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Strokes and Covid- 19

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic due to infection by the SARS- CoV- 2 virus started primarily as a respiratory illness. However as the pandemic has evolved since January 2020, it has brought to the fore varied presentations. Though uncommon, COVID- 19 associated stroke is now well known. Most are ischemic strokes; however, haemorrhagic venous strokes and intracerebral haemorrhage (ICH) have also been observed with COVID- 19. A recent meta-analysis noted that one fourth of patients with stroke symptoms did not experience any of the other typical COVID- 19 symptoms [1].

These patients can be a risk for nosocomial spread of infection who need to be identified and isolated. Stroke in COVID-19 can lead to significant morbidity and mortality [1, 2]. The occurrence of stroke in those with COVID- 19 ends leads to prolonged stay in the hospital and puts further burden on healthcare resources. The purpose of this review is to understand the prevalence of stroke in those with COVID- 19, associated risk factors, pathophysiology, management and prognosis as compared to those with non COVID- 19 strokes. This review focuses on acute ischemic strokes associated with COVID- 19.

Acute Ischemic Stroke (Ais) In Covid- 19: Stroke is an infrequent complication of COVID- 19; Incidence reported from various studies range from less than 1% to 1.74%. However, in those severely ill with COVID- 19 the incidence of strokes was higher at 9.8% (range 2.7% to 30.6%) [1] Stroke as a complication of COVID- 19 was reported initially by Mao et al from Wuhan in April 2020 [3]. The authors reported stroke to occur in those with severe COVID- 19. Also, most of the early data reported stroke as a complication during the second week of illness [3-5].

Even as the pandemic roars on, infecting large number of people through the world, many cities with large incidence of COVID-19 cases actually witnessed a decrease in the number of stroke patients getting admitted to the hospital (COVID- 19 paradox) [6-9]. Multiple reasons have been put forth to explain this paradox: The fear of the ravaging pandemic kept most of the mild stroke patients at home, due to strict isolation many strokes in the elderly may have been missed by their family members, COVID- 19 symptoms could have overshadowed the stroke symptoms, limited medical resources due to the overwhelming burden of pandemic may have resulted in less activation of stroke codes or there may be a true decline in the incidence of stroke cases in lieu of the behavioural modifications mandated by the pandemic [9].

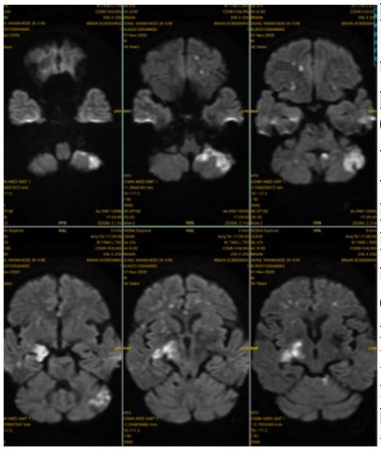
Stroke Can Occurly Early And Even In Those With Non- Severe Covid- 19: There is now sufficient literature evidence of early occurrence of stroke in those with COVID- 19 [1]. Benny et al reported strokes as a presentation of COVID- 19 in 67% of their patients [10]. These patients with stroke did not demonstrate features typical of COVID- 19 and they were often asymptomatic carriers. An abnormal CT scan of the chest for features typical of COVID- 19 is used in most centers to triage patients into suspected COVID- 19. However, of the patients with strokes in their study; 22.2% had normal CT chest results. This presentation of COVID- 19 has to be kept in mind by the treating physician and adequate precautions have to be taken to prevent nosocomial spread of infection.

Recent studies have observed AIS to occur even in those with non-severe COVID- 19 [10-12]. This implies that stroke mechanisms (discussed below) are active right from the onset of infection with the SARS- CoV- 2 virus.

Who are at a risk to get stroke in covid- 19?: Strokes with COVID-19 are more commonly seen in elderly (mean age 65.5 years) males [1,11]. But, even young patients can present with large vessel occlusion as a presentation of COVID- 19 [13,14]. Trifan et al found 89% of those with AIS to have at least one vascular risk factor (VRF) and 41% had three to four VRFs [11]. Most common VRF was hypertension, diabetes, dyslipidemia, ischemic heart disease, smoking, chronic kidney disease and in some studies, malignancy. Hence, those who are elderly, males and have at least one VRF with COVID- 19 should be monitored carefully for the occurrence of stroke.

Can presentation with stroke be a clinical predictor for conversion to severe covid- 19 eventually?

A pooled analysis by Aggarwal et al found cerebrovascular disease to be associated with a 2.5-fold increased disease severity in patients with COVID-19 [15]. Benny et al observed that patients with stroke who progressed to develop severe COVID-19 after admission were more likely to present with an altered sensorium, had low GCS on admission, had propensity for multiple territory strokes, large vessel occlusion and an abnormal finding on HRCT chest [10]. Most established criteria for COVID- 19 severity are based on oxygen saturation, HRCT chest and multi system involvement [16]. The presence of stroke in COVID- 19 already indicates a multi system involvement by the SARS- CoV- 2 virus and hence, stroke should be included as a risk factor for conversion to severe COVID- 19. However, the data to substantiate this statement is limited and needs to be verified by larger studies or pooled analysis.



Characteristics Of Stroke Associated With Covid- 19: Most studies have found COVID strokes to be large with an average median National institute of health stroke scale (NIHSS) on admission to be 17.9 (Range 9.1-29) [1]. Multiple territory strokes (including the three territory sign) and large vessel occlusions are common [5].

Another association is the presence of venous thromboembolism (deep vein thrombosis in the legs or pulmonary embolism) along with AIS in those with COVID- 19 [5]. Though the majority of COVID- 19 associated strokes are due to large vessel occlusion, lacunar strokes have also been observed [2].

Three Territory Sign

Pathophysiology

While traditional vascular risk factors are seen in patients with stroke and COVID- 19, several other factors also probably contribute. This is especially seen in young stroke patients who have elevated markers of inflammation (C reactive protein) and systemic coagulation abnormality (D-dimer) without the traditional risk factors for stroke. There are multiple, not mutually exclusive pathogenic mechanisms such as coagulopathy, vasculitis, endothelial dysfunction, cardioembolism etc. associated with COVID- 19 AIS.

Abnormality Of Coagulation: The hyperinflammatory response seen in patients with COVID- 19 (cytokine storm) may be the trigger for pathological thrombosis in these patients [17]. C reactive protein (CRP) is raised in many patients with COVID- 19 as a marker of the systemic inflammatory response. CRP can lead to thrombosis by initiating the extrinsic pathway of coagulation [18]. Most of the hospitalized patients with progression of COVID- 19 have a coagulopathy with elevated D dimer, prolonged prothrombin time and thrombocytopenia [19].

D-dimer is a broad biomarker for systemic thrombosis and can be elevated even in those with non COVID- 19 ischemic strokes [20]. Yaghi et al reported high levels of D-dimer in patients with stroke and COVID-19. As COVID- 19 progresses in severity nearly 50% of patients have an elevated D-dimer and this proportion increased to nearly 100% in those who died [14,21]. Benny et al found elevated D-dimer even in patients with non-severe COVID- 19 who had an ischemic stroke [10].

Viral invasion of the endothelium triggers complement activation and the coagulation pathway, leading to microvascular thrombosis [22]. Monocyte activation causes increased tissue factor expression, leading to activation of the extrinsic coagulation pathway. There is platelet activation and neutrophil recruitment leading to formation of neutrophil extracellular trap (NET) which further facilitates thrombosis [23].

Antiphospholipid antibodies (APA) have also been observed in COVID-19 patients with stroke [5,24]. Whether these APA are elevated transiently due to the viral infection or contribute to thrombosis is not yet clear.

Vasculitis

SARS-CoV-2 binds to ACE2 receptors which are widely expressed in the endothelial cells. This results in a cytotoxic effect to the endothelial cells and leads to a lymphocytic endotheliitis [25]. Endothelial dysfunction can lead to microvascular abnormality with subsequent inflammation and a procoagulant state [26]. This may be one of the possible mechanisms responsible for large vessel occlusive strokes in young patients who don't have the traditional VRFs [27].

The systemic immune response (cytokine storm) causes further vascular injury [28]. Several cytokines like IL1, IL6, IFNγ, TNFα etc. are elevated, causing endothelial activation and increased expression of adhesion molecules like VCAM-1. However their precise role in causing stroke is not clear. Endothelial activation also leads to increased Factor VIII and von Willebrand factor [29].

Cardiomyopathy

The myocardium may be damaged by direct viral infection or due to the cytokine storm [30]. Hypoxia and sympathetic overactivity may predispose to stress cardiomyopathy and arrythmias [31]. In the setting of a hypercoagulable state, it may predispose to intramural thrombosis and embolism. Other mechanisms which have been suggested include direct viral invasion of brain endothelial cells which express ACE-2 receptors. Depletion of ACE-2 receptors due to infection and endocytosis causes decreased production of angiotensin leading to impaired cerebral autoregulation [32].

Management of covid- 19 strokes

The management paradigm of AIS associated with COVID- 19 remains the same as those in non COVID- 19 strokes. However, strokes in those with COVID- 19 presents unique challenges: The prevalence of large vessel occlusion is high in those with COVID- 19 strokes (most may need mechanical thrombectomy and adequate care has to be taken in the angiography suite to prevent nosocomial spread of infection), the levels of inflammatory and procoagulant markers are high in these patients (may also have increased risk of intra cerebral hemorrhage after intravenous thrombolytic therapy) and the risk of contracting the infection.

Members of the stroke care team should take adequate precautions to prevent transmission of COVID- 19. These include maintaining a distance of two meters, wear surgical masks, gowns and a particulate filtering facepiece respirators (N95 or equivalent). The number of doctors monitoring these patients at a given time should be as minimal as possible.

Issues with administering intravenous recombinant tissue plasminogen activator (rtPA): Most patients with COVID- 19 have an abnormality of coagulation and thrombocytopenia; the severity of which worsens with disease progression. This may lead to an increase in the risk of ICH in those who receive thrombolytic therapy. Other than the traditional contra indications for intravenous rtPA, certain other factors also increase the risk of hemorrhage in those with associated COVID- 19 such as presence of severe COVID- 19 with multi organ dysfunction and elevated D-dimer levels. Even without COVID- 19, the presence of elevated D-dimer levels have been associated with an unfavorable outcome from AIS after intravenous thrombolysis and is an independent parameter to predict ICH [33]. Elevated D-dimer levels are not only a marker of systemic thrombosis but can also contribute to inflammation leading to tissue injury [34]. Also, the elevated D-dimer in COVID- 19 indicates the severity of the underlying infection with the associated coagulopathy and increases the risk of bleeding post treatment. On the other hand, it is not ethically and scientifically acceptable to deny these patients thrombolysis for fear of bleeding complications. A balanced decision needs to taken carefully considering the benefit and risk of thrombolysis. Compounding this issue is the non-availability of relatives who can be explained in person the treatment dilemmas. Where available; point of care evaluation of platelet count, D-dimer level, prothrombin time with INR and activated partial thromboplastin time should be done to help in decision making.

Primary Prevention Of Stroke In Those With Covid- 19: Hospitalized patients with COVID- 19 are at a risk for thrombosis including ischemic strokes. The benefit of the use of anti-coagulants to prevent thrombotic complications has to be weighed against the risk of developing hemorrhagic complications (including ICH). Also, there are case reports of occurrence of AIS even in those receiving thromboprophylaxis [5]. Use of low molecular weight heparin is associated with a better outcome in those in those with severe COVID disease or elevated D-dimer levels as compared to other anti-coagulants [35]. Gavioli et al [36] have proposed a clinical treatment pathway for the dose and use of anticoagulants in hospitalized patients with COVID- 19.

Outcome Of Covid- 19 Strokes As Compared To Non- Covid Strokes: Most studies have reported COVID- 19 ischemic strokes to have higher mortality and worse functional outcome as compared to non COVID- 19 strokes [2,14,37]. Large strokes (as documented by NIHSS) on admission, poor Glasgow coma scale, altered sensorium, need for an invasive ventilation, raised D- dimer and CRP levels were more likely to predict death in those with strokes [10].

Implications For Practise

Acute ischemic stroke patients may present without the typical features of COVID-19 and may also occur in the early stages of COVID- 19. In the current pandemic, many acute ischemic stroke patients are being detected to have associated COVID- 19 at the same encounter as the ischemic stroke. A COVID-19 infection is unlikely to be confirmed or excluded using laboratory assessment during the time frame for initial evaluation and decision making in acute stroke patients. Therefore, any patient with an acute stroke in a region where COVID- 19 infection is active has to be evaluated under the assumption that the patient has COVID-19 infection. A patient with AIS and COVID- 19 poses unique challenges: Risk of nosocomial spread of infection, large strokes with LVO, elevated markers for inflammation (CRP) and thrombosis (D-dimer), increase chances of hemorrhage with reperfusion or anticoagulant therapy, a higher mortality and poor functional outcome. On the other hand, current knowledge about the risks of thrombosis in those with COVID- 19, necessitate the use of LMWH for primary prevention of strokes. Treatment strategies for each patient with acute ischemic stroke and COVID- 19 has to be individualized carefully weighing the benefits and risks involved in the treatment.

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