SHORT COMMUNICATION

Transient changes in the olfactory bulb on MR follow-up of COVID-19 patients with associated olfactory impairment

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ABSTRACT

Olfactory dysfunction (OD) has been found to be common in mild to moderate COVID-19 patients. Previous reports indicate that the volume and signal intensity of Olfactory Bulbs (OB) are abnormal during the acute phase of COVID-19 anosmia, but a prospective MRI and clinical follow-up study of COVID-19 patients presenting with OD was lacking, with the goal of understanding how OB change during patients follow-up.

Key Words: *Anosmia; COVID-19; SARS-CoV-2; Magnetic Resonance Imaging, Olfaction disorders*

SHORT COMMUNICATION

Coronavirus Disease-2019 (COVID-19), which has been related to the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has been connected to a variety of clinical symptoms ranging from mild rhinitis to acute respiratory distress syndrome. In 50 to 86% of mild-to-moderate cases, the infection has been connected to smell and taste dysfunctions. Olfactory dysfunction (OD) can be caused by nasal blockage, as in a typical cold, or by neurological virus transmission across the olfactory cleft mucosa. More than 80% of patients with OD without accompanying rhinorrhea or nasal obstruction reported with OD in the initial publication describing OD as a major symptom of the COVID-19.

OB volume and signal intensity have been shown to be aberrant during the acute phase of COVID-19 anosmia. MRI results in individuals with prolonged COVID-19-induced OD were substantially linked with reduced olfactory bulb (OB) heights, compared to controls. These findings provide credence to the notion that SARS-CoV-2 may enter the central nervous system via the olfactory route, causing acute and perhaps irreversible damage to neuronal structures such as the OB. A prospective longitudinal investigation, however, was lacking to confirm the occurrence of OB alterations in terms of volume and aspect in tandem with clinical follow-up of patients recovering or not from COVID-19 anosmia. We provide a prospective MRI and clinical follow-up research of COVID-19 patients with OD, with the goal of understanding how OB changes with time.

COVID-19 patients with self-reported sudden OD were recruited prospectively from two University Hospitals from March to May 2020. (Foch Hospital and Garches Hospital, APHP, Paris, France). Serology or reverse transcription polymerase chain reaction (RT-PCR) results revealed that patients had mild to moderate COVID-19. Patients having a history of OD prior to the pandemic, nose surgery, chronic rhinosinusitis, head and neck trauma, degenerative neurological illness, or MRI contraindications were barred from participating in the research.

Psychophysical olfactory examinations (Sniffin'Sticks tests, Medisense, Groningen, Netherlands) aided patients. The Sniffin'Sticks test is a psychophysical olfactory exam that employs 16 scent pens. Each pen was handed to a different person, who had to pick the appropriate fragrance from four alternatives. The final score ranges from 0 (no olfaction) to 16 (complete olfaction) (perfect olfaction). Hyposmia was defined as a score of 9 to 11, and anosmia as a score of 94. The objective assessments were completed at two or four weeks after the commencement of the olfactory illness and continued throughout the follow-up period.

To measure cleft blockage, the Olfactory Cleft specific Lund-Kennedy scoring (OC-LK) was used, with this endoscopic score being

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connected with olfactory function in individuals with smell disorder.

The effect of COVID-19 on sinonasal symptoms was assessed using the French version of the sino-nasal outcome test-22 (SNOT-22), a validated patient-reported outcome questionnaire adapted from the US version.

Imaging tests were carried out using a 3 Tesla device (General Electric, Milwaukee, WI, USA) outfitted with a 20-element head and neck coil. The sequences used to evaluate the OB signal were 3D-FLAIR-CUBE and 3D-T2-FIESTA, which were obtained in the coronal and sagittal planes, respectively. TR/TE 8000/133ms; section thickness 2mm; matrix 240 240; FOV 230 230mm; flip angle 90°; and acquisition time = 4min-36sec were the 3D-FLAIR sequence parameters. TR/TE 5.9/2.5ms; section thickness 0.6mm; matrix 320 320; FOV 180 180mm; flip angle 55°; and acquisition time=4min-32sec were the 3D-T2 FIESTA sequence parameters. The identical protocol was used at the beginning of the infection and at the 6-month follow-up.

The pictures were evaluated separately by two expert neuroradiologists who were blinded to the clinical data. Potential discrepancies were resolved by a third neuroradiologist. Volumes of OB were quantified on a 3D-T2 sequence using a segmentation-specific post-processing application: ITK-SNAP® 3.8. (www.itksnap.org).

T2/FLAIR images were used to assess OC blockage, which was characterized as partial if it did not influence the complete anteroposterior length.

The average OB signal intensity was measured using quantitative analysis on a T2/FLAIR image by altering contours of a ROI centered on the OB on a coronal plane. At the same slice level, a Signal Intensity Ratio (SIR) was determined between the average signal of the OB and the average signal of a ROI implanted in the frontal white matter of normal appearance.

The Statistical Package for the Social Sciences was used to conduct statistical analyses (SPSS version 22.0; IBM Corp, Armonk, NY, USA). To test the repeatability of OC obstruction, SIR, and OB volume measures between readers, the intraclass correlation coefficient was employed. Consensual proofreading was used for SIR and OB volume measurements for statistical analysis. The Wilcoxon signed-rank test was used to compare the results from baseline to 6 months post-COVID-19. The significance threshold was set at p0.05.

Despite the fact that all patients were initially anosmic, just one patient remained hyposmic after 6 months of follow-up (9.09%). The latter recovered partially, with the Sniffin'Sticks test improving from 3 to 8.

In 8/11 patients, OC-LK was normal (score 0) at the time of the initial assessment (72.72%).

On the first exam, the mean SNOT-22 was 18.4519.65 (0-61) and on the follow-up exam, it was 10.3616.36 (range 0-47). The hyposmic patient's SNOT-22 score improved from 43 to 0 during the second test.

In 10/11 individuals, the psychophysical examinations revealed a 6-month recovery (90.9%). The mean OB-SIR readings declined considerably from baseline (1.660.24) to 6-month follow-up (1.350.27), with a mean variation of -17.8215.20% (p0.001).The mean OB volume values fell considerably from baseline (49.2210.46 mm3) to 6-month follow-up (43.709.88 mm3) (p=0.006).

MR imaging in COVID-19 anosmic patients revealed an early rise in signal intensity and volume of olfactory bulbs, followed by normalization on 6-month MRI follow-up, whereas 90% of our patients clinically recovered scent. This lends credence to the underlying mechanism of a transitory OB inflammation as a cause of OD in COVID-19 patients who recover. Inflammation would therefore cause an increase in initial signals and volumes, followed by a levelling of these parameters over time.

Laurendon et al. found comparable results in a 27-year-old COVID-19 anosmic patient who exhibited edoema and transitory enlargement of the OB. The first inflammatory response in the OB suggests that the SARS-CoV-2 has migrated neutrally into the OC mucosa.

In two recent investigations, the virus's spread in the brain was linked to simultaneous brain damage. As a result, COVID-19 RNA was found in the brains of patients, lending credence to the virus's neurological pattern. The virus spreads via the Angiotensin Converting Enzyme 2 receptor (ACE2) and Transmembrane Serine Protease (TMPRSS2), both of which are present in OC epithelium and OB sustentacular cells. The inflammatory response begins in the neuroepithelium, which may seem blocked on the first MRI. Eliezer et al. discovered that OD and OC blockage are evident in the early stages of the disease and ameliorate at one-month follow-up, implying that OD in Covid-19 patients is caused, at least in part, by reversible inflammatory alterations in the OC.

In our investigation, we discovered only partial OC blockage in 4/11 individuals on the initial MRI, which was completely regressive during follow-up, explaining just a portion of the OD. Our work confirms the occurrence of an early OB inflammation as a cause of OD by including a quantitative examination of OB signal intensity. Arago et al. also reported OB participation in COVID-19 OD, finding a hyper signal and/or enhancement of OB on T1-weighted images, explaining the OD by the existence of micro bleeding and/or blood-brain barrier rupture. Kandemirli et al. discovered a punctate hypo intense T2-weighted pattern inside the OB in 4/23 individuals with persisting COVID-19 OD, suggesting the possibility of micro hemorrhagic consequences. These anomalies might be a later sign of the severity of an inflammatory lesion.

Surprisingly, people with long-term OD may have OB atrophy. Tsivgoulis et al. found that prolonged SARS-CoV2-induced OD is related with reduced bilateral OB heights when compared to controls. On the follow-up evaluation of our patient with chronic hyposmia, MRI revealed a significant reduction in volumes, validating this notion.

Certain limitations of the current study should be noted, such as the small sample size of our population and the fact that the great majority of our patients recovered from anosmia, which was not expected at the outset.

CONCLUSION

COVID-19 anosmic patients observed a rise in signal intensity and volume of olfactory bulbs at 6 months MRI follow-up, followed by a levelling when the patient recovered smell. This lends credence to the underlying mechanism of a transitory OB inflammation causing Olfactory Dysfunction in COVID-19 individuals who later recover. In a setting where clinical evaluation of infected patients is still

prohibited due to the danger of aerosolization, our findings suggest that anosmia can be investigated using MRI.

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