

COVID-19 Infection an Individual Risk Factor of Stroke

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Abstract

Background: COVID-19 infection is associated with multi-organ involvement. Neurological manifestations are seen in COVID-19 infection due to endothelial damage and prothrombotic state. Thus the importance of early detection or identifying the patients with high risk for developing cerebrovascular manifestations that could end up in disability and a worse overall prognosis has lead to the study of stroke characteristics in association with COVID-19.

Objective: To study the acute cerebrovascular accident (CVA) manifestations in patients infected with coronavirus disease 19 (COVID-19).

Methods and Materials: Our study is a retrospective from July 2020 to September 2020 for a period of 3 months done in confirmed Covid-19 infection (SARS-CoV-2 RT-PCR-positive) who are admitted in our tertiary care hospital. Diagnosing of stroke was confirmed either by Computed Tomography(CT) or Magnetic Resonance Imaging (MRI) of the brain. The inclusion criteria were as follows: RT PCR confirmed Covid 19 cases, who developed acute cerebrovascular accident in the patient.

Exclusion Criteria Include: Known case of stroke, hyperlipidemia, diabetes mellitus, hypertensive cases and morbid obesity patients.

Result: Out of 8489 covid-19 confirmed cases in our hospital nearly 10 cases developed neurological manifestations who had no other co morbidities or risk factors. Out of 10 patients, 7 patients were male and 3 patients were female. Out of 10 cases 20% of cases were among the age group of 25-40 years of age, another 70% belongs to 40-50 years of age & 10% of cases belongs to age group 50-60years. Thus majority of our cases were around age group 40-50 years. Majority of our patients (60%) developed cerebrovascular accident on day 3-6 of onset of symptoms. All our patients had high sensitivity C- reactive protein above 10mg/ml and 60% had their serum ferritin value >550ng/ml. Majority of our patients had their D-dimer value >10000ng/ml. Most of our patients(50%) belongs to severe category of National Institute of Health Stroke Scale (NIHSS).Majority of our patients who developed stroke had improved (70%), nearly 10% had no improvement and 20% died. All our patients developed ischemic stroke.

Conclusion: From our study we seen that middle aged male between 40-50 yrs. who are infected with covid-19 infection with no comorbidities and with higher inflammatory markers had developed ischemic stroke when compared to the usual age >60 years with

comorbidities in non-covid patients. Thus we conclude that covid 19 infection is to be considered as an individual risk factor for developing stroke . D-dimer level more than 3 fold increase and high C-reactive protein should alarm the physician to start on early treatment of steroids and anticoagulants.. Thus early detection of inflammatory markers and early start of anticoagulants and steroids resulted in good outcome of the patients. Repeat inflammatory markers should be done at the end of the treatment and if it is still elevated, patient should be discharged with oral steroids, antiplatelets and statins even with no comorbidities and symptoms. Anyhow studies with bigger sample size is needed to validate these results.

Keywords: COVID-19, Stroke, D Dimer, Ferritin.

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Introduction

Novel corona virus (COVID 19) that started on December 2019 in China spread has become rapidly spreading pandemic disease. India reported its first Covid 19 case in March 2020 the causative agent being the Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). More than 35 million cases have been reported all over world with mortality rate of 1.04 million. Initially it was thought as a disease of respiratory symptoms but later it has been increasingly noted with multi organ involvement. Reports of ischemic stroke in patients affected with COVID-19 have been reported increasingly. Due to recency of the pandemic, most of studies are small case series, [1-3] as well as our study and so this evaluation should be regarded as preliminary. SARS-CoV-2 infection induces a severe inflammatory response and hypercoagulable state, making the patients more prone for thrombotic complications and there is elevation of D-Dimer and CRP levels and there is lymphopenia. [4,5] Direct vascular endothelial cell damage by the virus has been proposed to the main cause for neurological manifestations. There are reported cases where respiratory disease has occurred a few days prior to onset of neurological symptoms. On other hand cases of asymptomatic covid 19 patients debuting with stroke have been reported, rising concerns among physicians regarding adequate triage and

classification of stroke patients. This raises the need for further investigations and its correlations with acute ischemic stroke. World Health Organization panel review has reported incidence of ischemic stroke during covid 19 is around 5%. Covid 19 related hemorrhagic stroke are less common than the ischemic stroke. The medium time from diagnosis to ischemic stroke in one small single centre study was 10 days. Here we present a series of 10 covid -19 cases who developed ischemic stroke and their outcome.

Methods

On reviewing the current literature on the pathophysiology and clinical presentation of the published cases of stroke in Covid - 19 patients. Our study is a retrospective from July 2020 to September 2020 for a period of 3 months done in confirmed Covid-19 infection (SARS-CoV-2 RT-PCR- positive) who are admitted in our tertiary care hospital. Diagnosing of stroke was confirmed either by Computed Tomography(CT) or Magnetic Resonance Imaging (MRI) of the brain.

Inclusion Criteria

RT PCR confirmed Covid 19 cases, with newly developed neurological manifestation in the patient

Exclusion Criteria

Known case of stroke, hyperlipidemia, diabetes mellitus, hypertensive cases and morbid obesity.

Statistical Analysis

Statistical significance was analyzed using the SPSS (Statistical Package for Social Science) Software.

Results

Out of 8489 covid-19 positive confirmed cases in our hospital, nearly 10 cases developed neurological manifestations who had no other co morbidities or risk factors.

Table 1: Age wise distribution

Age	Number of Patients	Percentage
25-40	2	20%
40-50	7	70%
50-60	1	10%
>60	0	-

Our study showed out of 10 patients, 7 patients were male and 3 patients were female. Thus 70% of male developed cerebrovascular accident when compared to 30% of female among covid-19 affected cases.

Table 2: Sex wise distribution

Sex	Number of Patients	Percentage
Male	7	70%
Female	3	30%

Out of 10 cases 20% of cases were among the age group of 25-40 years of age, another 70% belongs to 40-50 years of age & 10% of cases belongs to age group 50-60years. Thus majority of our cases were around age group 40-50 years.

Table 3: Correlation of development of CVA with day of illness

Day of Fever	Day of Development of CVA	Percentage
1-2	2	20%
3-6	6	60%
7-14	2	20%

Majority of our patients (60%) developed cerebrovascular accident on day 3-6 of onset of symptoms.

hs CRP levels and stroke

Table 4: Correlation with CRP levels

hs CRP (mg/ml)	Number of Patients	Percentage
<10	0	-
>10	10	100%

Table 5: Correlation with serum ferritin levels

Serum Ferritin (ng/ml)	Number of Patients	Percentage
450-500	2	20%
500-550	2	20%
>550	6	60%

All our patients had high sensity C-reactive protein above 10mg/ml. Thus this

shows the significance of high C – reactive protein as a risk factor for development of

stroke in covid-19 patients. Majority of our patients (60%) had their serum ferritin value >550ng/ml and D-dimer value >10000ng/ml. thus it implies that higher

the serum ferritin and d-dimer value higher is the risk for development of stroke in covid 19 patients.

Table 6: Correlation with d - dimer levels

D-Dimer(ng/ml)	Number of Patients	Percentage
550-600	1	10%
600-650	1	10%
650-700	1	10%
700-10000	1	10%
>10000	6	40%

Table 7: Correlation with oxygen dependency

Severity	Number of Patients	Percentage
O ₂ Dependent	7	70%
Non O ₂ Dependent	3	30%

Most of our patients (70%) were oxygen dependent

Table 8: Correlation with NIHSS score

NIHSS Score	Number of Patients	Percentage
5-15	4	40%
16-20	1	10%
21-42	5	50%

Most of our patients(50%) belongs to severe category of National Institute of Health Stroke Scale (NIHSS).

Table 9: Stroke patients and their outcome

Outcome	Number of Patients	Percentage
Improved	7	70%
No Improvement	1	10%
Mortality	2	20%

Majority of our patients who developed stroke had improved (70%), nearly 10% had no improvement and 20% died.

Table 10: Type of stroke

Type of Stroke	Number of Patients	Percentage
Ischemic	10	100%
Hemorrhagic	0	-

All our patients developed ischemic stroke.

Table 11: Correlation between outcome and day of start of treatment

Day of Start of Steroids and Anticoagulant	Number of Patients	No of Patients Improved	Percentage
1-3	7	ALL 7	70%
4-6	1	NONE	10%
>6	2	NONE	20%

Most of our patients were started on treatment on day 2 of the onset of the

stroke and the had a better improvement and no mortality.

Discussion

COVID 19 increases the risk of stroke like other respiratory infections like influenza. [5] The proportion of patients with COVID-19 who have acute ischemic stroke was estimated to be 4.9%. [6] Out of 8489 covid-19 confirmed cases in our hospital nearly 10 cases developed neurological manifestations who had no other co morbidities or risk factors. Majority of our cases were around age group 40-50 years who developed ischemic stroke which is atypical when compared to more than 60 years of age in non-covid-19 patients. All our patients developed ischemic stroke with no other co morbidities. In literature COVID-19 patients who developed acute ischemic stroke were younger and without preexisting cardiovascular risk factors. [7,8] Out of 10 patients, 7 patients were male and 3 patients were female. Majority of them were male patients who developed stroke.

Usual stroke incidence is 85% ischemic and 15% hemorrhagic in non-covid-19 cases. Coagulopathy and vascular endothelial dysfunction have been proposed as the major mechanism of severity of disease in Covid-19 patients.

Nearly 60% of our patients developed cerebrovascular accident on day 3-6 of onset of symptoms. Fever is the main proceeding symptoms which lasted maximum 3 days before they developed neurological complications. One of our patient developed massive ischemic stroke post on day 9 and was started on steroids and anticoagulants on day 10 and he had poor outcome. All our patients had high sensitivity C- reactive protein above 10mg/ml. Serum ferritin value was >550ng/ml in majority of our patients and their D-dimer value >700ng/ml. Nearly 6 of our patients had serum D-dimer more than 10,000ng/ml, thus it implies that higher the inflammatory markers value higher is the risk for development of stroke in covid 19 patient. Increase in D-

dimer value by more than 3 fold should be monitored carefully and they have high risk for thrombotic phenomenon. Increase in CRP, D-Dimer, serum ferritin were associated with increased morbidity and mortality in COVID 19 patients with acute ischemic stroke. [9] Most of our patients (70%) were oxygen dependent. Their chest scan showed CORADS – 4/5 with severity scoring ranging between 8-15, which represents the moderate bilateral ground glass opacities of the lung parenchyma and 20% of them representing severity score more than 15 representing the severe lung involvement. Nearly half of our patients(50%) belongs to severe category of National Institute of Health Stroke Scale (NIHSS), 10% belongs to moderate category which suggests the severity of the stroke in covid-19 patients. In a study in-hospital mortality was increased in COVID-19 patients with ischemic stroke. [10]

All of them were started on anticoagulants, antiviral, steroids at the earliest. 2 of our patients who had atypical presentation were started on anticoagulants and steroids more than 6 days and they had very poor outcome. In literature, patients with COVID 19 and large vessel occlusion who were treated with mechanical thrombectomy had limited response compared to those without COVID 19 infection. [11] Seven of our patients who developed stroke had improved (70%) within 10 -12 days in both sensorium and motor power from hemiplegia to hemiparesis, nearly 10% had no improvement and 20% who had very poor GCS on admission died on their day 5-6 days of onset of symptoms. MRI brain of our patients showed infarct involving middle cerebral artery Territory mostly on the left side. Magnetic resonance arterial angiogram showed main stem occlusion of middle cerebral artery in 2 of our patients. The main mechanism of the virus to cause the disease in human beings is due to their affinity for the ACE2 receptors, which are

expressed in endothelial and arterial smooth muscle cells in the brain, allows the virus to damage intracranial arteries, causing vessel wall rupture. In addition, it is possible that the cytokine storm that accompanies this disorder could be the cause of hemorrhagic strokes, as reported in some studies in Covid-19 affected patients who developed an acute necrotizing encephalopathy associated with late parenchymal brain hemorrhages. This massive cytokines release damage and result in breakdown of the blood-brain barrier and cause hemorrhagic posterior reversible encephalopathy syndrome (PRES). Secondary hemorrhagic transformation of ischemic strokes has also been reported in Covid-19 patients, which may be due to endothelial damage or a consumption coagulopathy accompanying the disease. Some postmortem studies in patients dying of Covid-19 showed microvascular platelet fibrin rich thrombotic depositions in the lungs as well as in other organs. It has been suggested that the viral invasion of the vascular endothelium triggers activation of the contact and complement systems which results in thrombotic and inflammatory cascades leading to internal organ injury.

Conclusion

From our study we seen that middle aged male between 40-50 yrs. who are infected with covid-19 infection with no comorbidities and with higher inflammatory markers had developed ischemic stroke when compared to the usual age >60 years with comorbidities in non-covid patients. Thus we conclude that covid 19 infection is to be considered as an individual risk factor for developing stroke. D-dimer level more than 3 fold increase and high C-reactive protein should alarm the physician to start on early treatment of steroids and anticoagulants. Thus early detection of inflammatory markers and early start of anticoagulants and steroids resulted in good outcome of the patients. Repeat inflammatory markers

should be done at the end of the treatment and if it is still elevated, patient should be discharged with oral steroids, antiplatelets and statins even with no comorbidities and symptoms. Anyhow studies with bigger sample size is needed to validate these results.

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