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COVID-19 PATHOPHYSIOLOGY PREDICTS THAT ISCHEMIC STROKE OCCURRENCE IS AN EXPECTATION, NOT AN EXCEPTION: A SYSTEMATIC REVIEW

Agnes Annurul Maulidia[1*], Anni Rota Rimbun Silitonga[2], Media Yuni Kurniawati[2]

[1]Faculty of Medicine, Bandung Islamic University, Indonesia*
[2]Cibabat General Hospital, Indonesia

Coresponding Author:
maulidiaagnes@gmail.com

Abstract

Background: *Clinical reports of neurological manifestations associated with severe coronavirus disease 2019 (COVID-19), such as acute ischemic stroke (AIS) are increasing rapidly. However, there are comparatively few studies investigating the potential impact of immunological responses secondary to hypoxia, oxidative stress, and excessive platelet-induced aggregation on the brain.*

Aim: *This study attempted to elucidate potential pathophysiological mechanisms associated with peripheral and consequential neural (central) inflammation leading to COVID-19-related ischemic strokes.*

Methods: *A systematic search strategy was conducted across several electronic reference databases (MEDLINE, Cochrane Library, CINAHL) and included articles published between January 2000 and August 12th, was carried out up to August 15th, 2020. Duplicate publications, review articles, and incomplete articles were excluded.*

Results: *The databases search identified a total of 1.539 articles (Table 1) and resulted in 672 articles after duplicates removed. Of these, 206 articles passed the screening process, resulting in 20 articles for full-text assessment. Among them, 10 articles did not evaluate the outcome of interest and insufficient details. Hence, we found 10 appropriate studies included.*

Conclusion: *This study affirms that the immunological contribution to the pathophysiology of COVID-19 is predictive of the neurological sequelae particularly ischemic stroke, which makes it the expectation rather than the exception.*

Keywords: *COVID-19, stroke, ACE2, cytokines, pathogen associated molecular pattern, post COVID-19 neurology syndrome, PCNS*

INTRODUCTION

The World Health Organization (WHO) declared the 2019 novel coronavirus (SARS-CoV-2) a pandemic on March 11, 2019.[1] Since the first case of coronavirus disease 2019 (COVID-19) infection was reported in Wuhan, China in December 2019, a significant number of thrombotic complications affecting the venous and arterial systems have been published in the literature,[2–4] with the World Stroke Organization now recognizing that acute ischemic stroke (AIS) increases the severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) viral infection by 2.5-fold.[5,6] Similar associations between systemic infections, inflammation, and AIS are longstanding.[7] However, to date, few reports are reviewing the molecular bases of the peripheral and central mechanisms induced by SARS-CoV2 infection and potential neurological manifestations with focused attention on AIS.

Neurological manifestations of COVID-19 infection were first described by Mao et al. who observed six cases of acute cerebrovascular disease.[3] Subsequently, 19 cases of COVID-19-related strokes particularly affecting the young and involving medium to large arteries were reported from a tertiary center in New York,[8] highlighting the need for better understanding of the potential mechanisms linking COVID-19 and AIS. Stroke has been associated with other earlier coronavirus infections. In 2002, AIS was first detailed by Umapathi et al., in 4 of 206 patients who presented with large vessel occlusion associated with SARS-CoV infection in Singapore in 2002.[9] Two other patients with AIS were also described in Middle East respiratory syndrome corona virus (MERS-CoV)-infected patients in Saudi Arabia during the 2015 epidemic.[10]

SARS-CoV2 is known to initially bind to the angiotensin-converting enzyme 2 (ACE2) receptors of epithelial and endothelial cells where an immediate immunological activation occurs that can, in severe cases, eventually lead to hypercoagulability or thrombophilia and increased tendency of clots forming in the blood and potentially AIS.[11] However, there is limited information on the physiological abnormalities and mechanisms linking COVID-19 and AIS, although a number of mechanisms have been proposed. The major mechanisms that have been proposed to date include systemic innate immunity-mediated hyperinflammation, neurovascular endothelial dysfunction, endotheliitis, central nervous system renin–angiotensin–aldosterone system (RAAS) dysregulation, oxidative stress, and excessive platelet aggregation.[12,13] Thus, this study attempted to elucidate potential pathophysiological mechanisms predisposing patients with COVID-19 to a higher risk for neurovascular events.

Method

Identification and Development of the Research Question

This focused on the general research question: “Are there mechanisms associated with COVID-19 infection that are likely to predispose patients to ischemic stroke?”. Then, the following are the two specific areas of interest: (a) “Can current understanding of the immunological mechanisms associated with the inflammatory responses to severe COVID-19 potentially predispose a patient to AIS?” and (b) “Are there other potential pathophysiological mechanisms predisposing COVID-19 patients to upregulate procoagulable mechanisms leading to thrombi formation and potentially AIS?”.

Search Strategy

The search was conducted in multiple databases, including MEDLINE, Cochrane, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Subsequently, the identified keywords were used to search the same databases for relevant studies. The following keywords were used: COVID-19, coronavirus, mechanism, inflammation, thrombosis, embolism, endotheliitis, arteritis, neuroinflammation, and ACE2 receptors. The search was conducted on January 2000 till August 2020. The literature was first screened at the title and the abstract level; then, full-text articles were assessed for eligibility. The manual bibliographic search of identified studies was also done in the last step of the literature search.

Table 1. Literature search strategy

Database	Keywords	Results
MEDLINE	(covid-19) OR (coronavirus) AND (mechanism) AND (inflammation) OR (thrombosis) OR (embolism) OR (endothelitis) OR (arteritis) OR (neuroinflammation) OR (ACE2 receptors)	687
Cochrane Library	“covid-19” OR “coronavirus” in Title Abstract Keyword AND “mechanism” in Title Abstract Keyword AND “inflammation” OR “thrombosis” OR “embolism” OR “endothelitis” OR “arteritis” OR “neuroinflammation” OR “ACE2 receptors”	289
CINAHL	(covid-19) OR (coronavirus) AND (mechanism) AND (inflammation) OR (thrombosis) OR (embolism) OR (endothelitis) OR (arteritis) OR (neuroinflammation) OR (ACE2 receptors)	563

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were: (1) only studies (qualitative and quantitative studies, systematic reviews, metanalysis, case reports, and case series) that directly or indirectly link

pathophysiological mechanisms to ischemic stroke and COVID19 infection; (2) published between January 2000 and August 12th, was carried out up to August 15th, 2020; (3) full-text articles available; and (4) published in English. The exclusion criteria of the studies are articles that are not indexed by Scopus, editorials, reviews, and articles that did not evaluate the focus of interest of this study. The research selection was carried out in three successive phases. The titles and abstracts of all search results were initially screened and evaluated for relevance. Second, complete access was gained to all potentially eligible studies. Finally, the systematic review included only those studies that met our inclusion criteria. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline is used for the selection.

Data Extraction and Parameter Measured

All the authors extracted the data from the articles. The following parameters were taken into account: publication year, type of study, aims and objectives of the study, and study findings and conclusion. All disagreements regarding the methodology, article retrieval, and statistical analysis were resolved by consensus among the authors.

Results

The databases search identified a total of 1.539 articles (Table 1) and resulted in 672 articles after duplicates removed. Of these, 206 articles passed the screening process, resulting in 20 articles for full-text assessment. Among them, 10 articles did not evaluate the outcome of interest and insufficient details. Hence, we found 10 appropriate studies included (Figure 1). The summary of the main findings of the selected studies is presented in Table 2.

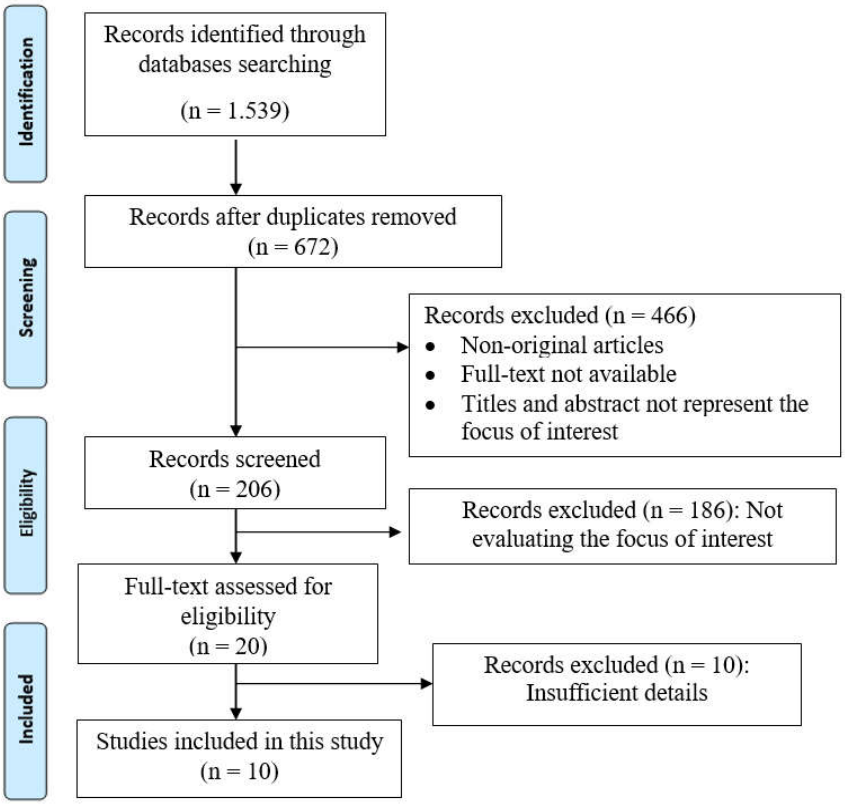

Figure 1. PRISMA flow diagram

Table 2. Summary of the studies on the mechanism of COVID-19-related strokes

Publication date	Author	Type of Study	Objectives	Conclusion
June 2, 2020	Tomar et al.[14]	Review article	To identify the role of enhanced neutrophil infiltration and the release of NETs, complement activation and vascular thrombosis during necroinflammation in COVID-19	NET formation induces production of proinflammatory cytokines leading to tissue inflammation responsible for cytokine storm and sepsis.
September 3, 2020	Wijeratne et al.[15]	Review article	To identify the role of inflammation affecting vascular systems as well as the importance of NLR as a potential biomarker in this context	NLR is a useful and easily available biomarker in atheromatous vascular disease supporting the same role in COVID-19 and large vessel disease
May 2010	Hermus et al.[16]	Review article	To identify the biomarkers associated with carotid plaque	Various biomarkers linked to inflammation, lipid accumulation,

			formation	thrombosis and angiogenesis have been related to plaque formation and vulnerability.
July 2020	Mohamud et al.[17]	Case series	To describe six cases of COVID-19 positive patients with associated intraluminal carotid artery thrombus.	Inflammation related to COVID-19 19 may lead to plaque rupture of previously known vulnerable atheroma leading to thrombosis an ischemic stroke.
May15, 2020	Wright et al.[18]	Prospective cohort	To determine the correlation between thromboelastography measurements of coagulation and thromboembolic events in COVID-19 19 patients.	Failure of clot lysis at 30 min on thromboelastography is predictive of thromboembolic events in critically ill COVID-19 19 patients
July 17, 2020	Kunutsor et al.[19]	Meta-analysis	To identify the association of CRP and VTE risk	Elevated CRP is associated with greater VTE risk, consistent with a linear dose–response relationship.
July 2020	Cheng et al.[20]	Review article	To identify the correlation between angiotensin-converting enzyme 2 (ACE2) and severe risk factors for coronavirus disease 2019	ACE2 is an essential part of the RAS, and it has extensive vascular and organ protection functions in hypertension, diabetes, cardio-vascular disease, and ARDS
May 7, 2020	Hess et al.[21]	Review article	To identify the role of ACE in COVID-19 related strokes.	Binding to and depletion of ACE2 may tip the RAS balance in favor of the ACE-1-angiotensin II-AT1 axis and contribute to endothelial dysfunction, organ damage, and stroke.
July 20, 2020	Spence et al.[12]	Review article	To identify the mechanisms of stroke in COVID-19	Vasculitis, hypercoagulability, endothelialinjury, microvascular thrombosis, cytokine storm, systemic hypoxia, fresh DVT, cardiac alterations.
June 26, 2020	South et al.[22]	Review article	To identify the risk of stroke in the context of preceding infection, including COVID-19	SARS-CoV-2 global pandemic is not the first viral infection to be linked with stroke. The current pandemic is an ideal opportunity to acquire valuable insight toward the relationship between stroke and infections

Discussion

The intrinsic pathogenicity of severe coronavirus infection in vulnerable people ensures that the acute severe inflammatory response to the COVID-induced respiratory distress results in decreased levels of circulating lymphocytes, secondary hemophagocytic lymphohistiocytosis (HLH)[23] shifts immune defenses toward natural killer (NK) and circulating macrophages (macrophage activation syndrome), and increased neutrophils.[24] An early and important mediator to this phenomenon is the significant elevation of proinflammator y cytokines that fuel various processes in cerebrovascular ischemia.[25]

Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasomes play an important role in innate immunity and are directly activated by the virus itself. In patients with stroke, it has been shown that the NLRP3 inflammasome plays a significant role in cerebral atherogenesis by similar activation of the immune system and increase in macrophages, neutrophils, lymphocytes, and vascular smooth muscle cell, which also play an important role in plaque instability.[26,27]

Among patients with coronary disease, evidence suggests that virally induced inflammatory infiltrates such as T cells, macrophages, and neutrophils populate the atheromatous plaque leading to a cascade of events including vascular permeability, endothelial disruption, and exposure of prothrombotic elements, which all play a role in thrombogenesis.[28,29] Furthermore, it is known that carotid artery plaques with features of a thin fibrous cap, large core lipid, intraplaque bleeding, and the abundance of monocyte-derived macrophages and activated smooth muscle cells cause instability and vulnerability to plaque rupture.[16] Indeed Mohamud et al. have described five cases of acute ischemic stroke associated with an intraluminal carotid artery thrombus with concomitant COVID-19 symptoms 0–14 days before the onset of stroke.[17] Another putative mechanism that can lead to plaque progression in patients with COVID-19 infection is the disruption of the receptor-mediated uptake of oxidized low-density lipoproteins (oxLDL) by the monocyte-derived macrophages with exposure to proinflammatory stimuli.[30] COVID-19 infection is associated with reduced leukocyte number and increased neutrophil to leukocyte ratio and so makes the recent evidence of dysregulated neutrophil extracellular traps (NETs) predictable.[31] NETs also play a role in thrombus formation.[32] Evidence indicates that, in patients with COVID-19 infection, there is an upsurge of NET production that further propagates inflammation and thrombosis.[33,34]

A component of Virchow's triad, endothelial dysfunction is another major contributor to SARS-CoV-associated thrombosis.[35] The virus has been shown to demonstrate a predilection to invade vascular endothelial cells by attaching to the ACE2 protein[36], which facilitates subsequent invasion. ACE2, which is ubiquitous in the brain, heart, and the vascular systems protects patients from the organ-damaging effects of the classical renin angiotensin aldosterone system (RAAS).[37] This COVID-19-related disruption of the RAAS axes is likely to contribute to stroke pathogenesis, as it promotes inflammation, vasoconstriction, and end-organ damage.[36] The summary of the the pathophysiological mechanism of COVID-19 related AIS is presented in Table 2.

Table 3. Summary of pathophysiological mechanism of COVID-19 related AIS

Inflammatory mediators of ischemic stroke	The role of cytokines	○ First released by the respiratory epithelium[24] ○ Further released by T lymphocytes activates other cellular mediators mediating secondary hemophagocytic lymphohistiocytosis[24,23]
	NLRP3 inflammasomes	○ Activated by viroporin protein 3a[26] ○ Drives production of inflammatory cytokines, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)[27] ○ May induce plaque instability by overdriving response of cellular mediators such as macrophages, neutrophils, lymphocytes and vascular smooth muscle cell[27]
	Inflammation-induced plaque vulnerability	○ Predominance of T cells, macrophages and neutrophils populating an atheromatous plaque leading to plaque rupture[28,29] ○ Characterized by elevation of proteolyic biomarkers such as metalloproteinases (MMPs) and cathepsin cysteine proteases (CCP's)[38,39]
	Oxidized LDL (oxLDL)	○ A marker of increased oxidative stress[30] ○ COVID-19-related disruption of the receptor-mediated uptake of oxLDL[30]
	Neutrophil extracellular traps (NETs)	○ Networks of chromatin, proteins and oxidant enzymes that protrude from membranes of activated neutrophil and mediate infection containment[31,33] ○ Also a marker of inflammation-related thrombosis[34,40]
Coagulatory disfunction	D-dimer	○ Mediates immunologic defense systems resulting in thrombi formation[41] ○ Increased level is a biomarker of fibrinolytic shutdown leading to massive fibrin formation resulting in thrombosis[41]
	Natural anticoagulants and antiphospholipid antibodies	COVID-19 induced decrease in the amounts of physiological anticoagulants and increased levels of coagulant factors and antiphospholipid antibodies[42,43]
Endotheliopathy	Endothelium-driven activation of the extrinsic coagulation system	○ Imbalance in the ACE2 and angiotension II (AT-II) receptors leads to the upregulation of tissue factor[36,44] ○ Tissue factor interacts with Factor VII to activate the extrinsic coagulation system[44]
	Endothelium-driven nitrous oxide deficiency	○ COVID-19 related endotheliopathy results in the suppression of nitric oxide synthase (NOS), resulting in nitric oxide deficiency[45] ○ Results in loss of vasodilatory effect and promotes adhesion of platelets and leukocytes to the vessel wall[45]
RAAS and ACE-2 deficiency	Alterations in the balance between the classical RAAS and the ACE2 pathways	○ Promotes organ damaging effects of the classical RAAS pathway[36,37] ○ Promotes overactivity of the sympathetic nervous system resulting in the exacerbation of traditional stroke risk factors[46]

Conclusion

Our systematic review shown that severe COVID-19 infection has the potential to lead to the disruption of most physiological systems and results in various multisystemic thrombotic phenomena including acute ischemic stroke. While inflammation orchestrates its pathogenesis, the further perturbation of the coagulation system resulting in fibrinolytic shutdown likewise contributes to neurological manifestation. Furthermore, the predilection of the virus to attach to ACE2 receptors in various cells, including the vascular endothelial system, may also disrupt the renin–angiotensin system, which further contributes to stroke pathogenesis. Clearly, there is a gap in the understanding of this phenomenon, and large-scale human and animal studies are necessary, as this co-occurrence results in deleterious outcomes.

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