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Peripheral facial paralysis during the COVID-19 pandemic

Sukru Aydin[1], Cigdem Firat Koca[2], Turgut Celik[1], Mehmet Kelles[2], Seyma Yasar[3]

[1]Malatya Training and Research Hospital, Department of Otolaryngology Head and Neck Surgery, Malatya, Turkey
[2]Malatya Turgut Ozal University, Faculty of Medicine, Department of Otolaryngology Head and Neck Surgery, Malatya, Turkey
[3]Inonu University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Malatya, Turkey

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Abstract

The mechanism surrounding idiopathic peripheral facial nerve paralysis remains unclear, though viral infections and even immunizations have been suspected of its origin. Thus, the relationship between COVID-19 and facial paralysis should be studied. With this research, we aimed to investigate the characteristics of facial paralysis during the COVID-19 illness as well as the relationship between facial paralysis and COVID-19, the length of time needed for recovery, concurrence with COVID-19 infection, and whether facial paralysis is a late complication or initial symptom of the disease. Forty-five patients thought to have had idiopathic peripheral facial paralysis were included in the study. Pure tone audiometry, COVID-19 PCR tests, and contrast-enhanced ear MRIs were performed on all participants. A standard prednisolone treatment protocol was followed. Participants were monitored for one month; we recorded whether they had COVID-19 previously, initially, or contracted it within the one-month testing period. At the same time, facial paralysis recovery rates were recorded and used in statistical analyses. PCR test at initial admission was reported as positive for COVID-19 in only one participant (2.2%). We discovered an improvement delay regarding facial paralysis in participants who had had COVID-19 previously ($p<0.001$). Prednisolone therapy used for peripheral facial paralysis did not pose an additional risk for COVID-19. Having had COVID-19 previously may cause delayed recovery of peripheral facial paralysis. Peripheral facial paralysis may be both a late manifestation as well as an early symptom of COVID-19.

Keywords: COVID-19, pandemic, peripheral facial paralysis, prednisolone therapy, SARS-CoV-2.

Introduction

On December 31st, 2019, the World Health Organization (WHO) was informed of patients diagnosed with pneumonia of an unknown origin in Wuhan, Hubei province, China. The novel microorganism was described on January 7th, 2020, as 2019 n-CoV; later, the virus was renamed—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—due to its similarity to SARS-CoV. The illness caused by the virus was named coronavirus disease 2019 (COVID-19) on February 11th, 2020, and on March 11th, 2020, WHO declared the outbreak a pandemic [1]. The respiratory system is the most affected, but the disease can also cause venous thromboembolism, acute kidney injury, acute liver injury, cytokine release, septic shock, diffuse intra-vessel coagulation, pregnancy-related complications, and neurological complications [2].

Viruses can travel to the central nervous system (CNS) by hematogenous or neuronal retrograde routes. The hematogenous path can be taken three ways: the virus infects the endothelial cells of the blood-brain barrier in the choroid plexus located in the brain's ventricles; it infects the epithelial cells of the blood-cerebrospinal fluid barrier; or it uses leukocytes, which act as vectors to spread the virus to the CNS. Using the neuronal retrograde path, the virus infects peripheral neurons and uses axons to access the CNS [3].

SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter human target cells. ACE2 receptors are found in many organs as well as the CNS; their presence in the CNS may explain the virus' effects on it [4]. Neurological complications associated with the COVID-19 infection may occur due to the direct invasion of the neurological system and/or cardiopulmonary insufficiency and metabolic abnormalities caused by autoimmune mechanisms triggered by the SARS-CoV-2 infection [5]. It is no surprise, then, that accompanying neurological problem were observed in 36.4% of participants with the COVID-19 infection, including dizziness, headache, loss of consciousness, olfactory and gustatory dysfunction, and epileptic seizures.

***Corresponding Author:** Sukru Aydin, Malatya Training and Research Hospital, Department of Otolaryngology Head and Neck Surgery, Malatya, Turkey
E-mail: dr.sukruaydin@gmail.com

Derollez et al. reported the case of a 57-year-old woman who presented with facial nerve paralysis as an initial symptom of COVID-19 [6-8]. The cause of facial nerve paralysis remains unclear, though viral infections have been suspected [9,10]. However, the increased number of cases reported with facial paralysis during vaccine trials have made an immune-mediated mechanism a possibility [11]. Thus, the relationship among immune-mediated activations, neurotropic features of the coronaviruses, and facial paralysis should be considered [12,13].

In this study, we aimed to investigate the characteristics of facial paralysis during about with COVID-19, the relationship between facial paralysis and COVID-19, the recovery period needed to overcome the facial paralysis, concurrence with COVID-19 infection, and whether facial paralysis is a late complication or initial symptom of the disease.

Materials and Methods

Patients with peripheral facial paralysis who were admitted to or consulted with the otorhinolaryngology outpatient clinic of Malatya Training and Research Hospital were included in the study. The study was conducted with the permission of the Malatya Turgut Ozal University Clinical Research Ethics Committee with protocol number 2021/15, which complied with the Helsinki declaration. All participants included in the study were informed and written consent was obtained. Thorough examinations of the participants included in the study were performed by the ear, nose, and throat physician upon application. Patients thought to have had idiopathic peripheral facial paralysis were included in the study. Patients who had peripheral facial paralysis that developed after trauma (and therefore thought to have developed as a complication of chronic otitis) were excluded from the study. Sociodemographic information about the study's participants, whether they had COVID-19 before developing peripheral facial paralysis, and whether they had had upper respiratory tract infection symptoms in the previous two weeks were recorded. Participants were also questioned if they had ever had COVID-19 before. We divided participants into two groups, positive (those with previous COVID-19 history) and negative (those with no COVID-19 history), and we compared recovery rates.

All participants underwent pure tone audiometry, COVID-19 polymerase chain reaction (PCR) tests (via oro-nasopharyngeal swabs), and contrast-enhanced ear magnetic resonance imaging (MRI). During pure tone audiometry, air and bone conduction frequencies of 250, 500, 1000, 2000, and 4000 Hz were measured and recorded. Nasopharyngeal and oropharyngeal samples were taken from 45 participants who presented with peripheral facial paralysis as defined by the Ministry of Health's COVID-19 Diagnosis and Treatment Guidelines. SARS-CoV-2 infection was verified by the Biospeedy RT-qPCR kit (USHAŞ, Ankara, Turkey) using the RT-qPCR method. All participants took 50 mg of prednisolone per day in two equal doses for five days. After five days, the total dosage of prednisolone was reduced to 10 mg per day and the medical treatment was discontinued after ten days [14]. A salt-free diet was recommended to all patients, and pantoprazole (a proton pump inhibitor) was given to prevent gastritis. The House-Brackmann (HB) grading system was used to rate the severity of peripheral facial paralysis of the participants; scores were measured on the first, 10th, 20th, and 30th days of the observation period. Artificial tears and lubricating eye pomade were administered to those with HB scores of 3 and higher to prevent eye dryness. During the one-month follow-up period, the participants were questioned about any complaints and/or diagnoses of COVID-19.

Statistical analysis

The IBM SPSS Statistics 26.0 program was used for analysis. Data was given with median (min-max), mean (standard deviation), and number (percentage). The Shapiro-Wilk test was used to ensure conformity to normal distribution. For statistical analyses, we used the Mann-Whitney U test, independent samples t-test, Friedman test, Pearson chi-square test, Yatesin corrected chi-square test, Fisher's exact chi-square test, and Spearman correlation test where appropriate. A p-value of <0.05 was considered statistically significant.

Results

Forty-six patients were initially included in the study. However, one patient developed a vesicular rash in the external auditory canal and auricle after receiving treatment; the participant was given acyclovir and was diagnosed with Ramsay Hunt syndrome. Consequently, the patient's data were excluded from the study. One patient had diabetes and did not receive prednisolone treatment because of unregulated blood glucose levels. Another participant had a retracted tympanic membrane; it was not pouched, and there was no middle ear pathology. In all other participants included in the study (29 male and 16 female), the external auditory canal was intact, and the tympanic membrane had a natural appearance.

The participants' mean age was 45.36±18.05. Seventeen participants (37.8%) had experienced COVID-19 previously, but most (86.7%) had not experienced peripheral facial paralysis before. The period between COVID-19 infection to facial palsy development ranged from 20 days to 150 days (mean=83 days). At the end of the first 30 days of follow-up, 38 patients (84.4%) had improved entirely, and 77.8% (n=35) had normal temporal MRI findings. Furthermore, the audiometric evaluation was normal for most patients (62.2%) (Table 1).

After analyzing the effect of previously having COVID-19 on the recovery of patients with facial paralysis and noting the differences between the positive (previously had COVID-19) and negative (no COVID-19 history) groups, we observed that there was a delay of improvement in patients who had already experienced COVID-19. In the control examination performed on the 10th day after facial paralysis, the complete recovery rate was 1/17 (5.8%) in the group who previously had COVID-19, while the full recovery rate was 10/27 (37%) in those who did not previously have COVID-19. On the 20th day, the complete recovery rate was 5/17 (29.4%) in the positive group and 20/27 (74.07%) in the negative group. At the last control examination on the 30th day, the rate rose to a maximum of 27/27 (100%) in the negative group and 10/17 (58.8%) in the positive group. Thus, there was a statistically significant difference ($p<0.001$) when the complete recovery rates between the groups were compared separately.

After a 30-day follow-up, seven patients still did not show complete recovery. Five improved moderately; their HB scores decreased from 4–5 to 2. One patient's HB score was 3, and one had an HB score of 4 (these two patients initially had HB scores of 5). These patients remain under observation. All of the seven patients who did not show complete recovery had previously had COVID-19.

Table 1. Descriptive statistic of patients with peripheral facial paralysis

		Mean±SD	Median (Min-Max)
Age		45.36±18.05	46.00 (17-82)
Days from onset to seeking medical attention		1.49±1.56	1(0-6)
		Count	**Percent (%)**
Gender	**Female**	16	35.6%
	Male	29	64.4%
Presence of active or recent upper airway infection symptom (recent 14 days)	**Yes**	4	8.9%
	No	41	91.1%
Previous Covid-19 positivity	**Positive**	17	37.8%
	Negative	28	62.2%
HB Grade at onset	**2**	16	35.6%
	3	14	31.1%
	4	10	22.2%
	5	5	11.1%
HB Grade at 10th day	**1**	11	24.4%
	2	22	48.9%
	3	9	20.0%
	4	3	6.7%
HB Grade at 20th day	**1**	25	55.6%
	2	15	33.3%
	3	4	8.9%
	4	1	2.2%
HB Grade at 30th day	**1**	38	84.4%
	2	5	11.1%
	3	1	2.2%
	4	1	2.2%
Recurrence	**No**	39	86.7%
	On the same side	4	8.9%
	On the other side	2	4.4%
Temporal MRI findings	**Normal**	35	77.8%
	Contrast enhencement	5	11.1%
	No applicable	5	11.1%
Comorbidities	**DM**	10	22.2%
	HT	9	20.0%
	Other	8	17.8%
Audiogram	**Normal**	28	62.2%
	Bilateral slight SNHL	2	4.4%
	Bilateral mild SNHL	5	11.1%
	Bilateral moderate SNHL	2	4.4%
	Bilateral moderately severe MHL	2	4.4%
	High-frequency SNHL	6	13.3%
Side of Palsy	**Left**	21	46.7%
	Right	24	53.3%

(SD: standard deviation, HB: House-Brackmann, MRI: magnetic resonance imaging, DM: diabetes mellitus, HT: Arterial Hypertension, Other comorbidities: cardiovascular disease, hypothyroidism, Turner syndrome, chronic renal failure, and familial Mediterranean fever, SNHL: sensorineural hearing loss, MHL: Mixed type hearing loss)

There were no statistically significant differences between groups when comparing gender, age, facial side of paralysis, recurrence, or temporal MRI findings. The groups were also similar when accounting for comorbidities (Table 2). Pathologies that could affect the facial nerve were ruled out via temporal MRIs. Five patients could not undergo MRIs due to contraindications. In four patients, contrast enhancement was noted in the facial nerve trace (Figure 1). This enhancement could be a secondary symptom of acute inflammation or may indicate tumors originating from the facial nerve; therefore, MRIs were scheduled six months later to check for tumoral formations. A benign parotid gland mass was detected in one patient, except for contrast enhancement of the facial nerve. The mass, which was located in the superficial lobe and distant from the facial trunk, was not associated with facial

paralysis. Another patient had what appeared to be a retrocerebellar arachnoid cyst and was not associated with facial paralysis.

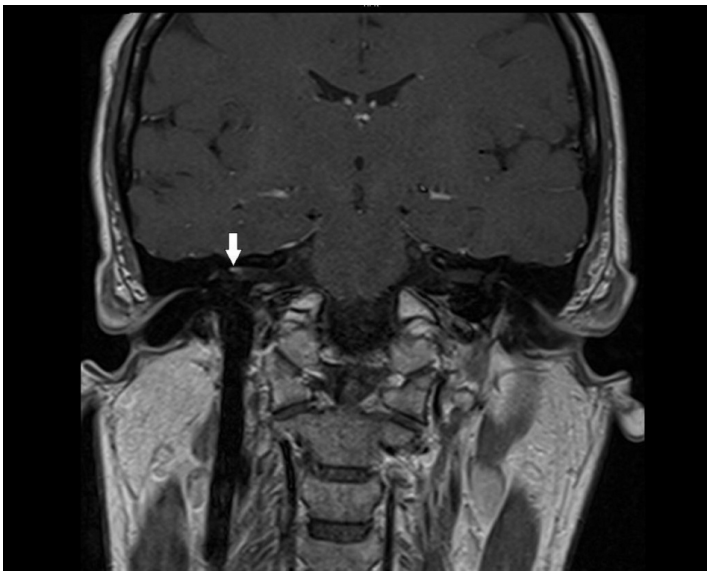

Figure 1. Contrast enhancement in the right facial nerve trace on contrast-enhanced MR image (white arrow)

The COVID-19 screening test was performed by PCR from oro-nasopharyngeal swabs taken from all patients at the time of admission. During this screening, the COVID-19 test was positive in one patient (2.2%). This patient had peripheral facial paralysis with an HB score of 4 at the time of admission but did not have any symptoms suggestive of COVID-19, such as fever, sore throat, or cough. In addition to prednisolone and the PPI, favipiravir was used in the patient's treatment, and the patient recovered completely at the end of the first month. During the follow-up period, no additional symptoms developed. After the quarantine period, an audiogram and MRI were performed; no pathological conditions were found. This patient's data were excluded from the statistics comparing those who had had COVID-19 before the time of application and those who had not. Forty-four patients who received prednisolone treatment did not voice complaints about COVID-19 during the follow-up period (the patient whose COVID-19 test was positive during the first application also received prednisolone and survived COVID-19 asymptomatically).

Other factors affecting the recovery rates of facial paralysis were investigated using the Spearman correlation test. A significant correlation was found between the first admission HB scores and the 10th, 20th, and 30th day HB scores (Spearman's rho: 0.636, p<0.001; Spearman's rho: 0.578, p<0.001; Spearman's rho: 0.527, p<0.001, respectively). Recovery was worse in patients with high HB scores at the time of admission. No correlation was found between the time it took to seek medical attention and the rate of recovery. This result may be due to the small number of patients in our study.

Table 2. The effect of previously positivity of Covid-19 on recovery in patients with facial paralysis and the differences between positive and negative groups

		Previous Covid-19 positivity		p-value
		Positive	Negative	
		Median (Min-Max)	Median (Min-Max)	
HB Grade at onset		3 (2-5)	3 (2-5)	0.117
HB Grade at 10th day		3 (1-4)	2 (1-3)	<0.001
HB Grade at 20th day		2 (1-4)	1 (1-2)	0.001
HB Grade at 30th day		1 (1-4)	1 (1-1)	<0.001
p-value		<0.001	<0.001	
Days from onset to seeking medical attention		1 (0-6)	1 (0-4)	0.118
		Mean ± SD	**Mean ± SD**	
Age		44.65 ± 19.77	45.74 ± 17.61	0.754
		Count (Percent)	**Count (Percent)**	
Gender	**Female**	7 (41.18%)	9 (33.33%)	0.838
	Male	10 (58.82%)	18 (66.67%)	
Side of palsy	**Left**	11 (64.71%)	10 (37.04%)	0.139
	Right	6 (35.29%)	17 (62.96%)	
Presence of active or recent upper airway infection symptom (recent 14 days)	**Yes**	2 (11.76%)	2 (7.41%)	0.634
	No	15 (88.24%)	25 (92.59%)	
Recurrence	**None**	15 (88.24%)	23 (85.19%)	0.475
	On the same side	2 (11.76%)	2 (7.41%)	
	On the other side	0 (0.00%)	2 (7.41%)	
Temporal MRI findings	**Normal**	14 (82.35%)	21 (77.78%)	0.613
	Contrast enhencement	2 (11.76%)	2 (7.41%)	
	No applicable	1 (5.88%)	4 (14.81%)	
Comorbidities	**DM**	5 (29.41%)	5 (18.52%)	0.473
	HT	5 (29.41%)	4 (14.81%)	0.275
	Other	4 (23.53%)	4 (14.81%)	0.690

(SD: standard deviation, HB: House-Brackmann, MRI: magnetic resonance imaging, DM: diabetes mellitus, HT: Arterial Hypertension, Other comorbidities: cardiovascular disease, hypothyroidism, Turner syndrome, chronic renal failure, and familial Mediterranean fever)

Discussion

We noticed that patients who had battled COVID-19 previously needed a longer time to recover from peripheral facial paralysis during this study. Moreover, patients with a high HB grade of facial paralysis at initial presentation had a significantly worse recovery rate. The period from COVID-19 infection to facial palsy onset ranged from 20 days to 150 days (mean=83 days). When the two research groups were compared, we found a statistically significant difference ($p<0.001$) in the rate of complete recovery (i.e., the recovery rate was higher in the negative group) on the 10th, 20th, and 30th days. Seven patients who partially recovered still had facial paralysis during the 30th-day examination: five scored a 2 on the HB scale, one scored 3, and one scored 4. These patients are still under care, and we continue to follow up with them. Interestingly, all of these seven patients previously had COVID-19.

Bell's palsy is an acute, peripheral paresis or paralysis caused by the dysfunction of the 7th cranial nerve. Herpes simplex virus (HSV), varicella-zoster virus(VZV), HIV, Lyme disease, and mycobacterium tuberculosis infections can all be associated with it; some non-infectious conditions, like sarcoidosis and neoplasms, can also cause facial nerve palsy. The definite mechanism of Bell's palsy is unknown, though several theories have been suggested, including inflammation, viral infection, ischemia, and immune-mediated disorders. Serum laboratory testing, viral serological testing, computed tomography, magnetic resonance imaging, and electrodiagnostic tests are important diagnostic methods that provide the best assessment of Bell's palsy cases. Acute facial paralysis is now accepted as a neurological manifestation of SARS-CoV-2. The prognosis of Bell's palsy is extremely positive and has a 90% improvement rate [15]. Indeed, in our study, at the end of the first 30 days of follow-up, 84.4% of patients (n=38) had completely recovered.

When analyzing blood to determine infection, SARS-CoV-2 IgM antibodies can be isolated five days after the virus takes hold. The elevated levels of the antibody continue for one month, then decline gradually. The median period of SARS-CoV-2 IgG antibody determination is 14 days. It is believed that both antibodies facilitate the diagnosis of COVID-19 after their corresponding window durations. Islamoğlu et al. investigated SARS-CoV-2 IgM and IgG antibodies in patients with Bell's palsy. They reported a 24.3% positivity rate of antibodies in their patients [16].

Corticosteroids are the mainstay of treatment; studies have shown that they are superior in treating Bell's palsy compared to no treatment or a placebo [17]. However, immunosuppression is a side effect of the high doses of corticosteroids needed to combat COVID-19 and may be harmful, and treatment should be individualized [15]. We applied standard steroid therapy for facial paralysis to all the patients in our study. COVID-19 infection was not transmitted among our patients during the period of steroid therapy. Although the number of patients in our study was limited, we observed that steroid therapy (50 mg/day) was reliable for treating facial paralysis.

A-viral-induced autoimmune reactivation causes peripheral demyelination of the influenced cranial nerve, which has been hypothesized to be related to Bell's palsy development. Inflammation-induced demyelination is another accepted mechanism of Bell's palsy. In terms of treatment options, Zammit et al. treated patients who had COVID-19 and concurrent Bell's palsy with either a prednisolone-only regimen or prednisolone plus antiviral regimen. Their results revealed that the benefits from the additional antiviral therapy were insignificant [18].

Zammit et al. also emphasized the increased incidence of spontaneous lower motor neuron facial nerve palsy in their emergency ENT clinic [18]. Similarly, Codeluppi et al. reported that the incidence of facial nerve palsy was higher during the COVID-19 pandemic and the patients who had facial paralysis at a younger age [19]. However, Mutlu et al. analyzed the incidence of Bell's palsy during the pandemic and compared the numbers to the previous four years to determine whether there was an increase during the pandemic; they found no significant difference [20].

SARS-CoV-2 can reach the CNS in two ways: the first mechanism is by the slow passage of the virus from the systemic circulation to cerebral circulation via damaging the endothelium. The second way is the direct entry via the cribriform wall and olfactory bulb [21]. The virus may spread from neuron to neuron by axonal transport when the virus enters the CNS via the olfactory nerve [22]. Especially during illness, the emerging cytokine storm increases the production of inflammatory cytokines and activates T-lymphocytes, macrophages, and endothelial cells. Subsequently, increased interleukin-6 (IL-6) release, vascular leakage, complement activity, and an activated coagulation cascade may result in organ damage [23]. The viral infection of glial cells may trigger cytokine release via a proinflammatory response. It is believed that the increased pro-inflammatory cytokines can cause neuron damage in the long term [24]. This mechanism may also explain the late development of facial palsy.

In this present study, the period from the COVID-19 to the facial palsy development ranged from 20 days to 150 days (mean 83 days). In the literature, we could not find any information to support the idea that facial paralysis could be a late symptom of COVID-19. However, there have been publications reporting that facial palsy was the first and sometimes the only symptom of COVID-19 [8,18-20]. We do not know if this late facial paralysis is directly linked to COVID-19. Thus, late peripheral facial paralysis may be caused by the inflammatory process associated with COVID-19, or it may be a side effect of the medications used in the treatment process. Studies with larger series are required to study and clarify this relationship. Still, we observed a delay of recovery in patients who previously had COVID-19 in each 10-day check, revealing a statistically significant difference between the two research groups.

Based on the preliminary outcomes of this study, it could be hypothesized that peripheral facial paralysis may be both a late and an initial manifestation of COVID-19. Further studies on larger sample sizes are essential to determine the pathophysiological mechanisms that emphasize the existence of the symptoms of a SARS-CoV-2 infection, the persistence of the symptoms over time, and the symptoms' possible transformation into chronic conditions.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study was conducted with the permission of the Malatya Turgut Ozal University Clinical Research Ethics Committee with protocol number 2021/15, was in compliance with the Helsinki declaration.

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