

Neurotological Manifestations of Patients with COVID-19

COVID-19 Hastalarında Nöro-otolojik Semptomlar

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ABSTRACT Objective: To evaluate the frequency, discomfort level, duration, and laboratory tests of neurotological symptoms (hearing loss, hyperacusis and vertigo) and their association with eustachian tube dysfunction (ETD), smell and taste impairment in hospitalized patients with coronavirus disease-2019 (COVID-19). **Material and Methods:** The study prospectively enrolled a consecutive series of patients with COVID-19, who were hospitalized and followed up for the first 3 months. In addition to demographic data and laboratory test (the highest value for D-dimer, ferritin, C-reactive protein and neutrophil; the lowest value for fibrinogen, lymphocyte and platelet during hospitalization) results, a record was made of visual analogue scale scores of symptoms that present. The results were evaluated in three separate categories according to the presence or absence of neurotologic symptoms, according to gender and according to age as >60 years and <60 years. **Results:** A total of 141 patients completed the study. The frequency of all neurotological symptoms in the whole study population was determined as approximately 10%. The laboratory test results were seen to be similar in patients who experienced or did not experience at least one neurotological symptom (p=0.181). Most neurotological symptoms were seen along with smell and/or taste impairment; 61% of the patients with vertigo, 81% with hyperacusis, and 91% with hearing loss. All patients who experience ETD were detected to also experienced at least one neurotological symptom. Regarding age groups, 93% of the patients with hyperacusis, and 86% of patients with taste and smell impairment were in the <60 years age category (p=0.032). **Conclusion:** Neurotological symptoms are present in patients with COVID-19 and should be questioned. The vast majority of these symptoms are associated with smell and taste impairments. It should be kept in mind that patients with ETD symptom may experience additional neurotological symptoms.

Keywords: COVID-19; coronavirus; neurological manifestations; vertigo; eustachian tube

ÖZET Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] enfeksiyonu geçiren ve hastanede yatışı gerçekleştirilen hastalarda nöro-otolojik semptomların (işitme kaybı, hiperakuzi, baş dönmesi) sıklığı, rahatsızlık düzeyi, semptom süreleri ve laboratuvar sonuçlarının araştırılması ve bunların östaki tüpü disfonksiyonu (ÖTD), koku ve tat kaybı ile birlikteliklerini değerlendirmek. **Gereç ve Yöntemler:** Çalışmaya, prospektif olarak hastaneye yatışı gerçekleşen COVID-19 enfeksiyonu geçiren hastalar dâhil edilmiştir ve hastaların ilk 3 aylık süreci takip edilmiştir. Demografik veriler ve laboratuvar test sonuçlarına (D-dimer, ferritin, C-reaktif protein ve nötrofil değerlerinin en yükseği; fibrinojen, lenfosit ve platelet değerlerinin en düşüğü) ek olarak, sorgulanan semptomlar hastada mevcut ise bunların vizüel analog skala skorları kayıt edildi. Sonuçlar, nöro-otolojik semptomların varlığına veya yokluğuna göre cinsiyete ve yaşa göre (>60 ve <60 yaş) 3 ayrı kategoride değerlendirildi. **Bulgular:** Çalışmayı toplam 141 hasta tamamladı. Tüm çalışma popülasyonunda tüm nöro-otolojik semptomların sıklığı yaklaşık %10 olarak belirlendi. En az bir nöro-otolojik belirti yaşayan veya hiç yaşamayan hastalarda laboratuvar test sonuçları benzer izlendi (p=0,181). Nöro-otolojik semptom yaşayan hastaların çoğunda koku ve/veya tat bozukluğu olduğu tespit edildi; baş dönmesi olan hastaların %61'i, hiperakuzili hastaların %81'i ve işitme kaybı olanların %91'i. ÖTD yaşayan hastaların en az bir nöro-otolojik semptom yaşadığı saptandı. Yaş gruplarına göre hiperakuzili hastaların %93'ü, tat ve koku bozukluğu olanların %86'sı <60 yaş kategorisindeydi (p<0,032). **Sonuç:** Nöro-otolojik semptomlar, COVID-19 hastalarında belirli oranda mevcuttur ve hastalar bu semptomlar açısından sorgulanmalıdır. Bu semptomların büyük çoğunluğu koku ve tat bozuklukları ile birliktedir. ÖTD semptomu olan hastalarda ek nöro-otolojik semptom olabileceği akıld tutulmalıdır.

Anahtar Kelimeler: COVID-19; koronavirüs; nörolojik manifestasyonlar; vertigo; östaki tüpü

Coronavirus disease-2019 (COVID-19) is the infectious disease caused by novel coronavirus [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)], which has spread all over the globe as a

pandemic. At the point of starting vaccination programs, the number of confirmed cases of COVID-19 and deaths related to the disease has exceeded 75 million and 1.6 million since the start of the pandemic,

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respectively.¹ Patients infected with COVID-19 experience various symptoms, the most common being fever, cough, myalgia and fatigue. In addition to these symptoms, taste and smell disturbance without association of other sinonasal symptoms is commonly recognized.² Elderly patients and those with comorbidities are susceptible to more severe infection, which is considered to be related to a cytokine storm. Together with the genetic similarity to SARS-CoV, it has been hypothesized that COVID-19 also has similar neurotrophic features and many of the neurological manifestations.³⁻⁵ The exact causes of neurological manifestations have not been clarified regarding whether they are the result of neurotrophic features, cytopathic effect or inflammatory response. New symptoms related to the neurotrophic effect have attracted increasing attention as the pandemic has continued and progressed. Therefore, the potential effects on the inner ear have been investigated in those presenting with hearing and balance problems. Together with some anecdotal reports, one of the previous studies on this issue revealed a reduction in transient evoked otoacoustic emissions (TEOAE) in asymptomatic patients with positive COVID-19 polymerase chain reaction (PCR) results.⁶ Another study reported that patients experience dizziness, vertigo, hearing impairment and tinnitus at varying frequencies.⁷ It has also been reported that several patients who presented with acute-onset hearing loss and vertigo symptoms were confirmed as COVID-19-positive.^{8,9} Nevertheless, there is a limited information in the literature regarding the effect of COVID-19 on the audio-vestibular system and to the best of our knowledge this is the first study that searches eustachian tube dysfunction (ETD) and hyperacusis in patients with COVID-19.¹⁰

This study aimed to contribute to the physiopathology mechanism of the neurotological symptoms through the evaluation of the frequency, discomfort level, duration, and laboratory tests of neurotological symptoms (hearing loss, hyperacusis and vertigo). This study also evaluates the association of neurotological symptoms with ETD, smell and taste impairment in hospitalized patients with COVID-19.

MATERIAL AND METHODS

This prospective observational study was approved by the Ministry of Health, Republic of Turkey (Necmettin Erbakan University, Meram Faculty of Medicine, Ethics Committee for Non-drug and Non-medical Device Researches; Approval Number and Date: 2020/2857, 23.10.2020) and the Local Ethics Committee (Number: 2020/2857). All procedures followed were in accordance with the Declaration of Helsinki. The study included a consecutive series of patients with COVID-19 infection confirmed with a positive reverse transcription-PCR (RT-PCR) test and who were hospitalized between October and November 2020. The swab samples tested with RT-PCR were obtained from the nasopharynx and oropharynx. The clinical, laboratory and thorax computed tomography imaging results were used to support the diagnosis of COVID-19 infections. The patients included were aged between 18-90 years and were followed up by the department of pulmonology. Patients were excluded from the study if they had a history of any otolaryngology intervention, any neurological or mental disease. All patients signed an informed consent form to participate in the study. All patients who were positive for the neurotological symptoms during hospitalization were followed up for 3 months with phone calls after discharge. Patients who were negative for the symptoms during the hospitalization period were called in the first and third month follow-up to ascertain whether any otological symptom has emerged after discharge. During the study period, patients who were transferred to the intensive care unit, and those who died after discharge were excluded from the study. The demographic data, laboratory test results (the highest value for D-Dimer, ferritin, C-reactive protein and neutrophil; the lowest value for fibrinogen, lymphocyte and platelet during hospitalization) and the symptom score scale that questioned hearing loss, hyperacusis, vertigo, ETD, smell and taste symptoms were recorded. Patients were asked if they perceived any alterations in hearing, smell and taste symptoms and if so, the visual analogue scale (VAS) was used. Patients were requested to score the symptom severity between 0 and 10, where 0 represented no changes and 10 repre-

sented total loss. In addition to these symptoms, patients were questioned whether they had perceived any new onset of symptoms related to hyperacusis, vertigo and ETD. Hyperacusis was questioned as the new onset of feeling discomfort from noise and sounds. ETD was questioned as the new onset of feeling that the ears are clogged or “under water”. Vertigo was questioned regarding whether the patient felt a peripheral vertigo (sensation of motion of environment) or central vertigo (dizziness). If positive, the VAS was used again and patients were requested to score these new onset symptoms between 0 and 10, where 0 represented normal and 10 represented severe discomfort. This questionnaire was applied to the patients by an otolaryngology resident on the first day of hospitalization before the COVID-19 treatment was started. Patients who were diagnosed in the outpatient clinic and started treatment of COVID-19 before hospitalization were excluded to eliminate confusion that may be related to medication. The duration and severity of the symptoms were followed up with the telephone calls after discharge.

Patients were classified according to whether or not they had at least one peripheral neurological symptom (hearing loss, hyperacusis and vertigo) and the laboratory test results were compared between these groups. The patients were also categorized into two subgroups according to gender and age as >60 years and <60 years to search whether there is a differentiation related to the presence of questioned symptoms.

The data of the present study were analyzed statistically using SPSS version 22 software (SPSS, Chicago, IL, USA). In the descriptive analysis of the data, continuous variables were presented as median [interquartile range (IQR)] [minimum (min), maximum (max)] and categorical variables as frequencies and percentages. The normality distribution analysis of the data was evaluated using the Kolmogorov-Smirnov test and according to the results, non-parametric tests were used. The Mann-Whitney U test was used for the comparisons of numerical data of laboratory tests. The Kruskal-Wallis H test was used to compare the duration times and VAS scores of the symptoms and Dunnett’s T3 test was used as the “post hoc” test. The Pearson chi-square test and Fisher’s exact test (when the expected count was <5)

were used for the comparison of categorical symptom presence data. The value of $p < 0.05$ was considered statistically significant throughout the study.

RESULTS

A total of 200 patients were enrolled and 59 left follow-up, thus 141 patients completed the study with a median age of 49 ± 7 years (range, 18-82 years). The patients comprised 78 (55%) males and 63 (45%) females. The frequencies of all symptoms that were questioned are seen in Table 1. In the study group, taste impairment (35%), vertigo (29%) and smell impairment (27%) were the most common of all questioned symptoms. The frequencies of all neurotological symptoms were approximately 10% in the study population.

The median (IQR) of VAS scores and duration times are demonstrated in Table 1. The comparison of the VAS scores of all symptoms revealed that the hearing loss VAS score was lower than that of all other symptoms ($p = 0.003$). The median duration of the symptoms in patients who recovered was similar ($p = 0.186$). The laboratory test results of patients who experienced or did not experience at least one neurotological symptom are presented in Table 2 and the two groups were similar ($p = 0.181$).

Vertigo was present in 41 patients (28 dizziness, 13 spinning sensation) on initial hospitalization. With the exception of two patients with the sensation of motion or spinning symptoms, all the others recovered. The median duration of symptoms was similar for dizziness and sensation of motion or spinning [3 (2) (min: 1, max: 5), 2 (2) (min: 1, max: 8), respectively] ($p > 0.227$). An isolated vertigo symptom was determined in 16 patients (39%) (12 dizziness and 4 sensation of motion or spinning) and the other 25 patients also experienced smell and/or taste impairment together with vertigo.

Hyperacusis was present in 16 patients on initial hospitalization and 93% (15 patient) recovered. The median duration of the symptom was 4 (6) (min: 1, max: 9) weeks in patients who recovered. Hyperacusis was an isolated symptom in 3 of the 16 patients, and 13 patients also experienced smell and/or taste impairment with hyperacusis.

TABLE 1: The frequencies, median VAS scores and median duration of the neurotologic and other symptoms.

	N (%)	VAS scores	The duration (week) of the symptom [Median (IQR) minimum, maximum]	
		[Median (IQR) minimum, maximum]		
Neurotological symptoms	41 (29%)			
Vertigo				
Dizziness	28 (20%)	5 (3.75) (2-10)		3 (2) (1-5)
Spinning	13 (9%)	4 (3.5) (1-10)		2 (2) (1-8)
Hyperacusis	16 (11%)	6 (3) (5-9)		4 (6) (1-9)
Hearing loss	14 (10%)	3 (3) (1-5)	p=0.003*	3 (2) (2-5)
Other symptoms				
Eustachian tube dysfunction	17 (12%)	6 (3) (1-10)		2 (2) (1-4)
Taste	50 (35%)	7 (5) (1-10)		3 (2) (1-8)
Smell	38 (27%)	9 (5) (1-10)		3 (2) (1-8)

N: Number; VAS: Visual analog scale; IQR: Interquartile range; Tests: VAS scores and durations of all symptoms were compared with *Kruskal-Wallis H test and only the VAS score of the hearing loss differentiated from other symptoms.

TABLE 2: The laboratory test results of patients who experienced and did not experience at least one neurotological symptom.

	Group without any neurotological symptom	Group with at least one neurotological symptom	p value*
D-dimer (µg/mL)	271±463	304±408	0.884
Ferritin (ng/mL)	248±466	273±498	0.444
Fibrinogen (mg/dL)	500±230	459±3060.965	
CRP (mg/dL)	42±67	53±106	0.181
Leukocyte (Count) (10 ⁻³ /µL)	7.9±3.9	7.0±5.4	0.581
Neutrophil (Count) (10 ⁻³ /µL)	5.2±3.3	5.1±5.2	0.589
Lymphocyte (Count) (10 ⁻³ /µL)	1.0±0.8	1.1±0.7	0.933
Thrombocyte (Count) (10 ⁻³ /µL)	207±81	187±72	0.192

*Mann-Whitney U test; CRP: C-reactive protein.

Hearing loss was present in 11 patients on initial hospitalization and it was experienced by 3 patients after discharge. The symptom continued in 4 of 11 hospitalized patients (VAS scores indicated that 3 patients remained stable, 1 increased the score by 2 points, and in 7 the symptom was resolved). In the patients with hearing loss after hospital discharge, the median time from initial hospitalization to onset of the symptom was 4 weeks and all of these cases recovered with 1mg/kg steroid treatment. The median duration of the symptom was 3 (2) (min: 2, max: 5) weeks in patients who recovered. This was an isolated symptom in 1 patient, and 10 patients also experienced smell and/or taste impairment together with hearing loss.

The symptom of ETD was present in 17 patients on initial hospitalization, and all patients recovered. The median duration of the symptom was 2.5 (2) (min: 1, max: 4) weeks. All the patients who experienced ETD symptom also experienced at least one of the symptoms of hearing loss, hyperacusis or vertigo and there were no cases of isolated symptom.

At the time of initial hospitalization, 50 patients experienced taste and 38 patients experienced smell impairment. With the exception of 3 cases with taste impairment and 1 with smell impairment, all the other patients recovered. The median duration of the symptoms was 3 (2) (min: 1, max: 8) weeks for both impairments in patients who recovered. Two patients experienced an isolated smell

impairment symptom, and all the other patients also experienced taste impairment together with smell impairment.

Age group analysis revealed that taste impairment, smell impairment and hyperacusis symptoms were more frequent in patients aged <60 years. 43 (86%) of 50 patients with taste impairment ($p=0.007$), 33 (86%) of 38 patients with smell impairment ($p=0.019$) and 15 (93%) of 16 patients with hyperacusis ($p=0.032$) were in the <60 age category. The rest of the questioned symptoms were similar regarding the age groups. As shown in Table 3, all the symptoms were similar regarding gender.

DISCUSSION

Research and reported incidence of neurotological symptoms in patients with COVID-19 are scarce in the literature. This study is the first to have focused only on neurotology symptoms and the first to have questioned hyperacusis and ETD symptoms in patients with COVID-19. The most common peripheral neurological symptoms of smell and taste impairments were also questioned to evaluate the association with the neurotological symptoms. The results of the study revealed that the most common symptom was vertigo at 29% frequency, close to the frequency of taste (35%) and smell (27%) impairment symptoms. However, two-thirds of the vertigo patients (20%) defined their symptom as dizziness and only one-third (9%) reported the symptom as a sensation of motion or spinning. Each neurotological symptom was present in approximately 10% of the hospitalized patients with COVID-19. Of all the

symptoms, the one with the lowest degree of discomfort was hearing loss. This shows that if the hearing loss is not questioned, it can be easily missed. Patients complained of similar levels of discomfort from hyperacusis, peripheral vertigo and ETD as from taste and smell impairments. Moreover, hyperacusis was more frequently present in the younger population, similar to taste and smell impairment symptoms. The main duration of all symptoms questioned was similar in patients who recovered.

The symptoms of COVID-19 have a broad range and in the initial period of the pandemic, the focus was concentrated on life-threatening symptoms. However, it is now being realized that the virus has deleterious effects on specific organs and new symptoms are emerging if questioned. There is an increasing number of cohort studies that showed that the most common peripheral neurological symptoms are smell and taste impairment.^{7,11} One of the early reports about neurological manifestations of COVID-19 revealed that dizziness and headache were the most common central neurological symptom at rates of 16.8% and 13.1%, respectively. The same report reported 5% hyposmia and hypogesia as peripheral nervous system symptom in the study population.⁵ In contrast to these, recent articles are showing higher frequencies for smell and taste impairments.⁷ The current study results are also consistent with these reports and it was seen that the frequency of these symptoms is higher (both are approximately 30%) compared to the early reports at the beginning of the pandemic.

TABLE 3: The frequencies of the symptoms according to age and gender groups.

	Age <60 102 (72%)	Age >60 39 (28%)	p value	Male 78 (55%)	Female 63 (45%)	p value
Vertigo	31 (75%)	10 (25%)	$p=0.578^*$	20 (48%)	21 (52%)	$p=0.317^*$
Eustachian tube dysfunction	13 (76%)	4 (24%)	$p=0.467^*$	7 (41%)	10 (59%)	$p=0.211^*$
Hearing loss	9 (81%)	2 (19%)	$p=0.368^*$	3 (27%)	8 (73%)	$p=0.051^*$
Hyperacusis	15 (93%)	1 (7%)	$p=0.032^*$	6 (37%)	10 (63%)	$p=0.128^*$
Taste	43 (86%)	7 (14%)	$p=0.007^*$	27 (54%)	23 (46%)	$p=0.815^*$
Smell	33 (86%)	5 (14%)	$p=0.019^*$	19 (50%)	19 (50%)	$p=0.440^*$

*Pearson Chi-square test; *Fisher's exact test.

Although the similarity of COVID-19 to previous coronavirus infections (such as Middle East respiratory syndrome and SARS) regarding neurotrophic features has been mentioned, there is no information about whether previous viruses have caused audio-vestibular symptoms since the incidence is low compared to COVID-19.^{3,10} However, in the COVID-19 pandemic, there are two case reports which have hypothesized that there could be a possible link between infection and sudden hearing loss.^{8,9} In addition, a study of 20 COVID-19 cases revealed an increase in high frequency thresholds and a decrease in the amplitude of TEOAE.⁶ In the present study, patients were detected who suffered from hearing loss symptom in the initial period and the discomfort from hearing loss was lower than other neurotological symptoms. This is consistent with the findings of the study by Mustafa, which reported subtle deteriorations in outer hair cells, even in asymptomatic patients.⁶ Therefore, if not questioned, it is difficult to detect such symptoms as the patient is struggling with more severe symptoms (fever, fatigue, shortness of breath, muscle and lumbar pain etc.). Although the exact mechanism of hearing loss or neurological symptoms has not been detected, there are some possible pathophysiological mechanisms.

The first possible pathophysiological mechanism is the neurotrophic mechanism of the virus, which binds to the angiotensin converting enzyme-2 (ACE-2) receptor.¹² With many other cells such as lung cells, it has recently been shown that middle ear mucosa, Eustachian tube mucosa, stria vascularis, spiral ganglions, neurons and glial cells also express this receptor.¹³ In the present study, the reported frequencies of the symptoms and the results demonstrate that in the majority of cases, hearing loss, vertigo and hyperacusis are not isolated symptoms, but accompany taste and/or smell impairments, which supports the theory of neurotrophic mechanism. Furthermore, as the transmission of the virus is mainly through airborne droplets, the first entry points of the eye and upper respiratory tract are the most affected body parts. This study is the first to have revealed that some patients have complaints of ETD and it was seen that all 17 patients in

the current study population who experienced this symptom also had at least one other neurotological symptom. It can be speculated that the Eustachian tube can be the transmission route for a direct viral effect on the audio-vestibular system, likewise the route of smell impairment is considered transneuronal transportation via ACE-2 receptors in the cribriform plate.^{12,14}

The second mechanism thought to be responsible is the increased immune reaction, cytokine storm and tendency to thrombosis. In contrast to this hypothesis, the current study showed no difference between patients with and without neurotological symptoms regarding blood counts. In a previous study, Cure et al. stated that the cytosolic pH decrease with age could be responsible, which hypothetically could lead to facilitating the process of the viral binding to ACE-2 receptors.¹⁵ Consequently, the viral load and the immune reaction increase and this whole process might be the cause of microthrombosis; hearing loss and hyperacusis. In contrast to this assumption, in the current study patients, all the neurotologic symptoms were seen to be more frequent in the younger age group and hyperacusis showed a statistical significance similar to the taste and smell impairment symptoms. Although some previous studies have revealed that some other symptoms are more frequent in the elderly, one study showed that taste and smell impairment symptoms were more common in the <60 years age group.^{7,16} Furthermore, during the follow-up of the current study, patients were detected who experienced hearing loss in the 4th weeks after discharge, but all of these cases recovered with steroid treatment.

In terms of the symptom of vertigo, a recent study reported a remarkably higher frequency (31% for dizziness symptom and a 6% for true peripheral vertigo).⁷ The current study results are also consistent with these higher percentages. In addition, similar to hyperacusis, the majority (61%) of patients with vertigo also had smell and/or taste impairment symptoms, which again support the neurotrophic mechanism. The aforementioned study found that vertigo symptom was more common in female patients and those aged <60 years and female gender. However,

the current study results showed no difference in all neurotological symptoms according to age. Again, the laboratory findings were similar in patients who experienced vertigo.

CONCLUSION

In conclusion, the current study results demonstrated that audio vestibular symptoms are present in some patients with COVID-19 and should be questioned. Moreover, some patients might experience hearing loss after discharge and therefore should be followed up for a period of time. The vast majority of neurotological symptoms are associated with smell and taste disorders. Patients with ETD symptom experience at least one neurotological symptom, the neurotrophic mechanism can be considered more likely than the pathophysiological mechanism for neurotological symptoms in patients with COVID-19. Additionally, the Eustachian tube might be the transmission path for direct neurotrophic viral damage resulting in neurotological symptoms.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Fakih Cihat Eravcı, Malik Alaflifi, Mehmet Akif Dündar; **Design:** Fakih Cihat Eravcı, Malik Alaflifi; **Control/Supervision:** Şebnem Yosunkaya, Hamdi Arbağ; **Data Collection and/or Processing:** Malik Alaflifi, Mehmet Akif Dündar, Celalettin Korkmaz, Soner Demirbaş, Hülya Vatansev; **Analysis and/or Interpretation:** Fakih Cihat Eravcı, Malik Alaflifi, Soner Demirbaş, Hülya Vatansev; **Literature Review:** Fakih Cihat Eravcı, Mehmet Akif Dündar; **Writing the Article:** Fakih Cihat Eravcı, Mehmet Akif Dündar; **Critical Review:** Şebnem Yosunkaya, Hamdi Arbağ.

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