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Effect of COVID 19 pandemic on the neurology department hospitalization with analysis of the neurological complications secondary to COVID 19 and vaccination against COVID 19

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Abstract

Objective: We investigated the effect of the pandemic on neurological hospitalizations and complications associated with severe acute respiratory syndrome coronavirus 2 infection or vaccinations.

Methods: We retrospectively analyzed data of patients hospitalized in our neurology division from 1 April 2019 to 31 March 2022 as the opt-out study. We classified the neurological diseases into nine subgroups, evaluated changes of neurological disease characteristics, and analyzed patients hospitalized with the complications from severe acute respiratory syndrome coronavirus 2 infection or after the coronavirus disease 2019 vaccination over three eras based on the pandemic stages: (1) pre-pandemic, (2) during the pandemic but before vaccines, and (3) during the pandemic with vaccines.

Results: Overall, 1756 patients were included in the analyses. The patient characteristics significantly changed throughout the pandemic ($p < 0.01$). Although the number of autoimmune cases did not change throughout the pandemic ($p = 0.53$), that of psychological cases and that of unknown cases were significantly changed ($p < 0.05$, $p < 0.01$). There were four infectious cases and 11 cases following vaccination from 1 April 2020 to 31 March 2022. The 11 postvaccination cases involved 10 kinds of neurological diseases.

Conclusions: The neurological characteristics significantly changed throughout the pandemic and there were diverse neurological complications following vaccinations.

Keywords

Autoimmunity, COVID-19, COVID-19 vaccines, neurologic manifestations, stroke

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Introduction

The coronavirus disease 2019 (COVID-19) outbreak was first reported in Wuhan, China, in December 2019 and soon spread throughout mainland China and overseas.[1] COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, became a worldwide health threat and was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. The COVID-19 pandemic profoundly affected society, for example, by encouraging and popularizing social distancing and mask-wearing.[2,3]

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SARS-CoV-2 infection can induce an uncontrolled inflammatory response and cytokine storm,[4] and some neurological complications have been reported following SARS-CoV-2 infection.[5,6] Although the comprehensive pathology of the COVID-19 was unclear at the initial phase, multiple and complex pathology was generally revealed.[7,8] Accumulating the knowledge of neurological complications of COVID-19 concerned with multiple pathology were revealed.[9–11] Suppressing the COVID-19 pandemic, a novel, lipid-nanoparticle-encapsulated messenger ribonucleic acid (mRNA) vaccine expressing the prefusion-stabilized spike glycoprotein was developed independently by Pfizer BioNTech and Moderna.[12,13] Both mRNA vaccines showed high effectiveness and safety in clinical trials involving large populations; thus, they were distributed among the general population. However, some cases of neurological complications were sporadically reported after receiving the COVID-19 vaccine[14,15] and the relationship between COVID-19 vaccine and neurological complications are recently focusing.[16]

The COVID-19 pandemic has had multifaceted effects on the neurological field. Furthermore, societal changes and COVID-19-specific guidelines have changed the approach to healthcare for patients with SARS-CoV-2 infection. Therefore, it is possible that the COVID-19 pandemic also affected neurological disease characteristics, but this remains unclear.

This ecological study investigated whether the characteristics of neurological diseases in hospitalized patients changed throughout the COVID-19 pandemic at our institution. In addition, most previous reports on COVID-19 vaccine complications are case reports,[17–19] and a direct relationship between neurological complications and the COVID-19 vaccine has rarely been demonstrated.[20,21] Thus, we performed the comprehensive analysis in order to validate whether the COVID-19 pandemic changed the character of the neurological disease hospitalization and to clear the neurological complications following the SARS-CoV-2 infections and the COVID-19 vaccination.

Methods

Participants

We retrospectively analyzed all consecutive patients admitted to our Division of Neurology, Department of Medicine, Jichi Medical University in Japan from 1 April 2019 to 31 March 2022. The Ethical Committee of Jichi Medical University approved the study, and we obtained exempted approval from the institutional review board based on our study protocol (approval #Rin-Fu 22-176). This study was performed as the opt-out study, and we announced the study in our website. Informed consent was not sought for this study because waiver of consent was approved by the institutional review board because of the opt-out approach. The inclusion criteria for this study were hospitalized cases in our division. Refusal to participate cases were excluded from this study.

All data in this work are submitted as supplemental material and can be made available based on reasonable request to the corresponding author.

COVID-19 pandemic timeline

To validate the changes in the characteristics of neurological disease hospitalizations, we classified the patients based on the COVID-19 pandemic stages in Japan. The first COVID-19 outbreak wave in Japan occurred in April 2020; before that, there were almost no patients with COVID-19. Furthermore, the vaccination rate radically increased after April 2021 as shown in Figure 1(a),[22] meaning that for almost 1 year (April 2020–2021), COVID-19 was present, but vaccines were not. Therefore, the patients were classified based on three pandemic eras in Japan: (1) COVID-19 (−) (i.e., the 2019 season), (2) COVID-19 (+) Vaccine (−) (i.e., the 2020 season), and COVID-19 (+) Vaccine (+) (i.e., the 2021 season) (Figure 1(b)).

Neurological disease hospitalization characteristics

We classified the neurological diseases into nine subgroups based on and modified from the original neuropathological subtypes[23,24]: vascular, autoimmune, infectious, functional, neurodegenerative, neoplastic, psychological, others, and unknown. We defined the functional category as epilepsy, muscle clamp, idiopathic normal-pressure hydrocephalus, cerebrospinal fluid hypovolemia, dystonia, myoclonus, facial nerve palsy, headache, sleep apnea syndrome, transient global amnesia, and sudden deafness. We defined the psychological category as somatic symptom disorder, schizophrenia, mood disorder, and personality disorder (But there was no hospitalization of schizophrenia, mood disorder, or personality disorder in our division through study period). We defined that unknown category that we were not able to reach any specific diagnosis. Other specific disease classifications are described in the Supplementary Manuscript.

Cases associated with SARS-CoV-2 infection or COVID-19 vaccination

To explore the link between the SARS-CoV-2 infection or COVID-19 vaccination and neurological disease requiring hospitalization, we analyzed patients hospitalized with suspected complications from SARS-CoV-2 infection or after COVID-19 vaccination through the 2019–2021 seasons. As a reference, we included patients hospitalized with suspected complications from the influenza virus infection or vaccine in the same period. Since proving a causal relationship between neurological disease and SARS-CoV-2 infection or COVID-19 vaccination is challenging, causality was determined based

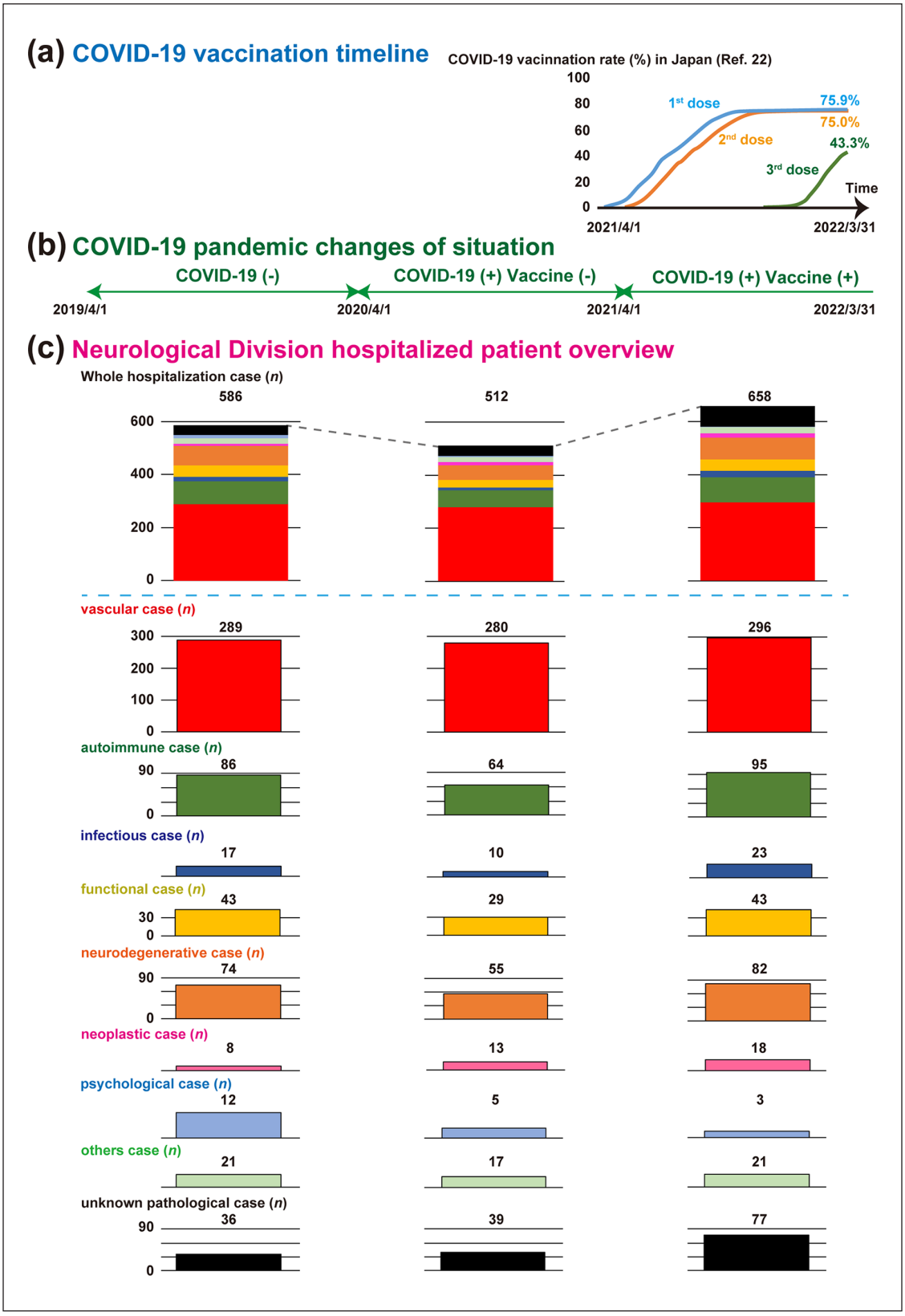

Figure 1. (a) The coronavirus disease 2019 (COVID-19) vaccination timelines in Japan based on data from the Statista based on data published.[22] (b) For this study, the pandemic eras in Japan are classified as pre-pandemic (COVID-19 (−)), with COVID-19 but without vaccines (COVID-19 (+) Vaccine (−)), and with both COVID-19 and vaccines (COVID-19 (+) Vaccine (+)). (c) The characteristics of neurological diseases in hospitalized patients significantly differ among the pandemic eras (**$p < 0.01$).

Table 1. Hospitalized patients with suspected associations with SARS-CoV-2 infection during the 2018–2021† seasons.

No.	Age (y)	Sex	Vaccine type	No. of vaccines	Admission date	Admission disease	COVID-19 information
#1	74	M	mRNA	3	2022.3.1	MG	Positive test after admission
#2	49	M	mRNA	2	2022.3.2	Stroke	Nosocomial infection‡
#3	51	M	mRNA	2	2022.3.2	Stroke	Nosocomial infection‡
#4	47	M	mRNA	2	2022.3.29	MD	Sequelae after domestic COVID-19 infection

COVID-19: coronavirus disease 2019; MD: myotonic dystrophy; MG: myasthenia gravis; mRNA: messenger ribonucleic acid; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
†SARS-CoV-2 infection (thus COVID-19) occurred during the 2020 and 2021 seasons.
‡Patients were in the same hospital room.

on the clinical diagnosis from multiple neurological experts, and the diagnosis must have been made within 60 days after real-time polymerase chain reaction or COVID-19 vaccination. The causality relationship was defined as (1) there is a possibility of the SARS-CoV-2 infection or COVID-19 vaccination introducing the disease, and (2) there are no obvious risk factors other than the SARS-CoV-2 infection or COVID-19 vaccination to the disease. We set the 60 days by considering the vaccination has the characteristic of boosting and by referring the previous report.[21] We examined with the real-time polymerase chain reaction method for all SARS-CoV-2 infection diagnosis.[25] We also measured the SARS-CoV-2 spike (S) and nucleocapsid (N) antibodies, which increase after COVID-19 vaccination and SARS-CoV-2 infection, respectively (Supplemental Manuscript).

Statistical analyses

All statistical analyses were performed using JMP 16 statistical software (SAS Institute Inc., Cary, NC, USA). Categorical data were analyzed by the Chi-squared test or the Cochran–Armitage trend test. p-values of <0.05 were considered statistically significant.

Results

Characteristics of neurological disease hospitalizations

We included 1756 patients in this study. Figure 1(c) presents the characteristics of neurological disease hospitalizations; 586 hospitalizations occurred during the COVID-19 (−) era, 512 occurred during the COVID-19 (+) Vaccine (−) era, and 658 occurred in the COVID-19 (+) Vaccine (+) era. The neurological subtypes significantly differed among the eras (Chi-squared test; $p < 0.01$).

Cases associated with SARS-CoV-2 infection

Four patients were hospitalized with suspected associations with SARS-CoV-2 infection (Table 1); all were admitted after March 2022. Two of the four cases (patients 2 and 3) were nosocomial infections, and three (patients 1–3) were discharged without sequelae. However, one case (patient 4) required total assistance (modified Rankin Scale score of 5). All patients had received at least two doses of the mRNA COVID-19 vaccine more than 60 days before admission. Contrary to SARS-CoV-2 infection, there was no case concerned with the influenza virus infection through the study period.

Cases associated with COVID-19 vaccination

Eleven patients were hospitalized with suspected associations with the COVID-19 vaccine (Table 2), and one patient was hospitalized with a suspected link to the influenza virus vaccine during the same period (Table 3). We note the COVID-19 vaccine period spanned only the 2021 season, shorter than that for the influenza virus vaccine through 2019–2021 seasons. The Supplementary Manuscript describes the detailed case information of the 11 patients in Table 2. Briefly, the average age was 58.9 ± 5.2 years, and 10 kinds of neurological diseases were reported after the COVID-19 vaccination. Ten patients received the mRNA vaccine, and one received the adeno-associated virus vaccine. The average number of days from vaccine administration to onset was 17.9 ± 6.2 days. The patients' SARS-COV-2 S antibody titer range was widely distributed, from 17.3 (minimum) to 10,600 (maximum) U/mL; SARS-COV-2 N antibody titers were negative (<0.1 U/mL) in all patients.

Many hospitalized patients with a suspected COVID-19 vaccine association had autoimmune neurological symptoms; thus, we focused on this subgroup. In addition, the numbers of psychological and unknown pathological cases considerably changed throughout the pandemic (Figure 1(c)). Thus, we validated the statistical differences for these three subgroups in a post hoc analysis. The number of autoimmune cases did not differ throughout the pandemic period ($p = 0.53$, Figure 2(a)), but the numbers of psychological and unknown pathological cases did ($p < 0.05$ (Figure 2b) and $p < 0.01$ (Figure 2c), respectively). Additionally, we used the Cochran–Armitage trend test to evaluate trends in

Table 2. Hospitalized patients with suspected associations with the COVID-19 vaccine during the 2019–2021† seasons.

No.	Age(y)	Sex	Vaccine information							SARS-COV-2 antibody(U/mL)		Disease
			Type	Manufacturer	Number	Vaccination date						
						1	2	3	‡	S§ (<0.80)	N¶ (<1.0)	
#1	72	F	mRNA	Pfizer	2	2021.6.25	2021.7.16	—	10	919	<0.1	ADEM
#2	84	F	mRNA	Pfizer	1	2021.6.19	—	—	44	17.3	<0.1	GBS
#3	73	M	mRNA	Pfizer	2	2021.6.24	2021.7.15	—	4	1,110	<0.1	Epilepsy
#4	46	F	mRNA	Moderna	1	2021.8.3	—	—	7	828	<0.1	SMS
#5	58	F	mRNA	Pfizer	2	2021.10.5	2021.10.26		2	90.8	<0.1	ADEM
#6	43	F	mRNA	Pfizer	1	2021.9.26	—	—	6	24.7	<0.1	PMR
#7	54	M	AAV	AstraZeneca	2	2021.8.1	2021.10.25	—	16	U	U	Stroke
#8	40	M	mRNA	Pfizer	2	2021.8.31	2021.9.21	—	48	324	<0.1	NSD
#9	75	F	mRNA	Moderna	3	2021.6.24	2021.7.15	2022.2.18	2	6,890	<0.1	SD
#10	32	F	mRNA	Pfizer	2	2021.9.17	2021.10.8	—	55	1,390	<0.1	NMOSD
#11	71	M	mRNA	Moderna	3	2021.6.24	2021.7.15	2022.2.26	3	10,600	<0.1	GFAP-A

AAV: adeno-associated virus; ADEM: acute disseminated encephalomyelitis; COVID-19: coronavirus disease 2019; GBS: Guillain–Barré syndrome; GFAP-A: Glial fibrillary acidic protein astrocytopathy; mRNA: messenger ribonucleic acid; N: immunoglobulin antibody to SARS-COV-2 nucleocapsid protein; NMOSD: neuromyelitis optica spectrum disorders; NSD: neuro-sweet disease; S: immunoglobulin antibody to the SARS-COV-2 spike protein; SARS-COV-2: severe acute respiratory syndrome coronavirus 2; SD: sudden deafness; SMS: stiff man syndrome; PMR: polymyalgia rheumatica; U: unknown.
†Vaccinations began in the 2021 season.
‡Time from vaccination to hospitalization.
§Increases after COVID-19 vaccination.
¶Increases after SARS-COV-2 infection.

Table 3. Hospitalized patient with a suspected association with the influenza virus vaccine during the 2019–2021 seasons.

No.	Age (y)	Sex	Vaccine type	No. vaccines	Vaccine date	Onset† (days)	Disease
#1	81	F	Inactivated	1	2021.10.28	10	GBS

GBS: Guillain–Barré syndrome.
†Time from vaccination to hospitalization.

the psychological and unknown pathological cases, finding significant results for both ($p < 0.01$ (Figure 2(b)) and $p < 0.001$ (Figure 2(c)), respectively). Specifically, the number of psychological cases significantly decreased, and the number of unknown pathological cases significantly increased throughout the pandemic period.

Discussion

Our study, conducted in a Japanese neurology division, demonstrated that the characteristics of hospitalized patients significantly changed throughout the COVID-19 pandemic. Furthermore, only 4 and 11 cases had suspected associations with SARS-CoV-2 infection and the COVID-19 vaccine, respectively, during the 2019–2021 seasons; this was compared to one case with a suspected association with the influenza virus vaccine during the same period. Moreover, although most patients hospitalized potentially due to the COVID-19 vaccine had autoimmune neurological symptoms, the number of autoimmune cases did not change throughout the pandemic, suggesting that the COVID-19 vaccine did not influence hospitalization. In contrast, the numbers of psychological and unknown pathological cases significantly changed throughout the pandemic.

Although recent reports have detailed the disease-specific effects of COVID-19, how COVID-19 affects neurology-related hospitalizations, including those associated with the COVID-19 vaccine, remains unclear. For instance, 55% of delayed and 63% of discontinued cancer treatments were due to the COVID-19 pandemic, emphasizing the pandemic's large-scale impact on cancer treatment.[26] Some studies have also focused on neurological manifestations during the pandemic,[27] such as encephalitis, GBS, and stroke, which have recently been associated with SARS-CoV-2 infection and COVID-19 vaccination.[27–30] However, most of these reports are case reports, and how the COVID-19 pandemic affects neurology departments within hospitals remains unclear. The most neurological symptoms reported in association with COVID-19 are nonspecific and several other pathologies than direct access to the nervous system are speculated.[31] Although we found that the pandemic influenced neurological hospitalizations, the influences of SARS-CoV-2 infection

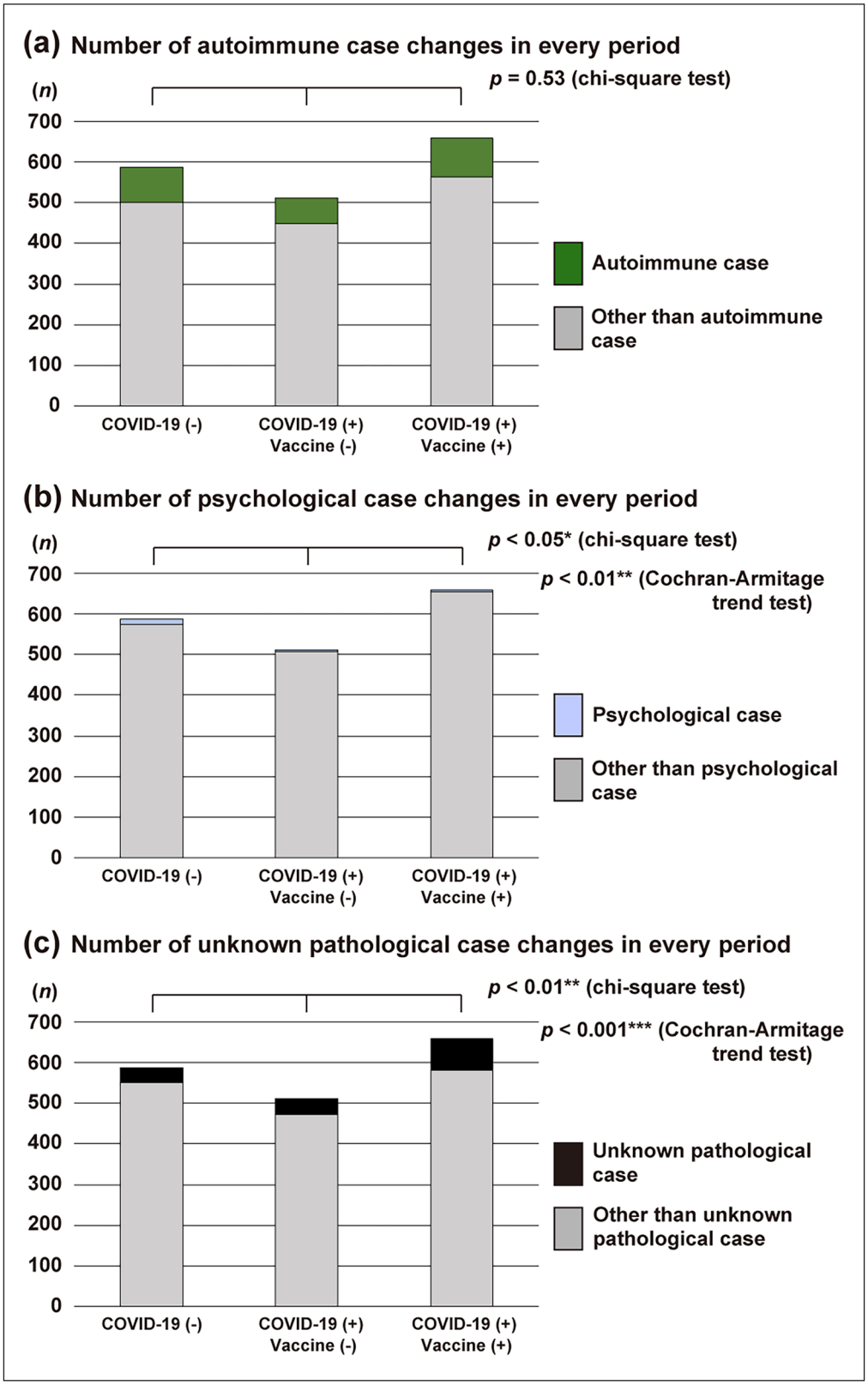

Figure 2. Statistical analyses based on the numbers of (a) autoimmune, (b) psychological, and (c) unknown pathological neurological cases throughout the pandemic. The numbers of psychological and unknown pathological cases significantly differ among the pandemic eras ($p < 0.01$), but the number of autoimmune cases does not.

and COVID-19 vaccination were limited. For instance, during the 2021 season, only four patients were hospitalized with a suspected link to SARS-CoV-2 infection. Moreover, 11 patients were hospitalized with a potential association with the COVID-19 vaccine, which seems considerably higher than the suspected influenza vaccine cases ($n=1$). However, the ecological analyses did not find a direct link to the COVID-19 vaccination. Moreover, our results support those of a previous study with a large sample size showing that the COVID-19 vaccination is neurologically safe.[32]

In 11 hospitalized patients with associations with the COVID-19 vaccine, there are one stroke case (No. #7) and one epilepsy case (No. #3) (Table 2). According to the stroke case, he received the adeno-associated virus (AAV) vaccine 16 days before the ischemic stroke onset. His cranial magnetic resonance image showed the ischemic stroke in the right posterior cerebral artery area, but no stroke cause or risk was detected without the COVID-19 vaccine. There are some reports showing the ischemic stroke after COVID-19 vaccine[33] and some scientists suggest that the AAV vaccine is associated with a higher risk of the postvaccination ischemic stroke than mRNA vaccine.[34] According to the epilepsy case, the seizure recurrence was occurred 4 days after second COVID-19 vaccination, although previously his epilepsy was well controlled for more than 2 years by treatment with levetiracetam 1000 mg/day. There was no statistically significant difference in the risk of new-onset seizure incidence between COVID-19 vaccinated individuals and placebo recipients.[35] However, a little proportion of the epileptic patients had a seizure worsening after COVID-19 vaccination.[36]

In contrast to autoimmune hospitalizations, the number of patients hospitalized for psychological and unknown pathological reasons significantly changed throughout the pandemic. Specifically, the number of psychological cases significantly decreased throughout the study period. However, others have reported that mental health disorders increased during the COVID-19 pandemic.[37] We speculate that these contrasting results are due to differences in the hospital department; our division is not a psychiatry division but a neurology division. Thus, most patients admitted to the neurology division for psychological symptoms are initially not diagnosed with psychological diseases. Furthermore, most of these patients have somatic symptom disorders, and we speculate that they avoid the hospital to avoid nosocomial COVID-19 infection.

The number of unknown pathological cases significantly increased throughout the study period. Explaining this result is challenging; however, we speculate that the COVID-19 burden, including prevention, influenced the neurological staff and patients. Additionally, some unknown pathological cases may have been misidentified.

Recent reports cleared the neurological complications of COVID-19 concerns with multiple pathology, the direct invasion of SARS-CoV-2 into the nervous system,[9] autoimmune disorders,[10] neuroinflammation,[11] exosomes,[8] etc. Because of the multiple pathology, there were diverse neurological complications of COVID-19 such as ischemic strokes, encephalopathy, GBS, depression.[11] Although most of our hospitalized cases associated with SARS-CoV-2 infection were nosocomial case, it is interesting that there were diverse neurological complications following the COVID-19 vaccinations. Clearing the pathological relationship between the neurological complications of the SARS-CoV-2 infection and those following the COVID-19 vaccination is the future issue.

Our study is a single-center study, which is a limitation. Multicenter participated study would be desired in future. Second, only Japanese patients were enrolled; thus, the findings cannot be applied to other cultural groups. Third, we did not perform the either calculation or justification of the sample size.

Conclusions

The characteristics of neurological diseases in hospitalized patients significantly changed throughout the COVID-19 pandemic, but SARS-CoV-2 infection and the COVID-19 vaccination did not influence these changes. Thus, other indirect factors influenced neurologic hospitalizations during the COVID-19 pandemic.

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Author contributions

KM collected data, calculated the results, and drafted the manuscript. MM helped interpret the results statistically. AK performed the anti-GFAP antibody analyses. TM, YA, and TO collected data. RK and RT helped draft the manuscript. SF conceived the study, participated in its coordination, and helped draft the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics approval

Ethical approval for this study was obtained from the Ethical Committee of Jichi Medical University (#Rin-Fu 22-176).

Informed consent

Informed consent was not sought for this study because waiver of consent was approved by the institutional review board because of the opt-out approach. This study was performed as the opt-out study, and we announced the study in our web site.

Trial registration

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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