

Report

Survey on Headache During COVID-19 Infection in People with Chronic Headache

Masakazu Ishii,^{*a} Ikumi Ito,^b and Hiroataka Katoh^c

^aDivision of Physiology and Pathology, Faculty of Pharmaceutical Sciences, Teikyo Heisei University, Tokyo, Japan;

^bDivision of Community Pharmacy, Faculty of Pharmaceutical Sciences, Teikyo Heisei University, Tokyo, Japan;

^cKuramae Kato Medical Clinic, Tokyo, Japan

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A questionnaire survey was conducted to clarify the headache situation in people with chronic headache during the new coronavirus disease 2019 (COVID-19) infection. A questionnaire survey was conducted on the internet. The subjects were 600 women in their 20s to 40s who were infected with the 7th wave of COVID-19 infection from July to October 2022. Subjects (55.7%) had headaches at the time of infection, and most of the infected people were recuperating at home. Other headaches (excluding migraine) accounted for about 60% of existing headaches in both the headache group and the headache-free group, but people with migraine accounted for 30.5% of the headache group, and those without headache accounted for 23.3% of the headache-free group. In the headache group, 40.3% had headaches even at the time of vaccination against COVID-19. In both the migraine group and other headache groups, compared to regular headaches, headaches during COVID-19 infection had a greater impact on daily life. Migraine headaches may have worsened in migraine carriers, as accompanying symptoms of migraine were observed at the time of infection. It is therefore important to note that chronic headache patients may develop severe headaches during COVID-19 infection.

Key words headache, COVID-19, migraine

INTRODUCTION

The new coronavirus disease 2019 (COVID-19) is highly contagious and has caused an explosive epidemic worldwide due to droplet infection, contact infection, and aerosol infection. The major difference from conventional viral infections is that there are many asymptomatic patients, and the virus spreads easily by acting without knowing that they are infected. Analysis of HER-SYS data from June 14 to July 18, 2021 showed 73% and 85% fever, 43% and 46% cough, 31% and 32% general malaise, and 22% and 27% headache in alpha and delta strains, respectively.¹⁾ In addition, a comparison of symptoms by age group among those who were positive for corona infection and had symptoms showed that 6.6% of those over the age of 65 had headaches, while 23% of those under the age of 65 had headaches.¹⁾ The 7th wave of the COVID-19, caused by the omicron strain substrain BA.5, which began in July 2022, had become an epidemic that surpasses the 6th wave in Japan. According to a survey by the French Public Health Agency, the most common clinical symptoms in 288 people infected with the Omicron strain BA.5 in France were general malaise (76%), cough (58%), and fever (58%), headache (52%) and runny nose (50%).²⁾

Vaccines have been developed with the aim of preventing the onset of COVID-19 infections, reducing the number of deaths and severe cases as much as possible, and preventing the spread of coronavirus infections. In fact, vaccination has been confirmed to be effective in preventing the onset of

symptoms,³⁾ and it is thought that symptoms such as fever and headache are reduced because it prevents the aggravation of COVID-19 infection. On the other hand, side effects such as pain in the injection site, fatigue, headache, muscle and joint pain, chills, diarrhea, and fever are known to occur after vaccination. In a female-biased group (hospital nurses), headaches after vaccination against the COVID-19 were more likely to occur as a side effect in those who had pre-existing headaches.⁴⁾ Therefore, even if infected with the COVID-19, it is likely that female with pre-existing headaches are more likely to have headaches after infection.

In this study, a questionnaire survey was conducted on female infected with the 7th wave of COVID-19 to clarify the headache situation in people with chronic headache during COVID-19 infection.

METHODS

Questionnaire Study Among the monitor members of Loyalty Marketing Inc., an Internet research company, the subjects were women in their 20s to 40s who were infected with COVID-19 between July and September 2022. An Internet research company sent questionnaire request emails to registered monitors (107,137 people), and 8,177 people responded to the screening. In this survey, the subjects were 600 women in their 20s to 40s, and the number of women in each age group was set to 100 for each gender. The response request email was sent on October 1, 2022, and the survey was dis-

*To whom correspondence should be addressed. e-mail: masakazu.ishii@thu.ac.jp

continued on October 2, 2022, when the planned number of responses was reached. As a result, 600 samples were collected. The questionnaire was multiple-choice and anonymous to protect the personal information of the respondents. In addition to the basic attributes, the question items were “situation during the 7th wave of COVID-19 infection”, “vaccination status”, “usual headache situation”, and “headache during the 7th wave of COVID-19”. This survey was conducted after obtaining approval from the human subject research ethics committee of Teikyo Heisei University (approval number: 2022-083).

How to Differentiate Headache To select people with migraine, we used the modified ID migraine screener Japanese version,⁵⁾ which included five items: headache exacerbation during daily activities, nausea, photophobia, osmophobia and phonophobia, covering the past 1 year. Respondents were asked to answer pre-existing headaches, excluding headaches associated with vaccination and headaches due to COVID-19 infection. Based on previous study by Lipton *et al.*,⁶⁾ we assessed headache exacerbation during daily activities, nausea, photophobia, osmophobia and phonophobia using the following criteria: “yes” assigned to response of “less than half the time” or “half the time or more”. Participants who answered yes to at least two of five questions were considered to have migraines. Of the people who had headaches in the past 1 year, those who did not meet the criteria of migraine were considered to have other headaches. Moreover, people with migraines who answered yes to the question about aura symptoms (visual symptom) were considered to have migraine with aura. In this way, migraine was evaluated according to the International Classification of Headache Disorders, Third

Edition (ICHD-3).⁷⁾ Usually, migraine screener cover the past 3 months, but in this study, the coverage period was 1 year. Therefore, many people with mild chronic headache were included in the subjects, and it was expected that the rate of chronic headache people would increase.

Statistical Analysis Data are expressed as mean \pm standard deviation or number of respondents (%). In this study, the subjects were classified into a “headache group” who developed headache due to the 7th wave of COVID-19 infection, and a “headache-free group” who did not have a headache. Furthermore, the headache group was classified into a migraine group and other headache groups, and analyzed. χ^2 test and Fisher’s exact method were used for categorical variables, and $p < 0.05$ was considered significant. The Fisher’s exact test is utilized since the sample size is small with expected frequency less than 5 in one cell. The statistical software used was Excel Statistics ver.3.21 (Social Information Service).

RESULTS

Subject's Situation During the 7th Wave of COVID-19 Infection Of the 600 subjects who were infected with the 7th wave of COVID-19, 334 had headaches at the time of infection, and 266 had no headaches (Table 1). In both groups, especially in headache group, many people complained of fever, sore throat, cough and sputum (Table 1). As for the route of infection, household infections accounted for about half of the cases in both groups (Table 1). The next most common was unknown route of infection, which accounted for

Table 1. Infection with COVID-19 Virus in the 7th Wave of the New Corona

	Headche		Headache-free		p-value
	n=334	%	n=266	%	
Age					
20's	112	33.5	88	33.1	0.973
30's	112	33.5	88	33.1	
Forties	110	32.9	90	33.8	
Have you ever been infected with the COVID-19?					
Until December 2021 (1st to 5th waves)	7	2.1	1	0.4	0.083
January to June 2022 (6th wave)	5	1.5	5	1.9	0.716
July-September 2022 (7th wave)	334	100.0	266	100.0	(-)
What were the symptoms of the 7th wave of infection? (Multiple answers allowed)					
Sore throat	284	85.0	198	74.4	0.001 *
Cough/sputum	281	84.1	175	65.8	< 0.001 *
Fever	309	92.5	212	79.7	< 0.001 *
Headache	334	100.0	0	0.0	(-)
Runny nose/stuffy nose	170	50.9	88	33.1	< 0.001 *
Taste disorders	94	28.1	46	17.3	0.002 *
Olfactory disturbance	69	20.7	32	12.0	0.005 *
General malaise	237	71.0	108	40.6	< 0.001 *
Diarrhea	68	20.4	27	10.2	< 0.001 *
Shortness of breath	42	12.6	14	5.3	0.002 *
Other symptoms	20	6.0	6	2.3	0.026 *
No symptoms	0	0.0	5	1.9	0.017 *
Please tell me about the route of infection.					
In the home	172	51.5	134	50.4	0.567
Workplace, school, part-time job	60	18.0	46	17.3	
Restaurant	11	3.3	6	2.3	
Others	5	1.5	9	3.4	
Infection route unknown	86	25.7	71	26.7	
Where did you receive treatment or recuperation? (Multiple answers allowed)					
Home care	332	99.4	262	98.5	0.414
Hotel recuperation	7	2.1	5	1.9	0.851
Hospital treatment	2	0.6	1	0.4	1.000

χ^2 test and Fisher's exact method (if expected frequency was < 5) were used.

*: $p < 0.05$, Headache vs. Headache-free

Table 2. Characteristics of Pre-Existing Headache

	Headache during COVID-19 infection				p-value	Pre-existing headache				p-value
	Headache		Headache-free			Migraine		Other headache		
	n=334	%	n=266	%		n=132	%	n=377	%	
Headache exacerbation during daily activities										
Never	159	47.6	194	72.9	< 0.001 *	10	7.6	252	66.8	< 0.001 #
Rarely	64	19.2	32	12.0		12	9.1	84	22.3	
Less than half the time	83	24.9	29	10.9		75	56.8	37	9.8	
Half the time of more	28	8.4	11	4.1		35	26.5	4	1.1	
Nausea										
Never	193	57.8	200	75.2	< 0.001 *	14	10.6	288	76.4	< 0.001 #
Rarely	61	18.3	36	13.5		22	16.7	75	19.9	
Less than half the time	67	20.1	17	6.4		72	54.5	12	3.2	
Half the time of more	13	3.9	13	4.9		24	18.2	2	0.5	
Photophobia										
Never	207	62.0	218	82.0	< 0.001 *	27	20.5	307	81.4	< 0.001 #
Rarely	61	18.3	23	8.6		26	19.7	58	15.4	
Less than half the time	47	14.1	16	6.0		52	39.4	11	2.9	
Half the time of more	19	5.7	9	3.4		27	20.5	1	0.3	
Osmophobia										
Never	237	71.0	235	88.3	< 0.001 *	42	31.8	339	89.9	< 0.001 #
Rarely	50	15.0	15	5.6		30	22.7	35	9.3	
Less than half the time	38	11.4	12	4.5		47	35.6	3	0.8	
Half the time of more	9	2.7	4	1.5		13	9.8	0	0.0	
Phonophobia										
Never	179	53.6	216	81.2	< 0.001 *	22	16.7	282	74.8	< 0.001 #
Rarely	75	22.5	26	9.8		26	19.7	75	19.9	
Less than half the time	59	17.7	16	6.0		57	43.2	18	4.8	
Half the time of more	21	6.3	8	3.0		27	20.5	2	0.5	
Type of headache										
No headache	29	8.7	62	23.3	< 0.001 *	(-)		(-)		(-)
Migraine	102	30.5	30	11.3		132	100.0	(-)		
Other headache	203	60.8	174	65.4		(-)		377	100.0	
Visual aura (flickering lights, spots of lines, and loss of vision)	n=102		n=30							
Never	53	52.0	13	43.3	0.033 *	66	50.0	(-)		(-)
Rarely	24	23.5	2	6.7		26	19.7			
Less than half the time	16	15.7	9	30.0		25	18.9			
Half the time of more	9	8.8	6	20.0		15	11.4			
Type of migraine	n=102		n=30							
MA	25	24.5	15	50.0	0.008 *	40	30.3	(-)		(-)
MO	77	75.5	15	50.0		92	69.7			
Influence of headache on daily life										
Stay in bed	50	15.0	30	11.3	< 0.001 *	36	27.3	44	11.7	< 0.001 #
Considerably hindrance (excluding stay in bed)	65	19.5	25	9.4		48	36.4	42	11.1	
Somewhat affected (excluding stay in bed)	134	40.1	72	27.1		44	33.3	162	43.0	
No influence	56	16.8	77	28.9		4	3.0	129	34.2	
Headache free	29	8.7	62	23.3		(-)		(-)		

χ^2 test and Fisher's exact method (if expected frequency was < 5) were used.

Respondents were asked to answer pre-existing headaches, excluding headaches associated with vaccination and headaches due to COVID-19 infection.

MA: migraine with aura; MO: migraine without aura

*:p < 0.05, Headache vs. Headache-free

#:p < 0.05, Migraine vs. Other headache

about one-fourth in both groups (Table 1). Most of the infected people were recuperating at home (Table 1).

Pre-Existing Headache Situation In pre-existing headache situation, compared with the headache-free group, the headache group had more accompanying symptoms, such as headache exacerbation during daily activities, nausea, photophobia, osmophobia and phonophobia (p < 0.001), and the degree of disability in daily life was higher (p < 0.001, Table 2). In both the headache group and the headache-free group, the most common type of headache was classified as other headaches, but migraine accounted for 30.5% of the headache group, and 23.3% of the headache-free group had no headaches on a regular basis. (Table 2). People with pre-existing headache were divided into the migraine group (132 people) and the other headache group (377 people), many people in the migraine group had accompanying symptoms (p < 0.001), and the degree of disability in daily life was high-

er (p < 0.001, Table 2). Migraine with aura accounted for 30.3% of the migraine group (Table 2).

Vaccination Status Against COVID-19 The number of vaccinations against the COVID-19 before the 7th wave infection was 3 times, accounting for 53.0% in the headache group and 55.6% in the headache-free group (Table 3). Approximately 80% of both the headache group and the headache-free group had received Pfizer's vaccine (Table 3). Fever was the most common adverse reaction after vaccination, which was 66.7% in headache group and 65.3% in no headache group (Table 3). In the headache group, injection site pain (p = 0.024), general malaise (p = 0.029), headache (p < 0.001), muscle pain (p < 0.001), and chills (p = 0.003) were more frequent (Table 3). In the headache-free group, 11.0% had no symptoms (p = 0.022, Table 3). In a comparison of the migraine group and other headache groups, among the side effects of vaccination, injection site pain (p = 0.028)

Table 3. Vaccination Status

	Headache during COVID-19 infection				p-value	Pre-existing headache				p-value
	Headache		Headache-free			Migraine		Other headache		
	n=334	%	n=266	%		n=132	%	n=377	%	
How many doses of vaccine against the new coronavirus did you have before you got infected with COVID-19 in the 7th wave?										
Once	3	0.9	4	1.5	0.142	3	2.3	4	1.1	0.384
Twice	90	26.9	79	29.7		34	25.8	109	28.9	
3 times	177	53.0	148	55.6		69	52.3	213	56.5	
4 times	3	0.9	5	1.9		2	1.5	4	1.1	
Not vaccinated	61	18.3	30	11.3		24	18.2	47	12.5	
What types of vaccines have you received so far? (Multiple answers allowed)	n=273		n=236			n=108		n=330		
Pfizer (Comirnaty)	223	81.7	191	80.9	0.828	90	83.3	265	80.3	0.486
Moderna (Spikevax)	111	40.7	86	36.4	0.330	42	38.9	132	40.0	0.838
AstraZeneca (Vaxzevria)	1	0.4	1	0.4	1.000	1	0.9	1	0.3	0.433
Novavax, Takeda (Nuvaxovid)	2	0.7	0	0.0	0.502	2	1.9	0	0.0	0.060
What side effects have you had with previous vaccinations? (Multiple answers allowed)	n=273		n=236			n=108		n=330		
Fever	182	66.7	154	65.3	0.737	80	74.1	211	63.9	0.053
Injection site pain	175	64.1	128	54.2	0.024 *	76	70.4	193	58.5	0.028 #
General malaise	148	54.2	105	44.5	0.029 *	65	60.2	163	49.4	0.051
Headache	110	40.3	35	14.8	< 0.001 *	46	42.6	90	27.3	0.003 #
Muscle pain	90	33.0	47	19.9	< 0.001 *	38	35.2	86	26.1	0.068
Chills	70	25.6	35	14.8	0.003 *	26	24.1	72	21.8	0.625
Nausea/vomiting	12	4.4	5	2.1	0.154	7	6.5	10	3.0	0.107
Diarrhea	6	2.2	4	1.7	0.758	3	2.8	6	1.8	0.542
Other symptoms	5	1.8	5	2.1	(-)	3	2.8	7	2.1	(-)
No symptoms	15	5.5	26	11.0	0.022 *	1	0.9	30	9.1	0.004 #

χ^2 test and Fisher's exact method (if expected frequency was < 5) were used.

*:p < 0.05, Headache vs. Headache-free

#:p < 0.05, Migraine vs. Other headache

and headache (p = 0.003) were more frequent in the migraine group (Table 3).

Situation of Headache During the 7th Wave of COVID-19 Infection Among those with headache during the 7th wave, 24.6% had headaches for 2 days, 23.7% for 3 days, and 13.5% for 5 or more days (Table 4). Regarding the situation at the time of the infection, in the headache group, “headache caused by fever” was 76.0%, “the headache site was the frontal region or the whole head” was 73.7%, and “the headache was pulsatile” was 60.5% (Table 4). Compared to other headache groups, 60.8% (p < 0.001) of the migraine group responded that “I felt noisy with the headache” 58.8% (p < 0.001) said that “The headache was non-pulsatile with a feeling of tightness or heaviness over the head”, 56.9% (p = 0.011) said that “I had trouble sleeping due to headaches”, and 44.1% (p < 0.001) said that “the headaches were accompanied by nausea and an upset stomach”, 40.2% (p < 0.001) said that “accompanied by a headache, I felt that the light was dazzling to the extent that I usually didn't notice it”, and 35.3% (p < 0.001) said that “accompanying the headache, I felt that the smell was unpleasant”.

The most common answer for headaches during the 7th wave infection was that they stay in bed (Table 4). Migraine and other headache groups, the degree of disturbance to daily life was greater than usual headaches (Fig. 1, p < 0.001). Approximately half of the headaches associated with infection were managed with prescription drugs (Table 4). Comparing the migraine group and other headache groups, more migraine group responded that they used over-the-counter medications (p = 0.008, Table 4).

DISCUSSION

Background of Respondents BA.5, one of the omicron strains, was the mainstream of the 7th wave of the COVID-19 in Japan.⁸⁾ Headache was a common symptom overseas, where the infection spread earlier than in Japan.⁸⁾ In this study, just like abroad,²⁾ headache was observed in 55.7% (334/600), and other symptoms such as fever, cough/phlegm, sore throat, and malaise were frequently observed. If the oxygen saturation is 96% or more and there are no respiratory symptoms, or if there is only a cough but no dyspnea, it is classified as mild and will be treated at home or in a hotel. If oxygen saturation is less than 96% and dyspnea or pneumonia findings are observed, hospitalization is indicated to prevent aggravation. Since 2022, when the omicron strain became mainstream, the mortality and severity rates have been declining.⁸⁾ Therefore, it was confirmed that the subjects of this survey are a group that has the characteristics of the 7th wave infected people in Japan.

Usual Headache Situation In our study, many of subjects had pre-existing headaches. In the migraine group, migraine with aura accounted for 30.3%, which is almost the same value as previous reports in Japan.⁹⁾ In addition, it was confirmed that the migraine group had a higher degree of disability in daily life than the other headache groups, and had the characteristics of migraine. However, in this study, there is a possibility that people with migraine headaches were included in other headaches because physicians did not conduct interviews or diagnoses.¹⁰⁾ Moreover, it cannot be denied that the population is biased, because it was an Internet survey and the subjects were limited to female.

Table 4. Situation of Headache During the COVID-19 Virus Infection in 7th Wave

	Headache during COVID-19 infection		Pre-existing headache				p-value
	Headache		Migraine		Other headache		
	n=334	%	n=132	%	n=377	%	
How long did your headache during the COVID-19 virus infection in 7th wave?							
Less than 6 hours	34	10.2	7	6.9	24	11.8	0.257
Less than 6-12 hours	30	9.0	8	7.8	22	10.8	
1 day	40	12.0	9	8.8	28	13.8	
2 days	82	24.6	23	22.5	50	24.6	
3 days	79	23.7	28	27.5	43	21.2	
4 days	24	7.2	9	8.8	13	6.4	
5 days or more	45	13.5	18	17.6	23	11.3	
Please answer about the headache caused by the COVID-19 infection.							
Headache caused by fever	254	76.0	77	75.5	156	76.8	0.792
Headache caused by dyspnea	16	4.8	6	5.9	10	4.9	0.724
The headache was pulsatile	202	60.5	70	68.6	118	58.1	0.075
The headache site was the frontal region or the whole head	246	73.7	81	79.4	143	70.4	0.094
The headache was non-pulsatile with a feeling of tightness or heaviness over the head	144	43.1	60	58.8	76	37.4	< 0.001 #
The headaches were accompanied by nausea and an upset stomach	80	24.0	45	44.1	30	14.8	< 0.001 #
Accompanied by a headache, I felt that the light was dazzling to the extent that I usually didn't notice it	66	19.8	41	40.2	22	10.8	< 0.001 #
Accompanying the headache, I felt that the smell was unpleasant	53	15.9	36	35.3	15	7.4	< 0.001 #
I felt noisy with the headache	116	34.7	62	60.8	52	25.6	< 0.001 #
I had trouble sleeping due to headaches	155	46.4	58	56.9	84	41.4	0.011 #
How much impact did your headaches during COVID-19 have on your daily life?							
Stay in bed	169	50.6	56	54.9	97	47.8	0.123
Considerably hindrance (excluding stay in bed)	73	21.9	24	23.5	45	22.2	
Somewhat affected (excluding stay in bed)	73	21.9	21	20.6	47	23.2	
No influence	19	5.7	1	1.0	14	6.9	
How did you deal with headaches when you were infected with COVID-19? (Multiple answers allowed)							
used prescription drugs	179	53.6	59	57.8	106	52.2	0.352
used over-the-counter drugs	112	33.5	44	43.1	57	28.1	0.008 #
sleeping/staying still	164	49.1	52	51.0	97	47.8	0.598
endured	46	13.8	15	14.7	28	13.8	0.829
didn't do anything	15	4.5	0	0.0	12	5.9	0.012 #

χ^2 test and Fisher's exact method (if expected frequency was < 5) were used.

#:p < 0.05, Migraine vs. Other headache

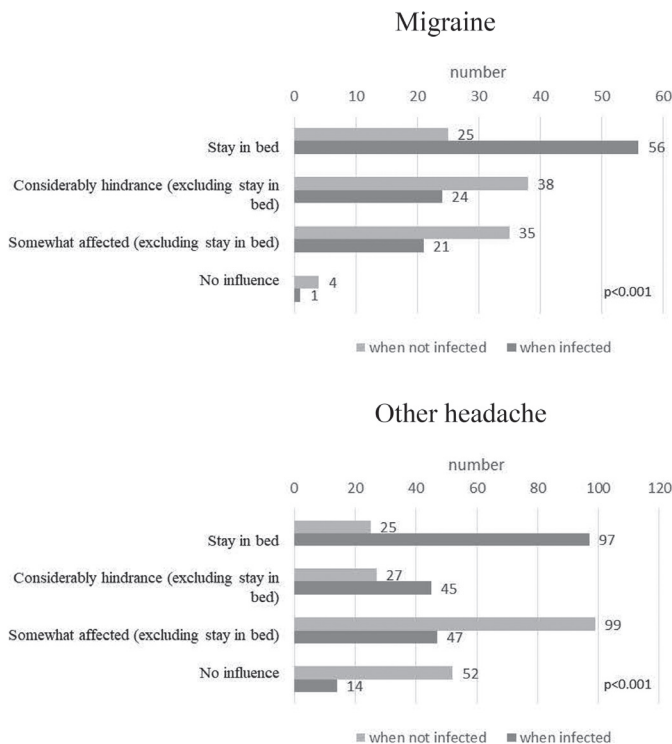


Fig. 1. Effects of Headache During COVID-19 Infection and Non-Infection on Daily Life.

Migraine and other headache. People with pre-existing headache were divided into the migraine group (132 people) and the other headache group (377 people). Headache during infection was worse than that during non-infection (p < 0.001).

Vaccinations for COVID-19 and Headaches There was no difference in the number of vaccinations or the type of vaccines taken between the headache group who had headaches due to the 7th wave infection and the headache-free group who did not have headaches. However, those who had headaches from the 7th wave of COVID-19 infection had headaches, injection site pain, general malaise, myalgia, and chills as side effects of vaccination compared to those who did not have headaches. Sekiguchi *et al.* also reported that people with pre-existing headaches, such as migraine, were more likely to have headaches after vaccination than people without headaches.⁴⁾ Furthermore, in our study, when comparing the subjects' pre-existing headaches, it became clear that the migraine group was more likely to have headaches after vaccination than the other headache groups. On the other hand, in the headache-free group, there were many people who did not usually have a headache, and compared to the headache group, a higher percentage of respondents answered that they had "no symptoms" after vaccination.

Headache During the 7th Wave of COVID-19 Infection Toptan *et al.* reported that COVID-19-infected people with migraine had different headaches (earlier onset, longer duration, stronger headache) than those without migraine.¹¹⁾ In this study, it was found that in migraine and other headache groups, compared to headaches during normal times, the headaches during the 7th wave COVID-19 infection was highly disabling. In both groups, more than 80% of the respondents said that headache was caused by fever. Therefore, the expansion of cerebral blood vessels due to fever may have caused a migraine. Even in the migraine group, more respondents reported that their headaches were non-pulsatile than in other headache groups. In addition, nausea, photophobia, osmophobia, phonophobia, and sleep deprivation were significantly more common in the migraine group than in the other headache groups, and headaches affect daily life. It was revealed that the migraine group suffered from symptoms other than headache. Thus, migraine headaches may have worsened in people with migraine, as accompanying symptoms of migraine were observed at the time of infection. Because migraine is a stress-associated disease,¹²⁾ stress due to COVID-19 infection, including movement restrictions and anxiety about infecting someone with COVID-19, might worsen migraine. Furthermore, more than half of the respondents in both groups reported using prescription drugs for headache, and it is thought that many of them used NSAIDs. In this study, since many migraine sufferers had exacerbated migraine during COVID-19 infection, it is important to use triptans if headache does not improve with NSAIDs.

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Conflict of interest The authors declare no conflict of interest.

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