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An Update on Interferon Gamma and C Reactive Proteins in Sickle Cell Anaemia Crisis

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Abstract

Sickle cell disease has been described by many scholars as a chronic inflammatory disease which is linked to many factors such as endothelial destruction, increased synthesis of reactive oxygen specie, haemolysis, increased synthesis of pro inflammatory cytokines among others. Inflammatory process play a major function in the activation of acute painful vaso-occlusion crisis that forms the main reason for the hospitalization of patients with sickle cell anaemia. Inflammatory processes, are key components of several complications of the disease including autosplenectomy, acute chest syndrome, pulmonary hypertension, leg ulcer, nephropathy and stroke and also ultimately initiates painful vaso-occlusion episodes that characterize Sickle Cell Disease. This study titled "Update on Interferon Gamma and C Reactive Proteins in Sickle Cell Anaemia in Crises, aims at finding out the recent updates on interferon gamma; a pro-inflammatory cytokine that plays a central role in inflammation and auto-immunity, and CRP; an acute phase protein used as a marker of inflammation in sickle cell anaemia patients in crisis. A lot of search engines were consulted in the course of writing this review such as scopus, Pubmed Central, Web of Science, Semantics, Google Scholar, Researchgate, Academia Edu, etc. Previous studies have suggested that levels of pro-inflammatory cytokines vary between steady-state and crisis states in SCA patients, hypothesized to help monitor clinical progression of the disease. . Newer therapies that target pathways downstream of the sickle are considered better options. This knowledge may have implications for the development of new treatments for sickle cell disease.

Keywords: Sickle cell anaemia, Crisis, Interferon-gamma, C - reactive protein, Inflammatory cytokines, Cytokines

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Introduction

Sickle cell anaemia is the result of homozygosity for a single amino acid change. Valine replaces glutamic acid at the sixth position of the beta-globin chain of the hemoglobin molecule. A person is homozygous for the disorder if the gene for HbS synthesis is inherited from both parents [1-3]. This result in the abnormal structure of haemoglobin S. Sickle cell disease can also result from HbS heterozygosity and another β-globin chain abnormality for example HbC or beta 0 thalassemia [4]. These present clinically as severe haemolytic anemia, punctuated by crises and usually painful. , which distorts the RBC. This crisis affects a variety of organs, including bones, spleen, and lungs. Under hypoxia caused by triggers such as infection, dehydration, and hypoxia, HbS polymerizes and erythrocytes assume a characteristic crescent shape. This makes the cell susceptible to many intracellular and membrane changes. These changes affect the ability of red blood cells to return to their original shape and stick to the walls of blood vessels. Attachment of RBCs to the vessel wall activates the complement and coagulation systems and contributes to the inflammatory process of SCD [2, 3, 5, 6]. Thus, SCD triggers hemolytic events and induction of inflammatory processes, resulting in vascular occlusion. Inflammation is protective,

but when in excess, as in sickle cell disease, it can be harmful. Decades of research have shown that inflammation plays a key role in many of the clinical complications that occur in patients with sickle cell anemia. As reported by [7] stated: Both IFN-γ and CRP are associated with inflammatory processes. IFN-γ is a glycoprotein produced by CD4+ and CD8+ T cells after activation by natural killer (NK) cells. The immunomodulatory functions of IFN-γ are diverse and include activation of mononuclear phagocytes, stimulation of NK cell cytolytic activity, and activation of neutrophils. On the other hand, C-reactive protein is an acute phase protein produced by the liver in response to inflammation. Its serum levels are elevated during acute inflammation. It is therefore used as a marker.

Sickle Cell Anaemia

Sickle cell disease is a common hereditary haemoglobinopathy that occurs primarily in individuals of African descent. The disease known as sickle cell disease is caused by a point mutation in the sixth codon of β-globin, replacing a valine residue with a glutamic acid residue. The resulting abnormal physicochemical properties of sickle haemoglobin (HbS) are the cause of this disease.

If a person inherits the mutated gene from his parents, all haemoglobin is derived from her abnormal HbS. Even at normal oxygen saturation. The disorder is fully developed. In heterozygotes, only part of the haemoglobin is HbS (the rest is HbA), so red blood cell sickling occurs only when the partial pressure of oxygen is reduced. This is called sickle cell trait to distinguish it from full-blown sickle cell anaemia There are two forms of sickle cell anaemia: homozygous (sickle cell anaemia) and heterozygous (sickle cell anaemia).

In sickle cell anaemia, the gene for HbS synthesis is inherited from both parents. It manifests clinically as severe haemolytic anaemia punctuated by painful attacks. This condition may be homozygous sickle cell anaemia HbSS, or a mixed syndrome in which HbS in combination with another Hb causes sickle cell anaemia. The most common combinations are with HbC, HbD, HbE, and beta-thalassaemia Hb0. Sickle cell trait occurs when HbS synthesis gene is inherited from only one parent and is a benign condition with no obvious anaemia.

Epidemiology of sickle cell disease

About 8-10% of African Americans, or about 2 million people, are heterozygous for HbS, a mostly asymptomatic condition known as sickle cell disease. Two heterozygous offspring have a 1 in 4 chance of being homozygous for the sickle mutation. There are about 70,000 people with sickle cell disease in the United States. In certain African populations, the prevalence of heterozygosity reaches as high as 30%. This high frequency is likely due to the protection that HbS offers against falciparum malaria. Sickle syndrome is most common in central Africa and among blacks, where P. falciparum is endemic. Patients with HbS are relatively protected from falciparum malaria.

The prevalence of sickle cell anaemia closely reflects the global spread of falciparum malaria. However, as a result of human migration to industrialized western countries, SCD has become more common in areas where malaria is not endemic. According to 2006 World Health Organization estimates, 5% of the world's population carries the haemoglobinopathy gene. Sickle cell anaemia is very common in sub-Saharan and equatorial Africa, with a low but significant prevalence in the Middle East, India, and the Mediterranean. The incidence of SCD in sub-Saharan Africa is 1-2%, equivalent to approximately 500,000 cases per year. In a Jamaican cohort study, newborn screening from 100,000 consecutive vaginal deliveries detected sickle cell trait in 10% of her newborns. The US Centers for Disease Control and Prevention estimates that sickle cell anaemia occurs in 1 in 500 African Americans. One in 12 of her African Americans has the trait, and about 100,000 Americans (mostly of African descent) have the disease. Among Hispanic Americans, the SCD rate is her 1 in her 36,000 live births. As of 2002, more than $1 billion is spent annually in the United States on her SCD hospitalizations.

Pathophysiology of sickle cell anaemia

HbS polymerization in SCD is associated with erythrocyte sickling, intravascular haemolysis with release of acellular haemoglobin, increased adhesion of erythrocytes to the vascular endothelium, platelet activation, production of inflammatory cytokines, and ultimately vascular occlusion.

The sickle cell crisis

State that the most important clinical feature of sickle cell anemia is acute painful attacks that often require hospitalization [8]. Sickle cell crisis is a term that describes several acute conditions, such as: B. Vasoocclusive crisis (acute painful crisis), aplastic crisis, splenic sequestration crisis, hyperhemolytic crisis, hepatic crisis, dactylitis and acute chest syndrome. Other acute complications include pneumonia, meningitis, sepsis, osteomyelitis, and stroke.

Interferon -$_{\gamma}$

Cytokines are a general term for a large group of secreted molecules involved in cell-to-cell signaling during immune responses. Interferons (IFNs) are cytokines that are particularly important in limiting the spread of certain viral infections. A group of interferons (IFNα and IFNβ, or type 1 interferons) are produced by virus-infected cells.

Another type of interferon gamma (IFN$_{\gamma}$) is released from her activated TH1 cells. IFNs induce a state of antiviral resistance in uninfected cells. They are produced very early in infection and are important in slowing viral spread until an adaptive immune response develops. Destruction of intracellular microbes growing in macrophages depends on activation of macrophage bactericidal activity by IFN$_{\gamma}$. When microorganisms are ingested by macrophages, macrophages secrete

IL-12 binds to IL-12 receptors on T cells and induces IFN$_{\gamma}$ secretion. Children with genetic defects in genes encoding IL-12, IL-12 receptor (IL-12R), or IFN$_{\gamma}$ receptor suffer from repeated infections with non-pathogenic mycobacteria and, to a lesser extent. These various defects are inherited as autosomal recessive or autosomal dominant traits.

C Reactive Protein (Crp)

CRP is the major acute-phase protein produced by liver

hepatocytes in response to IL-6. It is, for example, a pentameric protein that binds phosphorylcholine present in pneumococci and promotes phagocytosis of pneumococci by binding to C1q and activating the classical complement pathway. C-reactive protein (CRP) is an example of an acute phase protein. These are proteins whose serum levels rise rapidly during infection. It is called C-reactive protein because of its ability to bind to the pneumococcal C protein. Facilitates pneumococcal uptake by phagocytic cells.

A New Treatment for Sickle Cell Disease

The European Medicines Agency has recommended giving marketing authorization to his Oxbryta in the European Union for the treatment of haemolytic anaemia (excessive destruction of red blood cells) due to sickle cell anaemia in patients aged 12 years and older. I'm here. Oxbryta should be used alone or in combination with hydroxycarbamide (also known as hydroxyurea).

Currently, most patients with sickle cell anemia are treated with hydroxyurea and clizanlizumab (a drug used to prevent VOCs).

The active substance in Oxbryta is voxelotor, a small molecule that binds and stabilizes haemoglobin, preventing the polymerization of haemoglobin (i.e., the formation of abnormal haemoglobin) that causes red blood cells to sickle. As a result, preventing erythrocyte sickling also prevents the inflammatory cascade that leads to multiple organ damage.

Update on Interferon Gamma in Sickle Cell Anaemia Patients in Crises

A study by [9] 1990 found that he had significantly decreased IFN-γ production in both his SCD groups (steady state and crisis state) compared to normal healthy controls, indicating impaired IFN-γ production discovered. This suggests a possible reason for the increased frequency and severity of infections in sickle cell disease.

Contrary to the above, [10] in 2020, there are more patients with a history of frequent crises each year, but fewer patients receiving hydroxyurea therapy. Ischemia-induced cell death releases molecular patterns associated with major inflammatory damage (DAMPS). These then promote several inflammatory pathways. One of the effects of ischemia perfusion injury may be the activation of NK cells, which can induce pneumonitis by inducing IFY and IF-γ-induced chemokines. Ischemia-reperfusion injury causes damage through ROS production and calcium overload. In a study conducted in Oman, [11] showed that mean serum levels of IFN-γ were higher in SCA patients than in controls. This difference was significant in steady-state patients but not during crisis. In 2011; plasma levels of interferon gamma showed a trend towards a slight increase during painful attacks and a decrease at steady state, compared with levels in age-matched healthy controls.

Update on C Reactive Protein in Sickle Cell Anaemia Patients in Crises

A study (2014) aimed at determining C-reactive protein levels in patients with SCD showed that asymptomatic steady-state (ASS) HbSS subjects had significantly higher CRP levels compared with controls. HbSS crisis patients also had significantly higher CRP levels compared to ASS-HbSS patients. Disease severity and WBC have been found to be negatively correlated with CRP levels. Their study suggests that the biological role of her CRP in relation to inflammatory processes in patients with ASD-HbSS is protective. However, they suggested that more work needs to be done to confirm the results using larger HbSS populations.

Conducted a cross-sectional study in 2015 to measure CRP levels in patients with steady-state and critical SCA and to investigate the relationship between CRP levels and disease severity in patients with sickle cell anaemia in the West Indies [12]. Researched at Alkuwaity Hospital in El Obid. Their results also showed that at-risk patients exhibited a significant increase in CRP levels compared with resting patients is an indicator of inflammatory status and may be of therapeutic value. The above is also consistent with the study of [13]. In 2014, patients with SCD had elevated basal CRP levels, indicating that they may develop acute chest syndrome during a vascular occlusive crisis. Elevated CRP may precede severe her ACS, may be significantly associated with risk factors for ACS, and may also be an excellent diagnostic marker for patients with SCD and ACS. They suggested further studies to determine whether CRP can predict the development of ACS in VOC patients.

A study by [14,15] In 2021, we also found elevated levels of C-reactive protein, along with white blood cell and platelet counts, in pediatric subjects with stable sickle cell disease compared to apparently healthy children on haemoglobin AA.

Conclusion

From the above studies, we can conclude that both CPR and IFN-γ are substances produced during inflammatory processes in the body. Especially in his SCD, these inflammatory processes become excessive and can lead to many detrimental effects such as morbidity and multi-organ damage.

In this review, serum levels of CRP and interferon-gamma tended to be elevated during the development of sickle cell disease and play a key role in the inflammatory process, ultimately leading to the many complications associated with sickle cell disease. It is shown that it leads to New therapies focused on preventing the spread of the inflammatory process have shown promise as a therapeutic approach for sickle cell disease.

Recommendation

Sickle cell disease, like any other disease, is better prevented than cured. I highly recommend increased effort at creating awareness to educate the world population on ways to prevent birthing sickle cell children.

I also recommend that since this study has revealed the great role the inflammatory process plays in sickle cell pathology and

prognosis, it is important that more effort be geared towards the development of therapies aimed at preventing a vaso-occlusion crisis, which is a major driver of the inflammatory process in sickle cell anaemia crisis. Through this, other damaging effects caused by this disease will be averted, which will improve the quality of life of these patients.

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