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# Exploring MRI Changes in the Olfactory Bulb of COVID-19 Patients with Long-Term Anosmia

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**Abstract**

**Objective:** COVID-19 is a pandemic caused by SARS-CoV-2. Recent studies showed that it could infect the brain. The virus can cause a permanent loss of smell due to nerve damage. Magnetic resonance imaging (MRI) can help detect the structural changes in the olfactory bulb of patients with anosmia. In this article, we evaluated the morphological changes of the olfactory bulb in MRI in patients who suffered from persistent anosmia secondary to COVID-19 infection. Furthermore, we analysed the relationship between the severity of olfactory dysfunction and morphological changes in MRI.

**Material and Methods:** In this study, the MRI findings of patients who complained of isolated persistent anosmia after COVID-19 infection were presented. The study included patients aged 18 to 50 years who had confirmed COVID-19 and persistent anosmia for six months. We used a questionnaire to collect patient demographics, disease history, risk factors, and medical history. Patients underwent MRIs, and their olfactory bulb alterations were evaluated. The data was analysed using SPSS version 22 software.

**Results:** This study analysed the medical records of 15 COVID-19-positive patients admitted to the Loghman Hakim Hospital. Half of the patients had normal MRI scans. The most common disorder found was flattening or thinning of the olfactory bulb. The analysis revealed no significant relationship between Iran-SIT and MRI alterations. We categorised patients by gender. MRI abnormalities of the olfactory bulb were more prevalent in females, but this difference was not significant.

**Conclusion:** After conducting the research, half of the cases with post-COVID persistent anosmia had normal MRI findings. The MRI findings did not show a significant correlation with persistent anosmia in our sample.

**Keywords** Magnetic resonance imaging · COVID-19 · anosmia

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## INTRODUCTION

COVID-19, caused by SARS-CoV-2, which was the infective agent of a global pandemic, is a single-stranded RNA virus, closely related to SARS-CoV and MERS-CoV (1). Infection with this virus leads to respiratory symptoms and some non-specific symptoms such as headache and diarrhoea (2-7).

Moreover, olfactory dysfunction is very frequent. A meta-analysis revealed that nearly half of the patients infected by SARS-Cov2 suffer from olfactory dysfunction (8). The majority of cases of sudden-onset olfactory dysfunction are temporary, with a median recovery time ranging from 1 to 3 weeks (9).

The cause of the anosmia in COVID-19 patients is still being studied. However, evidence shows that it is different from other viral upper respiratory tract infections, which commonly cause nasal symptoms. In COVID-19-related anosmia, there is a lower prevalence of sinonasal symptoms (10). SARS-CoV-2 can enter the brain through nerve endings. It travels along the olfactory nerves and affects the thalamus and brain stem (2). Recent studies have raised questions about the effect of COVID-19 on odour processing and perception. The virus may damage the nasal epithelium, impair olfactory function, and increase the risk of nutritional deficiencies and psychiatric disorders in patients (11).

Magnetic resonance imaging (MRI) is the gold standard for assessing persistent OD, which can occur after a SARS-CoV-2 infection lasting over 2 months. MRI offers detailed images of the brain, helping clinicians identify abnormalities in the olfactory pathways. Imaging of the olfactory nerves using MRI is crucial for evaluating smell dysfunction associated with postviral infections, head injuries, and neurodegenerative conditions. This specialised MRI examines the volume and shape of the olfactory bulbs, the structure of olfactory nerve fibres, and the signal properties of the primary olfactory cortex. These evaluations can assist in distinguishing the underlying causes of smell dysfunction and offer insights into recovery, helping to inform treatment approaches in clinical practice (12, 13).

MRI assessment of the olfactory bulb in these patients improves our understanding of the underlying cause, guiding treatment options, and assessing brain health. As a result, in this article, we sought to explore the morphological alterations observed in the olfactory bulb through MRI among patients who experienced persistent anosmia following COVID-19 infection. Additionally, we investigated how the severity of olfactory dysfunction correlates with the observed morphological changes in the MRI findings. Our research aims to shed light on the underlying structural differences in the olfactory bulb that may contribute to the long-term loss of smell in individuals recovering from COVID-19.

## MATERIAL AND METHODS

### Study design

To obtain data as quickly as possible, a descriptive cross-sectional study was conducted on patients with PCR-confirmed COVID-19 and presenting with anosmia for six months or more duration, who were admitted to otorhinolaryngology clinics for 2 years during which this study was conducted. The study faced a significant limitation due to the rarity of patients experiencing persistent anosmia following a confirmed PCR diagnosis of COVID-19. As a result, the sample size was considerably low, which hampers the ability to generalise the findings to a broader population.

This study was ethically approved by the Shahid Beheshti University of Medical Sciences Ethics Committee (Date: 31/1/2021, No: IR.SBMU.RETECH.REC1399.1127). Eligible participants were informed of the study's purpose and process before providing written consent. The process of this study was compliant with the Declaration of Helsinki.

### Case definition and para-clinical data collection

The inclusion criteria for the study were patients aged between 18 and 50 years old, who had been diagnosed with COVID-19 by a definitive PCR test and complained of anosmia for six months or more. The anosmia must have developed during COVID-19 infection or within 2 days after its resolution. We obtained medical history with a specific focus on the onset and course of olfactory dysfunction and sinonasal symptoms, including nasal congestion and rhinorrhea. Then, patients who complained of anosmia for the past six months underwent olfactory assessment by the Iran Smell Identification Test (Iran-SIT), which is a modified version of the University of Pennsylvania Smell Identification Test (UPSIT) (14). The Iran-SIT test is interpreted in a manner similar to the UPSIT. The Iran-SIT test is interpreted as the UPSIT. Patients who scored less than 18 (anosmia) were considered to have complete anosmia and were included for further investigations. Those with severe microsomia scored between 19 and 25, while moderate microsomia was categorised as follows: for women, scores ranged from 26 to 30, and for men, scores ranged from 26 to 29. Mild anosmia was defined as scores of 31–34 for women and 30–33 for men. Scores above 34 for women and above 33 for men were interpreted as normosmia (15). Exclusion criteria were memory disorders (such as Alzheimer's disease), neurological diseases (such as Parkinson's disease), a history of olfactory problems due to any reason in the past except for COVID-19, lack of written and verbal consent of the patient to participate in the study, and inability to undergo MRI due to technical reasons or medical conditions.

Initially, the researchers used a simple questionnaire to collect patient demographics, disease history, risk factors (smoking and sinus diseases), and medical history. Subsequently, the patients underwent MRI, and their olfactory bulb alterations were evaluated. No control group was considered in this study. Our expert radiologists and otolaryngologists reported any abnormalities based on their experiences with healthy individuals.

According to the study by Kandermirli, a sample size of 21 was calculated using a confidence level of 90% and a statistical power (β) of 0.80 (16). Unfortunately, over the 2-year study period, we were unable to find 21 patients who met our inclusion and exclusion criteria. As a result, only 15 patients were evaluated.

### MRI evaluations

The morphology of the olfactory bulbs was examined using high-resolution coronal T2 sections. An MRI scan focused on the olfactory nerves was performed using a 3 Tesla MRI unit by Siemens in Erlangen, Germany. A 32-channel head coil was used for this imaging. Coronal T2 images were captured to encompass the entire range from the anterior pole of the olfactory bulb to the primary olfactory region. The scan parameters were as follows: TR (repetition time): 6550 ms, TE (echo time): 99 ms, flip angle: 150°, slice thickness: 1 mm, field of view (FOV): 100 × 100 mm2, matrix size: 269 × 384, voxel dimensions: 0.6 × 0.6 × 0.6 $mm^3$, and an acquisition time of 8.19 min.

A normal olfactory bulb is oval or has an inverted J shape. An abnormal olfactory bulb has a lobulated, rectangular, or atrophic appearance in more than two areas. An expert radiologist (MHM), along with an otorhinolaryngologist (ZA), evaluated the MRI of the patients, and based on their consensus, the morphological abnormality of OB was confirmed. Only the existence of MRI alteration was assessed, and the severity of these alterations was not determined.

### Statistical analysis

The data collected from the study were entered into SPSS (IBM SPSS Corp., Armonk, NY, USA) version 22 software. For descriptive statistics, the mean and standard deviation were used for quantitative data. For the qualitative data, percentage and frequency were used to report. Mann-Whiteney U test was conducted to evaluate the statistical difference between genders. Furthermore, the Spearman correlation test was performed to assess the correlation between the Iran-SIT score and the presence of MRI alterations. A p-value 0.05 was considered statistically significant.

## RESULTS

This study involved 15 patients who experienced loss of smell and had visited an otolaryngology clinic between September 2021 and March 2021. These patients had previously tested positive for COVID-19. The average age of the patients was 40.27 years old, with the youngest being 26 years old and the oldest 61 years old. Among the patients, seven were male (46.7%) and eight were female (53.3%). Only two of the admitted patients (13.3%) had a family history of olfactory disorder. most patients were housekeepers, while others were office and manual workers.

Most of the included cases had no risk factors (nine patients or 60%). Four patients (26.7%) had a history of smoking, and two (13.3%) had sinus diseases. The mean of the Iran-SIT scores for the patients was 14.3±3.7. OB showing normal MRI findings was found in 7/15 (46.7%) of the patients, while flattened/thinned OB was seen in 4/15 (26.7%), in 2/15 patients (13.3%) loss of normal oval/ inverted 'J' shape of the OB was evident, in 1/15 patient (6.7%) the OB had signal hyperintensity and in 1/15 patient (6.7%) there was asymmetric decrease in size of the OBs'. Figure 1 shows the MRI in the evaluated patients.

After conducting an analysis, it was revealed that there was no significant relationship between Iran-SIT and MRI alterations.

Based on the gender, patients were categorised. Table 1 shows the MRI alterations in patients regarding gender. Table 1 demonstrates that MRI abnormalities in the olfactory bulb were more frequently observed in female patients. A higher number of women exhibited bilateral neuropathy, while more men had normal MRI results. However, the difference between the two groups was not statistically significant (p-value = 0.1607).

## DISCUSSION

In this study, we evaluated the olfactory bulb of patients with persistent anosmia due to COVID-19 infection using MRI. As it was mentioned, seven out of 15 had normal OB morphology. Persistent anosmia in a patient with a normal MRI shows that the condition is not related to structural abnormalities. Instead, it may be associated with peripheral damage, such as injury to the olfactory epithelium in the nasal cavity (for example, due to a COVID-19 infection), functional abnormalities, or idiopathic cases where the cause is unknown (15). Because patients with neurological disorders were excluded from this study, neurological disorders cannot be considered a possible cause.

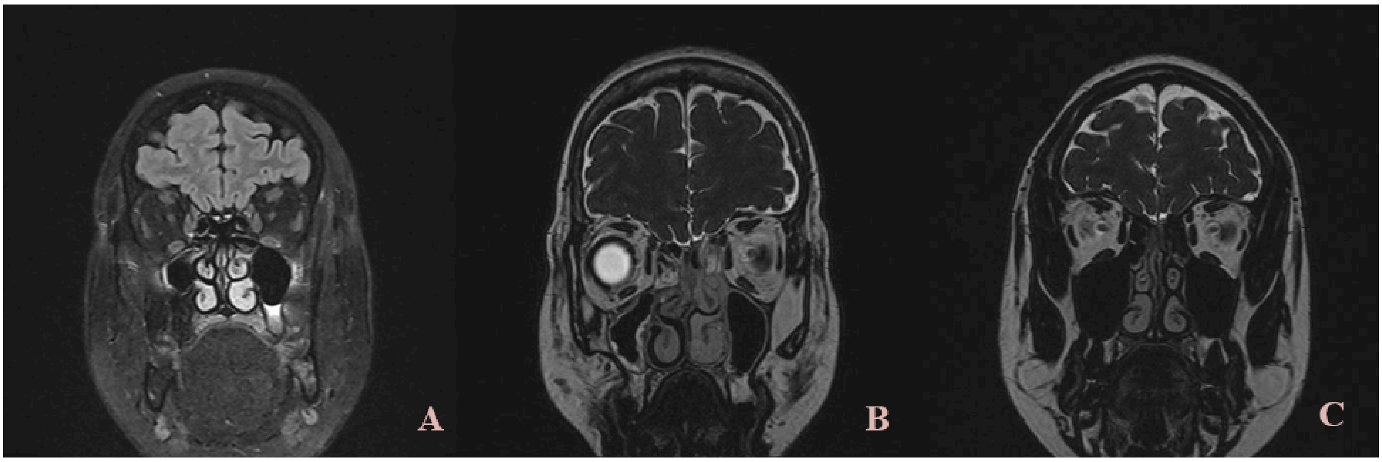


**Figure 1.** MRI alterations in evaluated patients. A: bilateral neuropathy, B: unilateral thinning of the olfactory bulb, C: asymmetrical decrease in the size of the olfactory bulb. )

**Tablo 1.** Distribution of MRI findings according to gender.

| Magnetic resonance imaging findings | Gender | |
|---|---|---|
| | Male | Female |
| Bilateral neuropathy | 1 | 4 |
| Unilateral atrophy | 0 | 1 |
| Bilateral atrophy | 1 | 1 |
| None | 5 | 2 |

Until 2002, coronaviruses were primarily seen as minor pathogens affecting humans, causing relatively mild illnesses. However, the emergence of more severe strains changed this perception. Both the Severe Acute Respiratory Syndrome (SARS) virus and the COVID-19 virus (SARS-CoV-2) exploit the angiotensin-converting enzyme 2 (ACE2) as their entry receptor. This receptor is crucial for the viruses to gain access to host cells, as it interacts with a trimeric glycoprotein located on the surface of the virion, facilitating the infection process. Despite sharing this common entry mechanism, the clinical outcomes of infections caused by these viruses differ significantly. SARS typically leads to a sudden onset of symptoms, which may include high fever and difficulty breathing, often resulting in severe respiratory distress. In contrast, COVID-19 has a wider range of symptoms, with some individuals experiencing mild to moderate respiratory issues, while others may suffer from severe complications, including pneumonia and acute respiratory failure. These differences in clinical presentation and disease progression highlight the diverse nature of coronavirus infections and the complexities associated with their management (17, 18).

The neurotropic and neuroinvasive characteristics of SARS-CoV-2 remain incompletely understood, leaving researchers with many unanswered questions. One striking feature of this virus is the sudden onset of anosmia along with hyposmia. These symptoms have been increasingly identified as specific markers indicating early infection. However, the precise biological processes and pathways through which the virus disrupts the olfactory system and leads to these sensory alterations are still not fully clarified. As such, an in-depth exploration of these mechanisms is essential to better understand the impact of SARS-CoV-2 on neurological functions (19-22).

Recent pooled prevalence estimates indicate that olfactory dysfunction occurs in approximately 50%–75% of individuals diagnosed with COVID-19. This rate is notably higher when compared with the prevalence of olfactory dysfunction in the general population, particularly among those who do not exhibit clear clinical signs of this condition. The implications of these findings revealed a strong association between COVID-19 and changes in the sense of smell, highlighting a potentially significant and widespread symptom experienced by patients across various demographics (22-24).

It is unknown whether the virus attacks neurons directly or spreads through the bloodstream. These gaps in knowledge are major obstacles to understanding the clinical effects of SARS-CoV-2 on the nervous system (25).

The heterogeneity of symptoms demonstrates that SARS-CoV-2 infection can affect olfactory function through various pathophysiological mechanisms, which are not mutually exclusive and occur at multiple anatomical levels. Most COVID-19 patients recover their olfactory function quickly and completely, along with other physical symptoms. However, in some cases, non-apparent hyposmia and perceptual distortions can persist even after the obvious recovery of olfactory dysfunction symptoms (26-28).

COVID-19 patients show localised abnormalities in MRI scans, suggesting sensitisation of olfactory brain regions. Follow-up MRI scans reveal that intracranial olfactory bulb oedema, observed during the acute phase, returns to normal after 24-28 days (29, 30).

Various studies have reported the radiological findings of patients with anosmia/hyposmia after COVID-19 infection.

A systematic review conducted by Keshavarz et al. investigated the neurological impact of post-COVID anosmia by analysing imaging data from 305 patients, some of whom experienced early symptoms while others reported late post-COVID anosmia. The findings indicated that the olfactory bulbs (OB), which play a crucial role in the sense of smell, appeared normal in 31.2% of the patients examined. In contrast, a significant presence of olfactory bulb atrophy was noted predominantly among those with late post-COVID anosmia, concluding a potential correlation between the duration of anosmia and the degree of olfactory bulb degeneration. This research highlights the variability in olfactory function recovery and the possible lasting effects of COVID-19 on olfactory pathways (31). Besides, a comprehensive meta-analysis conducted by Tan and colleagues revealed that there was a comparable prevalence of olfactory bulb signal abnormalities among both cases of individuals experiencing olfactory dysfunction and controls without the condition. The findings also indicated that 43.5% of patients suffering from olfactory dysfunction following COVID-19 exhibited morphological abnormalities in the olfactory mucosa. This shows that a significant portion of post-COVID patients may have structural changes affecting their sense of smell, highlighting the potential lingering effects of the virus on olfactory function (32). Although our study encompassed a relatively small number of cases, the outcomes we observed aligned closely with those reported by Tan et al. Notably, a significant portion of our participants presented with normal MRI results. It is important to highlight that our research specifically focused on patients experiencing persistent anosmia, which is the loss of the sense of smell that continues over time. This targeted approach could elucidate the differences in findings when compared with the results published by Keshavarz et al., who may have examined a broader or different cohort of patients.

Brudasca et al. evaluated 67 patients with olfactory dysfunction after COVID-19 infection. They showed that 85 % of patients had normal MRI (33). The findings of our study indicate a higher rate of morphological abnormalities in the OB compared with the results reported by Brudasca et al. Both studies focused on patients experiencing persistent anosmia. However, Brudasca et al. defined persistent olfactory dysfunction under a condition lasting more than two months. In contrast, our study specifically examined persistent anosmia, which we defined as an olfactory dysfunction that lasts for more than six months. This essential distinction in the definition of the duration of olfactory dysfunction may help explain the differing conclusions drawn by the two studies. Brudasca et al. concluded that MRI in the early stages of olfactory dysfunction may be unnecessary, citing a low rate of morphological abnormalities in the structure of the olfactory bulb. Conversely, our research demonstrated a significantly higher incidence of such abnormalities in the olfactory bulb among patients with persistent anosmia lasting over six months. This disparity in findings led us to reconsider the implications for clinical assessment and the timing of imaging techniques in relation to olfactory disorders.

In their study, Casez et al. explored the MRI results of a patient experiencing anosmia, which is the loss of the sense of smell (34). The patient tested positive for PCR analysis of CSF, indicating an underlying viral infection. The MRI findings revealed characteristics consistent with encephalitis, an inflammation of the brain often caused by infection. While the effectiveness of imaging methods in diagnosing such conditions has been the subject of ongoing debate, the advanced MRI techniques used in this case demonstrated notable changes in the OB. Specifically, the images showed thickening and shrinkage of the olfactory bulb, which may indicate the presence of post-infectious inflammatory neuropathy, a condition that arises as a response to a previous infection. This study highlights the potential of MRI as a valuable tool for understanding the neurological impacts of infectious diseases (34). Several research studies have documented the presence of atrophic changes in the olfactory bulb, as revealed through MRI scans, among individuals who have survived COVID-19 and are experiencing lingering issues with their sense of smell. These changes are particularly associated with persistent post-viral olfactory dysfunction, which affects many patients long after their initial COVID-19 infection has resolved. These findings highlight the potential impact of the virus on brain structures involved in olfactory processing (35, 36). In this study, a greater number of patients were included compared with the studies mentioned. This study evaluated patients with persistent anosmia, whereas Tsivgoulis et al.'s study evaluated MRI findings of all forms of post-COVID olfactory dysfunction.

In a very similar survey conducted by Kandemirli et al, 23 patients with persistent olfactory dysfunction after COVID-19 infection were assessed. Among them, approximately half of them had normal olfactory bulb volume, and 54.2% had changes in normal inverted J shape of olfactory bulb and 43.5% of patients had below the normal of OB volume (37). The findings reported by Kandermirli et al. closely align with the results we observed in our study. Notably, approximately one-third of their patient cohort exhibited abnormalities in olfactory cortical signals (36). It is important to highlight that Kandermirli et al. specifically evaluated individuals who had been experiencing anosmia for a duration exceeding one month. In contrast, our investigation considered an even longer period of olfactory dysfunction in our participants. Despite this difference in the length of time that anosmia was present between the two studies, the prevalence of olfactory signal abnormalities remained strikingly similar. This shows that regardless of the duration of the condition, there are consistent patterns in the olfactory dysfunction observed in patients.

MRI findings alone cannot diagnose olfactory bulb infections, as they may not detect viral pathosis that resolves quickly. COVID-19 patients may have normal MRI findings but still exhibit functional neuronal electrical activity abnormalities, as seen in those with olfactory impairment and normal functional MRI and PET-CT scans (38, 39).

## Limitations

The study included some patients and was conducted in a single centre. To establish a definite relationship, multi-centre prospective studies with more cases and longer follow-up periods would be helpful. Furthermore, to establish the aetiology of persistent anosmia in patients who were previously affected by COVID-19, assessing patients with neurofunctional imaging is necessary.

## CONCLUSION

In summary, out of the 15 patients surveyed, seven had normal MRI results. This conclude that the morphological changes seen in the MRI of the olfactory bulb (OB) may not be responsible for the persistent loss of smell (anosmia) in individuals who have recovered from COVID-19. In cases where the MRI results are normal, it is possible that functional abnormalities or peripheral damage could be the underlying causes of the loss of smell.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Shahid Beheshti University of Medical Sciences (Date: 31.01.2021, Number: IR.SBMU.RETECH.REC.1399.1127).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer Review: Externally peer-reviewed.

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