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Hypercoagulability in COVID-19: A review of the potential mechanisms underlying clotting disorders

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Abstract

Severe acute respiratory syndrome coronavirus-2 has emerged as a new viral pandemic, causing Coronavirus disease 2019 (COVID-19) leading to a wide array of symptoms ranging from asymptomatic to severe respiratory failure. However, coagulation disorders have been found in some patients infected with SARS-CoV-2, leading to either a clotting disorder or hemorrhage. Several mechanisms attempt to explain the mechanism behind the pro-coagulant state seen with COVID-19 patients, including different receptor binding, cytokine storm, and direct viral endothelial damage. SARS-CoV-2 has also been recently found to bind to CLEC4M receptor, a receptor that participates in the clearance of von Willebrand Factor and Factor VIII. The competitive binding of SARS-CoV-2 to CLEC4M could lead to decreased clearance, and therefore a promotion of a pro-coagulative state; however, an experimental study needs to be done to prove such an association.

Keywords

CLEC4M, coagulopathy, COVID-19, fibrinolytic shutdown, infectious diseases, mechanism, SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2, a virus belonging to the same family as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), was first identified in Wuhan, China in December of 2019.[1,2] On January 30, 2020 the World Health Organization (WHO) declared COVID-19 as a public health emergency of international concern (PHEIC).[3] The disease started spreading at an alarming rate causing widespread illness and mortality.[4,5] The main mode of transmission of COVID-19 is human to human via droplets, with asymptomatic carriers possibly acting as a silent source of transmission.[6] Lockdown measures were therefore implemented in most countries, at a different rate and level. These containment measures predictably caused a large disruption in the economy, prompting countries to evaluate the risk versus benefit of maintaining lockdown.[7]

Although infections range from mild to severe, and usually affect the respiratory system, patients with COVID-19 have shown various degrees of coagulation disorders ranging from thrombosis to bleeding, with markedly altered D-dimer levels.[8,9] While a multicenter retrospective study found the overall thrombotic complication rate was 9.5%, the overall and major bleeding rates were lower at 4.8% and 2.3%, respectively.[10]

I, therefore, aim to provide a concise review on the potential mechanisms of increased clotting in COVID-19 patients.

Search strategy

Pubmed/Medline, Science Direct, Google Scholar, and Medrxiv were used to search original articles and review articles published in the English language with the following keywords "SARS-CoV-2," "COVID-19," "thrombosis," "coagulopathy," "coagulation," "bleeding," "hemorrhage," and "CLEC4M."' Keywords in the results obtained were further used to expand the search strategy and included "fibrinolytic shutdown in COVID-19," "hypofibrinolysis in COVID-19," "cytokine storm in COVID-19," "complement

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in COVID-19," "autoimmunity in COVID-19," "ACE2 and COVID-19," and "endothelial damage in COVID-19."

Discussion

Coronaviruses are large, enveloped, positive-stranded RNA viruses that contain spike-like projections of glycoproteins on their surface, which appear like a crown under the electron microscope.[11] The structural proteins encoded by the viral genome allow host infection, membrane fusion, viral assembly, and release of virus particles.[12–16] The structure proteins include the membrane (M), the envelope (E), and the spike protein (S). The S protein assembles into trimers protruding from the virus envelope, with a membrane-distal N-terminal S1 portion and a stalk formed by the S2 region. The S1 region contains the receptor-binding determinants, whereas S2 mediates virus-cell fusion for membrane penetration.[17,18] The S protein is therefore the key mediator that allows viral entry into host cells.[11,19] Viral replication and transcription, on the other hand, are mediated by nonstructural proteins.[20]

Recent studies have shown that SARS-CoV-2 S proteins utilize angiotensin-converting enzyme 2 (ACE2) to gain host cell entry.[21,22] The SARS-CoV-2 receptor binding domain (RBD) has been also shown to have higher ACE2 binding affinity than SARS-CoV RBD.[23]

However, other molecules also act as receptors for SARS-CoV-2, namely, the neuropilin-I receptor and CD147 (also known as Basigin or EMMPRIN).[20,24] Alternatively, the molecules CD209 and CD209L (DC-SIGN and L-SIGN, respectively) act as receptors for SARS-CoV, promoting viral dissemination.[25] Both CD209L and ACE2 are expressed largely in type II alveolar cells and lung endothelial cells, with CD209L sharing almost 80% sequence homology with CD209.[26,27]

In addition, three genes encoding three distinct receptors have been proposed as determinants of VWF plasma levels: stabilin-2, CLEC4M, and LRP1.[28] This is significant because C-type lectin domain family 4 member M (CLEM4, CD299) gene encodes the L-SIGN (CD209L, CLEC4M).[29] As such, not only does CLEC4M act as viral receptor as mentioned above, but it also has the intrinsic capacity to recognize glycan structures present on the Von Willebrand Factor (VWF) molecule, internalize it, and clear it.[30] The role of CLEC4M in the coagulation disorder caused by COVID-19 is yet to be defined.

Thrombotic complications are emerging as important issues in patients infected with COVID-19. A meta-analysis of 22 Chinese studies involving 4,889 confirmed COVID-19 inpatients showed the prevalence of coagulopathy to be high, with elevated D-dimer levels and prolonged prothrombin time (PT) in more severe patients.[31] Several potential mechanisms could explain the clotting disorder caused by COVID-19 which is likely the result of a cooperation between all these different processes.

Cytokine storm

The first mechanism involves the ability of severe COVID-19 infections to cause a "cytokine storm," through the ability of SARS-CoV 2 to rapidly activate Th1 cells to secrete pro-inflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6). GM-CSF, in turn, activates CD14+ CD16+ inflammatory monocytes to produce large quantities of IL-6, tumor necrosis factor-α (TNF-α), and IL-1.[32,33] These cytokines are usually found at high levels in patients with sepsis associated with hypercoagulable status, as seen in disseminated intravascular coagulation (DIC).[34] However, IL-6 seems to be the key mediator in initiating hyper-coagulation. A study done by Folman et al. showed that IL-6 has an important role in the induction of tissue factor (TF) expression in inflamed tissues and the stimulation of megarkyopoiesis.[35] An increase in TF expression could be seen in patients with COVID-19 due to the lungs tissue damage and inflammation leading to induction of IL-6.[36,37] Fibrinogen and Factor VIII production are also stimulated by IL-6, which acts as well on endothelial cells to induce vascular permeability by stimulating vascular endothelial growth factor (VEGF) secretion.[38–40]

The complement pathway

The second proposed mechanism involves the activation of the complement pathway.[41] The extrinsic and intrinsic coagulation pathways interact with complement factors to maintain homeostasis.[42] In the setting of infections, complement activation favors pro-coagulation through the actions of C5a which activates tissue factor, mannan binding lectin serine protease (MASP)-1 which cleaves fibrinogen and factor XIII and therefore activates coagulation, and MASP-2 which amplifies complement activity, creating a positive loop.[43–45] Post-mortem studies of COVID-19 patients have shown increased interalveolar endothelial deposits of MBL, MASP-2, C4b, C3b, and C5b-9, as well as C5b-9 deposits in the glomeruli of kidneys.[46–48]

Autoimmunity

A third mechanism of coagulopathy could be linked to viral-induced autoimmunity with the induction of antiphospholipid antibodies (aPL). aPL are recognized risk factors for both arterial and venous thrombosis and have been associated with different viral infections.[49] However, data regarding aPL in COVID-19 patients are scarce, and what is available shows that the patients who had aPL did not have the same type of antibodies as seen in antiphospholipid syndrome.[50]

ACE2 expression

As COVID-19 binds to its receptors, ACE2 expression is decreased leading to activation of the renin-angiotensin system (RAS), promoting platelet adhesion and aggregation.[51]

Attachment can also cause direct endothelial dysfunction promoting the formation of a platelet plug.[52] The accumulation of angiotensin II can result in the production of reactive oxygen species (ROS) leading to oxidation of beta 2 glycoprotein 1 (β2GP1), which depletes non-oxidized β2GP1 from binding Von Willebrand Factor, leading to a cascade of platelet adhesion, activation, and aggregation.[53]

Endothelial damage

Severe inflammation might trigger endothelial injury and resulting thrombosis. Endothelial cells, when activated, trigger exocytosis and microvascular inflammation and thrombosis. This process is mediated by VWF, P-selectin, and other cytokines released during exocytosis.[54] While VWF facilitates platelet adherence and aggregation, and P-selectin leukocyte adherence to the vessel wall, these two molecules exhibit a synergistic relation that enhances inflammation and thrombosis.[55] Endothelial exocytosis can be triggered by SARS-CoV-2 directly binding to ACE2 receptor on the endothelial surface, indirectly through cytokines upregulation, or directly through the infection of endothelial cells by the virus.[54] This endothelial damage could also be linked to the cytokine storm seen in severe COVID-19 cases, whereby inflammation leads to the release of several cytokines that mediate endothelial exocytosis and thereby create a cycle of inflammation and vascular injury.[54] Among the inflammatory cytokines, IL-6 inhibits ADAMTS13 enhancing platelet adhesion and aggregation.[56]

Fibrinolysis shutdown

In septic patients with severe COVID-19 infection, hypofibrinolysis, leading to severely increased fibrinogen, has been well documented and has been linked to hypercoagulability and increased morbidity and mortality.[57,58] A recent study utilized thromboelastography (TEG) performed on 44 patients with severe COVID-19 infection and showed an elevated maximum amplitude (MA) in line with a hypercoagulable state, and low lysis at 30 min almost half the patients, suggestive of fibrinolysis shutdown.[59] The mechanism of this shutdown is still poorly understood but a few hypotheses exist. The liver and the plasma are the primary sites of production and distribution of fibrinogen, respectively.[60,61] Fibrinogen is converted into fibrin and cleaved by plasmin yielding products such as D-dimer.[62] An important relationship exists between the fibrinolytic system and the RAA system. In fact, binding of COVID-19 to ACE2 prevents degradation of angiotensin 2 leading to excess and causing plasminogen activator inhibitor (PAI-1) which acts as the main inhibitor of fibrinolysis.[63,64] In addition, PAI-1 expression is enhanced by complement activation, and specifically by C5a.[65] A pilot observational study showed significantly increased levels of PAI-1 in COVID-19 patients at sepsis onset with a sustainment of the fibrinolytic shutdown throughout the observation period especially in two groups of patients: non-surviving septic patients and septic patients with multiorgan failure.[54]

However, it is also important to mention the role of tissue plasminogen activator (tPA) as an activator of fibrinolysis. The fibrinolytic system may play a double role in COVID-19-induced coagulation disorder, either favoring coagulation or bleeding. As severe inflammation is caused by COVID-19, bradykinin is increased, favoring tPA production via upregulation of the kinin-bradykinin pathway. This increase might theoretically favor bleeding; however, the increased tPA has not yet been decisively proven to counterbalance the effects of increased PAI-1.[66] One possible explanation for the dual risk of hemorrhage and thrombosis in severe COVID-19 patients relates to the different sites that express either elevated tPA (leading to intra-alveolar hemorrhage) or elevated PAI-1 (leading to microthrombosis).[67]

CLEC4M

A seventh possible mechanism that has not yet been studied is the role of the CLEC4M receptor. As mentioned above, SARS-CoV-2 has been found to bind to ACE2 receptors, CD147, CD209, and CD209 L (L-Sign, CLEC4M). A recent study evaluating Factor VIII (FVIII) interactions with CLEC4M showed that CLEC4M is not only the clearance receptor for VWF, but it can also bind and internalize human FVIII in both a VWF-dependent and independent manner.[68] Genetic variation in the C-type lectin receptor CLEC4M in type 1 von Willebrand Disease has been demonstrated, showing the effect on CLEC4M on the alteration of VWF levels.[69,70] Factor VIII is proteolytically activated by thrombin into VIIIa, which serves as a cofactor for factor IXa, which, in the presence of Ca2+ and phospholipids, forms a complex that converts factor X to the activated form Xa, which then binds to factor II to form thrombin activates factor V and factor VIII, which serves as a cofactor in prothrombinase complex and accelerates the activation of Factor II by FXa and of FXa by FIXa, respectively. This cascade allows for continuous generation of thrombin and subsequently fibrin to form a sufficiently large clot.[71] Viral infections lead to inflammation which increases generation of thrombin, therefore increasing the activation of factor VIII and favoring a procoagulant state.[49] Parallels can be drawn between CLEC4M and Thrombocytopenic thrombotic Purpura, and specifically ADAMTS13, as the unavailability of CLEC4M (due to SARS-CoV-2 competitive binding) can be likened to the deficiency of ADAMST13 which leads to an excess of VWF and therefore favors coagulation.[72] We are therefore able to hypothesize that the ability of SARS-CoV-2 to bind to CLEC4M would decrease the body's ability to clear both VWF and FVIII, favoring a procoagulant state. However, this mechanism is still a hypothesis with a need for experimental data to prove the role of CLEC4M in COVID-19-related coagulation.

Limitations

This review presents information mainly based on literature reviews with data accumulated via different collection modalities, target population, and sampling and selection methods. In addition, coagulopathy in COVID-19 is still under study and other mechanisms could exist, while some of the already proposed mechanisms could be invalidated by further experimental studies. A major limitation is the role of CLEC4M receptor as it is still hypothetical, and no experimental studies were designed to demonstrate its role in COVID-19. Finally, this review is not meant to be an exhaustive list of the possible mechanisms underlying clotting disorders caused by COVID-19 as new data are constantly produced that could invalidate one of these mechanisms or suggest new, not previously discussed, mechanisms.

Conclusion

Aside from the respiratory symptoms, SARS-CoV-2 can also cause coagulation disorders leading to both increased clotting and increased bleeding. Several hypotheses attempt to explain the mechanism behind increased clotting which include cytokine storm, complement activation, and direct viral interaction with receptors. However, the effects of SARS-CoV-2 binding to CLEC4M, a receptor that clears VWF and FVIII, have not yet been studied, and warrant further research. In all likelihood, the coagulopathy caused by COVID-19 is likely attributable to a combination of factors rather one sole mechanism.

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