REVIEW ARTICLE

Adv Psychiatry Neurol 2022; 31 (2): 69-73
DOI: https://doi.org/10.5114/ppn.2022.116881

Stroke in the COVID-19 pandemic era

Małgorzata Wiszniewska[1,2], Małgorzata Sankowska[3]

[1]Emergency Medical Services, University of Applied Sciences, Piła, Poland
[2]Neurological Department with Stroke Unit, Specialist Hospital, Piła, Poland
[3]Central Clinical Hospital of Medical University of Warsaw, Poland

Correspondence to:
Dr Małgorzata Wiszniewska
Emergency Medical Services
University of Applied Sciences
10 Podchorążych St.
64-920 Piła, Poland
e-mail: mpwisz@gmail.com

Submitted: 27.01.2022
Accepted: 28.03.2022

Abstract

Purpose: The aim of this article is to outline the impact of COVID-19 on the frequency of occurrence, course of stroke treatment, and to highlight the cause-effect relationship between SARS-CoV-2 infection and stroke on the basis of a literature overview.

Views: Since the end of 2019, the whole world has been struggling with the effects of the pandemic caused by the coronavirus SARS-CoV-2. The virus induces a wide spectrum of symptoms, ranging from mild or serious ones, which may lead to a severe multiorgan failure. Acute ischaemic stroke (AIS) might be associated with COVID-19 as a potentially fatal complication, while hemorrhagic stroke is less frequent. In most cases, stroke is caused by large artery occlusion. One of its reasons is hypercoagulation with a complex mechanism, which has not been fully explained. Research has shown that during COVID-19 pandemic, the number of patients admitted to hospitals due to AIS decreased. During the first pandemic wave there was no change regarding the proportion of patients with cerebral vessel obstruction who received endovascular treatment.

Conclusions: In the COVID-19 pandemic era, rapid intravenous administration of tissue plasminogen activator remains the main treatment for acute ischaemic stroke. Patients often fail to report to hospital for the fear of SARS-CoV-2 infection. It is of the utmost importance to raise society's awareness of the necessity to report to hospital when experiencing serious symptoms, including stroke.

Key words: stroke, coagulopathy, COVID-19, SARS-CoV-2.

INTRODUCTION

SARS-CoV-2 infection inducing COVID-19 (coronavirus disease) often starts with general, non-specific, and respiratory system symptoms, such as: fever, cough, dyspnea, ageusia, and anosmia. These respiratory system symptoms may progress into acute respiratory distress syndrome (ARDS), which has proven to be highly fatal. The virus is transmitted through face-to-face contact with an infected person or through indirect transmission by touching an infected surface and then subsequent transmission in the mucous membrane [1, 2]. Even though COVID-19 is widely associated with pulmonological symptoms, several neurological complications, such as headaches, dizziness, insomnia, encephalopathy, Guillain-Barré syndrome and stroke, mainly of the ischemic variety, have been observed [3-5]. It has been found that SARS-CoV-2 infection results in systemic hypercoagulation, elevation of D-dimers and fibrinogen levels, which are factors increasing coagulation, which in turn may lead to ischemic stroke [4, 6-8].

COVID-19 AND ACUTE ISCHEMIC STROKE

Acute ischemic stroke (AIS) is a life-threatening complication of SARS-CoV-2 infection, affecting 1-3% of hospitalized patients and 6% of intensive care unit patients. Beyrouti *et al.* carried out an analysis of COVID-19 patients with AIS and concluded that the latter occured within 8-24 days from the onset of COVID-19 [4, 9]. Based on neuroimaging data with comprehensive meta-analysis, Tan *et al.* stated that the majority of strokes (62.1%) were caused by large vessel occlusion (thrombosis, embolism). This is probably due to the hypercoagulability observed in SARS-CoV-2 infection [10]. Binding to ACE2 receptors on the vascular endothelial cells, SARS-CoV-2 might directly infect these cells. Platelets might be infected as well, and therefore aggregate and form clots in the arteries. It is worth emphasizing that in COVID-19 infection, inflammatory changes within endothelial cells, with damage to the structure of the cell membrane and necrosis, are more severe compared to other infections [4, 6-8].

Moreover, the clotting process in this infection is also initiated by an abnormal immune response. The clots are mainly located in the larger arteries and are believed to be a hallmark of COVID-19 disease. The same mechanisms work in the heart, which promotes myocardial infarction, heart failure and contributes to heart arrythmias. Ultimately, all of these may in turn lead to cerebral embolism [6-8, 10]. In addition, studies of 2020 showed that strokes involving multiple vascular territories were observed, accounting for 26% of cases, while small-vessel strokes occurred rarely (8.7%) [11, 12]. According to the statistics, the incidence of ischemic stroke is more frequent among men, whereas the rate of mortality associated with it is higher among women. Wang *et al.* conducted a comparative analysis comprising 4,453 Asian patients affected by ischemic stroke and treated by thrombolysis during the pandemic. It turned out that women (especially over 70 years old) developed a greater risk of worse results on Rankin scale (mRs) 3 months after experiencing a stroke compared to men (odds ratio 1.14) [13]. Moreover, data from a European register of 10,000 patients also showed that women had poorer functional outcomes 3 months after stroke compared to men. Women are more prone to severe stroke caused by cardioembolism, with a higher mortality risk [13, 14]. Based on a systematic review, Szegedi *et al.* identified the fact that most stroke patients infected by COVID-19 suffered from serious stroke (median score National Institutes of Health Stroke Scale, NIHSS 16). Only 29 of the 198 patients did not present any previous diseases as risk factors [15]. The most common stroke risk factors among the remaining patients were hypertension, diabetes, and hyperlipidemia [11, 16]. Strokes in patients under 50 were also reported [17]. In this age group, in certain cases the symptoms of stroke were sometimes the first manifestation of SARS-CoV-2 infection. Large artery occlusion was a common stroke etiology in young patients with COVID-19 comorbidity [18-21].

SARS-COV-2 INFECTION AND THE TENDENCY TO THROMBOSIS. COAGULOPATHY ASSOCIATED WITH COVID-19

Thrombotic complications and coagulopathy are frequently observed in SARS-CoV-2 infection and are the reason for increased mortality in COVID-19-positive patients. Coagulopathy associated with COVID-19 (CAC) differs from sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC). In the case of CAC, elevated levels of D-dimers and fibrinogen are witnessed, with minimally prolonged prothrombin time and associated thrombocytopenia. The elevated levels of D-dimers are a hallmark of a severe infection [4, 22, 23]. Furthermore, the tendency towards arterial and venous thromboses is more frequent in CAC than in SIC/DIC [24]. The underlying molecular mechanisms of hypercoagulation have not yet been fully explained. However, it is believed that there is a direct link between inflammation and hemostasis, i.e. thromboinflammation [25, 26]. The complex interaction between inflammation, thrombocytopathy, and endotheliopathy leads to hypercoagulation in COVID-19 infection.

CYTOKINE STORM IN COVID-19

During SARS-CoV-2 infection the cytokine storm (immunological overreaction to a pathogen) can be observed. The cytokine storm results in elevated levels of IL-1, IL-2, IL-6, IL-8, IL-10, IL-17 and TNF-α [15]. Inflammatory reaction may induce thrombosis via various mechanisms, including activation of and damage to the endothelium, initiation of coagulation through activation of VIIa factor tissue, platelets, white blood cells or dysregulation of natural anticoagulation and fibrinolysis pathways. Activation of neutrophiles and formation of neutrophil extracellular traps (NET) seems to play a key role in COVID-19-associated thrombotic complications. NET can activate a contact pathway via an interaction between histions and platelet phospholipids. The thromboinflammatory response induces further damage of the endothelium and leads to increased thrombin production [15, 27].

ENDOTHELIOPATHY

SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptors, which are widely expressed on the host cells and through that directly infect endothelial cells in many tissues [28]. The high expression of ACE2 receptor has also been reported in the central nervous system. Having crossed the blood-brain barrier, the SARS-CoV-2 virus causes brain endothelial cell damage, inducing hypercoagulability. Ultimately, all these may induce ischemic stroke [4, 29].

THROMBOCYTOPENIA

Xu *et al.* advanced the hypothesis that there are three main mechanisms of thrombocytopenia in COVID-19 infection. Firstly, a reduction in platelet production, secondly, platelet destruction and, lastly, platelet consumption. Platelets can aggregate at the vascular endothelium damaged by the virus, leading to the formation of microthrombi. Although the number of platelets is reduced, they are more active and are used to form microthrombi despite their lower numbers. Activated platelets release microparticles (MPs), von Willebrand factor (vWF) and plasminogen activator inhibitor (PAI). Activation

of platelets by promoting hypercoagulability can lead to AIS [30].

THE PROPHYLAXIS OF ACUTE ISCHEMIC STROKE

Due to CAC, anticoagulant prophylaxis should immediately be implemented. Nevertheless, it is still uncertain whether anticoagulants or antiplatelet drugs ensure better primary or secondary stroke prevention in COVID-19 patients. One study has observed AIS despite treatment with anticoagulants [20]. Before the administration of anticoagulants the benefit-risk ratio must be assessed because these drugs may increase the risk of intracranial hemorrhage. Further research evaluating the role of anticoagulants in treating AIS in COVID-19-positive patients is needed [31].

INTRAVENOUS THROMBOLYSIS AND MECHANICAL THROMBECTOMY IN THE ERA OF COVID-19

Current international guidelines of all neurological societies, including the Polish Neurological Society, recommend the intravenous administration of t-PA if no more than 4.5 hours have passed since the onset of stroke symptoms [32]. Those infected with COVID-19 often experience hypercoagulation and elevated inflammatory factors (D-dimers, leukocytosis). In previous research carried out in COVID-19-negative patients with AIS with similar laboratory abnormalities, higher mortality, and disability rate, as well as intracranial hemorrhage after thrombolysis, have been described. The principles of eligibility for thrombolytic therapy are the same for patients with and without COVID-19 infection.

The guidelines also recommend mechanical thrombectomy (MT) in adults suffering from ischemic stroke caused by internal carotid artery or middle cerebral artery occlusion, based on angio-CT, if no more than 6 hours have passed since the onset of stroke symptoms [32-34].

COVID-19 AND INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage (ICH) in COVID-19 occurs less frequently compared to ischemic stroke [8]. Cytokine storm caused by SARS-CoV-2, apart from the mechanism described above, may lead to the destruction of blood-brain barrier, causing hemorrhagic stroke. Moreover, binding SARS-CoV-2 to the ACE2 receptors may increase angiotensin-2 synthesis and may thus elevate blood pressure, thereby increasing the risk of hemorrhagic stroke [35]. Many cases of ICH relate to anticoagulant treatment. Dogra *et al.* have proven that 4.4% of a group of 755 COVID-19-positive patients experienced intracerebral hemorrhage. The majority of these patients were administered anticoagulant drugs, in particular unfractioned heparin (UFH) [36].

CHANGES BROUGHT ABOUT BY THE COVID-19 PANDEMIC

Numerous studies have shown that in the era of COVID-19 pandemic the number of patients admitted to hospitals due to stroke has decreased significantly, from 40% to 25% [12, 14]. The authors have proven that patients with transient ischemic attack, TIA or minor stroke may not have reported to hospital for fear of SARS-CoV-2 infection and social isolation, preventing family members from identifying symptoms of stroke in elderly patients [20, 21, 33, 37, 38]. Romoli *et al.* conducted a meta-analysis in the first wave of the pandemic of 29 studies comprising 212,960 patients comparing the pre-pandemic timeframe with the COVID-19 era. A thirty-one percent decrease in stroke-related admissions was observed, most of cases being connected with large vessel occlusion, i.e. the internal carotid artery and middle cerebral artery. It has also been noted that the average admission time to hospital increased by 32 minutes, and CT examination time by 5 minutes, while the time it takes to administer an rt-PA drug has not changed [3, 14, 39]. Interestingly, the ratio of patients undergoing endovascular treatment has not changed compared to pre-pandemic period [39].

CONCLUSIONS

Ischemic stroke may take place in the context of SARS-CoV-2 multiorgan infection. The exact mechanisms through which COVID-19 triggers a hypercoagulable state, and thus stroke, remain unclear. Understanding the underlying mechanisms of hypercoagulability is essential to the effective treatment of these patients. In ischemic stroke immediate intravenous t-PA administration remains the main treatment method in acute cases. The faster t-PA is administered (within 4.5 hours from onset), the better the prognosis for the patient. It should be remembered that the principle "time is brain" is still used in patients with COVID-19. Therefore, it is of the utmost importance to raise society's awareness of the necessity to report to hospital when experiencing serious symptoms, including stroke.

Conflict of interest

Absent.

Financial support

Absent.

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