REVIEW ARTICLE

Ischemic Stroke and Acute Coronary Syndrome (ACS) in COVID-19 Patients: Mechanisms and Role of Coagulopathy

Syed Mujtaba Azhar Bokhari[1*] and Muhammad Irfan Kaleem[2]

[1]*Doctors Hospital and Medical Centre, Johar Town, Lahore, Pakistan*
[2]*Anjum Clinic, Samanabad, Lahore, Pakistan*

Abstract

COVID-19 has a devastating impact on patients not only due to the severity of pulmonary disease but also the multitude of other manifestations. We discuss here myocardial ischemia and stroke, associated with COVID-19, from a hyper coagulation perspective. Original studies, case reports, and systematic reviews from different databases were studied for this review article. Elevated inflammatory markers (*e.g.* ferritin, C reactive protein, interleukins, antiphospholipid antibodies) together with elevated D-dimer levels point to an inflammatory source of activation of the coagulation cascade. Furthermore, the features of macro and micro thrombi, because of dysregulated coagulation, point to local thrombosis as well as distant thrombo-embolism. Inflammation cascade and changes in coagulation markers leading to coagulopathy in COVID-19 patients emphasize the need to develop investigation techniques that can independently guide therapy.

Keywords: *Coagulation, inflammatory, COVID, stroke, Acute coronary syndrome (ACS), D-dimer.*

INTRODUCTION

The COVID-19 index case was presented in Wuhan, the capital city of Hubei province in China, in late December 2019 [1]. It was declared a pandemic by WHO on 11 March 2020 [2]. Currently, there have been a total of more than 524 million cases and more than 6.2 million deaths [3]. Although, it has proven to be a mild disease for a greater proportion of patients but has also been severe and fatal in a significant proportion throughout the world [4], while long-lasting effects continue to be reported [5]. The disease symptoms range from cough, flu-like illness, and shortness of breath to other non-specific sets of symptoms affecting multiple organ systems [6]. Of the many presentations, patients have also been reported with ischemic stroke and acute coronary syndrome. The rate of stroke in COVID-19 patients has been reported at 1-2% [7] while the rate of ACS reported at more than 7% [8]. Previous studies have highlighted that COVID-19 causes thrombotic complications which could result in an ischemic event [9, 10]. Ischemic stroke and ACS in critically ill COVID-19 patients presented [11] in a greater number than the general population and mild COVID-19 infection patients. 1.13% of a COVID-19 cohort was diagnosed with an acute cerebrovascular event [12]. No singular mechanism is solely responsible for the development of ischemia in COVID-19. In the case of stroke, the worst consequence can range from residual functional loss, and hemorrhagic transformation, to death [13].

Established mechanisms of ischemia in ACS are atherosclerotic narrowing of coronary arteries, rupture of atherosclerotic plaque and thrombus formation, vasospasm of the coronary arteries, and imbalance of oxygen supply due to myocardial hypertrophy [14-16] and mechanisms of ischemia in stroke are similar and also include embolization from a remote site (*e.g.* carotids, left heart due to atrial fibrillation), paradoxical emboli in case of atrial septal defects, *etc.* [17, 18].

Due to the severity of the disease in COVID-19, patients underwent rigorous testing and this has led to the realization of unique pathological processes and triggered further testing to define the exact mechanisms of the multitude of presentations. We present here the different mechanisms and pathological findings that have been defined in the COVID-19 cases of ACS and stroke and how these mechanisms are different from those described previously for non-COVID patients.

MATERIALS AND METHODS

We searched PUBMED database with the terms: COVID-19, ischemia, myocardial ischemia, infarct, stroke, pathophysiology, mechanism, and pathology* (all variations). Relevant articles were selected for review from the resultant 173 titles.

RESULTS

Different mechanisms and pathologies have been proposed which lead to changes in the vessels, myocardium, and brain parenchyma causing ACS or stroke accordingly:

Acute Coronary Syndrome (ACS)

Gross and Microscopic Findings

Other than chronic pathologies, findings peculiar to an acutely ischemic event included fibrin microvascular thrombi, thrombi in cardiac veins, and mural thrombi

**Corresponding author: Syed Mujtaba Azhar Bokhari, Doctors Hospital and Medical Centre, Lahore, Pakistan; Email: syedmujtaba922@gmail.com*
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including atria [19] and ventricle [9]. Autopsy results show no specific new gross findings related to COVID-19. Findings relevant to coagulation include significant blood clots in the (right) ventricle. Clot formation in the epicardial vessels has also been noted [9].

Microscopic changes were also variable. Evidence supportive of coagulopathy includes macro and microthrombi in cardiac vessels within and out of the myocardium. Other associated findings include lymphocytic myocarditis and pericarditis [9]. Constituents of thrombi in COVID-19 and non-COVID-19 hearts have been found to differ such that microthrombi, associated with focal myocyte necrosis, was more fibrin rich in patients with COVID-19 than with thrombi in COVID-19 negative or ST-elevation myocardial infarction patients [10].

Stroke

Gross and Microscopic Findings

A systematic review done by Pajo *et al.* commonly showed diffuse brain edema, and glial scars representing chronic infarcts. Infarctions were located in diverse areas: watershed areas, basal ganglia, and brainstem [20]. However, gross abnormalities may not be found at all in all the patients. A case of an occlusive thrombus adhesive at the carotid bulb and extending into the internal carotid artery has also been reported [21]. But such cases may only be outliers of the actual spectrum.

Non-specific to COVID-19 findings such as intimal thickening, atherosclerotic plaque, calcification, and intimal mononuclear cells were also found [21]. In a wide number of patients microscopic findings in the brain of COVID-19 patients showed gliosis in different stages, punctate hemorrhages, and microbleeds that were not localized to a specific region of the brain. Hypoxic changes were also seen in a significant number of patients. other findings included microthrombi and recent microscopic cortical infarcts [20].

Laboratory Findings in Stroke and ACS with COVID-19

Investigations to guide treatment have also provided evidence of the linkage of inflammatory markers and coagulation factors. A d-dimer level ≥ 2.0 µg/dl has been associated with higher mortality (18% vs. 0.4%) [22]. Similarly, high levels of vWF (when compared to non-COVID patients) [23] have been found in COVID-19 patients and are also related to worse outcomes [24, 25]. Theoretically, these factors may trigger the activation of the coagulation cascade. In this perspective it is important to note that lupus anticoagulant (la) has also been found elevated in some cases [26, 27] and pointing to one of many possible causes of hypercoagulability and thrombogenesis [28]. Serum ferritin levels have an established predictive role in disease severity and mortality [29]. Hyperferritinemia in COVID-19 could hypothetically be linked with coagulopathy through acute inflammation by macrophage activation leading to microvascular thrombosis [29, 30].

COVID-19 therefore predisposes to an increased propensity to form microvascular thrombi. this is supported by the fact that COVID-19 patients have higher levels of d-dimer [31], c-reactive proteins, and increased sensitivity to troponin [32].

DISCUSSION

This review aims at discussing the underlying pathophysiological mechanisms and features of coagulopathy leading to acute coronary syndrome and acute ischemic stroke in COVID-19.

In patients with COVID-19, ischemic stroke also affected the younger population who would not have prior risk factors for stroke [33]. Patients who presented with ACS and were later on found to be COVID positive and underwent an interventional procedure, had a post-procedure re-stenosis rate of the stent significantly higher compared to the patients who were COVID-19 negative [34-36]. Reported rates of incidence of stroke in COVID-19 have also been variable, 0.9% in a large observational study from New York while 2.5% in studies from Wuhan and Italy. This may be due to risk factors, disease severity, and health facilities across populations [37].

Ischemia could result from endothelial damage propagated thrombosis or from derangement in the coagulation cascade due to inflammation. on the endothelial note, cells with higher expression of ACE-2 receptors [38] are more targeted by the virus and these include type 2 pneumocytes, enterocytes, vascular endothelium, and renal tubules [39].

SARS-COV-2 infection causes a proinflammatory state. Cytokine cascade mediates an imbalance of homeostatic mechanisms. Coronavirus may harm endothelium by direct invasion or indirectly by inflammatory cytokines. As a result, coagulopathy occurs, leading to the formation of thrombi in microvasculature [28]. Given that cardiac cells have binding sites for SARS-COV-2, there is a suggested possibility of direct viral entry into the heart cells causing cell injury and myocarditis in patients with covid-19 [40]. However, against this hypothesis of direct invasion is the evidence that viral RNA was not detected significantly in endothelial cells with and without associated cardiomyonecrosis [10]. On the other hand, endotheliitis together with coagulopathy does increase the propensity of thrombus formation in mild carotid atherosclerotic lesions [21].

Comparison between ischemic events incidence and severity due to COVID-19 and those due to other respiratory viruses warrants discussion. The incidence of ischemic episodes in severe disease is starkly greater than not just in the general population or mild COVID cases but also compared to patients suffering from other respiratory viruses [41, 42]. In this respect, the most consistent and useful information would not

be a single test but a combination of high-sensitivity inflammatory and coagulation lab markers. This sensitivity is well highlighted by the raised levels of trop I even in non-ischemic cases [43]. Similarly, there have been raised levels of inflammatory and coagulation markers in COVID-19. These levels are also raised in other inflammatory disorders *e.g.* vasculitides and SLE. The linkage between inflammation-led coagulopathy therefore needs to be compared with other inflammatory states also featuring hypercoagulability.

Endothelial damage due to immune dysregulation in patients suffering from intraluminal thrombo-embolic stroke without significant atherosclerotic disease points out that the cause needs not to be local to cause stroke but can be from an embolus from a distant vessel [44]. Furthermore, it is important to know if the severity of high-resolution computed tomography (HRCT) abnormalities correlates with the incidence of ACS and stroke. Or are the two phenomena independent of each other? It has been suggested that stroke after micro-emboli may not necessarily occur only in patients with severe pulmonary features [45].

The rise in troponin levels (through highly sensitive assays) in many patients also demands attention from a resource and clinical management perspective, because it will be followed by repeated testing [46]. A trend or a correlation with other COVID-19 markers could lead to the formulation of a protocol for the management of suspected ACS in COVID patients and rule out whether the changes in cardiac markers are temporary due to stress with ongoing COVID infection [47].

There is also a need to find how incidence rates of ACS and stroke vary in patients already on anticoagulants (*e.g.* Warfarin). SARS COV 2 adds insult to an already damaged vascular endothelium in diabetics and hypertensive patients, therefore a worse prognosis for patients with these comorbid disorders [48]. Treatment strategies aimed at management through the identification of the mechanisms by which COVID-19 causes coagulopathy will help improve patient outcomes. Sirtuin-1 (a gene implicated in thrombotic phenomenon) activity levels may form a good investigational ground in coagulopathy in COVID-19 due to its relation with hypoxia-induced thrombosis [49, 50].

CONCLUSION

Coagulopathy occurs due to disruption in the balance of the coagulation cascade, inflammatory mediators lead to microthrombi in the vessels of the heart and the brain causing features of ACS and stroke. However, thrombo-emboli from remote sites also play a part in causing critical ischemia.

RECOMMENDATIONS

Different population groups will need their own set of investigations and treatment guidelines as incidence rates of cerebral and cardiovascular ischemic events are heavily dependent on demographic characteristics. Troponin I levels should be measured and carefully interpreted in patients with or without cardiac disease history due to the increased sensitivity in the inflammatory state of COVID-19. Moreover, it is important to find out if the severity of HRCT abnormalities can be a significant indicator of the rate of ACS and stroke, and if treatment can be guided by HRCT findings alone.

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CONFLICT OF INTEREST

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