European Review for Medical and Pharmacological Sciences 2023; 27: 3201-3207

Diffusion-weighted imaging measurements of central smell regions in COVID-19 patients: insular gyrus, corpus amygdala, and thalamus

V. BURULDAY[1], N. BAYAR MULUK[2], M.H. AKGÜL[3], M.S. SAYAR[4]

[1]Department of Radiology, Faculty of Medicine, Inonu University, Malatya, Turkey
[2]Department of ENT, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey
[3]Neurosurgery Clinics, Yuksek Ihtisas State Hospital, Kırıkkale, Turkey
[4]Infectious Diseases and Clinical Microbiology Clinics, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

Abstract. – OBJECTIVE: The aim of this study was to investigate central smell centers with cranial magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) in COVID-19.

PATIENTS AND METHODS: This retrospective study evaluated cranial MRI images of 54 adults. The experimental group (Group 1), consisting of 27 patients with positive COVID-19 real-time Polymerase Chain Reaction (RT-PCR) assays, was compared to the control group (Group 2), comprising 27 healthy controls without COVID-19. The apparent diffusion coefficient (ADC) values were measured in the corpus amygdala, thalamus, and insular gyrus in both groups.

RESULTS: Thalamus ADC values of the COVID-19 group were significantly lower compared to the control group bilaterally. However, no differences were found in the insular gyrus and corpus amygdala ADC values between the two groups. Positive correlations were observed between the insular gyrus and corpus amygdala ADC values and the thalamus ADC values. Insular gyrus ADC values (right) were higher in females. Left insular gyrus and corpus amygdala ADC values were higher in COVID-19 patients with smell loss. Right insular gyrus and left corpus amygdala ADC values were lower in COVID-19 patients with lymphopenia.

CONCLUSIONS: Diffusion restriction in olfactory areas can be considered an obvious indicator that the COVID-19 virus affects and damages the immune system at the neuronal level. Given the urgency and lethality of the current pandemic, acute onset odor loss should be considered a high suspicion-adhesive index for patients with SARS-CoV-2 infection. Therefore, the sense of smell should be considered and evaluated simultaneously with other neurological symptoms. DWI should be widely used as an early imaging method for central nervous system (CNS) infections, especially in relation to COVID-19.

Key Words:
COVID-19, Diffusion-weighted imaging (DWI), Apparent diffusion coefficient (ADC), Cranial MRI, Central smell centers.

Introduction

Diabetes The coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), appeared in Wuhan, China in December 2019, causing a global pandemic. Recently, in addition to systemic and respiratory symptoms, it has been reported[1-4] that patients with COVID-19 have developed neurological symptoms, including headaches, disturbed consciousness, and paresthesia. Patients who are severely affected are more likely to develop neurological symptoms than patients with mild or moderate disease. COVID-19 has been shown[5,6] to have the potential to cause nerve system damage after confirming the presence of SARS-CoV-2 in cerebrospinal fluid with genome sequence. It is essential for clinicians to be aware of the effects of COVID-19 on the nervous system.

Central nervous system (CNS) infections and the recent SARS-CoV-2 pandemic remain a health problem worldwide. Viral infections have detrimental effects on neurological functions and can cause serious neurological damage. Therefore, an accurate diagnosis of a CNS infection should be made as soon as possible to ensure effective treatment options. Clinical and laboratory data are useful for differential diagnosis, but medical imaging is also important[1-3]. As magnetic resonance (MR) diffusion imaging provides high anatomical resolution and tissue contrast and multi-plane acquisition, it is the preferred

Corresponding Author: Veysel Burulday, MD; e-mail: vedoctor@hotmail.com

method for patients with a CNS infection. In addition, advanced MR imaging techniques, such as MR diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI), help in the diagnostic evaluation by providing metabolic and functional information about lesions. Of these advanced techniques, DWI provides potentially unique information about the viability of brain tissue because the findings in the image depend on the molecular movement of water that can be significantly altered by infectious diseases. Therefore, DWI is the most widely used evaluation method for CNS infections because it gives findings according to the placement of each infection[7,8].

It has been found[9] recently that coronaviruses (CoVs), particularly SARS-CoV-2, exhibit neurotropic properties and can also cause neurological diseases. As the pathobiology of these neuroinvasive viruses in the brain or cerebrospinal fluid is still not fully known, it is essential to investigate the effect of CoV infections on the nervous system. Recent reports[10] also indicate that anosmia, the loss of smell, is among the symptoms associated with SARS-CoV-2.

It has long been known[9] that viral neurotropic viruses begin with symptoms such as decreased or loss of odor or taste. The clinical evaluation of the first cranial nerve was usually unquestioned during the physical examination of the patients[11,12].

Odor impairment is often seen in the most serious cases or occurs late in the diagnosis. However, the absence of advanced neuroimaging studies in the acute stage, difficulty evaluating the odor, and the lack of histopathological tissue samples and/or infected olfactory neuroepithelial viral cultures make it difficult to examine this event. In addition, sensorineural viral anosmi patients tend to be rare in the context of normal transnasal airflow of olfactory molecules and in the absence of intranasal disease[12].

Therefore, until the recent SARS-CoV-2 pandemic, the prevalence of sensorineural viral anosmia in society was low overall. It is the end protein that performs the front-line action for the virus by performing the initial receptor recognition with the human angiotensin converting enzyme-2 receptor (hACE2). hACE2 has this interaction with viral spike protein, which is at the center of viral infection[13]. Here, we investigated the radiologic findings of CoV infections on central smell centers using cranial MRI diffusion-weighted imaging (DWI).

Patients and Methods

This retrospective study was conducted at the Van Training and Research Hospital, in the Infectious Diseases and Radiology Departments and at the Kırıkkale University Faculty of Medicine, in the Otolaryngology Department according to the principles of the Declaration of Helsinki. Cranial magnetic resonance imaging (MRI) values images were obtained from a database of the Van Training and Research Hospital Radiology Department. TR Ministry of Health, COVID-19 Scientific Research Evaluation Commission approval was obtained (2020-06-12T08_07_57), and Ethics Committee approval was obtained from Van Training and Research Hospital, Clinical Research Ethics Committee (Date: August 20, 2020, Number: 2020/16).

Subjects

This study was performed retrospectively. Cranial MRI images of 54 adult patients were screened and selected from a database of Van Training and Research Hospital. Group 1 consisted of 27 patients (16 males and 11 females) with positive COVID-19 real-time polymerase chain reaction (RT-PCR) (Qiagen Rotor GeneQ) assays. Diagnoses of COVID-19 were detected using examples of oropharyngeal and nasopharyngeal sweep. The mean age of the patients was 35.25 ± 13.99 (18-75) years. Cranial MRIs were taken because COVID-19 (+) patients reported having a headache.

In the COVID-19 group, smell loss, nasal obstruction and nasal discharge presence were evaluated from the Hospital data. Thoracal CT was taken from all COVID-19 patients and involvement were evaluated. Disease duration and treatment duration were also noted. Leukocyte count and lymphocyte count were measured for all patients, and lymphopenia (Lymphocyte count $\leq 800/mm^3$) were evaluated. Moreover, C-reactive protein (CRP) (mg/L), D-dimer (ng/mL) and ferritin (ng/mL) values were also detected.

The control group (Group 2) consisted of 27 healthy controls without COVID-19 (16 males, 11 females) with normal cranial MRI results. They were selected from Van Training and Research Hospital's database of Radiology Clinics. The mean ages of them were 35.62 ± 13.47 (20-74) years.

Subjects with previous trauma, sinonasal or cranial surgery, sinonasal polyposis, sinonasal

cerebrospinal fluid (CSF) leak, marked facial and/or nasal septal deformity, multiple sclerosis, Alzheimer, Parkinson's diseases and epilepsy were not included in the study.

Cranial MRI Measurements

MRI examinations were performed by 1.5 Tesla MRI (General Electric MRI Systems, Signa 12/2010, General Electric Company, Milwaukee, WI, USA.), using the cranial coil.

Diffusion-weighted imaging (DWI) echo-planar pulse sequence [TR msn/TE msn; 8500/100, deflection angle 90°, field of view (FOV) 200 x 200 mm, matrix 128 x 128 mm] was achieved in the axial plane using a 5-mm slice thickness and 1-mm intersection gap; and 20-25 sections were obtained. All images were used with two different *b*-values (0 and 1,000 s/mm^2). Apparent diffusion coefficient (ADC) mapping was reconstructed from these images with the commercially available software.

All regions of interest (ROI) were elliptical and were drawn on to the ADC mapping images by the software system. The areas of ROIs were 50-80 mm^2 in corpus amygdale (Figure 1), 50-120 mm^2 in the thalamus (Figure 2). The three ROIs (25-50 mm^2) were placed in the right and left sides for the Insular gyrus (Figure 3) and the mean ADC values were calculated for statistical comparisons.

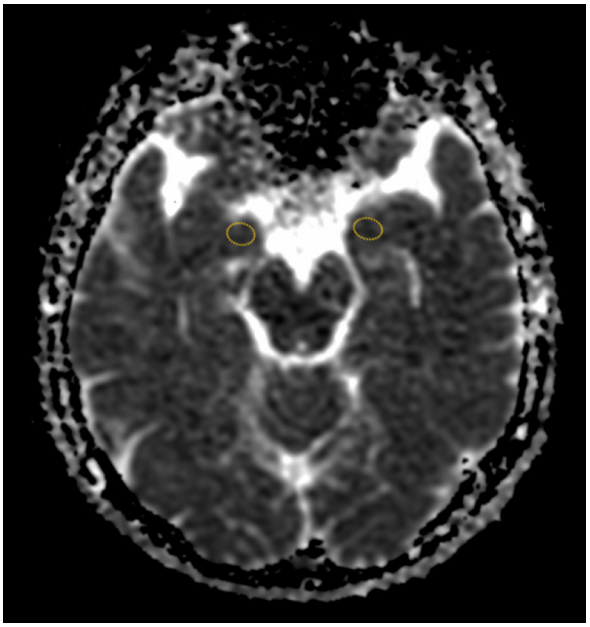

Figure 1. An adult male with COVID-19 disease. On axial ADC map of bilateral corpus amygdala was demonstrated. ADC values (magnification: x 10^{-6} mm^2/s) were measured (right corpus amygdala; 827, left corpus amygdala; 809).

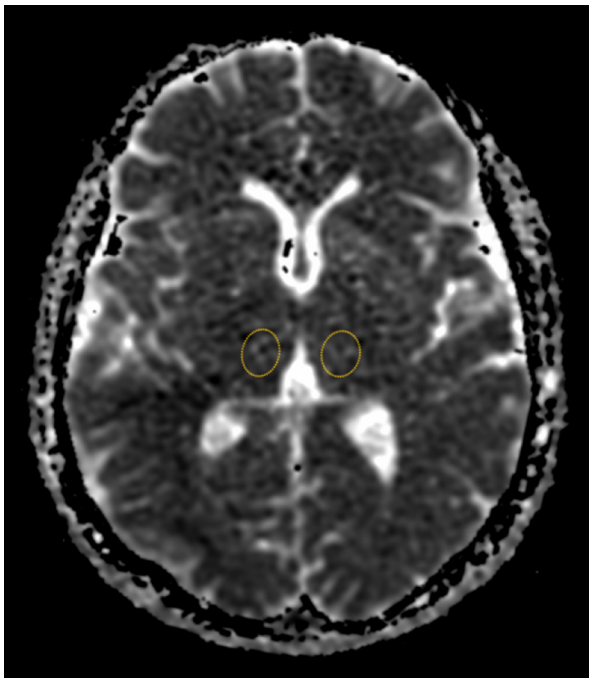

Figure 2. An adult male with COVID-19 disease. On axial ADC map of bilateral thalamus was demonstrated. ADC values (magnification: x 10^{-6} mm^2/s) were measured (right thalamus; 774, left thalamus; 771).

All measurements were evaluated by a single radiologist.

Statistical Analysis

SPSS for Windows 16.0 (SPSS Inc., Chicago, IL, USA), independent samples *t*-test, paired samples *t*-test, Pearson's correlation test and Spearman's correlation rho efficient tests were used. *p*-value<0.05 was considered as statistically significant.

Results

Features of the COVID-19 Group

Smell loss was present in 11 (40.7%) and absent in 16 (59.3%) of the patients. In none of the patients there were nasal obstruction or nasal discharge.

Thoracal CT involvement was detected in 12 (44.4%) and absent in 15 (55.6%) of the COVID-19 patients.

The mean of the disease duration was 2.81 ± 2.38 days (0-10 days). The mean of the treatment duration was 5.55 ± 1.60 days (5-10 days).

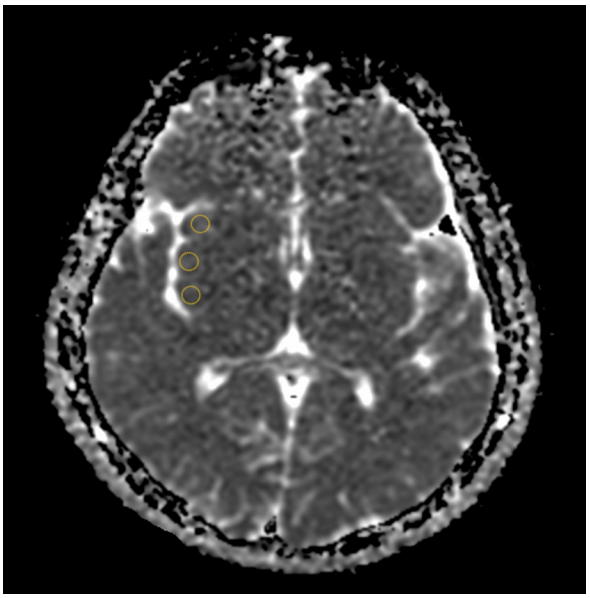

Figure 3. An adult female with COVID-19 disease. On axial ADC map of right insular gyrus was demonstrated. Mean ADC values (magnification: x 10^{-6} mm^2/s) were measured (right insular gyrus; 864).

The mean of the leukocyte count was 5,928.14 ± 1,738.57/mm^3 (1,380-9,570/mm^3). The mean of the lymphocyte count was 1,457.03 ± 713.82/mm^3 (450-3,350/mm^3).

Lymphopenia was present in 6 (22.2%) and absent in 21 (77.8%) patients. The mean of the CRP was 7.70 ± 8.87 mg/L (0.21-43.10 mg/L). The mean of the D-dimer was 179.33 ± 279.96 ng/mL (11-1,125 ng/mL). The mean of the ferritin was 176.79 ± 225.41 ng/mL (5.64-1,094.00 ng/mL).

Diffusion-weighted imaging (DWI) ADC values measurement results in both groups are shown in Table I.

Insular Gyrus ADC Value

There were no significant differences between the insular gyrus ADC values of the Group 1 (COVID-19 group) and the control group bilaterally ($p>0.05$). In each of the groups, 1 and 2 separately, there were no significant differences between insular gyrus ADC values on the right and left sides ($p>0.05$) (Table I).

Corpus Amygdala ADC Value

There were no significant differences between corpus amygdale ADC values of the Group 1 (COVID-19 group) and control group bilaterally ($p>0.05$). In each of the groups, 1 and 2 separately, there were no significant differences between corpus amygdale ADC values on the right and left sides ($p>0.05$) (Table I).

Thalamus ADC Value

Thalamus ADC values of Group 1 (COVID-19 group) were significantly lower than those in the control group bilaterally ($p<0.05$). In COVID-19 group, the mean of the thalamus ADC values were 781.85 and 780.03 (x 10^{-6} mm^2/s) in the right and left sides, respectively. However, these

Table I. ADC measurement results in both groups.

		Group 1 (COVID-19 Group) (n=27)			Group 2 (Control group) (n=27)			p*
		Mean	Median	Std. Dev	Mean	Median	Std. Dev.	
Age		35.25	35.00	13.99	35.62	33.00	13.47	0.921
Measurements results								
Insular gyrus ADC values (x10^{-6} mm^2/s)	R	853.96	854.00	44.77	855.51	860.00	27.98	0.879
	L	846.70	841.00	47.36	851.40	852.00	29.21	0.662
	p**	0.220			0.371			
Corpus amygdala ADC values (x10^{-6} mm^2/s)	R	820.48	815.00	38.83	837.5185	839.0000	32.61	0.087
	L	813.88	809.00	36.99	828.3704	830.0000	24.87	0.097
	p**	0.308			0.145			
Thalamus ADC values (x10^{-6} mm^2/s)	R	781.85	788.00	42.48	811.07	813.00	36.08	0.009
	L	780.03	786.00	44.45	806.74	809.00	34.69	0.017
	p**	0.781			0.364			

* *p*-value shows the results of independent samples *t*-test. ** *p*-value shows the results of paired samples *t*-test.

values were 811.07 and 806.74 (x 10^{-6} mm^2/s) respectively in the control group. In both groups separately, there were no significant differences between thalamus ADC values on the right and left sides ($p>0.05$) (Table I).

Correlation Test Results in Group 1 (COVID-19 Group)

- There were positive correlations between the insular gyrus and corpus amygdala ADC values bilaterally ($p<0.05$) (Table II).
- There were positive correlations between right and left thalamus ADC values ($p<0.05$) (Table II).
- In females, right insular gyrus ADC values were higher than that of the males ($p<0.05$) (Table II).
- In COVID-19 patients with smell loss, left insular gyrus and corpus amygdala ADC values were higher than that of the COVID-19 patients without smell loss ($p<0.05$) (Table II).
- In COVID-19 patients with lymphopenia, right insular gyrus and left corpus amygdala ADC values decreased compared to COVID-19 patients without lymphopenia ($p<0.05$) (Table II).

Discussion

The Previous studies[13] on SARS-CoV and MERS-CoV has been related to transgenic mice being infiltrated into their brains through the nose. The infiltration of the virus to the brain occurs through the olfactory nerves and eventually affects the thalamus and the brain stem. Mitral cells are reflected in the limbic structures for the smell, including the anterior olfactory nucleus, smell tubercule, smell cortex, amygdale, and entorhinal cortex. On the other hand, the olfactory bulb has retrograded connections with the cholinergic diagonal part, serotonergic dorsal raphe, and noradrenergic locus coeruleus[14]. In addition, dopaminergic neurons in the ventral tegmental region are reflected in the pre-odor smell nucleus. After entering the olfactory bulb, neurotropic viruses can infect the brain in both anterograde and retrograde ways. The olfactory system has several unique features that are not unique to other sensory systems. First, receptor molecules of olfactory neurons are exposed directly to the external environment so that they can respond to volatile chemical stimuli. Second, these neurons have the capacity to take exogenous substances to CNS and transsynaptic transport. Third, the smell system makes direct connections to the frontal cortex without a thalamic warning, while other sensory paths of visual, auditory, and somatosensory modalities are constantly passed on to the thalamus[14-16].

Affecting the brain stem is accepted as a serious indicator of infection. Apart from hematologic spread, retrograde neuronal transport of the virus from lungs to CNS *via* vagal nerve afferents is also possible[17]. In some cases, parenchymal changes detected on DWI and characterized by hyperintensity before abnormalities are recorded in traditional MR imaging sequences such as DWI, T2 weighted and fluid-attenuated inversion recovery (FLAIR) images. The decrease in water diffusion causes cytotoxic edema and is usually associated with irreversible neuronal damage and poor outcome, which is related to necrosis. DWI can also reveal[7,8] more expansion and more lesions than T2-DWI and is the preferred method for monitoring treatment responses. Facilitated diffusion with apparent diffusion coefficient (ADC) values, then occur in parallel with the development of vasogenic edema and encephalomalacia.

In the present study, we investigated diffusion-weighted imaging (DWI) ADC values measurements of central smell regions (insular gyrus, corpus amygdale, and thalamus) in COVID-19 positive patients by MRI. In COVID-19 positive patients, thoracal CT involvement was detected in 44.4% and smell loss complaint was present in 40.7%. Lymphopenia was present in 22.2%; and CRP, D-dimer, and ferritin values increased.

Our measurements showed that thalamus ADC values of Group 1 (COVID-19 group) were significantly lower than the control group bilaterally. However insular gyrus and corpus amygdala ADC values were not different between the COVID-19 and control groups. In each of the groups, ADC values were not different between the right and left sides.

Insular gyrus and corpus amygdala ADC values, and thalamus ADC values showed positive correlations. Insular gyrus ADC values (right) were higher in females. Left insular gyrus and corpus amygdala ADC values were higher in COVID-19 patients with smell loss. In terms of smell, this shows that women's odor receptors are affected earlier than men[18].

In COVID-19 patients with olfactory loss, left insular gyrus and corpus amygdala ADC values were higher than COVID-19 patients with no odor loss. In addition, another analysis result of

Table II. Correlation test results in Group 1 (COVID-19 group).

			Insular gyrus ADC values		Corpus amygdala ADC values		Thalamus ADC values	
			R	L	R	L	R	L
Insular gyrus ADC values	R	r		0.789	0.406	0.442	0.228	0.098
		*p**		0.000	0.035	0.021	0.253	0.626
	L	r	0.789		0.387	0.573	0.175	0.130
		*p**	0.000		0.046	0.002	0.382	0.517
Corpus amygdala ADC values	R	r	0.406	0.387		0.623	0.302	0.302
		*p**	0.035	0.046		0.001	0.126	0.126
	L	r	0.442	0.573	0.623		0.239	0.125
		*p**	0.021	0.002	0.001		0.230	0.534
Thalamus ADC values	R	r	0.228	0.175	0.302	0.239		0.702
		*p**	0.253	0.382	0.126	0.230		0.000
	L	r	0.098	0.130	0.302	0.125	0.702	
		*p**	0.626	0.517	0.126	0.534	0.000	
Age		r	0.249	0.191	0.309	0.409	0.030	-0.133
		*p**	0.211	0.340	0.117	0.034	0.883	0.507
Gender (Code 1: Male, Code 2: Female)		r	0.383	0.126	0.068	0.126	-0.034	-0.121
		*p***	0.049	0.532	0.737	0.532	0.867	0.548
Smell loss (Code 1: Present, Code 0: Absent)		r	0.291	0.470	0.208	0.653	0.073	-0.208
		*p***	0.141	0.013	0.298	0.000	0.719	0.297
Disease duration (days)		r	-0.066	-0.188	0.293	0.152	0.173	0.142
		*p**	0.745	0.347	0.138	0.450	0.387	0.479
Treatment duration (days)		r	0.053	0.053	0.166	0.030	0.114	0.136
		*p***	0.793	0.793	0.407	0.881	0.573	0.498
CRP (mg/L)		r	-0.044	-0.160	-0.020	-0.004	-0.100	-0.123
		*p**	0.829	0.424	0.923	0.986	0.621	0.540
D-dimer (ng/mL)		r	-0.064	-0.213	-0.100	-0.063	-0.109	-0.224
		*p**	0.752	0.285	0.621	0.753	0.588	0.261
Ferritin (ng/mL)		r	-0.190	-0.257	0.014	0.079	0.138	0.135
		*p**	0.341	0.196	0.943	0.694	0.492	0.503
Leukocyte count/mm3		r	-0.036	0.032	0.031	0.121	-0.241	-0.226
		*p**	0.857	0.874	0.878	0.547	0.226	0.257
Lymphopenia (Lymphocyte count ≤800/mm3) (Code 1: Present, Code 0: Absent		r	-0.412	-0.240	-0.240	-0.400	0.120	-0.006
		*p***	0.033	0.227	0.227	0.038	0.551	0.977
Thorax CT involvement (Code 1: Present, Code 0: Absent)		r	0.062	0.091	0.000	0.316	-0.062	-0.187
		*p***	0.758	0.652	1.000	0.108	0.758	0.351

**p*-value shows the results of Pearson's correlation test. ***p*-value shows the results of Spearman's correlation rho efficient test.

the clinical imaging and blood test supporting each other, in COVID-19 patients with lymphopenia, the ADC values of the right insular gyrus and left corpus amygdala decreased compared to COVID-19 patients without lymphopenia. Right insular gyrus and left corpus amygdala ADC values were lower in COVID-19 patients with lymphopenia. Restriction of diffusion in olfactory areas can be considered as an indicator of damage at the neuronal level that maybe associated with the involvement of the immune system with the COVID-19 virus.

Looking at the assessment of the central smell areas, this study revealed that the most affected area is the thalamus[19].

Conclusions

In SARS-CoV-2[20], given the urgency and lethality of the current pandemic, patients with acute onset odor loss should be considered as a high suspicion-adhesive index for the accompanying SARS-CoV-2 infection. However, it is still too early

to definitively determine the incidence of these symptoms and full-spectrum clinical benefit. CoV infections can affect the nervous system and CoV's host immune mechanisms. These infections can cause permanent damage that can lead to neurological diseases. Therefore, the sense of smell should also be considered and evaluated simultaneously with other neurological symptoms, including headaches, consciousness disorders, paresthesia, and other pathological symptoms in patients with CoV infection. DWI should be widely used as an early imaging method for CNS infections and especially in relation to COVID-19. Treatment of infectious neurological complications is key to improving the prognosis of critical patients.

Conflict of Interest

The Authors declare no conflict of interests.

Funding

There are no financial disclosures of the authors.

Informed Consent

There is no need to take informed consent, because the data were evaluated retrospectively.

Ethics Approval

TR Ministry of Health, COVID-19 Scientific Research Evaluation Commission approval was obtained (2020-06-12T08_07_57), and Ethics Committee approval was obtained from Van Training and Research Hospital, Clinical Research Ethics Committee (Date: August 20, 2020, Number: 2020/16).

References

1) Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol 2020; 19: 767-783.
2) Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg 2020; 194: 105921.
3) Bridwell R, Long B, Gottlieb M. Neurologic complications of COVID-19. Am J Emerg Med 2020; 38: 1549.
4) Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol 2020 1; 70: 311-322.
5) Domingues RB, Mendes-Correa MC, de Moura Leite FBV, Sabino EC, Salarini DZ, Claro I, Wagner S, de Jesus JG, Ferrira NE, Romano CM, Soares CAS. First case of SARS-COV-2 sequencing in cerebrospinal fluid of a patient with suspected demyelinating disease. J Neurol 2020; 267: 3154-3156.
6) Hung EC, Chim SS, Chan PK, Tong YK, Ng EK, Chiu RW, Leung CB, Sung JJY, Tam JS, Dennis Lo YM. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. Clin Chem 2003; 49: 2108-2109.
7) Gasparetto EL, Cabral RF, da Cruz LC Jr, Domingues RC. Diffusion imaging in brain infections. Neuroimaging Clin N Am 2011; 21: 89-113, viii.
8) Bulakbasi N, Kocaoglu M. Central nervous system infections of herpesvirus family. Neuroimaging Clin N Am 2008; 18: 53-84.
9) Xydakis MS, Mulligan LP, Smith AB, Olsen CH, Lyon DM, Belluscio L. Olfactory impairment and traumatic brain injury in blast-injured combat troops: a cohort study. Neurology 2015; 84: 1559-1567.
10) Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, Rusconi S, Gervasoni C, Ridolfo AL, Rizzardini G, Antinori S, Galli M. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis 2020; 28: 889-890.
11) Xydakis MS, Belluscio L. Detection of neurodegenerative disease using olfaction. Lancet Neurology 2017; 16: 415-416.
12) Desforges M, Le Coupanec A, Brison E, Pinard MM, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. Adv Exp Med Biol 2014; 807: 75-96.
13) Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020; 92: 552-555.
14) Xu F, Greer CA, Shepherd GM. Odor maps in the olfactory bulb. Comp Neurol 2000; 422: 489-495.
15) Tsodyks M, Gilbert C. Neural networks and perceptual learning. Nature 2004; 431: 775-781.
16) Wilson DA, Stevenson RJ. Olfactory perceptual learning: the critical role of memory in odor discrimination. Neurosci Biobehave Rev 2003; 27: 307-328.
17) Toljan K. Letter to the Editor Regarding the Viewpoint "Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanism. ACS Chem Neurosci 2020; 11: 1192-1194.
18) Oliveira-Pinto AV, Santos RM, Coutinho RA, Oliveira LM, Santos GB, Alho ATL, Leite REP, Farfel JM, Suemoto CK, Grinberg LT, Pasqualucci CA, Filho WJ, Lent R. Sexual Dimorphism in the Human Olfactory Bulb: Females Have More Neurons and Glial Cells than Males. PLoS ONE 2014; 9: e111733.
19) Shepherd GM. Perception without a Thalamus: How Does Olfaction Do It? Neuron 2005; 46: 166-168.
20) Meo SA, Meo AS, Al-Jassir FF, Klonoff DC. Omicron SARS-CoV-2 new variant: global prevalence and biological and clinical characteristics. Eur Rev Med Pharmacol Sci 2021; 25: 8012-8018.