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Review Article

COVID-19 and cerebrovascular stroke: a mini review

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ABSTRACT

The novel corona virus has shown accelerated effect on stroke and stroke care. Worlds stroke organization has reported a decline in stroke admission due to use of FAST tool and usage of thrombolysis and thrombectomy. FAST stands for F=facial weakness, A=arm weakness, S=slurred speech T=time to call 911 in USA, 120 in China, 999 in England, 112 in EU. In case of 911, 9=word nine (slurred speech), 1 one arm weakness, 1=one side facial weakness. It has a record that 72% of the confirmed stroke patients had speech disturbance, 62% had facial drooping, and 87% had arm weakness. The most appropriate way to diagnose stroke is motor dysfunction or slurred speech than facial drooping. Articles have been selected from Google scholar, PubMed, PubMed Central, Scopus, Web of Science, Medline, Embase, Scimago, and Publon. Studies on stroke from these articles has shown that speech disturbance has a worse outcome after stroke compared with individuals where speech is unaffected. The incidence of speech disturbance is as high as 84.4% in stroke patients, and a speech disturbance persists at discharge in 75.8% of patients who survived their stroke. Therefore, presence or absence of speech disturbance has predictive value for outcome of a stroke patient. D dimer is very important haematological marker to diagnose Disseminated intra vascular coagulation (DIC). Again, it is known that sepsis is a common cause of DIC. This biomarker is released when a fibrin blood clot undergo degradation. Tassiopoulos et al mentioned about anticoagulant administration according to D-dimer level can improve respiratory or kidney function in a COVID-19 patient.

Keywords: COVID-19, Stroke, D-dimer, Speech, Facial drooping

INTRODUCTION

The novel corona virus has shown accelerated effect on stroke and stroke care. Worlds stroke organization has reported a decline in stroke admission due to use of FAST tool and usage of thrombolysis and thrombectomy. FAST stands for F=facial weakness, A=arm weakness, S=slurred speech T=time to call 911 in USA, 120 in China, 999 in England, 112 in EU. In case of 911, 9=word nine (slurred speech), 1 one arm weakness,1=one side facial weakness. It has a record that 72% of the confirmed stroke patients had speech disturbance, 62% had facial drooping, and 87% had arm weakness. The most appropriate way to diagnose stroke is motor dysfunction or slurred speech than facial drooping. Studies on stroke has shown that speech disturbance has a worse outcome after stroke compared with individuals where speech is unaffected. The incidence of speech disturbance is as high as 84.4% in stroke patients, and a speech disturbance persists at discharge in 75.8% of patients who survived their stroke. Therefore, presence or absence of speech disturbance has predictive value for outcome of a stroke patient.[1] Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is an enveloped, single-stranded, positive-sense RNA virus of the coronaviridae family and it has a phospholipid bilayer capsule containing spike proteins(S). Since it's a RNA virus, it can undergo several fastest mutatic changes as compared to other type of DNA viruses. SARS-CoV-2 gains access to human body through the interaction of its spike (S) protein and angiotensin-converting enzyme 2

(ACE-2), found in many tissues such as lung, kidney, heart, and intestines.[2] Electron microscopy studies have proved that SARS-CoV-2 virus 'spikes' ('S' glycoprotein) act like 'keys' to enter human cells by binding to the ACE-2 receptor, similar to other coronaviruses. RNA sequencing studies have determined that ACE-2 expression is high in lung, heart, ileum, kidney and bladder as well as brain, vascular endothelium and testis. In the brain the ACE-2 receptors have been found in glial cells and neurons, with highest expression in pons and medulla. The ubiquitous presence of ACE-2 receptors may explain the multiorgan involvement in COVID-19.[3] In patients with stroke, the presence of SARS CoV-2 infection worsens a cerebrovascular stroke. The virus SARS CoV-2 can enter the CNS through two different pathways: retrograde neuronal diffusion and the blood-brain barrier. Spread of SARS CoV-2 through the cribriform plaque of the ethmoid bone can lead to brain involvement which could happen during the initial phase or at subsequent infection. Notably, the presence of ACE-2 receptors on both neuronal and capillary endothelial cells could lead to CNS injury, without much inflammatory load.[6] As the virus is present in the general circulation including the cerebral circulation, the sluggish cerebral microcirculation enhances the interaction between the virus spike protein and ACE-2 on cerebral endothelial cells. Viral proliferation and release from endothelial cells could lead to endothelial damage leading to formation of thrombosis and embolism causing ischemic or haemorrhagic stroke. Also, ACE-2 receptors have been detected on neurons and glial cells, making them a potential target for SARS-CoV-2. While the exact mechanism of transcribiform invasion of SARS-CoV-2 is not fully understood, a rodent model of SARS-CoV-1 infection, a close "cousin" of SARS-CoV-2, shows the presence of the virus in areas of the brain connected to the olfactory bulb after transnasal exposure which is associated with neuronal death. Presence of anosmia, hypogeusia, and other neurological findings in COVID-19 patients support the theory of a direct effect of the virus on the brain.[2]

Pathogenesis and pathophysiology

Endothelial dysfunctions

ACE-2 receptors are expressed in cerebrovascular endothelial cells and regulate the sympathoadrenal system, vascular autoregulation, and cerebral blood flow.[2] Virus binding to the CNS ACE-2 receptors can lead to disruption of its autoregulatory function causing blood pressure elevations leading to vessel wall rupture.[3] By binding to ACE-2, SARS-CoV-2 induces receptor endocytosis, thereby leading to depletion of the "protective" endothelial ACE-2 and tilting the balance in favor of ACE-1 and angiotensin 2, with an increased vasopressor, proinflammatory disposition and endothelial injury . mechanism of endothelial injury in patients with COVID-19 is the immune hyper reaction referred to as a cytokine storm. Elevated levels of cytokines such as IL1-β, IL-7, IL-8, IL-9, IL-10, granulocyte-macrophage colony-stimulating factor (GMCSF), IFN-γ, monocyte chemoattractant protein (MCP-1), and tumor necrosis factor-α (TNF-α) has been reported in COVID-19 patients.[12] Inflammatory cytokines cause endothelial activation, increased expression of endothelial leukocyte adhesion molecules (ELAMs) such as intercellular adhesion molecule 1 (ICAM-1), E-selectin, and vascular cell adhesion molecule 1 (VCAM-1) which interact with leukocyte surface receptors.[20] The effect of the cytokines and leukocyte-mediated injury could disrupt the integrity of the endothelial cells. Endothelial activation and endothelitis can therefore occur due to direct viral activity and also via downregulated receptors ACE-2 and other receptors.[2]

Blood coagulopathy

In COVID-19 patients there are rise in D-dimer and fibrinogen level at a higher level in severe cases as compared to milder form of the disease. Again, there are release of cytokines, Von Willenbrand factors, tissue factors due to destruction of endothelial cells. These are the potential cause of thrombosis.[3] SIC is an earlier phase of disseminated intravascular coagulopathy (DIC) characterized by elevated D-dimer, prolonged prothrombin time, and low platelet count, increase fibrinogen level. It follows systemic inflammatory response syndrome triggered by an immune response to the virus leading to endothelial dysfunction leading to release of cytokines and thrombosis of the microcirculation. In addition, there is increased production of plasminogen activator inhibitor-1, thereby increasing the risk of thrombosis. Unlike DIC, there is no bleeding.[2]

Aims and objectives

The main aim of this COVID-19 review article is to find out the absolute management plan with the help of the following objectives: pathogenesis and pathological changes in COVID-19; age wise occurrence of COVID-19; sexwise occurrence of COVID-19; blood pressure changes in COVID-19; cerebrovascular accidents in COVID-19; and D-dimer level in COVID-19.

METHODS

Data's have been collected from online databases for example - Google Scholar, PubMed, PubMed Central, Scopus, Web of Science, Medline, Embase, Scimago, and Publon. Study duration is from November 2021 to March 2022.We have included case reports, case series, original articles, letter to the editor. Total 108 articles have been downloaded showing SARS COV-2 structures and their functions, pathogenesis caused by it, stroke related changes, d-dimer levels, age wise and sex wise distribution of COVID-19 patients. Here we have mentioned about the results obtained by other researchers. Articles mentioning about vascular events during the viral infections are taken and only stroke related data have been mentioned. Review articles include previous review articles, case reports, case

series, original articles, letter to editors etc**.** Duplicate articles have been subtracted, articles from which data could not been extracted, review articles, data regarding COVID-19 infected patients with other systems except CNS (stroke) data, same articles downloaded, are rejected and only those eligible articles from which required data are available have been selected for this study. This is according to PRISMA chart. The PRISMA chart is shown below.

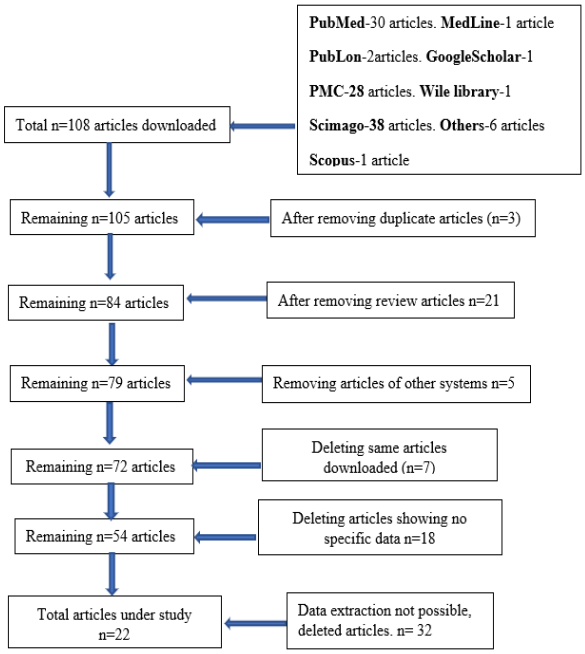

Figure 1: PRISMA chart.

RESULTS

Age group effected in SARS CoV-2

Out of 26 COVID-19, patients with either ischemic or hemorrhagic stroke, 27% of them were younger than 50 years of age. Patients with COVID-19 who have stroke have worse in clinical outcomes than patients without COVID-19 with stroke.[7] The mean age of sarscov-2 patients with stroke was 65.5 years.[8] Four patients were admitted in hospital due SARS CoV-2 infection with age group ranging from 55-60 years.[9] Of 143 patients admitted for stroke, 61.1% were between age group 69-70 years of age.[10] Among patients with Ischemic stroke, the mean age was 64.16±14.73 years (range 27–92 years).[2]

Sex group effected SARS CoV-2

Out of 4089 patients admitted in hospital due to COVID-19, only 44% were female.[8] There is no difference in the proportion of COVID-19 cases between sexes, but men have a higher risk of intensive therapeutic unit admission and death as compared to female.[11] Among the admitted cases of ischemic stroke more than 50% were male.[12]

Blood pressure in SARS CoV-2

The most common comorbidities found in COVID-19 patients are hypertension, diabetes and cardiovascular disease. According to several studies hypertension is the most common comorbidity, followed by diabetes mellitus and cardiovascular disease.[3] A total of 82.4% (662/803) of COVID-19 patients had good BP control, and 17.6% (141/803) had poor BP control during hospitalization. Compared to those with good BP control, the patients with poor BP control had higher SBP and DBP, and higher MAP and PP during the period. The patients with poor BP control were more likely to have COPD and chronic kidney disease.[4] Compared with patients without hypertension, patients with hypertension were older, more likely to have a prior history of diabetes mellitus or chronic kidney disease. The C-reactive protein (CRP) level was significantly higher in hypertensive patients than in no hypertensive patients.[5]

Type of stroke

Out of 1683 COVID-19 infection admitted to the hospital, 73.9% had cerebral ischaemia, two of whom had arterial dissection. 21.7% had an intracerebral haemorrhage and one patient had leukoencephalopathy. Patients with haemorrhage included subarachnoid haemorrhage, parieto-occipital leukoencephalopathy, multiple microbleeds, and focal haematoma.[8] Four patients admitted due to covid 19 had punctate multiple cortical infarcts. There was no history of intra cerebral haemorrhage.[9] Out of 275 cases of COVID-19 associated stroke, 226 were of ischemic stroke and remaining 35 were of intracerebral haemorrhage.[12]

D dimer

D dimer is very important haematological marker to diagnose disseminated intra vascular coagulation (DIC). Again, it is known that sepsis is a common cause of DIC. This biomarker is released when a fibrin blood clot undergo degradation.[14]

Shi et al studied d dimer level in COVID-19 patients in China and found that out of all infected patients admitted to hospital from age groups 35-71 years males are most commonly affected than females and usually the elder age groups >70 years are affected more than the younger age groups around 35 years of age groups and among these younger age groups D dimer levels are much higher in non-survival patients as compared to survival patients. Normal D dimer levels of non-survival: (0.8-31.5) microgram/ml, survival (0.29-4.16 microgram/ml).[15]

Ayusha et.al examined COVID-19 patients older than 60 years of age with co morbid conditions-like DM, hypertension, hypothyroidism, hyperthyroidism, anxiety, depression, dyslipidemia, CKD, atrial fibrillation and divided them into two groups – D dimer value <1.5 microgm/ml and D-dimer value >1.5 microgm/ml. In the

first group hospital stay was compared to second group. The mean admission D-dimer among patients who survived was 1.067 µg/ml (±1.705 µg/ml), while patients who died was 3.208 µg/ml (±2.613 µg/ml). Those patients whose D dimer value is higher, they needed more mechanical ventilatory support than non-invasive ventilation as compared to low D dimer value who mostly required non-invasive ventilation as compared to mechanical ventilation. With increase in weight there is increase in D dimer level as well as severity of COVID-19 under cut-off value for D dimer 1.5 microgram/ml sensitivity=70.6% and specificity of 78.4%.[16]

Zhan et.al have mentioned that diagnostic sensitivity specificity of D dimer in COVID-19 patients were 90% and 60% respectively.[17]

Yao et al all patients with normal D-dimer (<0.5 mg/l) at admission survived, patients were grouped into D-dimer levels of <1 mg/l, 1–2 mg/l, and >2 mg/l.

Patients with COVID-19 with pneumonia can be divided into three groups according to the involvement of lung area, <30%, 31-50%, and >50% of lung area.

Predominant changes seen in lungs are – decreased ground glass opacity, patchy consolidation, fibrous septa, and irregular consolidated nodule.

When compared between patients who survived and who died during hospitalization, a significantly higher D-dimer level was detected in non-survivors versus survivors 6.21 mg/l versus 1.02 mg/l. D-dimer level above 2.14 mg/l had a sensitivity of 88.2% and specificity of 71.3%. It can be considered as cut-off level to discriminate between survivors from nom-survivors.[18]

Mahajan et al mentioned that severity of COVID-19 and associated mortality is higher in patient with elevated d dimer. In a study with COVID-19 patients in China, some patients are found with elevated levels of D-dimer (0.5 mg/l) with less worsening condition than those whose D-dimer level >1mg/l. D-dimer >2.4 mg/l require ICU admission. With progress of the disease, D-dimer level keeps on increasing but if we inject anticoagulant like heparin start continuous venovanous haemofiltration (CVVH) there is rapid decrease of D-dimer and a rapid improvement of pulmonary and renal function. This shows anticoagulant has a therapeutic role in COVID-19. At the same time, we should be very much careful during anticoagulant therapy because it may increase risk ICH.[19]

Tassiopoulos et al mentioned about anticoagulant administration according to D-dimer level as showed below sliding scale- D-dimer <1000 ng/ml: enoxaparin 40 mg/day; D-dimer 1000-3000 ng/ml: enoxaparin 40 mg BD/day; and D-dimer >3000 ng/ml: enoxaparin 1 mg/kg BD/day.

Or, therapeutic anticoagulant with IV heparin (target 60-90) based on physician preference. Escalation of anticoagulant occurred within 24 hours of a change in the D-dimer level.[20]

DISCUSSION

Occurrence of stroke in COVID-19 patients is less in younger age groups as compared to 64 years of age group where occurrence is more than half. Elkheider et al found that acute ischemic stroke in COVID-19 cases is more among >60 years of age group secondary to vasculitis due to infection by virus and intracranial cytokine storm.[9]

Occurrence of COVID-19 is equal in both sexes but admission to therapeutic intensive unit and death is more in men as compared to female. Vahidy et al, found in their study that white males are more effected than black females in COVID-19. Proportion of hospitalization due to covid is more in male than in female. Patients effected with COVID-19 who had a poor blood pressure control were mostly elder persons who likely to have COPD and chronic kidney disease. As it is considered as most common comorbid condition followed by diabetes and cardiovascular diseases in patients with COVID-19.[13]

According to Yao et al, patients with normal D-dimer (<0.5 mg/l) at admission survived. With a significantly higher D dimer level detected in COVID-19 non-survivors (6.21 mg/l) versus survivors (1.02 mg/l). D-dimer level above 2.14 mg/l had a sensitivity of 88.2% and specificity of 71.3%. In our present review the average D dimer level in COVID-19 survivors and non-survivors are corresponding to previous literatures. Along with it the average sensitivity and specificity of the study is corresponding with previous study.[18]

CONCLUSION

From the above-mentioned results and data, if a patient comes to the emergency department with facial deviation to one side along with paralysis of one half of the body and RTPCR and for COVID-19 physicians can directly come into a quick diagnosis of stroke and can take an appropriate measure within short time to remedy it with the help of d-dimer and blood pressure follow-up.

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