bone, where blood flow via collateral vessels is limited. Sickle red blood cells cause the blockage of capillaries, resulting in a lack of oxygen and the destruction of bone tissue. Age, frequency of painful episodes, hemoglobin level, and alpha-gene deletion are all risk factors for avascular necrosis (AVN) of the femoral head. The total frequency of HbSS in patients reaches 50 percent by the age of 33. Individuals with HbSS-alpha thalassemia and HbSS-Beta-0 thalassemia have an increased susceptibility to developing avascular necrosis (AVN) at an early age (Ankit Mangla et al., 2023).

Leg Ulcers:
Prevalent in the SCA population relative to other genotypes of SCD. Leg ulcers are seen in about 2.5% of people with sickle cell anemia who are older than 10 years. Leg ulcers have a higher prevalence among males and older individuals, whereas they are less prevalent among individuals with elevated total hemoglobin, alpha-gene deletion, and increased levels of HbF. Leg ulcers are more likely to occur in those who have had trauma, infections, or severe anemia. Ulcers are more often seen on the inner and outer sides of the ankles. Ulcers exhibit variations in both size and depth, and if they become chronic, they might potentially result in osteomyelitis, particularly when they penetrate deep enough to expose the bone (Ankit Mangla et al., 2023).

Pulmonary Artery Hypertension (PAH):
Impacts around 6 to 11% of individuals with SCA. PAH in SCA is categorized as Group V by the World Health Organization (WHO). Nevertheless, persistent destruction of red blood cells results in alterations in the blood vessels of the lungs, which are categorized as WHO group 1 in around 10% of individuals with sickle cell anemia. Pulmonary arterial hypertension (PAH) may also arise as a result of left heart malfunction (Group II), chronic lung illness associated with sickle cell anemia (Group III), chronic thromboembolism (Group IV), or reasons originating beyond the chest (Group V).

The patient may have dyspnea during physical activity, edema in the lower extremities, or manifest signs indicative of an underlying condition (such as a history of thrombosis, heart failure, etc.). An echocardiography is useful for determining the velocity of the tricuspid regurgitant jet (TRV). Higher levels of TRV are linked to a greater risk of death in adults. Nevertheless, temporary elevation of TRV may occur with acute chest illness. The level of Serum NT-pro-BNP is positively associated with mortality. The conclusive diagnosis is established using a procedure known as right cardiac catheterization (Ankit Mangla et al., 2023).

Renal complications:
Approximately 30% of adult individuals with sickle cell anemia (SCA) have chronic kidney disease (CKD). The kidney's acidic, osmotic, and hypoxic conditions heighten the likelihood of polymerization of HbS, resulting in the deformation of red blood cells known as sickling. Patients with SCA have abnormal secretion of large amounts of creatinine in their proximal tubules. Therefore, it becomes difficult to detect early indications of renal disease, since the levels of creatinine take a longer period to increase. Microalbuminuria, which refers to the presence of 30-300mg of albumin in a 24-hour urine sample, is often the first indication of chronic kidney disease (CKD). The use of spot urine-creatinine ratio is not validated in individuals with sickle cell anemia (SCA) owing to excessive production of creatinine (G M Brittenham et al., 1994; Remacha et al., 2013).

Ophthalmologic Complications:
Proliferative Sickle Retinopathy is caused by the blockage of blood vessels in the vitreous, resulting in reduced blood flow and the development of new blood vessels. Neovascular tissue is prone to bleeding and the pulling forces of the vitreous may cause bleeding in the vitreous (which is the most serious consequence of proliferative sickle retinopathy) (Ankit Mangla et al., 2023).

Serum Ferritin:

The protein ferritin was first identified in 1937 by the French scientist Laufverger V. (Laufverger V, 1937). He extracted this protein from horse spleen, which was shown to have an iron content of up to 23% by weight when dried. The presence of ferritin in human serum was recorded a few years later (Addison et al., 1972). Nevertheless, the measurement of serum ferritin was delayed until the isolation of ferritin and anti-ferritin antibodies, as well as the development of very sensitive immunoassay methods. In 1972, Addison et al. successfully established the reliable detection of ferritin in human serum using an immunoradiometric technique (Addison et al., 1972). The authors investigated serum ferritin levels in a normal population, patients with iron shortage, and persons with iron overload to establish the correlation between serum ferritin levels and total body iron storage. The study revealed that individuals with iron excess had higher levels of serum ferritin, whereas those with iron deficient illnesses showed lower levels of serum ferritin(Mayer et al., 1996). In 1975, Jacobs and Worwood proposed that measuring serum ferritin levels may be a valuable and easy way to evaluate iron storage levels (A Jacobs & M Worwood, 1975).

Ferritin is mostly found in the cytoplasm of most tissues; however, a mitochondrial variant has been recently identified (S Levi et al., 2001; Sonia Levi & Paolo Arosio, 2004) and there have been suggestions of its localization and functions inside the nucleus (Cindy X. Cai et al., 1997; Surguladze et al., 2005). Ferritin is crucial for storing iron inside cells and has been the focus of comprehensive recent studies(Frank M Torti & Suzy V Torti, 2002; Koichi Orino & Kiyotaka Watanabe, 2008).

Ferritin is a protein consisting of 24 subunits, which are categorized into two types: H and L subunits. The term "H" is used to refer to the first separation of isoforms of ferritin from the human heart, which are abundant in the H subunit (Elizabeth C Theil, 2004; Paolo Arosio & Sonia Levi, 2002). It may also describe the electrophoretic movement of the heavier of the two subunits. L refers to ferritin derived from the liver of humans, which has a higher proportion of a lighter component. The proportion of H to L subunits in the formed ferritin protein changes based on the type of tissue and stage of development. The genes responsible for encoding the H and L subunits of human ferritin are situated on chromosomes 11q and 19q, respectively (M Worwood et al., 1985). Both high (H) and low (L) ferritin also possess many pseudogenes, numbering between 15 and 17. The amino acid sequence similarity between ferritin H and L subunits in mammals is around 50%. The sequence conservation within subunit types is significantly higher, with approximately 90% homology among mammalian H subunits and roughly 80% homology among L subunits (Andrews et al., 1992; Koichi Orino & Kiyotaka Watanabe, 2008).

Serum ferritin is also made in the liver, just like fibrinogen. Ferritin is a well-known risk factor for heart disease because it shows how much iron is in the body. Serum ferritin levels have been linked to the risk of myocardial infarction (Salonen et al., n.d.) and carotid atherosclerosis and its progression in a number of epidemiological studies (Wolff et al., 2004) (Kiechl et al., 1997). In the same way, studies on animals showed that a higher iron load in the body was linked to a faster progression of atherosclerosis, and clinical studies found a link between genetic markers linked to a higher iron load in the body and impaired endothelial function, which is an early functional marker of atherosclerosis (Araujo et al., 1995; Duffy et al., 2001; Lee et al., 1999).

Hyperferritinemia may sometimes occur due to inherited diseases that do not result in an excessive accumulation of iron. This encompasses genetic variants in the tissue ferritin L gene, which provide as evidence supporting the notion that the gene encodes serum ferritin. Individuals with hyperferritinemia cataract syndrome, who possess mutations that enhance the formation of tissue ferritin L, also have elevated levels of serum ferritin (Mario Cazzola et al., 1997). A novel missense variation in the coding sequence of ferritin L has been recently discovered. This mutation has been shown to be linked to hyperferritinemia, without causing excessive iron accumulation in the body (Dey et al., 2019). The mutation, located at the amino terminus of the L ferritin subunit and not resulting in clinical symptoms, was suggested to induce hyperferritinemia by enhancing the secretion of ferritin (Dey et al., 2019).

The reduction in serum iron levels, elevation in macrophage iron levels, and decrease in dietary iron absorption observed in anemia of inflammation can be attributed to the upregulation of hepcidin expression caused by inflammatory cytokines. Conversely, the increase in serum iron levels, depletion of macrophage iron levels, and enhanced dietary iron absorption seen in hereditary hemochromatosis are consequences of abnormal regulation of hepcidin expression due to genetic abnormalities (Wang et al., 2010).

The theory behind elevated iron levels in SCA is that the condition is characterized by chronic red blood cell transfusions, hemolysis, recycling, and buildup of iron. Anemia and other sickle cell disease consequences are common reasons for transfusions of red blood cells. Multiple studies have linked the iron status alterations brought about by this treatment to substantial morbidity and death (Oyiro Peter et al., 2018).

OBSERVATIONS & DISCUSSION:

The status of elevated serum ferritin levels, which suggest an accumulation of iron in the body, aligns with the predictions made by previous researchers who have investigated serum ferritin levels in individuals with SCA under medical supervision. Based on previous research, we have observed that a significant proportion of individuals with SCA had elevated levels of serum ferritin.

Eneh I Chizoma, Nwankwo A. Chinweoke and Ihuoma C. Juliet (2023) were observed significantly raised level of serum ferritin in the individuals with Sickle cell anemia (Chizoma I. Eneh et al., 2023). Sukla Kumar S. et. al; (2021) were reported increased mean level of serum ferritin in the subjects with SCA than control group (Sukla et al., 2023). Peter O. et. al; (2018) were found high serum ferritin level (>300 ng/ml) in SCA patients which was statistically significant (Oyiro Peter et al., 2018). They also found statistically significant association of serum ferritin with sickle cell anemia (Oyiro Peter et al., 2018). Okoh D. A. and Nwabuko C. O. (2016) were also observed high serum ferritin level (>300 ng/ml) in the subjects of SCA. And they found weak correlation of serum ferritin with iron and weak association of serum ferritin with SCA. They recommended successive iron examination for individuals undergoing repeated blood transfusions (D. A. Okoh & C. O. Nwabuko, 2016). A cross sectional study of Akinbami A. A. et. al; (2013) were reported normal serum ferritin level in homozygous patients with sickle cell anemia and found high serum ferritin level in men with sickle cell anemia than female subjects (Akinbami et al., 2013). S. O. Akodu et.al; (2013) were reported statistically high serum ferritin level in SCA children, according to their study, serum ferritin mostly reflects reticuloendothelial iron reserves.

Serum ferritin is a sensitive indication of bodily iron storage, hence elevated levels may indicate high iron stores. Children with sickle cell anaemia may have elevated blood ferritin levels due to increased iron in reticuloendothelial cells caused by hemoglobin breakdown (Akodu et al., 2013). Koduri R. Prasad (2003) was described that, the sensitivity of low serum ferritin to diagnose iron shortage is limited in SCA compared to other conditions because of the non-specific rise caused by accelerated red cell turnover. Even though iron deficiency is more prevalent than thought, particularly in males, there is no proof of iron excess in SCA. In order to diagnose iron deficiency, the absence of bone marrow iron is still considered the gold standard in these individuals treated (Koduri, 2003). According to Brownell A. Lowson S. and Brozovic M. (1986) were reported raised level of serum ferritin level along with serum AST, ALT, and ALP, they said that, the use of serum ferritin as an indicator of iron balance in sickle cell disease is only reliable when the patient is in a stable condition. The significant increase in serum ferritin content seen during a crisis may serve as a valuable indicator of the severity of vaso-occlusion and tissue injury(Brownell et al., 1986). Hussain M.A.M. et. al; (1978) were reported that, patients with sickle cell anaemia have greater mean serum ferritin levels compared to control children of the same age range, corroborating previous research (Hussain et al., 1978). Siimes et al. (1974) and Peterson et al. (1975) discovered elevated blood ferritin levels in the patients with sickle cell anaemia of similar ages, and our patients' median value was comparable to theirs (Martti A Siimes et al., 1974; Peterson et al., 1975).

CONCLUSION:

Based on previous research articles and published report we have concluded that, Serum ferritin mostly reflects reticuloendothelial iron reserves. Serum ferritin is a sensitive indication of bodily iron storage, hence elevated levels may indicate high iron stores. Subjects with sickle cell anaemia may have elevated serum ferritin levels due to

increased iron in reticuloendothelial cells caused by hemoglobin breakdown.

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