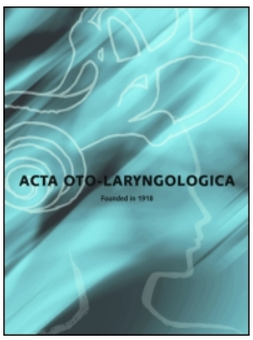

Acta Oto-Laryngologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ioto20

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To cite this article: Bünyamin Güney, Ferda Bacaksızlar Sarı, Murat Yunus Özdemir, Neşat Çullu, Emrah Doğan & Turhan Togan (2021): Changes in olfactory bulbus volume and olfactory sulcus depth in the chronic period after COVID-19 infection, Acta Oto-Laryngologica, DOI: 10.1080/00016489.2021.1946138

To link to this article: https://doi.org/10.1080/00016489.2021.1946138

Published online: 21 Jul 2021.

ACTA OTO-LARYNGOLOGICA
https://doi.org/10.1080/00016489.2021.1946138

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RESEARCH ARTICLE

Changes in olfactory bulbus volume and olfactory sulcus depth in the chronic period after COVID-19 infection

Bünyamin Güney[a], Ferda Bacaksızlar Sarı[b], Murat Yunus Özdemir[a], Neşat Çullu[a], Emrah Doğan[a] and Turhan Togan[c]

[a]Department of Radiology, Muğla Sıtkı Koçman University Medical Faculty, Muğla, Turkey; [b]Ministry of Health Muğla Training and Research Hospital, Muğla, Turkey; [c]Department of Infectious Diseases, Muğla Sıtkı Koçman University Medical Faculty, Muğla, Turkey

ABSTRACT

Background: Although there are a limited number of studies investigating the changes in olfactory bulb volume (OBV) and olfactory sulcus depth (OSD) values in the acute and subacute periods after COVID-19 infection, there are no studies conducted in the chronic period.

Purpose: The aim of this study is to reveal the changes in OBV and OSD after COVID-19 in the chronic period.

Material and methods: A total of 83 people were included in our study, including 42 normal healthy individuals (control group) and 41 patients with COVID-19 infection (10–12 months after infection).

Results: The COVID-19 group included 41 patients with the mean age 40.27 ± 14.5 years and the control group included 42 individuals with the mean age 40.27 ± 14.4. The mean OBV was 67.97 ± 14.27 mm^3 in the COVID-19 group and 94.21 ± 7.56 mm^3 in the control group. The mean OSD was 7.98 ± 0.37 mm in the COVID-19 group and 8.82 ± 0.74 mm in the control group. Left, right, and mean OBVs and OSD were significantly lower in patients with COVID- 19 than the control individuals (all $p < .05$).

Conclusion: Our findings show that COVID-19 infection causes a significant decrease in the OBV and OSD measurements in the chronic period.

ARTICLE HISTORY
Received 22 April 2021
Accepted 9 June 2021

KEYWORDS
COVID-19; olfactory bulbus volume; olfactory sulcus depth; 3 Tesla MRI

Introduction

Considering the current literature information, it is now known that the SARS-CoV-2 virus causes olfactory dysfunction in some cases besides the symptoms caused by respiratory tract involvement [1]. Several recent studies have found that the frequency of developing odor disturbance symptoms in COVID-19 infection patients is as high as 74–85% [2–4]. However, there are studies in which this rate was found to be very low (5–11.5%), and the literature on this subject has a heterogeneous structure [5,6]. As a result of the meta-analysis study conducted on this subject, the rate of development of olfactory dysfunction was found to be 45% [7]. The pathogenesis of the highly developing olfactory dysfunction in COVID-19 infection is currently not fully defined. Possible causes for this include viral inflammation or blockage of the olfactory cleft and/or damage to the olfactory bulb [8].

Magnetic resonance imaging (MRI) method is a useful anatomical imaging technique that is successfully used to evaluate olfactory dysfunction in normal individuals and those who develop olfactory disorders for many different reasons (such as infection, trauma, psychiatric diseases, metabolic diseases, and neurodegenerative processes) and to measure Olfactory bulbus volume (OBV) and olfactory sulcus depth (OSD) [9].

There are limited studies on radiological imaging of the olfactory bulbus in COVID-19 infection related olfactory dysfunction. The unvarying radiological findings in all studies observed in the olfactory bulb were decreased size and olfactory bulb micro-bleeding. However, the signal intensity changing is described as one of the findings in some paper, while the others claim that this finding is not a part of olfactory bulb atrophy [10–13]. In a recent study from these studies, the shape of the olfactory bulb, signal characteristics, OBV and OSD measurements and olfactory tests were evaluated together in patients with olfactory dysfunction due to COVID-19 infection [13]. All of these studies were conducted either in the acute phase of COVID-19 infection or in the 1–4 months following the infection. Considering the heterogeneity in the literature regarding olfactory dysfunction associated with COVID-19 infection, we could not find a study investigating the changes in OBV and OSD values in the chronic period after COVID-19 infection, regardless of whether or not olfactory dysfunction developed in these cases.

This study aims to reveal the differences between OBV and OSD measurements at least 10–12 months after the disease in chronic postinfectious cases whose COVID-19 infection.

CONTACT Bünyamin Güney bunyaminguney@mu.edu.tr Department of Radiology, Muğla Sıtkı Koçman University Medical Faculty, Muğla 48000, Turkey

Material and methods

Patient selection

This study is a prospective study that includes the measurements of OBV and OSD 10–12 months after the disease in patients who developed olfactory dysfunction due to COVID-19 between March and May 2020. All of the patients included in the study had olfactory disturbances during viral infection, and the diagnosis of COVID-19 infection was confirmed by a polymerase chain reaction (PCR) being a stick test. The control group consists of adult healthy individuals who have been proven to be free from COVID-19 infection by PCR test and serum antibody test. As for both groups, pediatric and pregnant patients were not included in the study. In addition, patients with previous olfactory disorders, head trauma, psychiatric disease, chronic allergic rhinitis, and neurological-neurodegenerative disease were excluded from the study.

With the approval of our ethics committee, informed consent was obtained from all individuals who participated in the study. The study was conducted on the basis of and in accordance with the declaration of Helsinki.

Evaluation of olfactory dysfunction

In this study, we used visual analog scale (VAS) to demonstrate olfactory dysfunction. The VAS consists of a 10 cm line with maximum and minimum extremes at both ends. The subjects participating in the study were asked to indicate their sense of smell by marking the appropriate point between the two extreme expressions defined as 1 (anosmia) and 10 (normal).

MRI evaluation

OBV and OSD measurements were made on T2-weighted brain MRI in the coronal plane obtained on a 3 Tesla MRI (Siemens Skyra, Berlin, Germany) device. Our imaging parameters were 256 × 256 matrix and 22 cm field of view (FOV), repetition time = 3500 ms (TR 3500 ms), echo time = 75 ms (TE 75 ms), excitation number = 2 (NEX 2), and a slice thickness of 3 mm. OBV and OSD measurements were made by two experienced radiologists who had no knowledge of the cases.

Volumetric measurement of OBV was made using 3D Slicer software (3D Slicer software ver. 4.2.2-1, http://www.slicer.org). The Slicer volumetric measurement program is a free open-source software package developed by Harvard University and approved for medical research. After dividing the olfactory bulbus into sections with appropriate threshold values in the coronal image, separate MRI numbers were assigned to each image with the slicer software. Region of interest (ROI) was adjusted to not exceed the anatomical contours of the bulb. After each slice containing the relevant OB sections was revealed, a 3D graphical model of the OB was created and volume calculation was made. Intra-observer variability was set at less than 5%.

Statistical analysis

Statistical evaluation was done using the IBM SPSS version 20.0 software (IBM Corp, Armonk, NY). Normal distribution was checked with the Shapiro–Wilk test. Descriptive data were shown as mean ± standard deviation. Independent samples *t*-test was used for evaluating the statistical differences between COVID-19 infection and control groups for OBV and OSD. Pearson chi-square (χ^2) analysis was used to determine the gender distribution for both groups. p value $<.05$ was accepted as statistically significant.

Results

A total of 83 patients, 41 of whom had a history of smell disorder due to COVID-19, and 42 of whom were adult healthy individuals, were included in the study. Patients with COVID-19 consisted of 21 (51.22%) females and 20 (48.78%) males. In the VAS test performed to evaluate olfactory dysfunction in this group, 3 patients were anosmic and 38 patients were hyposmic (mean 3.39 ± 1.46, minimum 1 and maximum 6). The control group consisted of 20 men (47.62%) and 22 women (52.38%).

The mean age for the COVID-19 group was 40.27 ± 14.5 years, while the mean age for the control group was 40.27 ± 14.4 years. There was no statistical difference in the evaluation in terms of age for both groups. In addition, the significant gender distribution difference was not found ($p > .743$). The mean OBV in the COVID-19 group was 67.97 ± 14.27 mm^3 (range 40.5 and 99 mm^3). In the control group, OBV was calculated as 94.21 ± 7.56 mm^3 (range 75.2–115.2 mm^3). In the COVID-19 group, the right, left and mean OBV were significantly lower than the control group ($p < .05$) (Figures 1 and 2).

When we compare both groups in terms of OSD, the mean OSD value in the COVID-19 group was measured as 7.98 ± 0.37 mm (range 6–9.8 mm). The OSD value in the control group was found to be 8.82 ± 0.74 mm (range 7.1–10.8 mm). Similar to OBV, OSD values were significantly lower in the group of post-COVID-19 compared to the control group ($p < .05$). Right, left, and average OBV and OSD values for both groups are shown in Table 1.

Discussion

Our study has several important results. The first of these is that OBV significantly decreases in the chronic period in individuals who have had COVID-19 infection and who have smell disorder during their disease. Second, OSD values were found to be lower in the chronic period compared to normal healthy cases.

In a study showing changes in the brain and central olfactory system in patients with recovering COVID-19 infection, it is stated that SARS-Cov-2 uses the olfactory bulbus-mediated neuronal retrograde pathway according to the volume changes in the central olfactory regions [14]. In addition, there are studies in the literature showing a decrease in OBV in patients who develop olfactory

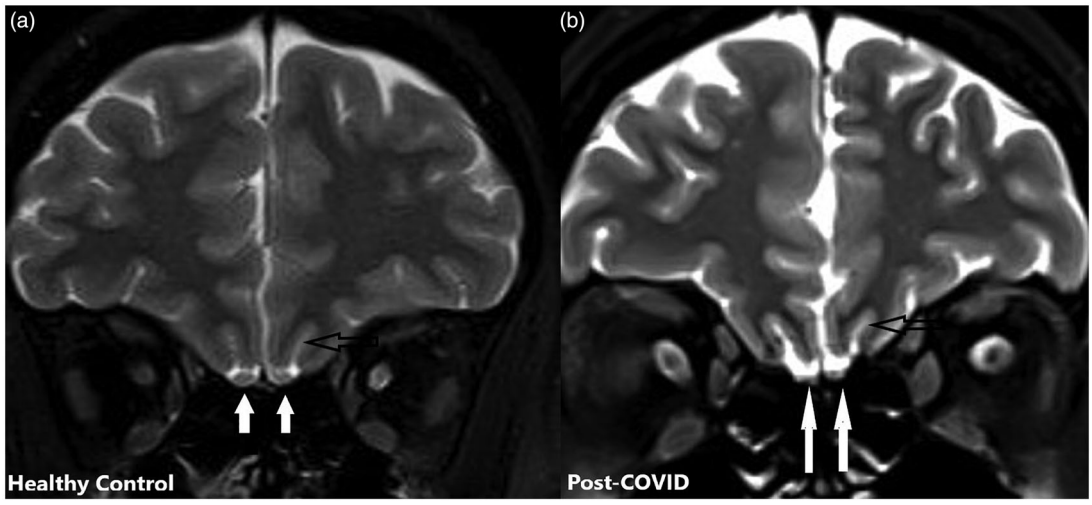

Figure 1. A healthy adult 39-year-old male case (a) and a 40-year-old male COVID-19 case (b) chronic period appearance, in fat-suppressed coronal T2-weighted images with 3 mm slice thickness. In the right image (b), there is a loss of volume in the olfactory bulb and an increase in CSF distances around the olfactory nerve (arrows). Also, note the shallowness of the olfactory sulcus in the picture (hollow arrow).

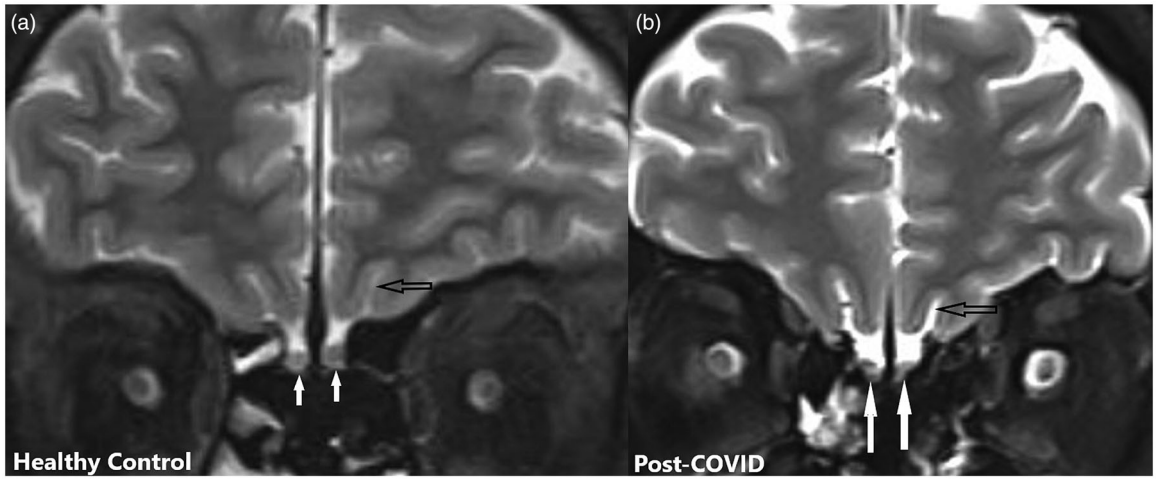

Figure 2. A healthy adult 43-year-old female case (a) and a chronic stage 49-year-old female COVID-19 case (b) in fat-suppressed coronal T2-weighted images with 3 mm slice thickness. The volume loss in the olfactory bulb and an increase in perineurinal CSF distances are also observed in the right image (b) (arrows). The shallowness of the olfactory sulcus is present similar to first case (hollow arrow).

Table 1. The distribution of mean and both sides olfactory bulbus volume (OBV) and olfactory sulcus dept (OSD) in according to COVID-19 infection and control groups.

	COVID-19 infection ($n = 41$)	Control ($n = 42$)	p value
Age (years)	40.27 ± 14.5	40.27 ± 14.4	0.994
OBV (mm^3)			
Mean	67.97 ± 14.27	94.21 ± 7.56	0.001
Right	68.68 ± 14.75	94.13 ± 8.15	0.001
Left	67.27 ± 14.31	94.30 ± 8.11	0.001
OSD (mm)			
Mean	7.98 ± 0.37	8.82 ± 0.74	0.001
Right	8.02 ± 0.87	8.85 ± 0.76	0.001
Left	7.94 ± 0.68	8.79 ± 0.74	0.001

dysfunction due to COVID-19 infection. In a case report, in a 19-year-old female patient who developed anosmia due to COVID-19 infection, OBV was found to be significantly lower in the measurement performed 2 months after the onset of anosmia (before infection: right OBV 49.5 mm^3 and left 47.46 mm^3 After 2 months of beginning anosmia: right OBV 29.96 mm^3 and left 35.51 mm^3) [15]. In the study conducted by Altundağ et al., OBV and OSD values of cases with anosmia due to SARS-Cov-2 and cases with anosmia due to other viruses were compared and no significant difference was found between the two groups [16]. In another study on olfactory dysfunction associated with COVID-19, early (1–4 months) OBV and OSD values were measured in 23 cases, but the study was not compared with healthy cases. The comparison in the study was made considering the cut-off values of a study conducted on normal cases in the literature, and a decrease in OBV was found in 43.5% of the cases and a decrease in OSD values in 60.9% of the cases [13]. Considering all this literature information and findings, our prospective study is the first study to compare the OBV and OSD values of cases with COVID-19-related olfactory dysfunction and normal healthy cases, as well as the first study conducted in the chronic period (10–12 months). Studies on OBV and OSD in the period after COVID-19 infection are summarized in Table 2.

The pathogenesis of the olfactory dysfunction in COVID-19 disease is not known exactly. However, there are some distinct features that distinguish COVID-19 related olfactory

Table 2. Comparison of previous studies in terms of OBV and OSD in COVID 19 infection.

Study	Year	Number of Cases	Time after COVID	OBV values (mm^3)	OSD values (mm)
Chiu et al.	September 2020	1	2 months	R: 29.6	–
				L: 35.5 29.6	–
Altundağ et al.	June 2020	24	No information	R: 59.76 ± 13.80	R: 6.77 ± 2.21
				L: 58.33 ± 17.46	L: 6.37 ± 1.99
Kandemirli et al.	June 2020	23	1–4 months	R: 62 (50.1-66.2)	R: 6.8 (5-4-8.1)
				L: 60.8 (47.4-67.8)	L: 6.3 (4.6-7.6)
Our Study	2020	42	10-12 months	R: 68.68 ± 14.27	R: 8.02 ± 0.87
				L: 67.27 ± 14.31	L: 7.94 ± 0.68

dysfunction from post-viral olfactory dysfunction due to other viruses. Olfactory dysfunction after viral upper respiratory tract infection other than COVID-19 is generally associated with mucosal congestion and nasal congestion, and this may cause a conductive loss of smell, even with an intact olfactory epithelium [8,17]. However, it has been determined that other mechanisms other than sinonasal symptoms play a role in olfactory dysfunction due to COVID-19 infection [18]. In the first studies in the literature, it is hypothesized that there may be mechanisms such as direct damage to the olfactory epithelium and olfactory cold by the virus and damage to the olfactory epithelium secondary to inflammatory changes as a possible cause [8].

In recent studies, the presence of SARS-Cov-2 RNA and protein in the neurinal tissues of the olfactory system, as well as in the brain and brain stem, has been demonstrated anatomically [19,20]. Autopsy study including 33 COVID-19 patients, it has been shown immunohistochemically that the SARS-CoV 2 spike (S) protein is present in the highest rate in olfactory sensor neurons in the nasal cavity [19]. In another study by Meinhardt et al., the neurotropism of the SARS-CoV-2 virus was shown. With this study, it was shown that the virus enters the nervous system by crossing the neural-mucosal interface in the olfactory mucosa, then penetrates into defined neuroanatomical areas, including the primary respiratory and cardiovascular control center in the medulla oblongata, following neuroanatomical structures [20]. As a result of our study, we think that the decrease in OBV and OSD values developing in the chronic period in patients with olfactory dysfunction due to COVID-19 may be the neuroglial response caused by the direct damage of the SARS-Cov-2 virus to the olfactory bulbus and adjacent neuroanatomical structures and/or neuroinflammation.

Our study had some limitations. The first of these is that the VAS we use to evaluate olfactory dysfunction is subjective because it is based on patient statements. In addition, inter-observer variability was not taken into account in our study.

Conclusion

Our findings show that chronic SARS-Cov-2 infection, which develops smell disorder during the disease, causes a significant decrease in OBV and OSD measurements compared to healthy cases. This finding is important both in showing the damage and neurotropism of the virus to the olfactory system, which is the retrograde neurinal spreading route, and in the follow-up of patients with COVID-19 disease. In conclusion, in patients with COVID-19 infection, this reduced OB volume and depth of OS and associated impaired odor functions may adversely affect the daily living activities of these patients.

Consent to participate

Written consent was obtained from each case participating in the study.

Disclosure statement

The authors declare that there is no conflict of interest.

ORCID

Bünyamin Güney http://orcid.org/0000-0002-0853-4184
Ferda Bacaksızlar Sarı http://orcid.org/0000-0002-6293-9481
Murat Yunus Özdemir http://orcid.org/0000-0002-7192-5110
Neşat Çullu http://orcid.org/0000-0002-5045-3919
Emrah Doğan http://orcid.org/0000-0002-9446-2294
Turhan Togan http://orcid.org/0000-0002-5490-8888

Data availability statement

Our data are transparent, reliable, and reusable.

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