Research Article

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Incidence of Cryptogenic Stroke in Covid-19 Patients

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Abstract

Introduction

The risk of ischemic stroke during COVID-19 is approximately 5% reported by WHO. Hemorrhagic strokes are less common compared to ischemic ones, but few cases have been reported. The strokes are called a cryptogenic strokes which means an unknown origin. Diagnostic investigations were incomplete in patients with COVID-19 leading to a high rate of cryptogenic stroke.

Materials and Methods

It is a prospective observational study conducted at a single centered hospital in Hanamkonda the data was collected from January 2020 to April 2020 and all Parameters were expressed as Mean ± Standard Deviation (SD). Data analysis was performed using MS Excel and Graphpad Prism (9.0 version). A One-Way ANOVA (Analysis of variance) followed by Dunnett's Multiple Comparison test was done to assess the significant difference between visit 1and visit 3 cryptogenic parameters. A p-value <0.0001 was considered significant.

Results

There were significant changes observed from visit 1 to visit 3 in evaluating the parameters and treatment of coagulation and inflammation.

Conclusion

The risk of cryptogenic stroke in COVID-19 infected patients was assessed by considering parameters such as TLC, CRP, LDH, RBS, FERRITIN, D-DIMER, IL-6 and it can be concluded that the evaluation of the above parameters is to be evaluated in every patient irrespective of comorbidities, age, and anti-coagulants, anti-diabeticandanti-inflammatoryagentswillplayasubstantialroleinthe management of cryptogenic stroke in COVID-19.

Keywords: ACE-2-Angiotensin Converting Enzyme-2, COVID-19-Coronavirus Disease 2019, LDL-Lactate Dehydrogenase, SARS COV 2-Severe Acute Respiratory Syndrome CoronaVirus 2, TLC-Total Leucocyte Count, WHO-World Health Organization.

Introduction

Cryptogenic stroke is defined as a stroke of undetermined etiology due to two or more underlying causes. Patients with COVID-19 who had a stroke were more likely to get older with comorbidities, lower platelet count, and patients had high levels of total leukocyte, lactate dehydrogenase, D-dimers, interleukin-6, ferritin, random blood sugar, C-reactive protein. Stroke in patients with COVID-19 may be due to common causes such as atherosclerosis, high blood pressure, and atrial fibrillation. However, in this review, we focus on stroke pathways that appear to be directly related to COVID-19. It appears that these COVID-19related approaches may also increase the risk of stroke in infected individuals with common risk factors for stroke. The main mechanisms appear to be responsible for the occurrence of ischemic stroke in COVID-19(Fig. 1) [1, 2]. These include hypercoagulable conditions, vasculitis, and cardiomyopathy. While the pathogenesis of hemorrhagic strokes in the case of COVID-19 has not been fully elucidated, it is possi-

ble that the SARS-CoV-2 affinity for ACE2 receptors, expressed in endothelial cells and arterial smooth muscle in the brain, allows the virus to damage intracranial arteries causing rupture[3]. In addition, the cytokine storm associated with these disorders may be the cause of hemorrhagic stroke, as reported in a patient of COVID-19 who developed acute necrotizing encephalopathy associated with late parenchymal hemorrhage [4]. This excessive release of cytokines can also damage and lead to the blood-brain barrier and lead to hemorrhagic posterior reversible encephalopathy syndrome (PRES) [5]. Second hemorrhagic reversal of ischemic stroke has also been reported in COVID-19 patients [6, 7]. Such changes may occur in the case of endothelial injury, or the use of coagulants associated with COVID-19 disorders [7].

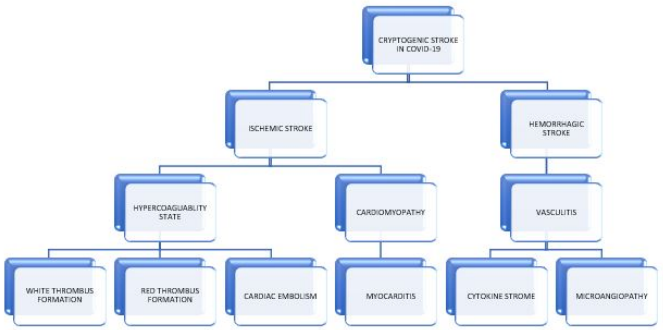

Figure1: Potential Mechanism of Cryptogenic Stroke

Methods

Study design and Ethical conduct of research

It is a Prospective, observational study conducted in patients who tested covid positive from Sri Bhadrakali clinic, Hanmakonda, Warangal, Telangana.150 patients were included in this study based on the inclusion criteria.The project protocol was submitted to the Institutional Human Ethics Committee (IHEC) and was approved (Approval No.: IHEC/VCOP/PHARM.D/NRCT/2020/006) before the initiation of the research work.

Inclusion criteria

Patients tested with covid positive RTPCR (Reverse Transcriptase Polymerase Chain Reaction) Rapid Antigen Test & HRCT. Patients aged between 25-80 years are included.Patients with Hypoxia, SOB, and low oxygen saturation (SPO2<95%).

Exclusion criteria

Patients with Von Willebrand's disease, liver disease, vitamin k deficiency, and fibrinolytic disorders are excluded.Patients with autoimmune disorders such as Rheumatoid arthritis, Systemic lupus erythematosus, Inflammatory bowel disease, and Multiple sclerosis are excluded.

Objectives

Evaluation of parameters such as C - reactive protein (CRP), D-DIMER, Interleukin-6 (IL-6), Ferritin, Total Leukocyte Count (TLC), Random Blood Sugar (RBS), and Lactate Dehydrogenase (LDH) is done before and after covid treatment.

Statistical Analysis

All Parameters were expressed as Mean ± Standard Deviation (SD). Data analysis was performed using MS Excel and Graphpad Prism (9.0 version). A ONE-WAY ANOVA (Analysis of variance) followed by Dunnett's Multiple Comparison test was done to assess the significant difference between visit 1an visit 3 cryptogenic parameters. A p-value <0.0001 was considered significant.

Results

The evaluation of the parameters such as TLC, D-DIMER, CRP, LDH, FERRITIN, and IL-6 is necessary to avoid cryptogenic stroke exposure in covid-19 patients which reduces the mortality rate.

Age Distribution

Table 1 explains the age distribution of covid patients out of 136 covid positive patients,93 patients were males (68.30%) and 43 patients were females (31.60%). The percentage of participation each band of 4 age bands (20-40, 40-60, 60-80, >80) was 14.70%, 50.7%, 31.60%, 2.90% respectively.

Table-1: Age Distribution

Age	No. of patients	Percentage
20-40 Years	20	14.70%
41-60 Years	69	50.70%
61-80 Years	43	31.60%
>80 Years	4	2.90%

Gender distribution

Figure 2 explains the gender distribution of covid patients out of 136 covid positive patients,93 patients were males (68%) and 43 patients were females (32%).

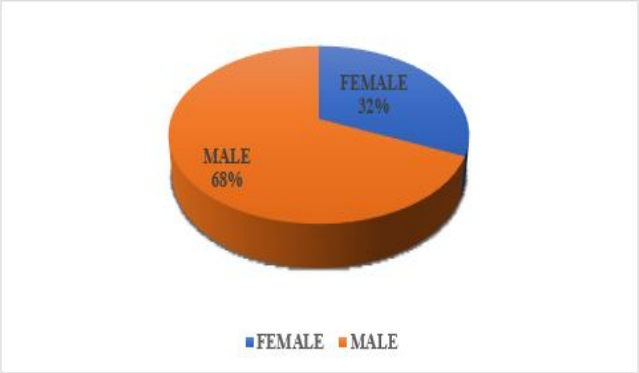

Figure-2: Gender Distribution

During the study period,150 patients are assessed and 136 patients are included based on inclusion criteria.The standard and mean deviation of TLC were found to be 13157.36±3100.191 on visit 1 followed by 10386.55±2998.379 and 8367.897±2926.268 on visit 2 and visit 3 respectively. Elevated levels of Total Leucocyte count were observed in 109 (80.17%) in visit 1, 55(40.44%) in visit 2, 25(18.9%) in visit 3. In visit one there was an unusual increase in TLC and there was a significant change(P-value <0.0001) from visit 1 to visit 2 and visit 3. The mean and standard deviation of136 patients with CRP diagnosis was 51.49578±41.46674 at visit 1 followed by 28.70478±28.18661 at visit 2 and 15.99471±22.0.77866 at visit 3. Elevated levels of CRP were observed in 122 (89.7%) in visit 1, 105(77.2%) visit 2, 60(44.11%) visit 3. There is a significant change (P <0.0001)

from visit 1 visit 2 and visit 3. Serum LDH was validated for its potential usefulness as a marker for evaluating clinical severity and monitoring therapeutic response in COVID-19 pneumonia. From this study, the mean and standard deviation of 136 patients' LDL was found to be 466.0463±216.1088 on visit 1 followed by 353.5772±178.3556 on visit 2 and 252.9603±131.5888 on visit 3. Elevated levels of LDH were observed in 88 (64.7%) in visit 1, 60(44.11%) visit 2, 28(20.5%) visit 3.There is a significant change (P-value <0.0001)from visit 1 to visit 2 and visit 3 in covid treatment. Patients with COVID-19 who have high blood sugar levels without any previous history of diabetes may be at greater risk of death and an increased risk of serious complications such as stroke and infectious disease. 136 Covid-19 patients RBS mean and standard deviation values found that 271.5382±98.56849 in visit 1 followed by 220.0147±86.89167 in visit 2 and 162.2941±62.99103 in visit 3. Elevated levels of RBS were observed in 106(77.9%) in visit 1, 87(64.7%) in visit 2, 44(32.35%) in visit 3. There is a significant change (P <0.0001) from visit1 to visit 2& visit 3on treatment with antidiabetic agents. Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm. From this study, the mean and standard deviation values of Ferritin were found to be 630.1889±884.0982 on visit 1 followed by 434.0724±632.9865 on visit 2 and 238.9443±199.7582 on visit 3. Elevated levels of FERRITIN were observed in 89(65.44%) in visit 1, 57(41.9%) in visit 2, and 23(16.9%) in visit 3. There is a significant change (P-value <0.0001) from visit 1 to visit 2 and visit 3 on treating with iron cheaters. Elevated D-dimer in COVID-19 patients is associated with higher mortality. From this study, the mean and standard deviation values of D-dimer were found to be 1412.607±2044.307 on visit 1 followed by 996.7393±1691.491 on visit 2 and 638.7554±1193.976 on a visit 3. Elevated levels of D-DIMER were observed in 100 (73.5%) in visit 1, 59(44.3%) in visit 2, and 35(25.7%) in visit 3.There is a significant change (P-value <0.0001) from visit 1 to visit 2 and visit 3 on treating with prophylactic anticoagulation. Levels of IL-6 seem to be associated with inflammatory response, respiratory failure, need for mechanical ventilation and/or intubation, and mortality in COVID-19 patients. From this study, the mean and standard deviation values of IL-6 were found to be 50.09169±49.2996 on visit 1 followed by 29.8225±25.99163 on visit 2 and 14.37353±14.37088 on visit 3. Elevated levels of IL-6 were observed in 129(94.8%) in visit 1, 122(89.7%) in visit 2, and 93(68.38%) in visit 3. There is a significant change (P-value <0.0001)

b	PARAMETER	MEAN±SD			ELEVATION%		
		VISIT 1	VISIT 2	VISIT 3	VISIT 1	VISIT 2	VISIT 3
1	TLC	13157.36±3100.191	10386.55±2998.379	8367.897±2926.26	109 (80.17%)	55(40.44%)	25(18.9%)
2	CRP	51.49578±41.46674	2870478±28.18661	15.99471±22.0.77	122 (89.7%)	105(77.2%)	60(44.11%)
3	LDH	466.0463±216.1088	353.5772±178.3556	252.9603±131.58	88 (64.7%)	60(44.11%)	28(20.5%)
4	RBS	271.5382±98.56849	220.0147±86.89167	162.2941±62.99	106(77.9%)	87(64.7%)	44(32.35%)
5	D-DIMER	1412.607±2044.307	996.7393±1691.491	638.7554±1193.97	100(73.5%)	59(44.3%)	35(25.7%)
6	FERRITIN	630.1889±884.0982	434.0724±632.9865	238.9443±199.75	89(65.44%)	57(41.9%)	23(16.9%)
7	IL-6	50.09169±49.2996	29.8225±25.99163	14.37353±14.370	129(94.8%)	122(89.7%)	93(68.38%)

from visit 1 to visit 2 and visit 3 on treatment with anti-inflammatory agents

Discussion

During a pandemic, assessing the impact of strategies to alleviate the strain placed on health care systems is necessary to guide effective response. Evidence-based practices that reduce the mortality rate will ultimately prevent the overwhelming of hospital resources.

For this study, the patients with COVID-19 infection are selected irrespective of comorbidities, age,gender, and an evaluation of different parameters which are directly or indirectly biomarkers of Cryptogenic stroke is done. The mortality rate was high in thosepatients whose cryptogenic stroke parameters are not evaluated. Even though the infection is reduced, in the post covid time there is an enormous increase in the inflammation and coagulation effect which is the direct risk of the cryptogenic stroke. So even after covid infection also these parameters need to be monitored until they come to normal ranges.

Lee et al. [9] reported that 20-55% of hospitalized patients with COVID-19 had laboratory evidence of coagulopathy, with increased levels of D-dimer to more than double the normal, slightly extended prothrombin duration (1-3 seconds above normal) , mild thrombocytopenia, and latedisease, decreased fibrinogen levels. D-dimer levels above 4 times normal were associated with a 5-fold increase in the risk of serious illness.

Ackermann et al. [8] reported an autopsy series of 7 cases of COVID-19 compared to 7 influenza cases. They noted that different lung features in COVID-19 include alveolar injury and perivascular T-cell infiltration, endothelial damage associated with the presence of intracellular virus and disturbed cell membranes, widespread thrombosis with microangiopathy,and angiogenesis.

An earlier report from China and an earlier report from Singapore on SARS-CoV-1 infection resulting from a stroke during the 2002-2003 outbreak showed cardioembolic pathways in 36 and 60% of their cases, respectively. [11]. Yagi et al. [10] reported that patients who had a stroke those with COVID-19 are more likely to be young men with high troponin levels compared to historical controls.

In this observational study of patients who are admitted with COVID-19 infection, there is a 2-3 fold increase in the cryp-

togenic stroke parameters. By evaluating and treating with anti-inflammatory and anticoagulants besides the antiviral agents there is a gradual decrement in these parameters which can be compared with the study conducted by Lee et al, Ackermann et al,Yaghi et al[8 -11].

Conclusion

Thestudywasconductedtoassesstheriskofcryptogenicstrokein-COVID-19infected patients. A total number of 136 patients were included in this study. The risk of cryptogenic stroke was assessed by taking into consideration the mean and standard deviation values of TLC, CRP, LDH, RBS, FERRITIN, D-DIMER, and IL-6 by the application of descriptive statistics. Several mechanisms are involved in cryptogenic stroke in COVID-19, including a hypercoagulable state, DIC, necrotizing encephalopathy, vasculitis, and cardiomyopathy.It can be concluded thatthe evaluation of the above parameters is to be evaluated in every patient irrespective of comorbidities, age, and anti-coagulants,anti-diabetic and anti-inflammatoryagentswillplayasubstantialroleinthe management of cryptogenic stroke in COVID-19. Further evidence is needed from largerstudies.

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Conflict of Interest

The authors declare no conflict of interest.

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