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Clinical Characteristics of Patients with Acute Ischemic Stroke Previously Vaccinated Against COVID-19

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Objectives: The aim of this study was to examine the clinical characteristics of patients with acute ischemic stroke which were previously vaccinated against Coronavirus Disease 2019 (COVID-19) and determine whether the vaccine had impact on outcome. *Materials and Methods:* In this observational cohort study we analyzed the clinical characteristics of 58 patients with ischemic stroke, previously vaccinated against COVID-19. We analyzed demographic characteristics, risk factors, type of stroke and outcome. We also compared outcome of those patients with outcome in stroke patients hospitalized in the same period but not vaccinated, patients hospitalized during the pandemic, before vaccination began, and stroke patients hospitalized before the pandemic. Further, we compared mortality rate with mortality rate in patients who had acute ischemic stroke and COVID-19 simultaneously. *Results:* The mean age of the patients was 71.0 years, most were male (58.6%), mostly with risk factors for stroke. In the largest number of patients, 17 (29.3%), the etiopathogenetic mechanism of stroke was atherosclerosis of the large arteries. Mortality in vaccinated patients was identical to mortality in stroke patients before pandemic, without significant difference from mortality in unvaccinated patients (13.8% versus 8.6%; p= 0.23). The mean NIHSS and mRS score at discharge for all examined groups were without significant difference. A significant difference in mortality was found between COVID-19 positive and COVID-19 negative stroke patients (37.8% versus 18.1%; p=0.001). *Conclusions:* There are no significant differences in clinical characteristics of stroke in vaccinated compared to unvaccinated patients. We did not find a connection between vaccination and stroke.

Key Words: Ischemic stroke—Covid-19—Vaccines—Clinical presentation

Introduction

Coronavirus disease 2019 (COVID-19) was primarily considered only as a respiratory tract infection, but it soon became clear that it is a systemic disease associated with coagulation disorders. The question of the impact of the prothrombotic state on the occurrence of cerebrovascular diseases has been raised. According to reports from China and north-eastern United States, cases of ischemic stroke have been reported in young patients with severe forms of COVID-19, otherwise healthy people.[1-5]

An increase in mortality worldwide after a COVID-19 pandemic was declared clearly emphasizes the need for an urgent solution. Active immunization is the only way to prevent further spread of the virus and control the disease which negatively affects the quality of life for two years worldwide.[6,7] The process of vaccine development and duration of the obligatory phases are maximally

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accelerated. This fact has initiated numerous scientific and social debates, especially after the occurrence of thrombotic events, including stroke, which may be related with the use of some vaccines.[8-11] In order to detect vaccine side effects as quickly as possible, regulatory agencies around the world have prepared safety strategies.[8-11]

The following vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been approved in Serbia: Pfizer-BioNTech COVID-19 Vaccine (Comirnaty); Gam-KOVID-Vak; SARS-CoV-2 Vaccine (Vero Cell), Inactivated; ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) COVISHIELD/AstraZeneca SKBio AZD1222-COVID-19 Vaccine (ChAdOx1-S (recombinant))/COVID-19 Vaccine AstraZeneca.[12]

Since the available literature has not yet reviewed the clinical characteristics of stroke in patients vaccinated against SARS-CoV-2, the aim of this study was to examine those characteristics. In addition, the aim was to determine whether the vaccine against SARS-CoV-2 can be considered as one of the significant triggers for the development of ischemic stroke, and whether it affects poor stroke outcome.

Materials and methods

In this observational cohort study, we retrospectively analyzed the clinical characteristics of patients with ischemic stroke, previously vaccinated against SARS-CoV-2, which were hospitalized from 1 January to 30 June 2021 in the Clinical Center of Vojvodina, Clinic of Neurology. Patients with acute ischemic stroke were consecutively included if they had data on previous vaccination against severe acute respiratory syndrome coronavirus 2, a total of 58 of them.

Data on demographic characteristics of patients, risk factors for stroke, conducted vaccination/ revaccination against SARS-CoV-2 (type of vaccine, time from the conducted vaccine / revaccination to the appearance of neurological symptoms) were collected.

Clinical severity of stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS). The functional status at discharge was quantified using a modified Rankin Scale (mRS). The type of brain infarction was determined according to the Oxfordshire Community Stroke Project (OCSP) classification.[13]

The etiopathogenetic mechanism of ischemic stroke was determined on the basis of neuroimaging (computed tomography of the brain and / or magnetic resonance imaging of the brain) and additional diagnostics (duplex scanner of cervical arteries, transcranial doppler of vertebro-basilar basin, 24-hour Holter electrocardiogram, transcranial echocardiography, duplex of lower extremity veins, Transcranial Doppler (TCD) Bubble test). A division was made on the basis of etiopathogenetic mechanisms of stroke: cardioembolism, atherosclerotic disease of large arteries, small blood vessels occlusion and unknown cause. Initial X-ray of the lungs, laboratory findings, and the occurrence of somatic complications were also noted.

In the second part of the study, an analysis of the total number of examined and hospitalized patients with ischemic stroke was performed, as well as of their hospital mortality in three six-month periods: before the pandemic (from 1 July to 31 December, 2019); during the pandemic, and before the vaccination period (from 1 July to 31 December, 2020) and during the pandemic, when vaccination began (from 1 January to 30 June, 2021). The number of patients with ischemic stroke who were COVID-19 positive and their mortality in the period from 1 July, 2020 to 30 June, 2021 was also examined.

The outcome of stroke patients in three previous mentioned six-month periods, was also expressed though neurological (NIHSS score at discharge) and functional (mRS score at discharge) status and it was compared with outcome of previously vaccinated stroke patients.

The research was conducted in accordance with the principles of the Declaration of Helsinki on Human Clinical Research and was approved by the Ethics Committee of the Clinical Center of Vojvodina.

The data were coded and entered into a specially created database, and further analyzed using the statistical software Statistical Package for the Social Sciences, version 21.0. Statistical data analysis included methods of descriptive statistics. The arithmetic mean and standard deviation (SD) were used to describe the distributions of measurement variables. Pearson's chi-square (χ^2) test, t-test, and Fisher's exactness test were used to determine the difference in the arithmetic means between the groups. Test values with probability $p<0.05$ were considered statistically significant.

Results

Out of a total of 58 patients with ischemic stroke previously vaccinated, 34 (58.6%) were male, 24 (41.4%) were female, mean age was 71.0 years. The demographic characteristics of patients and the presence of risk factors for stroke are shown in Table 1.

A total of 45 (77.6%) patients had been previously vaccinated with both doses. The vast majority of patients, 48 of them (82.7%), received Sinopharm vaccine, while only 2 of them received AstraZeneca. The first neurological symptoms occurred in most patients within two months after revaccination. Vaccination status and time of onset of first neurological symptoms are shown in Table 2.

In the largest number of patients, 17 of them (29.3%), the etiopathogenetic mechanism of ischemic stroke was atherosclerosis of the large arteries. The second most frequent etiopathogenetic mechanism was small blood vessel occlusion, recorded in 14 (24.1%) patients. The prevalence of individual causes of stroke and division according to the OCPS classification is shown in Table 3.

Table 1. *Demographic characteristics and risk factors for stroke*

		No./Total No.(%)
Demographic characteristics		
Gender	female	24/58 (41)
	male	34/58 (59)
Average age (X), (SD)	71.03, (9.31)	
Risk factors and medical history		
Hypertension	yes	53/58 (91)
	no	5/58 (9)
Atrial fibrillation	yes	16/58 (28)
	no	42/58 (72)
Other cardiovascular diseases	yes	17/58 (29)
	no	41/58 (71)
Diabetes mellitus	yes	21/58 (36)
	no	37/58 (64)
Hyperlipoproteinemia	yes	21/58 (36)
	no	37/58 (64)
Previous stroke	yes	15/58 (26)
	no	43/58 (74)
Smoking	yes	18/58 (31)
	no	27/58 (47)
	unknown	13/58 (22)
Excessive alcohol use	yes	5/58 (9)
	no	38/58 (65)
	unknown	15/58 (26)

The clinical severity of stroke was estimated by the NIHSS scale on admission and discharge. The median NIHSS score on admission was 8.5, and 5.5 at discharge.

According to the mRS score, a total of 10 (17.2%) patients were asymptomatic or without significant disability at discharge. The functional status at discharge is shown in Table 4.

The platelets count in all patients was normal. In 40 (69.0%) patients the initial X-ray of the lungs was normal, in 9 (15.5%) pneumonia was described, and 9 (15.5%) of them had some other pathology described. In the total sample, 25 (43.1%) patients had somatic complications, and the most common was urinary tract infection, 15 (25.9%) patients. The second most frequent complication was pneumonia, 9 patients (15.5%), while 10 patients (17.2%) had some other complications. None of the patients had thrombophlebitis, pulmonary thromboembolism or pressure ulcers.

The vast majority of patients (82.7%) were previously vaccinated with Sinopharm vaccine, 7 of them died, while in the group of patients that were previously vaccinated with other types of vaccine, there was one fatal outcome. This difference was not significant (14.6% vs 11.1, p=0.70).

The trends in the number of examined, hospitalized and deceased stroke patients in different follow-up periods are shown in Table 5. Comparing the three six-month periods, it was found that during the period before COVID-19 pandemic the most patients were examined (838) and the highest number of them was admitted to the hospital, 435 (51.9%). On the other hand, fewer patients were examined during the pandemic (604 in the second half of 2020 and 633 in the first half of 2021) and a significantly lower percentage was retained in hospital (46.2% in the second half of 2020 and 42.2% in the first half of 2021; p=0.001).

Table 2. *Vaccination status and the time when neurological symptoms began*

		No./Total No.(%)
Vaccination status	Vaccinated with the first dose	13/58 (22)
	Vaccinated with both doses	45/58 (78)
Type of vaccine	Sinopharm	48/58 (83)
	Pfizer	3/58 (5)
	Sputnik V	4/58 (7)
	AstraZeneca	2/58 (3)
	Unknown	1/58 (2)
The first neurological symptoms in patients who received both doses of vaccine	Within 7 days after the second dose	5/58 (9)
	8-14 days after the second dose	2/58 (3)
	15-21 days after the second dose	2/58 (3)
	22-30 days after the second dose	7/58 (12)
	31-60 days after the second dose	20/58 (34)
	61-90 days after the second dose	5/58 (9)
	Unknown	4/58 (7)
The first neurological symptoms in those vaccinated with the first dose	Within 7 days of vaccination	2/58 (3)
	8-14 days after vaccination	5/58 (9)
	15-21 days after vaccination	4/58 (7)
	22-30 days after vaccination	1/58 (2)
	31-60 days after vaccination	1/58 (2)

Table 3. *Etiopathogenetic mechanisms of stroke and OCSP classification*

		No./Total No.(%)
Stroke etiology	Cardioembolism	13/58 (23)
	Large artery atherosclerosis	17/58 (29)
	Small blood vessel occlusion	14/58 (24)
	Unknown	14/58 (24)
OCSP classification	Total anterior circulation infarct (TACI)	5/58 (9)
	Partial anterior circulation infarct (PACI)	27/58 (46)
	Lacunar infarct (LACI)	12/58 (21)
	Posterior circulation infarct (POCI)	14/58 (24)

The outcome of stroke patients is shown through neurological and functional status at discharge and through mortality. The average NIHSS score at discharge in the second half of 2019 was 5.2, which was not significantly different from the average NIHSS score at discharge for previously vaccinated stroke patients (5.2 vs 5.5, p=0.05). The similar results were obtained with average NIHSS score in second half of 2020 (6.4 vs 5.5, p=0.34) and the first half of 2021 (7.0 vs 5.5, p=0.48). The mean value of mRS score at discharge in the second half of 2019 was 3.1, which was not significantly different from the average mRS score at discharge for previously vaccinated stroke patients (3.1 vs 3.2, p=0.32). Significant difference was not observed for average mRS score in the second half of 2020 (2.9 vs 3.2, p=0.13) and the first half of 2021 (3.4 vs 3.2, p=0.32), as well.

Mortality rate in the second half of 2019 was 13.8%, and in the period during the pandemic (July 1, 2020 to June 30, 2021) was 18.1%, which was not significantly different (p=0.07). Mortality in previously vaccinated patients with ischemic stroke was 13.8%, which was identical to the mortality in the period before the pandemic, and was not significantly different from the mortality of unvaccinated stroke patients who were treated in the same period at the Clinic of Neurology (13.8 vs 8.6%; p=0.23).

We registered in total 45 stroke patients who were COVID-19 positive in the analyzed period of the pandemic. Mortality in this group of patients was 37.8%, which was significantly higher compared to the mortality of COVID-19 negative patients with ischemic stroke treated in the same period (37.8% vs 18.1%; p=0.001). Among them, five patients died from pneumonia, one from pulmonary thromboembolism and two patients died from acute respiratory distress syndrome. The remaining nine patients died from the stroke itself (two patients had a cardioembolic stroke, seven patients had a stroke of undetermined cause).

Table 4. *The functional status at discharge*

mRS	No./Total No.(%)
0	4/58 (7)
I	6/58 (10)
II	12/58 (21)
III	12/58 (21)
IV	10/58 (17)
V	6/58 (10)
VI	8/58 (14)

Discussion

Numerous studies were aimed to investigate the relation between stroke and COVID-19 disease. In general, according to the results of meta-analyses, stroke is marked as a very serious, life-threatening complication of COVID-19 disease. Further, an increase in the incidence of cryptogenic stroke has been observed in young patients and patients without significant risk factors for stroke.[14,15] Hypercoagulability, dehydration, inflammation and patient immobility have been described as possible risk factors for stroke in patients infected with SARS CoV-2.[14]

On the other hand, complications and side effects of vaccines against this disease have been the subject of numerous studies, where great importance was attached to rare but severe thrombotic events, even to ischemic stroke itself, without completely explained mechanisms so far.[10] Actually, cases of thrombocytopenia with thrombotic events (reported cases of ischemic stroke and cerebral venous thrombosis (CVST)) have been reported in the literature after receiving AstraZeneca vaccine, which has been investigated, but there is still no evidence that this vaccine increased the risk of thrombotic events in general population.[8-10,16]

A recently published study monitoring serious vaccine adverse events found that 6.2 million people who received 11.8 million doses of mRNA vaccine had no significant association between vaccination and serious health outcomes, including ischemic stroke, with a note that further monitoring is required.[6] The studies mainly investigate serious thrombotic events due to vaccine-induced thrombotic thrombocytopenia (VITT), and consequent cerebrovascular events, emphasizing CVST. According to the results of one systematic review, the largest number of CVST occurred one week after the first dose of the vaccine, and mostly from the fourth to the nineteenth day after the first dose of the vaccine.[16] Almost half of our patients had a stroke within two months or more after

Table 5. *Examined, hospitalized patients and their mortality in the three examined periods of time*

	First period (July 1 to December 31, 2019)	Second period (July 1 to December 31, 2020)	Third period (January 1 to June 30, 2021)	p
Patients with ischemic stroke COVID-19 negative				
Examined (No.)	838	604	633	
Hospitalized No./Total No. (%)	435/838 (51.9)	279/604 (46.2)	267/633 (42.2)	**0.001**
Fatal outcome No./ Hospitalized No. (%)	60/435 (13.8)	73/279 (26.2)	26/267 (9.7)	**<0.0001**
Patients with ischemic stroke COVID-19 positive				
Hospitalized No.	-	29	16	
Fatal outcome No./Hospitalized No. (%)	-	14/29 (48)	3/16 (19)	**0.001**
Unvaccinated patients with ischemic stroke				
Hospitalized No.	-	-	209	
Fatal outcome No./Hospitalized No. (%)	-	-	18/209 (8.6)	
Vaccinated patients with ischemic stroke				
Vaccinated No.	-	-	58	
Fatal outcome No./Vaccinated No. (%)	-	-	8/58 (14)	0.23

revaccination. This period is longer compared to the results of the mentioned study, which reduces the probability of the connection between stroke and vaccination in our sample.

Since the available literature has not yet reviewed the clinical characteristics of stroke in individuals vaccinated against SARS CoV-2, those characteristics were analyzed in this study.

Considering the demographic characteristics and risk factors for stroke in this group of patients, we found that those were elderly patients (mean age 71.0 years), mostly male (58.6%), and almost all of them had some conventional risk factor for stroke.

The vast majority of patients (91.4%) had arterial hypertension, 33,3% patients had diabetes mellitus, 25% patients had atrial fibrillation. Hypercholesterolemia was detected in more than a third of patients, as was the case with smoking.

According to the results of previous studies on stroke, the majority of patients are male (56%-59%), noting that the risk of stroke increases significantly in women after age of 75, especially if they have atrial fibrillation. Also, according to their results, the predominant risk factor is arterial hypertension (65% and more), but diabetes mellitus (about 15-30%) and atrial fibrillation (15-25%) are also very important.[17-19] Comparing demographic data (age and gender), as well as data on risk factors for stroke in our study with the epidemiological studies conducted both in world and in our country, we did not find significant differences.[18-22] Thus, in our study published in 2017, the majority of patients were female in the group of patients with atrial fibrillation (43.2% vs. 28.9%), while in the group without atrial fibrillation, male patients were more dominant (71.1%).[20] In that study, the most common risk factors were hypertension, diabetes mellitus, and atrial fibrillation.[20] The same is in our group of stroke patients who had previously received vaccines against COVID-19.

As for stroke characteristics, according to the OCSP classification, most patients were patients with partial anterior circulation infarction (PACI), (46.5%), which is in accordance with the results of studies conducted both in our country and in the world.[20,21] Thus, a similar prevalence of PACI infarction of 44.5% was observed in the group of patients without atrial fibrillation in the above-mentioned study conducted in our country,[20] and even higher prevalence (48.6%) was found in one Chinese study.[21]

Using the TOAST (trial of ORG 10172 in acute stroke treatment) classification, in our study stroke was predominantly caused by atherosclerotic disease of the large arteries of the head and neck (29.3%), followed by other causes: small-vessel occlusion (24%) and cardioembolism (23%), while in 24.1% of patients the etiology remained undetermined.

Numerous studies have shown similar results, thus the results of a large study in 2014 also showed that the most common cause of ischemic stroke was atherosclerotic disease of the large arteries of the head and neck (37.3%), followed by small blood vessel disease (22.9%) and cardioembolism (20.6%), while the cause was undetermined in about 17% of patients.[23] In the mentioned research, the results were compared with the data from large registers, which were also without significant differences (Lausanne registry: large artery-atherosclerosis 43.2%, small vessel occlusion 13.2%, cardioembolism 20.4%; Besancon registry: large artery-atherosclerosis 30.5%, small vessel occlusion 10%, cardioembolism 31%;).[18,23,24]

Also, we would highlight the fact that the frequency of cryptogenic stroke in our study (24.1%) was not

significantly different from the results of large epidemiological studies (Besancon registry 26.1%, Lausanne registry 12.6%).[18,23,24]

The mean NIHSS value on admission in our sample was 8.5, and 5.5 at discharge. Comparing the mean values of both NIHSS and mRS score at discharge in previously vaccinated stroke patients with results for stroke patients hospitalized in three six-month periods previously mentioned, showed no significant difference. Thus, we can conclude that there is no significant difference in neurological and functional status at discharge in stroke patients previously vaccinated against COVID-19 infection. COVID-19 positive patients with acute stroke mostly had a more severe stroke than COVID-19 negative patients, according to a recent study, where they had a higher admission NIHSS score (median NIHSS score: 19 vs 8, P=0.007).[5]

Considering that somatic complications could have a significant impact on stroke outcome, we analyzed their frequency in vaccinated stroke patients. Somatic complications occurred in 43.1% of vaccinated patients with stroke, where infections were most frequent (urinary tract infection 25.9%, pneumonia 15.5%), while no case of pulmonary thromboembolism was reported. Compared with the results of our recent study in 2018, we can see that there are no significant differences. At that time, the prevalence of somatic complications was 40.2%, with also the highest percentage of infections (urinary tract infections 20.3%, pneumonia 16.3%), while pulmonary thromboembolism was diagnosed in 3.46% of patients.[25]

The results of our study showed that the incidence of stroke did not increase from the period when vaccination against SARS-CoV-2 virus began. Also, no significant increase in the incidence of stroke has been recorded in our institution since the pandemic began.

The number of examined and hospitalized patients with ischemic stroke in the Clinical Centre of Vojvodina was lower in the follow-up period during the pandemic compared to the period before the pandemic. Worldwide, in accordance with our observations, a decrease in the number of hospitalized stroke patients was observed. The possible explanations could be the fear of infection and the consequent possibility that patients with stroke are hesitant to present for medical treatment, as well as the fact that numerous stroke patients with a mild clinical picture were treated on an outpatient basis due to reorganization and overloaded health systems with COVID-19 positive patients.[2,26-29]

However, in the group of vaccinated stroke patients, the mortality rate did not differ significantly from the mortality observed in unvaccinated patients (13.8 vs. 8.6, p=0.23). Mortality in patients with ischemic stroke which were hospitalized in the first period of the pandemic was higher than in those who were hospitalized before the pandemic, which can be explained by the fact that only clinically severe forms of stroke were hospitalized due to the reorganization of the health system.

Similar results were published in other centers.[2,15] However, important to point out is the fact that the mortality in COVID-19 positive patients with ischemic stroke was very high, even ranging up to 48%. This data does not differ significantly from the data in the literature, where in some studies the mortality rate in such patients is around 38%.[15] All of these data highlight the fact that patients are much more at risk for a poor stroke outcome if they also have SARS-CoV-2 virus infection than if they do not have it, or have previously been vaccinated against it. On the other hand, previous vaccination against SARS-CoV-2 virus did not lead to a worse stroke outcome compared to unvaccinated patients with ischemic stroke.

The main limitation of our study is the relatively small number of patients. Also, considering the redistribution of health capacities due to pandemic, we can assume that a number of patients with mild neurological symptoms were treated on an outpatient basis, so they could not be included in this research. Further, it is possible that a number of COVID-19 patients, especially those treated in intensive care units, had a stroke that was not recognized due to severe general condition of the patient, and those patients could not be included in the analysis, too.

Conclusions

The clinical characteristics of stroke in patients vaccinated against SARS CoV-2 virus do not differ significantly from the clinical characteristics of other stroke patients. Vast majority of patients had conventional risk factors. Neurological and functional status at discharge and mortality in this group of patients did not differ significantly compared to other stroke patients. On the other hand, mortality after stroke in COVID-19 positive patients was extremely high, which is why it is necessary to continue to insist on the importance of vaccination against this severe systemic infection. Based on our results, we cannot conclude that there is a connection between vaccination against SARS-CoV-2 virus and the occurrence of ischemic stroke, nor that previous vaccination affects a worse stroke outcome. Further monitoring and detailed analysis of all adverse events after vaccination against SARS-CoV-2 virus is certainly needed.

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