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Von Willebrand Factor Effect on Pro-Thrombotic State in Sickle Cell Disease

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Annotation: Background: sickle cell disease (SCD) is a serious kind of hemolytic anaemia that marked by persistent haemolysis, hypercoagulation, and changes in hemostatic parameters.These variables have the potential to cause thrombosis in SCD patients. Multimeric plasma hemostatic protein von Willebrand factor (VWF), which is produced and secreted by platelets and endothelial cells, is elevated in SCD and rises much more during a vaso-occlusive crisis (VOC). Nevertheless, it is unclear how VWF affects the pathophysiology of VOC.

Objective: The purpose of the review is to present a concise scientific summary of thrombotic risk in SCD, which has a significant morbidity and mortality on patient's life.

Conclusion: Previous research evaluating these markers indicates that, when comparing SCA to control, there was no discernible difference in VWF Ag, ADAMTS13, or VWF Ag: ADAMTS13 antigen ratio. According to other research, patients' VWF and ADAMTS 13 activity levels were much higher than those of control.

Keywords: Sickle cell disease, Vaso-

occlusive crises, Von Willebrand factor, Thrombosis ADAMTS 13.

Introduction

Sickle cell disease is a chronic condition that belongs to a diverse set of illnesses inherited in an autosomal recessive manner. It had a highly variable clinical spectrum including sickle cell anemia (SCA), which results from homozygous inheritance of the sickle cell gene. Additional variations consist of compound heterozygosity, in which the mutated gene is inherited alongside additional defective hemoglobin gene, such as HbC, β thalassaemia, and hemoglobin D[1][2].

The mutation occurs when a valine replaces a glutamic acid in the sixth position at the NH2-terminal end of the β-globin gene. Under conditions of low oxygen tension, the hemoglobin S polymerized, leading to the sickling of red blood cells[3],[4].

Sickle cell disease is the prevailing form of hemoglobinopathy, with an estimated annual incidence of around 300,000 new cases and a global impact on millions of people. [5]. It is highly prevalent across extensive regions of sub-Saharan Africa, the Mediterranean basin, the Middle East, and India[6].

In Iraq, patients with sickle cell anemia (SCA) are concentrated in two specific regions, posing a significant health challenge. The Arabs in the extreme south, particularly in Basra, have the highest prevalence of the sickle cell trait, with 6.48% of the population being carriers[7]. The second most common region affected is the northern Kurdish community, with a carrier rate of 1.2% among individuals in Dohuk[8],[9].

In 1910, sickle cell disease emerged in Western medicine as a "strange" or, as Herrick described it, a "new, unknown disease." In this condition, the abnormal sickle-shaped appearance of the red blood cells intrigued medical practitioners[10].

Literature Review

The identification of hemoglobin S by Linus Pauling and his colleagues in 1949 marked the initial evidence that the presence of a defective protein may be responsible for a genetic condition. This discovery gave rise to the idea of "molecular disease," with sickle cell disease serving as the inaugural example[11], [12].

Ingram found the genetic cause of the disease in 1958 and showed that it happened when a valine (GTG) was switched out for a glutamic acid (GAG) at the sixth position in the amino acid sequence in the hemoglobin beta chain. A single point mutation (A to T) in the hemoglobin gene substitutes this amino acid, generating notable changes in the haemoglobin molecule's structure and function in those who have that illness. [10],[13].

Sickle cell disease is an established hyper-coagulation and prothrombotic state characterized by a marked change in the hemostatic parameters. marked by elevated VWF levels, increased platelets P-selectins expression, elevated adhesion and aggregation of platelets, marked activation of coagulating proteins along with concomitant rise in thrombin and thrombin-antithrombin production, reduced levels of ADAMTS13, protein C and S with compromised fibrinolytic activity. Each of these factors increases the risk of thrombosis[14].

The exposure of hydrophobic motifs on single deoxygenated HbS tetramers is facilitated by intra-erythrocyte HbS deoxygenation in high oxygen-demanding tissues. Consequently, the nucleation of HbS polymers is initiated when βS globin chains on various deoxygenated HbS tetramers link to one another in order to cover the hydrophobic motifs. These polymers growing speedily to form elongated fibers that enhance cellular rigidity and distort the red cell membrane, are responsible for cell sickling, dehydration, cellular energy failure and stress, decreased rheology, and premature

hemolysis[15].

These long polymers "melt" or dissolve during oxygenation, causing the sickle erythrocyte to lose the majority of its pathological characteristics. Polymerization of HbS correlates exponentially with the level of HbS withen erythrocytes and with the composition of others hemoglobin that variably participate in the polymers[16].

Von Willebrand factor

Von Willebrand factor (VWF) is a complex glycoprotein consisting of multiple different-sized units. It has a crucial function in the process of blood clotting, namely by facilitating the attachment of platelets to damaged and activated blood vessels. [17],[18]. Von Willebrand factor (VWF) is exclusively synthesized and stored by endothelial cells and megakaryocytes. Initially, VWF dimers are created, which then come together to form ultralarge VWF (ULVWF) multimers. These substances have kept in endothelium, specifically in the Weibel-Palade bodies, as well as in α-granules of platelets. They can release either continuously or as needed.[19],[20]. The ULVWF released into the bloodstream can be highly hazardous. If not metabolized, they have the ability to bind spontaneously with platelets, forming clusters that can obstruct the blood flow in small blood vessels [17].

Proteolytic enzyme of von Willebrand factor

A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif member 13 (ADAMTS13), a circulating metalloprotease, was initially cloned and determined as member of (ADAMTS) family in 2001. It is mainly produced by hepatic stellate cells, but can also be found in other cells such as endothelial cells, and megakaryocytes or platelets[21].

ADAMTS13 is released into the bloodstream as an enzyme that is constantly active, with a concentration of roughly 1µg/ml. It cleaves a substantial adhesive glycoprotein called VWF, which has a crucial function in primary hemostasis by attracting platelets to the location of damaged blood vessel[22].

Prior reports indicated that the VWF/ADAMTS13 axis is implicated in SCD due to the inhibition of ADAMTS13 activity by elevated levels of extracellular haemoglobin in the plasma of patients with SCD. Furthermore, reduced ADAMTS13/VWF antigen ratio has been observed during both steady state and at painful crises, accompanied by elevation of both VWF and ULVWF multimers in circulation[23].

Materials and Methods

So, giving recombinant ADAMTS13 could possibly prevent blood cells from sticking together, improve blood flow, and lower the risk of vasoocclusions. A recent study demonstrated that the use of recombinant ADAMTS13 decreases platelet adhesion in the blood of mice with sickle cell disease (SCD) and also lowers the acute organ damage associated with SCD in a mouse model that mimics human SCD[24].

Crizanlizumab, a monoclonal antibody that targets P-selectin; L-glutamine, an antioxidant that reduces painful crisis; hydroxyurea, which increases fetal haemoglobin production and limits HbS polymerization; and voxelotor, a small molecule that modifies HbS binding to oxygen to decrease polymerization, are the only available treatments for SCD. Sadly, these therapies lessen the VOC by only about 45% [25].

The structure and expression of Von Willebrand factor

A large multimeric glycoprotein von Willebrand factor is produced as pre-pro-VWF, which consists of a 741-residue propeptide and a 22-residue signal peptide. It comes from a large gene (180 kb, 52 exons). Golgi, post-Golgi, and endoplasmic reticulum organelles are the sites of substantial posttranslational processing for von Willebrand Factor, which includes glycosylation, sulfation, and assembly[26],[27].

Results and Discussion

Disulfide-linked multimers of 500–20,000 kDa are formed from the ~ 250-kDa monomeric subunits. The 2050 amino acids that make up a mature VWF monomer are composed of conserved domains ordered as follows: D1-D2-D'-D3-A1-A2-A3-D4-B1-B2-B3-C1-C6-CK. (Figure1)[26].

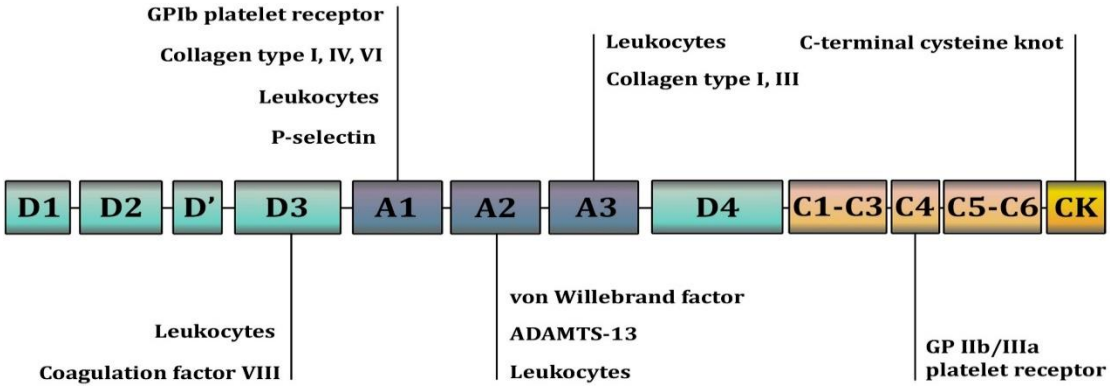

Figure (1): Von Willebrand factor structure displaying the binding sites and domains[28]

Von Willebrand factor is expressed specifically in endothelial cells and megakaryocytes. It is also found in the plasma, sub-endothelial matrix, and platelets. The factor is maintained within elongated vesicles in endothelial cell known as Weibel-Palade bodies and in α-granules of platelets. Endothelial damage triggers the activation of Weibel-Palade bodies, making them discharge their contents into the bloodstream, which includes VWF[29],[30].

Function of von Willebrand factor

Recently released VWF attaches itself to the cell surface to form incredibly enormous "string-like" structures, which ADAMTS13 then cleaves. Platelets quickly adhere and firmly attach to the site of damaged endothelium. This process, which is known as primary hemostasis, mediated by VWF by serving as a link between platelets and subendothelial collagen[31],[32]. In fact, VWF multimers bridge the extracellular matrix's collagen fibrils to the GpIb/IX/V platelets receptor[33].

VWF immobilization on sub-endothelial collagen creates a binding surface that allows platelets to be obtained from flowing blood[34].

When the immobilized VWF's A1 domain is bound by the platelet GpIbα receptor, the platelets undergo a continuous surface translocation, which is the hallmark of the initial platelets attachment. [35].

After interacting with the GpVI collagen receptors of platelets and α2 β1 integrin (GpIa/IIa), this pathway eventually results in stable platelet adhesion, aggregation, and activation of the GpIIb/IIIa receptor complex of platelet[36],[37].

In addition, VWF is also a carrier protein for procoagulant factor VIII (FVIII). It can attach to both neutrophils and macrophages and is very important for linking the primary haemostatic process to innate immune responses.[38].

Association between von Willebrand factor and prothrombotic state in SCD

There is mounting evidence that VWF contributes significantly to atherosclerosis, venous and arterial thrombosis, and thrombotic consequences seen in SCD and other thrombotic micro-angiopathies[39].

A little decline in the level of ADAMTS13 can occur from VWF release into the circulation as a result of endothelial activation brought on by the inflammation present in these clinical situations[40].

Sickle RBC adherence to endothelium is increased by multimeric VWF, which is two to 27 times greater than that of healthy RBCs. Research reveals that SCD patients experience a higher

elevation in VWF during occlusive crisis, which connects to rise inflammatory markers, without a significant ADAMTS-13 deficit[41].

Large, extremely adhesive VWF strands (ULVWFs) that are very good at attaching platelets, leukocytes, and sickle erythrocytes were released into the circulation during endothelium activation. The high level of VWF in patients with SCD may facilitated the adherance of sickled RBCs in the microcirculation, slow down their passage and encouraging deoxygenation, polymerization, hemolysis, and, possibly vaso-occlusion[42].

According to the authors, increased VWF level in SCD may result from increased VWF production as a result of endothelial activation, as well as decreased VWF sensitivity to cleavage. It documented that reactive oxygen species (ROS), produced by activated neutrophils, block VWF proteolysis by oxidizing the ADAMTS-13 cleavage site in VWF[43].

Extracellular hemoglobin also functions as an ADAMTS13 inhibitor. In both static and shear circumstances, extracellular hemoglobin is attached to VWF and ADAMTS13. However, its affinity for binding to the VWF A2 proteolytic cleavage site was about three times higher than that of ADAMTS13[44],[45].

It was discovered that there is a saturation-dependent relationship between the localization of VWF and extracellular hemoglobin. This suggests that excessive levels of hemolysis, as observed in SCD patients, particularly during acute crises, have a competing inhibitory effect on ADAMTS13 activity. Consequently, patients with SCD complaint from accelerated haemolysis may benefit from therapeutic targeting of the Hb-VWF interaction to alleviate thrombotic and vaso-occlusive consequences[44]. Microvascular thrombosis, which is observed in SCD patients, may be caused by disruptions in the complex equilibrium between VWF secretion and its breakdown by ADAMTS-13[46], [47],[48].

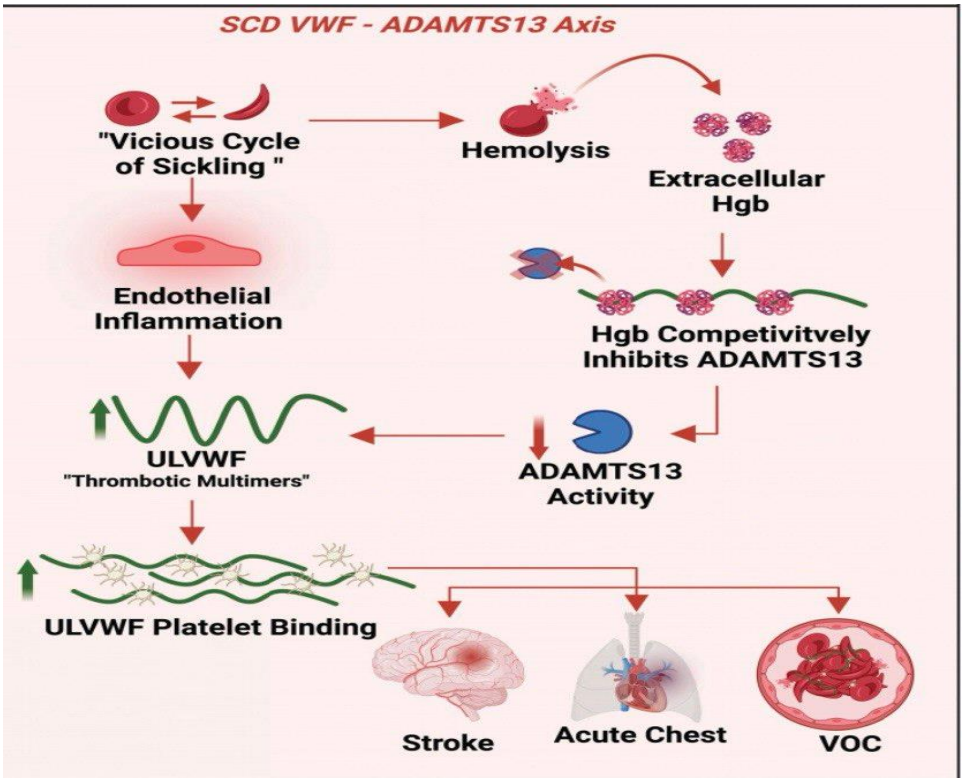

Figure (2) the rule of VWF on prothrombotic state in SCD[49]**.**

Conclusions

VWF and ADAMTS 13 level disturbance have a significant role in the pathophysiology of SCD, making them excellent targets for therapeutic intervention. Prior research has demonstrated that VWF is a major factor in the development of VOC, hemolysis, anaemia, and inflammation in SCD

patients. The von Willebrand factor is crucial in defining the clinical severity of sickle cell disease.

Conflict of interests

There is no conflict of interest

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