Antiphospholipid Antibody Role in Acute Ischemic Stroke Patients with COVID-19: A Narrative Review

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ABSTRACT

Antiphospholipid antibodies (aPL) are commonly found in humans after an infection. Its action can promote thrombosis via the activation of endothelial cells, platelets, and neutrophils. This autoantibody is the leading cause of antiphospholipid antibody syndrome (APS), characterized by widespread thrombosis in various vascular beds. COVID-19 also causes acute ischemic stroke (AIS) in the younger demographic, who previously was not considered a population at risk for AIS, which may be related to APS. This narrative review will discuss the role of aPL in COVID-19 patients who experienced AIS during infection.

Keywords: Antiphospholipid antibody, Acute Ischemic Stroke, COVID-19, Antiphospholipid antibody syndrome

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel contagious disease caused by a Coronaviridae family named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] By the beginning of 2021, there were 92 million cases found, with 1.9 million death cases worldwide.[2]

The SARS-CoV-2 virus infects the human body primarily via interaction with angiotensin-converting enzyme 2 (ACE2) in the human respiratory tract. A recent study found that SARS-CoV-2 can cause disease in other organs which express ACE2 receptors, such as the heart, kidney, gastrointestinal tract, male genitals, and blood vessels.[3]

Antiphospholipid antibody (aPL antibody) is an autoantibody that binds to phospholipids and phospholipid-binding protein. Its action can promote thrombosis via the activation of endothelial cells, platelets, and neutrophils. This autoantibody is the leading cause of antiphospholipid antibody syndrome (APS), characterized by widespread thrombosis in various vascular beds.[4] Several reports found aPL antibody in COVID-19 patients. Guerra *et al.* reported that 12 of 21 severe COVID-19 patients tested positive for this antibody.[5] A cohort study in New York found that 44% (30 out of 68) of patients who tested positive for aPL antibody also tested positive for COVID-19, compared to 22% (27 out of 118) COVID-19 negative group. Also, this study reported that 63% (19 out of 30) patients in the COVID-19-positive and aPL antibody-positive group had experienced thrombosis events.[6]

One manifestation of COVID-19 is acute ischemic stroke (AIS). The incidence of AIS in COVID-19 is reported between 1 to 6%. COVID-19 also causes AIS in

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the younger demographic, who previously was not considered a population at risk for AIS. A study in New York found a 7-fold increase of large vessel stroke in young people compared with the previous year. Other studies also found that the mean age of large vessel stroke patients who tested positive for COVID-19 is younger than that of large vessel stroke patients who tested negative for COVID-19 (59 years vs. 74 years).[7] Currently, the pathophysiology of AIS in COVID-19 patients is not well established.

Nonetheless, several mechanisms of COVID-19-induced-AIS have been proposed, such as hypercoagulability, vasculitis, new-onset atrial fibrillation, and direct infection by the SARS-CoV-2 virus.[8] It has been suggested that the AIS in COVID-19 is linked with the presence of aPL autoantibody. We conducted a thorough literature search to find articles and peer-reviewed journals related to possible interactions between COVID-19, AIS, and aPL autoantibody. This paper aims to give an update of current knowledge about aPL in COVID-19 patients who experienced AIS.

AIS in COVID-19

Several studies reported the occurrence of AIS in COVID-19 patients. A systematic review by Kiat-Tan *et al.* noted that 54 out of 4466 COVID-19 patients experienced AIS (1.2% pooled incidence). This data was collected from five observational cohort studies. The mean severity score of AIS in COVID-19 patients was 19 ± 8, measured with NIHHS score.[9] Another systematic review from Nannoni *et al.* found that the stroke incidence rate in COVID-19 patients was 1.4%, of which 87.4% of stroke cases were ischemic type. This study also reported that compared to the stroke cases in non-COVID-19 patients, stroke in COVID-19 occurred at a younger age, had a higher National Institutes of Health Stroke Scale (NIHSS) score, and had higher mortality.[10] These findings are in line with another systematic review conducted by Siow *et al.* The majority of strokes in COVID-19 patients were the ischemic type (an average of 82.8% from 27 studies). Large vessel ischemic stroke was the most common pattern found in this group of patients.[11] Mortality rate in AIS patients tested positive for COVID-19 was nine times higher than COVID-19-negative AIS patients.[12] In conclusion, AIS has already been recognized as one of the consequences of COVID-19 infection.

aPL antibody in general

Phospholipids are substances in the blood that are required for the blood to clot.[13] A group of antibodies directed against phospholipid called Antiphospholipid antibodies (aPL). aPL can target the anionic and neutral phospholipids that form cellular membranes.[14] It consists of immunoglobulins IgG, IgM, and IgA isotypes that target phospholipid (PL), PL-binding plasma proteins, or both.[15] The most common aPL finding in Antiphospholipid syndrome is Lupus anticoagulants (LAC) and anticardiolipin antibodies (aCL). LAC works by interfering with the phospholipid-dependent coagulation test, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT). aCL has autoantigen properties towards negatively charged phospholipids such as cardiolipin, beta2-glycoprotein I, prothrombin, protein C, etc.[16] The other antibody that is frequently mentioned is anti-beta2-glycoprotein I (aB_2GP1). This antibody has been proposed as the most critical factor in the development of thrombotic events in APS and could increase the specificity in the diagnosis of APS.[16,17]

aPL antibody role in the vascular system

aPL antibodies are commonly found in humans after an infection. A previous literature review found that this antibody is frequently present during an episode of viral infection, such as HIV, Hepatitis B, and Hepatitis C.[18] This antibody usually disappears after the infection is over. Memory B-cells can produce this antibody, suggesting that antibodies may have a role in the typical human immune system. It might be acting like a "vacuum cleaner" that clears cellular debris in human blood circulation. aPL effect is instigated by its binding to phospholipid-binding protein β2 glycoprotein I (β_2GPI). Then, this complex binds and removes any apoptotic cells, microparticles, and bacterial products present in blood circulation. Autoantibodies regulate this function against β_2GPI naturally found in the human body. When these autoantibodies increase in titer and avidity, the physiological role of aPL- β_2GPI is altered into a pathologic state.[19] These pathologic complexes can form immune complexes and modify standard coagulation steps that could cause arterial or venous thrombosis.[20]

aPL antibody findings in COVID-19-positive AIS patients

There are several aPL that is usually used for classification criteria for antiphospholipid syndrome; aCL antibodies or $a\beta_2GPI$ antibodies, LAC, and anti-phosphatidylserine/prothrombin autoantibodies (aPS/PT antibodies).[4] Reports from several studies found that these antibodies can also be found in COVID-19-positive AIS patients. Beyrouti *et al.* reported a case series of 6 patients with COVID-19 and AIS, 5 of which tested positive for at least one aPL antibody mentioned above.[21] A case report presented by Goldberg *et al.* noted a 64-year-old male with ischemic stroke in the right middle cerebral artery (MCA) and bilateral anterior cerebral artery (ACA). This patient was tested positive for IgM aCL antibody.[22] One patient from a case series reported by Zayet *et al.* tested positive for IgG $a\beta_2GPI$ antibody.[23] Another case series from Zhang *et al.* mentioned that three patients with multiple cerebral infarctions tested positive for IgA aCL antibodies, IgG $a\beta_2GPI$ antibody, and IgA $a\beta_2GPI$ antibody.[24] These studies showed that aPL antibody was prevalent among COVID-19-positive AIS patients. However, another study failed to find any aPL in these patients. Case reports from Deliwala *et al.*, Viguier *et al.*, and Gunaransekar *et al.* were unable to found these

antibodies.[25-27] We reckon this difference arose because no standard aPL panel testing was available to test COVID-19-positive AIS patients. Therefore, we postulated a need to establish which aPL antibody is directly associated with AIS in COVID-19 patients and develop a standard panel testing to find these aPL antibodies.

Table 1 below summarized AIS case reports in COVID-19-positive patients and their reported aPL antibody findings. We also mentioned the patient's NIHSS score in this table. NIHSS is a score that measured stroke severity. It consists of 15 items of impairment scale, covering the level of consciousness, eye movements, the integrity of visual fields, facial movements, arm and leg muscle strength, sensation, coordination, language, speech, and neglect. It is ranged from 0 to 42. A higher score indicates a more severe stroke.[28]

There are several postulation-related antibody anti-phospholipid in COVID-19 patients. The first mechanism is the S1 and S2 subunit from S protein SARS-CoV-2 mimic phospholipid epitope, inducing PL antibodies. This process includes cell T mechanism antibody-dependent T cell which the virus triggers the immunologic response. This is confirmed with the occurrence of β2-glycoprotein in the cell host, suggesting oxidative stress from SARS-CoV-2 infection, which then produces antibodies (Figure 1).[29,30] The second mechanism is the two-hit hypothesis related to thrombogenesis. The increase of reactive oxygen by endothelial and macrophages downregulates the antioxidant pathway. This phenomenon, along with the first mechanism, contributes to thrombus formation and activation in the coagulation cascade.[31]

Hypercoagulable state and role of aPL in COVID-19-positive AIS patients

The imbalance between procoagulant and anticoagulant can result in a hypercoagulable state.[33] It can result from various causes, including an inherited or an acquired one. The most common cause of contracted hypercoagulable state is an aPL syndrome which one of the criteria is the presence of aPL antibodies.[34,35] To initiate a clinical event, aPL antibodies

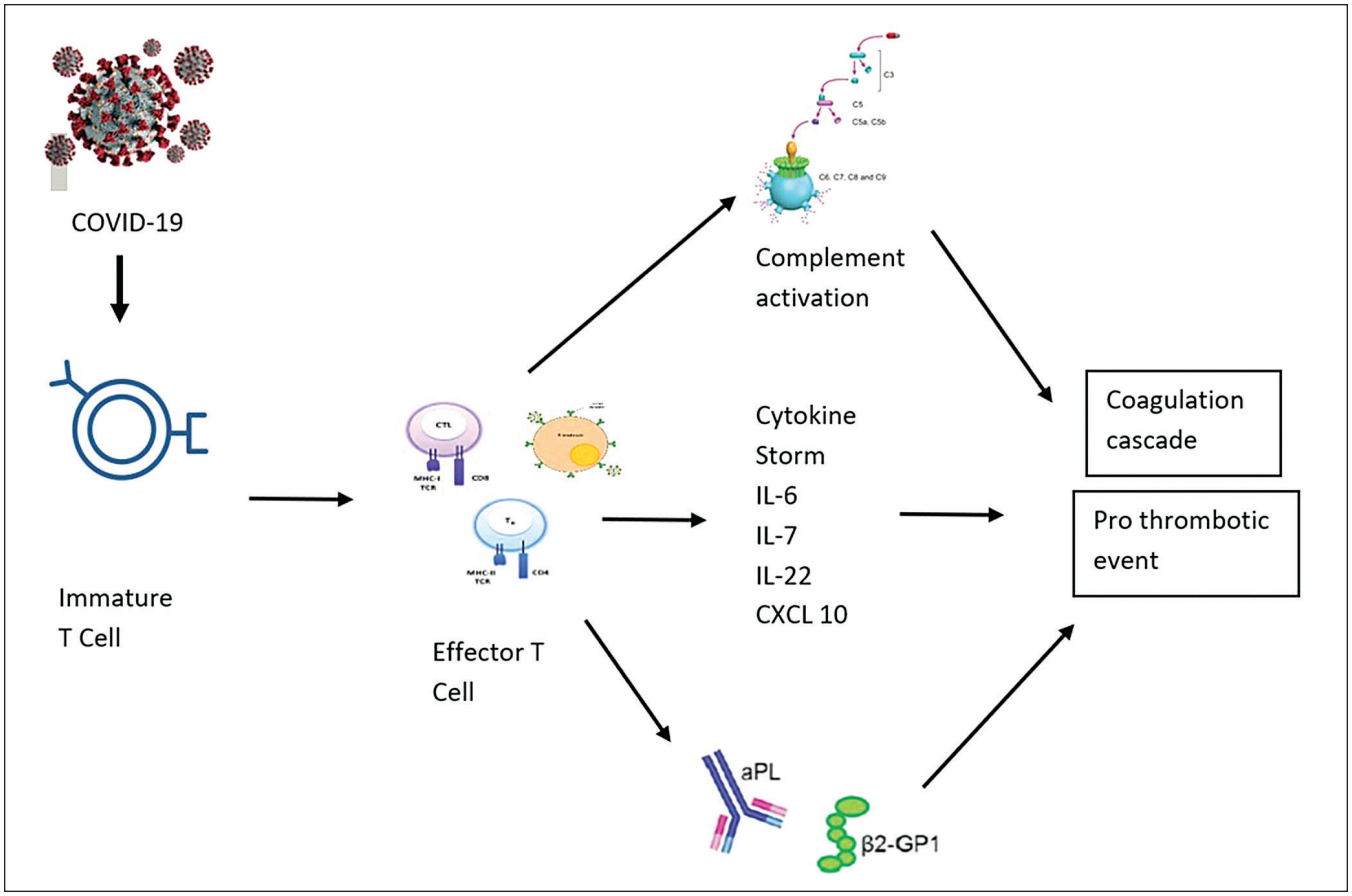

Figure 1. Supporting mechanism of COVID-19 trigger antiphospholipid antibody. There are two hypotheses of aPL and β2-glycoprotein 1 production. Molecular mimicry from SARS-CoV-2 and respiratory epithelium invasion, which results in endothelial damage, triggers the effector T cell to produce the antibody. This process also increases the complement activation and cytokine release, such as cytokine storm syndrome. All of these cascades promote platelet aggregation and increase thrombin generation.[32]

Table 1. AIS in COVID-19 case reports and reported aPL findings

Author, Year	Design	Population	Number of Patients with positive mortality	Laboratory and CT Findings	NIHSS (admission, discharge)	aPL Antibody Detection	Comment
Beyrouti et al. (2020)	Case Report	Patients with AIS and COVID-19 (confirmed by RT PCR). Assessed between 1st and 16th April 2020 in The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.	1	All patients were either tested with MRI or non-contrast-CT, and all showed cerebral infarctions.	Not stated	All patients were tested for aCL and aB_2GP1. 5/6 patients tested positive for LAC. One patient tested positive for IgM aCL and IgG, IgM aB_2GP1	The aPL may be related to the severity of the disease
Goldberg et al. (2020)	Case Report	64-year-old male admitted because of hemiparesis and shortness of breath. Sixteen days before admission patient was tested positive for SARS-CoV-2 infection.	1	Elevated prothrombin time, D-dimer level, and ferritin level. Head CT showed ischemia	Not stated	aCL IgM positive	The presence of an aPL may be related to an increase in odds of mortality in a stroke patient with COVID-19
Zayet et al., 2020	Case report	Patient with presumed thrombotic stroke during the pandemic of COVID-19	1	All head CT show multiple cerebral infarctions.	Not stated	1 of 2 patients tested positive for aCL IgM	The presence of an aPL may be a predictor of mortality in a patient stroke with COVID-19
Zhang et al. (2020)	Case Series	69-year-old male, 65-year-old female, and 70-year-old male with confirmed SARS-CoV-2 infection also developed cerebral infarctions.	Not stated	All patients have elevated D-dimer and CRP levels; one patient has elevated ferritin levels. All head CT show multiple cerebral infarctions.	Not stated	All cases tested positive for aCL IgA, aB_2GP1 IgA, and IgG	The presence of aPL may lead to poor morbidity
Deliwala et al. (2020)	Case Report	A 31-year-old female developed a cerebral infarction after eight days admitted with respiratory symptoms and confirmed SARS-CoV-2 infection.	0	Elevated Ferritin, CRP, and D-dimer level. Head CT shows cerebral infarctions.	Not stated	Tested negative for LAC and IgG IgM aCL	The presence of an aPL may be related to severe morbidity in patient stroke with COVID-19
Viguier A et al. (2020)	Case Report	A 73-year-old patient developed an AIS a week after respiratory symptoms related to SARS-CoV-2 infection.	0	Elevated Ferritin, CRP, and D-dimer	10,3	Negative (not explicitly stated)	Case Report weighs more about COVID and Stroke. aPL only tested for screening.
Gunasekaran et al. (2020)	Case Report	A 40-year-old female came to ER with respiratory symptoms and tested positive for SARS-CoV-2 infection. Seven days after being admitted patient developed cerebral infarctions.	0	Elevated ferritin level. Head CT showed cerebral infarctions.	Not stated	LAC negative	The presence of an aPL antibody may be related to severe morbidity in patient stroke with COVID-19

Abbreviations: AIS – acute ischemic stroke; aB_2GP1 – anti-B_2-glycoprotein-1; aCL – anticardiolipin; aPL antibodies – antiphospholipid antibodies; LAC - lupus anticoagulant; NIHSS – National Institutes of Health Stroke Scale

activate cells via several pathways, including the activation of platelets and the complement system.[33] The thrombotic mechanism involves activating endothelial cells, monocytes, platelet, coagulation factor, and complement proteins.[36]

Though the mechanism is uncertain, some studies describe the unique hypercoagulable state caused by aPL antibodies. It can strike almost every vessel, artery and vein, large vessel, and microcirculation and interfere with the various coagulation process mechanism.[35]

One of the pathogenesis of thrombosis can be explained by the "two-hit" model. The first hit is the presence of aPL antibodies, provided by conditions that can alter the vascular endothelium and increase oxidative stress, such as infection. The first hit or the antibody will induce a thrombophilic state. The second hit is the triggering risk factor which facilitates thrombus formation. These thrombotic events only occur when there is a persistent presence of aPL antibodies.[37-39]

Infectious agents have been proposed as a possible trigger because of the molecular mimicry mechanism.[40] Infection could initiate an inflammatory response as a part of innate immunity. aPL antibodies could transiently appear in patients with various infections or critically ill patients. Those appearances of antibodies could lead to thrombotic events.[41]

The hypercoagulable state has been observed in COVID-19 patients. Data from several studies found that COVID-19 patients have suffered from coagulation abnormalities, such as elevated von Willebrand factor (vWF), factor VIII, D-dimer, and fibrinogen.[42]

The World Health Organization (WHO) has mentioned that coagulopathy is common in severe COVID-19 infection. Therefore, monitoring of thrombotic events, AIS included, is recommended.[43] Usually, D-dimer is used as a tool to detect if there was a hypercoagulable state that happened in COVID-19 patients.

Based on the findings above, we suggest that aPL antibodies can be added as an additional tool to detect these events, especially whenever AIS is manifested in COVID-19 patients. Our suggestion is in line with Zhang *et al.*'s review that proposed aPL antibodies as one of the possible mechanisms that cause hypercoagulability in COVID-19 patients, which eventually cause AIS in COVID-19 patients.[44]

Other possible mechanisms of COVID-19-induced AIS

Other potential mechanisms have been proposed to explain the occurrence of AIS in COVID-19. We will briefly describe them in the following:

Vasculitis

As mentioned above, SARS-CoV-2 virus interaction with a human cell is primarily mediated by the ACE2 receptor. Besides lung, this receptor can also be found in vascular endothelium.[45] SARS-CoV-2 binding to the ACE2 receptor could deplete the amount of endothelial ACE2 and subsequently promote the action of ACE1, a homolog to ACE2. This homolog promotes inflammation and tissue injury in the brain endothelium.[46] Several cases have been reported regarding this mechanism. Hanafi *et al.* reported a case of extensive cerebral small-vessel ischemic lesions resembling cerebral vasculitis.[47] Sousa *et al.* also reported a case of a 28-years old male who was diagnosed with vasculitis-related stroke.[48]

New-onset atrial fibrillation

Atrial fibrillation (AF) has been established as a significant risk factor for developing AIS. Framingham's study in 1978 has found AIS incidence in AF patients is five times higher than in non-AF patients.[49] Several recent reports from other studies mentioned AF occurrence in COVID-19 patients. Gawalko *et al.* stated that AF was found in 19 to 21% of COVID-19 patients. They noted that reliable data for newly diagnosed AF was scarce. Based on current data, they estimated the prevalence of newly diagnosed AF in COVID-19 patients was between 3.6% and 6.7%. There are several hypotheses proposed to explain this finding, which includes cytokine storm, endothelial dysfunction, electrolyte imbalance, and hypoxemia, all of which leads to a prothrombotic state and eventually make a person susceptible to AF.[50]

Direct viral infection

A study from Merkler showed that COVID-19 patients have a higher risk of experiencing AIS than influenza patients.[51] This finding is in line with past finding that influenza-like viral infection could slightly increase the risk of developing AIS. However, the exact mechanism of how SARS-CoV-2 directly causes AIS is still unknown.[8]

SUMMARY

COVID-19 can manifest itself as a cerebrovascular accident (CVA), mostly AIS. Several studies reported this occurrence. It is suspected that AIS in COVID-19 patient may be caused by aPL that increases when SARS-CoV-2 infect a human body. This may lead to a hypercoagulable state in the blood vessel, which eventually causes thrombosis in the vasculature; in this context, brain vasculature leading to AIS. Some studies noted the presence of aPL in COVID-19 patients who had AIS.

A more comprehensive study is warranted to establish this correlation and explore whether these findings can be helpful in a clinical setting, whether as an additional tool for examination or as a target for therapy.

Statement of Authorship

All authors participated in the data collection and analysis, and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

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