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Does COVID-19 increase risk of stroke?

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Abstract

Aim: In this study, it was aimed to compare the epidemiological characteristics and frequency of patients diagnosed with stroke in Kayseri City Hospital in the pre-COVID-19 pandemic period and during the COVID-19 pandemic and investigate whether COVID-19 increases the frequency of stroke.The true relationship between COVID-19 and the incidence of stroke has yet to be determined.

Materials and Methods: A meta-analysis study reported that 1.4% (95%CI: 1.0–1.9) of 108,571 patients with COVID-19 developed acute cerebrovascular disease (CVD). Additionally, although the number of hospital admissions due to clinical presentation of suspected stroke decreased due to the pandemic, it has been suggested that the COVID-19 infection itself may cause a stroke.

Results: In the literature, there have been reports of patient groups who developed ischemic stroke 1-2 weeks after diagnosis with typical COVID-19 symptoms, as well as patient groups who developed symptoms such as fever, dry cough, and shortness of breath during follow-up with ischemic stroke and who were subsequently diagnosed with COVID-19 . It was observed that patients presented with sudden onset loss of strength showing side without typical COVID-19 symptoms (such as cough, fever), and thoracic CT scans of these patients in the later period revealed pulmonary findings.

Conclusion: In other words, COVID-19 patients may present with neurological symptoms such as acute cerebrovascular disease as the first symptom.

Introduction

On 31 December 2019, World Health Organization (WHO) - China Country Office was informed of cases of pneumonia of unknown etiology detected in Wuhan city of Hubei province of China. On January 7, 2020, it was defined as a new strain of coronavirus (2019-nCoV) that has not been previously identified in humans. Later, 2019-nCoV disease was designated as COVID-19. Reports made during the COVID-19 (SARS CoV-2) pandemic, accepted as a pandemic by WHO, revealed that the disease not only causes severe acute respiratory failure (SARS) by affecting the respiratory tract, but also affects the neurological systems together and sometimes only. Approximately 30% of patients with COVID-19 are known to display neurological symptoms and signs [1,2].

In COVID-19 infection, neurological symptoms related to central and peripheral nervous system involvement through various mechanisms have been reported. With the increase in cases, the diversity of these symptoms is progressively increasing. Although headache is the most commonly reported neurological symptom, altered level of consciousness, impaired sense of taste, hyposmia, acute cerebrovascular diseases, encephalitis, myelitis, epilepsy and Guillan-Barre syndrome can be included in other neurological diseases observed. In patients with comorbidities such as hypertension, the neurological presentation is more severe and the inflammatory response is more pronounced (such as low levels of lymphocytes, elevated CRP). COVID-19 has been suggested to increase the risk of stroke in several ways. COVID-19 has been associated with hypercoagulation, which is possibly a "coagulation disorder due to sepsis" and causes predisposition to stroke [3]. On the other hand, it has been reported that widespread microvascular thrombosis develops with prothrombotic activation, accompanied by increased cytokine levels, in COVID-19 infection, and these patients have high D-dimer levels in clinical practice. In the guideline published by AHA/ASA in 2020, it was emphasized that 5.9% of patients had a stroke after an average of 10 days after symptom onset in COVID-19 [4].

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SARS-CoV-2 infection is associated with a prothrombotic state that causes venous and arterial thromboembolism and elevated D-dimer levels [2]. In severe COVID-19 infection, endothelial and mononuclear cell activation can trigger the coagulation process and increase thrombin formation. The circulation of free thrombin that is not controlled by natural anticoagulants can activate platelets and cause thrombosis. Although ischemic stroke has been recognized as a complication of COVID-19 (usually in severe disease), the mechanism has not been understood yet. Therefore, it has been reported that early anticoagulant treatment with low molecular weight heparin will reduce the risk of COVID-19-associated ischemic stroke [5,6].

The true relationship between COVID-19 and the incidence of stroke has yet to be determined. A meta-analysis study reported that 1.4% (95%CI: 1.0–1.9) of 108,571 patients with COVID-19 developed acute cerebrovascular disease (CVD) [7]. Additionally, although the number of hospital admissions due to clinical presentation of suspected stroke decreased due to the pandemic, it has been suggested that the COVID-19 infection itself may cause a stroke [8]. In the literature, there have been reports of patient groups who developed ischemic stroke 1-2 weeks after diagnosis with typical COVID-19 symptoms, as well as patient groups who developed symptoms such as fever, dry cough, and shortness of breath during follow-up with ischemic stroke and who were subsequently diagnosed with COVID-19 [9]. It was observed that patients presented with sudden onset loss of strength showing side without typical COVID-19 symptoms (such as cough, fever), and thoracic CT scans of these patients in the later period revealed pulmonary findings. In other words, COVID-19 patients may present with neurological symptoms such as acute cerebrovascular disease as the first symptom [10].

In this study, it was aimed to compare the epidemiological characteristics and frequency of patients diagnosed with stroke in Kayseri City Hospital in the pre-COVID-19 pandemic period and during the COVID-19 pandemic and investigate whether COVID-19 increases the frequency of stroke.

Materials and Methods

Our study was a cross-sectional and descriptive study, and the research was started after obtaining permissions from the Ministry of Health and local ethics board. Ethics approval of Kayseri City Hospital with was obtained (Decision no. 149 of 03.09.2020). During the study, the ethics principles specified in the Declaration of Helsinki were followed.

G-Power 3.1 analysis program was used to determine the sample size in the study. Sampling method was not used in the research of the g power part. All patients who met the inclusion and exclusion criteria were included in the study. The epidemiological characteristics, complaints at admission, type of stroke (ischemic or hemorrhagic), department in the hospital where the patient has stayed (service or intensive care unit), length of stay in the hospital, and clinical outcomes (discharge or ex) of the patients included in the study were recorded in the patient follow-up form and compared.

Patients admitted to the Emergency and Neurology clinics of Kayseri City Hospital due to a diagnosis of stroke in the 6-month period (10 October 2019-10 March 2020) before 11 March 2020, the date of the first COVID-19 infection in Turkey, and all patients, female or male, over the age of 18 were grouped as Group 1, and patients who tested positive for COVID-19 by real-time PCR test during their hospitalization period in the 6-month period after the pandemic (11 March 2020- 11 September 2020) and all patients, female or male, over the age of 18 who tested negative for COVID by PCR test, who developed stroke and who was transferred to neurology clinic were grouped as Group 2 and recruited for the study.

Patients under the age of 18, patients with incomplete information on hospital information management system (HIMS) and hospital file, male or female patients hospitalized due to COVID-19 with negative or positive PCR but without clinical presentation of a stroke, patients hospitalized in the neurology clinic for non-stroke reasons in the 6-month period from 10 September 2019 to 10 March 2020 and male or female patients hospitalized in the neurology clinic for non-stroke reasons in the 6-month period from 11 March 2020 to 11 September 2020 were excluded from the study.

Statistical analysis

A total of 954 people, of female or male gender, who were diagnosed with stroke in the pre-pandemic period (10 September 2019- 10 March 2020) (Group 1) and a total of 513 people, of female or male gender, who were diagnosed with stroke during the pandemic (11 March 2020 - 11 September 2020) (Group 2) based on HIMS records were included in the study.

The data obtained for the study were recorded using SPSS 22 (IBM; Armonk, NY, USA) program and analyzed in this program. Frequency, percentage, mean value, standard deviation, highest and lowest values were used for descriptive statistics in research data and analysis. The Kolmogorov-Smirnov test was used to check the conformity of the data to the normal distribution, Mann-Whitney U test was used for the statistical analysis since the quantitative data did not show normal distribution, Pearson Chi-square test was used for the statistical analysis of the categorical data, and Fisher's Exact Test was used for the values below five in the four-eyed tables. Pearson correlation coefficient was used to show the relationship between the variables. Statistically, significant difference was accepted as $p<0.05$.

Results

A statistically significant difference was found between the distributions of intracranial pathology determined by group ($p<0.001$). 91% of group 1 and 92.3% of group 2 had ischemic stroke. A statistically significant difference was found between the distributions of clinical outcome determined by group ($p<0.001$). The percentage of patients in the groups discharged from the hospital were 88.9% for group 1 and 81.01% for group 2. A statistically significant difference was identified between the distribution of B complaints by group ($p<0.001$), arising from the fact that

Table 1. Distribution of some demographic and clinical variables in Group 1 and Group 2 patients.

Variables		All patients		Group 1		Group 2		χ^{2*}	p
		n	%	n	%	n	%		
Gender	Male	770	52.5	495	51.9	275	53.6	0.396	0.529
	Female	697	47.5	459	48.1	238	46.4		
Age groups	Under 65	468	31.9	294	30.8	174	33.9	1.476	0.224
	65 years and older	999	68.1	660	69.2	339	66.1		
Intracranial pathology	Ischemic stroke	1381	94.1	868	91.0	513	100.0	49.125	<0.001
	Hemorrhagic stroke	86	5.9	86	9.0	0	0.0		
Unit in hospital	Service	909	62.0	575	60.3	334	65.1	3.309	0.069
	Intensive care	558	38.0	379	39.7	179	34.9		
Clinical outcome	Discharge	1361	92.8	848	88.9	513	100.0	61.439	<0.001
	Exitus	106	7.2	106	11.1	0	0.0		
Age		Ort.	ss.	Ort.	ss.	Ort.	ss.	U	p
		64.48	13.48	69.91	13.49	68.69	13.03	229412.0	0.048
		Median	Min/Max	Median	Min/Max	Median	Min/Max		
		19	19/97	71	19/97	70	28/94		

Column percentage used, * Pearson Chi-square Test.

Table 2. Distribution of patients' symptoms according to groups.

Symptoms		All patients		Group 1		Group 2		χ^{2*}	p
		n	%	n	%	n	%		
Weakness in the arms	available	579	39.5	464	48.6	115	22.4	96.001	<0.001*
	unavailable	888	60.5	490	51.4	398	77.4		
Weakness in the legs	available	579	39.5	471	49.4	108	21.1	111.981	<0.001*
	unavailable	888	60.5	483	50.6	405	78.9		
Speech disorder	available	454	30.9	369	38.7	85	16.6	76.315	<0.001*
	unavailable	1013	69.1	585	61.3	428	83.4		
Headache	available	373	25.4	329	34.5	44	8.6	118.109	<0.001*
	unavailable	1094	74.6	625	65.5	469	91.4		
Dizziness	available	194	13.2	165	17.3	29	5.7	39.406	<0.001*
	unavailable	1273	86.8	789	82.7	484	94.3		
Consciousness change	available	166	11.3	96	10.1	70	13.6	4.266	0.039*
	unavailable	1301	88.7	858	89.9	443	86.4		
Facial asymmetry	available	55	3.7	53	5.6	2	0.4	24.669	<0.001*
	unavailable	1412	96.3	901	94.4	511	99.6		
Defect of vision	available	40	2.7	29	3.0	11	2.1	1.009	0.315*
	unavailable	1427	97.3	925	97.0	502	97.9		
Watch	available	37	2.5	27	2.8	10	1.9	1.053	0.305*
	unavailable	1430	97.5	927	97.2	503	98.1		
Reduction in odor	available	4	0.3	4	0.4	0	0.0	2.157	0.304**
	unavailable	1463	99.7	950	99.6	513	100.0		
Taste change	available	3	0.2	3	0.3	0	0.0	1.617	0.556**
	unavailable	1464	99.8	951	99.7	513	100.0		

Column percentage used, * Pearson Chi-square test, ** Fisher's exact test.

the percentage of patients with headache, speech disorder, facial sagging asymmetry, loss of strength in arm, loss of strength in leg, dizziness vertigo, and altered level of consciousness varied by group. 49.4% of patients from group 1 and 21.1% of those from group 2 had loss of strength in leg. There was no statistically significant difference between

Table 3. Distribution of patients' symptoms by age groups.

Symptoms		All patients		Group 1		Group 2	
		Under 65 years	65 years and older	Under 65 years	65 years and older	Under 65 years	65 years and older
		n/%	n/%	n/%	n/%	n/%	n/%
Weakness in the arms	available	186/39.7	393/39.3	138/46.9	326/49.4	48/27.6	67/19.8
	unavailable	282/60.3	606/60.7	156/53.1	334/50.6	126/72.4	272/80.2
		χ^2=0.022 p=0.883		χ^2=0.491 p=0.484		χ^2=4.045 p=0.044	
Headache	available	140/29.9	233/23.3	120/40.8	209/31.7	20/11.5	24/7.1
	unavailable	328/70.1	766/76.7	174/59.2	451/68.3	154/88.8	315/92.9
		χ^2=7.302 p=0.007		χ^2=7.537 p=0.006		χ^2=2.858 p=0.098	
Consciousness change	available	42/9.0	124/12.4	31/10.5	65/9.8	11/6.3	59/17.4
	unavailable	426/91.0	878/87.6	263/89.5	595/90.2	163/93.7	280/82.6
		χ^2=3.754 p=0.053		χ^2=0.109 p=0.742		χ^2=11.985 p=0.001	
Defect of vision	available	20/4.3	20/2.0	14/4.8	15/2.3	6/3.4	5/1.5
	unavailable	448/95.7	979/98.0	280/95.2	645/97.7	168/96.6	334/98.5
		χ^2=6.200 p=0.013		χ^2=4.276 p=0.039		χ^2=2.134 p=0.144	
Reduction in odor	available	4/0.9	0/0.0	4/1.4	0/0.0	-	-
	unavailable	464/99.1	999/100.0	290/98.6	660/100.0	-	-
		χ^2=8.562 p=0.003		χ^2=9.017 p=0.003		-	
Taste change	available	3/0.6	0/0.0	3/1.0	0/0.0	-	-
	unavailable	465/99.4	999/100.0	291/99.9	660/100.0	-	-
		χ^2=6.417 p=0.011		χ^2=6.765 p=0.009		-	

Column percentage used, Pearson Chi-Square Test (symptoms that were not significant according to age groups in Group 1 and Group 2 were not included in the table).

Table 4. Length of hospital stay according to some variables.

Variables		Average	ss	Average	Min/max	p
Group	Group 1	6.63	7.52	5	1/113	0.947
	Group 2	6.84	10.19	5	1/183	
Gender	Male	6.56	9.15	4	1/183	0.086
	Female	6.86	7.82	5	1/113	
Age groups	Under 65 years	6.35	7.21	5	1/80	0.386
	65 years and older	6.87	9.10	5	1/183	

Mann Whitney U test.

the distributions of other variables by group (p>0.050). (Table 1).

1467 patients in our study, 770 (52.5%) were male, and the mean age of all patients was 69.48±13.34 (min-max:19-97) years. Of all the patients, the mean age of males was 67.72±12.61 (min-max:19-97& median:68), and females were 71.43±13.86 (min-max:23-96&median:74) years (p<0.001). Group 1 patients were 954 (65.0%) and Group 2 patients were 513 (35.0%). The gender distribution, intracranial pathology, hospitalization unit and clinical outcome frequencies of the patients according to Group 1 and Group 2 are given in Table 1. There was no significant difference between Group 1 and Group 2 in terms of gender and age groups. However, all 86 patients with hemorrhagic stroke and all 106 patients with clinical outcome were group 1 (p<0.001) (Table 1). Although there was no significant difference between Group 1 and Group 2 patients in terms of hospitalization unit (p=0.069), the frequency of intensive care hospitalization was slightly higher in group 1 patients. Of 106 patients whose clinical outcome was exitus, 62 (58.5%) were women (p=0.019).

The most common symptoms seen in the patients were weakness in the arms, weakness in the legs, speech disorder and headache, respectively. Decreased odor and change in taste were the least common symptoms. p<0.05). There was no statistically significant difference between group 1 and group 2 patients in terms of visual impairment, seizures, decreased smell and taste changes, but patients with these symptoms were more common in group 1 (p>0.05) (Table 2).

The distribution of all these symptoms by gender was examined and only headache was found to be significantly higher in women (χ^2=5.085 p=0.024). While headache was significantly higher in women in Group 1 (χ^2=5.827

p=0.016), there was no significant difference between genders in terms of headache in Group 2 (p>0.05). Headache, visual impairment, decrease in smell and taste changes were significantly higher in the group below 65 years of age in all patients, while changes in consciousness were higher in those aged 65 and over. Headache, visual impairment, decrease in smell and change in taste were more common in group 1 under 65 years of age, while weakness in arms in group 2 was significantly higher in those under 65 years of age, and changes in consciousness were significantly higher in those aged 65 and over (Table 3).

Percentage column was used, Pearson Chi Square Test (symptoms that were not significant according to age groups in Group 1 and Group 2 were not included in the table). The mean hospital stay of all patients was 6.70±8.54 (min-max:1-183) days. The duration of hospitalization of the patients according to some variables is given in Table 4. There was no significant difference in terms of hospital stay according to group 1 or group 2, gender and age groups of the patients. In addition, no significant correlation was found between the age of the patients and the length of hospital stay (p=0.083 cor. Coefficient=0.077).

Discussion

In this study, it was aimed to compare the epidemiological characteristics and frequency of patients diagnosed with stroke in Kayseri City Hospital in the pre-COVID-19 pandemic period and during the COVID-19 pandemic and investigate whether COVID-19 increases the frequency of stroke, and the results revealed that the number of patients presented with acute stroke statistically decreased after the pandemic, compared to the pre-pandemic period.

The first COVID-19 case in Turkey was reported in 11 March 2020. This rapidly spreading pandemic had a significant impact on the health system of Turkey, as in the case of the entire world. In order to prevent the spread of COVID-19, which is highly contagious and has a high rate of infection, a number of national protective measures that restrict the movement of the population, except for the needs, working and health conditions, have been taken in many countries of the world, including Turkey. During this extraordinary time, the attention of healthcare providers was primarily focused on infected patients. Restriction of free movement, quarantine and isolation measures were encouraged. In healthcare institutions, full-fledged hospitals were assigned as pandemic hospitals, to which patients with suspected COVID-19 were admitted. In addition, the admission of green-zone patients in the emergency services was terminated; and the practice flexible hours was introduced, and the number of outpatient clinics was reduced. Our hospital was assigned as a pandemic hospital, in which COVID-19 patients were primarily admitted to emergency department, the number of outpatient clinics was reduced, and neurology clinics were transformed into pandemic services.

In Chinese series in the COVID pandemic, it has been shown that in addition to systemic symptoms such as cough, fever, diarrhea, and shortness of breath, neurological symptoms such as headache, dizziness, impaired consciousness, encephalitis, encephalopathy, cerebrovascular disease, peripheral nervous system damage and neuromuscular disorders can be observed in approximately one third of the patients [11,12]. Based on available information, COVID-19 viremia does not appear to be a "direct" cause of ischemic stroke. However, as in other infection processes, it can trigger stroke through various pathophysiological mechanisms [13]. COVID-19 patients have been reported to have stroke up to a percentage of 6%, i.e., they have an increased frequency of stroke. This may immediately suggest that the frequency may have increased due to the fact that the patients are mostly elderly and have multiple comorbidities. On the other hand, once severe pneumonia and acute severe respiratory failure syndrome, induced by new type of corona virus that causes COVID-19, progress and reach a level difficult to control, the risk of stroke increases with addition of multi-organ failure and coagulopathy similar to sepsis, diffuse intravascular coagulation or cardiac involvement to the existing condition [14]. Since the patients participating in our study did not have clinical symptoms of COVID-19 and contact history, polymerase chain reaction test was not performed. In this respect, our study does not claim whether COVID-19 is a direct cause to be included in stroke etiology.

A French study conducted using the national database covering the periods of March-April-May and June found that the number of stroke patients decreased by 18% compared to the previous year [15]. Reported rates were as follows: United Kingdom (48%), China (40%), Belgium (40%), the United States (39%), Germany (35%), Italy (26%), and Spain (25%) [16-20]. In their observational study, Dula et al. found a decrease in the number of patients with acute ischemic stroke who received iv thrombolytic therapy in the emergency department after the epidemic, compared to the pre-epidemic [21]. Altunışık et al.'s study conducted in their own region found that they treated 44 patients with acute stroke during the two-month period during the pandemic period and 89 patients with acute stroke in the same period one year ago [22]. In our study, we found that there was a statistically significant decrease in the number of stroke patient admissions in the first six-month period of the pandemic compared to the previous period. In addition, all of our stroke patients who were followed up and treated in the post-pandemic period were discharged. We think that the main reason for the decrease in the number of emergency department stroke admissions during the pandemic is that patients who had mild stroke or transient ischemic attack (TIA) applied to the emergency department less frequently due to their fear of going to the hospital. During the course of our study, the diagnosis of patients with mild and transient symptoms may have been omitted, as our hospital focused on identifying and treating patients with COVID-19, and the service and intensive care beds were allocated to this patient group. Another factor that might have contributed to the lower stroke numbers might be omission of patients with silent infarcts due to the decrease in the use of cranial imaging, as a result of maximizing the use of radiodiagnostic facilities for pulmonary pathologies during the COVID-19 period.

Stroke symptoms are often noticed by another family member, friend, or anyone outside the household earlier

than they are noticed by the patient himself/herself. We think that other reasons contributing to the decrease or delay in stroke admissions include strict lockdown measures applied particularly to the elderly population during the pandemic period, and reduced contact with the elderly members of young people in the household, who have continued to go outside, for fear of infecting the elderly. Our study covering the pandemic period revealed once more the importance of increasing patient education and awareness about the warning signs and symptoms of this decreasing patient rate, as well as the importance of the fact that undiagnosed and untreated strokes did not cause more serious health problems that might develop.

During the pandemic period, Oxley et al. shared remarkable observations that there was an increase in the number of young ischemic stroke patients presenting with severe stroke findings in a healthcare center in New York. All of these young stroke patients were diagnosed with COVID-19 [23]. In our study, the mean age of the patients diagnosed during the pandemic was lower than that before the pandemic.

The limitations of our work include the fact that the study was a single-center, retrospective, observational study for a short period in the early phase of the COVID-19 pandemic and that it could not show the direct effect of ischemic stroke risk factors during the COVID-19 pandemic. Therefore, it may not be generalizable to the whole country and may not indicate major changes in the epidemiology of stroke.

Conclusion

To conclude, it is still unclear how the effects of the pandemic on human behavior and functioning in healthcare institutions will affect the diagnosis, treatment and long-term follow-up of diseases other than COVID-19. Our results showed that the number of patients admitted to the hospital with the diagnosis of ischemic stroke in the first months of the pandemic decreased, compared to the pre-pandemic period. We think that among the potential reasons for this decline are decreased number of admissions to the emergency department of patients with mild stroke symptoms due to the fear of contracting COVID-19 infection and that healthcare providers give priority to patients with COVID-19. In order to prevent undiagnosed and untreated strokes from causing more serious health problems, it should be aimed to prevent possible morbidity and mortality in terms of stroke by reviewing healthcare policies and practices. We believe that longitudinal, multicenter studies to be conducted on large patient populations are needed to elucidate the effects of the pandemic on acute stroke.

Ethics approval

Ethics approval of Kayseri City Hospital with was obtained (Decision no. 149 of 03.09.2020).

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