ARTICLE

Loss of smell in patients with COVID-19
MRI data reveal a transient edema of the olfactory clefts

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Abstract

Objective
To assess the physiopathology of olfactory function loss (OFL) in patients with coronavirus disease 2019 (COVID-19), we evaluated the olfactory clefts (OC) on MRI during the early stage of the disease and 1 month later.

Methods
This was a prospective, monocentric, case-controlled study. Twenty severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)–infected patients with OFL were included and compared to 20 age-matched healthy controls. All infected patients underwent olfactory function assessment and 3T MRI, performed both at the early stage of the disease and at the 1-month follow-up.

Results
At the early stage, SARS-CoV2–infected patients had a mean olfactory score of 2.8 ± 2.7 (range 0–8), and MRI displayed a complete obstruction of the OC in 19 of 20 patients. Controls had normal olfactory scores and no obstruction of the OC on MRI. At the 1 month follow-up, the olfactory score had improved to 8.3 ± 1.9 (range 4–10) in patients, and only 7 of 20 patients still had an obstruction of the OC. There was a correlation between olfactory score and obstruction of the OC ($p = 0.004$).

Conclusion
OFL in SARS-CoV2–infected patients is associated with a reversible obstruction of the OC.

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Glossary

ACE2 = angiotensin-converting enzyme 2; **COVID-19** = coronavirus disease 2019; **FLAIR** = fluid-attenuated inversion recovery; **OB** = olfactory bulbs; **OC** = olfactory clefts; **OFL** = olfactory function loss; **SARS-CoV2** = severe acute respiratory syndrome coronavirus 2; **VOS** = visual olfactive score.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), infects mostly the human upper respiratory tracts, causing dry cough and dyspnea.[1–4] Some patients also experienced non-specific symptoms such as diarrhea and headache.[5,6] A recent meta-analysis has reported a prevalence of self-reported olfactory function loss (OFL) among SARS-CoV2–infected patients as high as 52.7%.[6] However, 2 studies have demonstrated that some patients with COVID-19 were aware of their olfactory deficit, while a quantitative olfactory deficit (with objective olfactory function tests) was observed in a greater proportion.[7,8] In contrast, it has recently been reported that only 62% of patients with COVID-19 with self-reported OLF had a deficit on objective psychophysical olfactory evaluation.[9] Recent studies have shown a high rate of quick recovery of olfactory disorders.[10,11] On the basis of this observation, Vaira et al.[11] questioned the link between olfactory disorders and viral damage to the neurosensory cells.

In some studies, the virus directly infects sensorineural cells, similar to other coronaviruses.[12,13] According to this model, one expects direct damage to the olfactory sensory tract, with structural changes in the olfactory bulbs (OB) and pathways. Recent research studies demonstrated that angiotensin-converting enzyme 2 (ACE2) receptors are expressed in the olfactory epithelium but not in the olfactory neurons.[14,15] These receptors are targeted by SARS-CoV2, which might explain the obstruction of the olfactory clefts (OC), as previously reported.[16–18] In effect, edema of olfactory mucosa could be the result of the interaction between SARS-CoV2 and the ACE2 protein, the first mechanism of the OFL, preventing odorant molecules from reaching the olfactory epithelium.[16]

The main aim of this study was to assess both olfactory function and morphologic changes of the OC on MRI in patients with COVID-19 with OFL during the early stage of the disease and at the 1-month follow-up.

Methods

Standard protocol approvals, registrations, and patient consents

This study has been approved by the ethics committee of our hospital (No. 00006477). All participants provided informed consent.

Patients

This was a single-center prospective case-controlled imaging study. All participants gave their informed consent to the study. Patients with confirmed SARS-CoV2 infection, as confirmed by real-time PCR, and presenting with OFL for <15 days were prospectively included between March 23 and April 27, 2020. All patients underwent real-time PCR to confirm SARS-CoV2 infection.

The following baseline data were collected: age; sex; OFL history; associated olfactory symptoms; taste disorders; other ear-nose-throat symptoms, especially nasal obstruction; clinical history; and chronology of SARS-CoV2 symptoms.

Exclusion criteria included a history of olfactory dysfunction, in particular after head trauma, congenital olfactory dysfunction, chronic rhinosinusitis, nasal surgery, neurologic disorders, or contraindication to MRI.

Age-adjusted (±5 years) 1:1 controls were recruited among the medical staff on a voluntary basis. Exclusion criteria for controls included any history of olfactory dysfunction, chronic rhinosinusitis, neurologic disorders, or contraindication to MRI.

Olfactory functional assessment

All patients and controls underwent 2 olfactory functional assessments: at baseline (e.g., within the first 15 days after the onset of OFL) and then 1 month later.

A visual olfactive score (VOS) from 0 to 10 was recorded, and evaluation was performed to assess the ability to detect and identify odorants. With the forced choice method,[19] 5 odorants were tested for both detection and identification—acetic acid (vinegar), eugenol (clove), vanillin (vanilla), curry, and cinnamaldehyde (cinnamon)—and trigeminal sensitivity (acetic acid, vinegar). An olfactory detection and identification assessment was performed and scored from 0 to 10 (0 = presumed anosmia and 10 = normal perception).

Imaging

All patients and controls underwent 3T MRI (Skyra; Siemens, Erlangen, Germany) with a 64-channel head coil on the same day as the consultations and the olfactory tests. We performed 2D coronal and 3D T2-weighted images covering the anterior and middle segments of the skull base. The 2D fast-spin echo coronal T2-weighted images were performed with the following parameters: repetition time 2,230 milliseconds, echo time 90 milliseconds, slice thickness 2 mm, without interslice gap, field of view 130 × 130 mm, matrix 320 × 256, and scan time 2 minutes 45 seconds. We also performed a 3D-T2 sampling perfection with application optimized using different flip angle evaluation (SPACE) sequence with the

following parameters: field of view 160 × 160 mm, repetition time 2,000 milliseconds, echo time 423, matrix 320 × 288, flip angle 120°, number of excitations 2, generalized autocalibrating partial parallel acquisition 2, and scan time 2 minutes 46 seconds. A second MRI was performed at the 1-month follow-up.

Image analysis

For each patient, MRIs were evaluated with Carestream Vue 12.1 (Capterra, Arlington, VA) by 2 radiologists (M.E. and E.H.) with 6 and 30 years of experience in head and neck imaging who were blinded to the clinical data.

The permeability of the OC was evaluated on 2D fast-spin echo coronal T2-weighted images. The OC is delimited superiorly by the cribriform plate, below the OB, medially by the nasal septum, and laterally by the upper part of the middle and superior turbinates (figure 1). Obstruction of the OC was considered complete when the entire length (anterior and posterior) was involved.

We also evaluated the volume of the OB on 3D-T2 SPACE sequence and calculated it by contouring the OB manually. The software then calculated the volume (in cubic millimeters) of the OB (figure 1). The posterior landmarks of the OB were defined on MRI as when a round-shaped of the OB was still observed on the coronal slice, contrasting with the flattened shaped of the olfactory tract on the next slice.

Statistical analysis

Data were analyzed with R software version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). Between-group comparisons were analyzed with the Student t test for continuous data to assess significant differences between the groups. The χ^2 test was used for categorical data to evaluate significant differences in each group for the presence of OC obstruction.

Interrater agreement in OC obstruction was estimated with the Cohen κ coefficient. For statistical analysis, in cases of discrepancies, the presence of OC obstruction evaluated by the most experienced radiologist was taken as an abnormal finding.

Continuous data are presented as the mean with SD. Sensitivity was estimated by taking the clinical examination as the gold standard. We report categorical data as frequency and percentages.

Data availability

Researchers can apply for access to anonymized data from the present study for well-defined research questions that are in line with the overall research agenda for the cohort. Please contact the corresponding author.

Results

Population

All patient characteristics are listed in the table.

There were 20 patients with SARS-CoV2 infection (10 men, 10 women) with a mean age of 34.6 ± 8.8 years (range 21–53 years). There were 20 healthy controls (12 men, 8 women) with a mean age of 33.9 ± 7.8 years (range 26–51 years). No significant differences in the mean age ($p = 0.85$) and sex ($p = 0.41$) of the healthy control and the patient groups were observed.

A sudden OFL was experienced by 18 of 20 (90%) patients with SARS-CoV2 infection. The remaining 2 patients reported a progressive OFL. None of the patients had associated nasal obstruction. Dysgeusia was claimed by 17 of 20 patients (total 9 patients, partial 8 patients). Typical symptoms of SARS-CoV2 infection were present in all patients (fever 6 patients, cough 11 patients, myalgia 16 patients, dyspnea 2 patients).

Figure 1 Fifty-two-year-old female healthy control
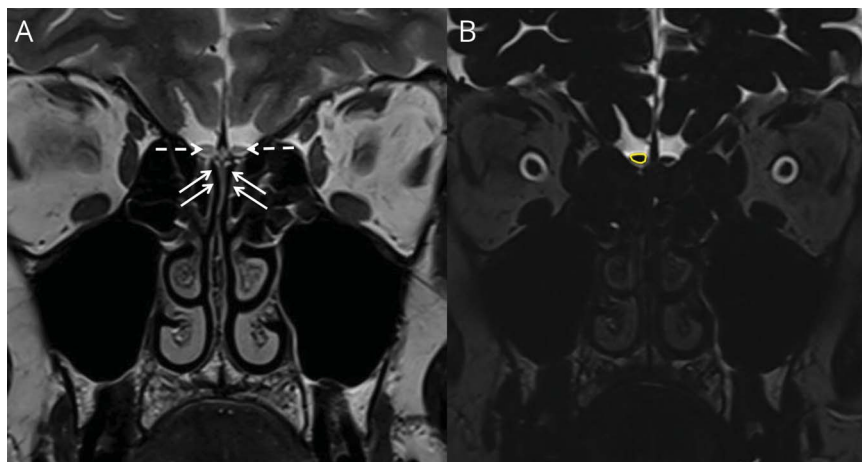
Coronal section of the olfactory clefts and bulbs on MRI on (A) 2D T2-weighted and (B) 3D T2-weighted sequences. Olfactory bulbs (white dotted arrow) are normal (right 32.3 mm³, left 37.9 mm³), and the olfactory clefts (white arrow) are patent without inflammatory obstruction.

Table Clinical and radiologic characteristics of patients with SARS-CoV2 infection and OFL

Patients			Early-stage MRI and olfactory functional assessment					Follow-up MRI and olfactory functional assessment at 1 mo				
			MRI					MRI				
			OC obstruction		OB volume, mm^3			OC obstruction		OB volume, mm^3		
No.	Age, y	Sex	R	L	R	L	Olfactory score	R	L	R	L	Olfactory score
1	27	M	Yes	Yes	33.9	51.3	0	No	Yes	49	43	8
2	27	M	Yes	Yes	43.1	41.4	2	No	No	30	26.6	8
3	31	M	Yes	Yes	32.7	34.8	0	No	No	25.5	17	10
4	27	F	Yes	Yes	36.8	32	0	No	No	20.6	19.5	10
5	26	M	Yes	Yes	60.2	61	7	No	No	57.7	54.5	10
6	50	M	Yes	No	36.7	40.4	0	No	No	44.8	38.3	10
7	32	F	Yes	Yes	33.2	43.4	1	Yes	No	39.8	30	8
8	53	M	Yes	Yes	33.2	39.1	0	Yes	Yes	38.2	41.9	5
9	47	F	Yes	Yes	56.2	43.2	1	Yes	No	49.2	51.2	9
10	34	F	Yes	Yes	31	32.5	5	No	Yes	33.8	27.3	9
11	38	F	Yes	Yes	32.8	42.1	3	No	No	29.2	39.3	10
12	40	F	Yes	Yes	38.1	36.3	1	No	No	36.9	41.9	7
13	29	F	No	Yes	48.3	40.9	7	No	No	39.8	41.9	9
14	41	F	Yes	Yes	24.1	32.1	8	No	No	28	33.8	10
15	27	F	Yes	Yes	32.2	31.6	5	No	No	33.3	32.4	9
16	21	F	Yes	Yes	46.8	45	7	No	No	49.5	51.4	10
17	27	M	Yes	Yes	42.3	46.2	4	No	Yes	42.8	55	4
18	35	M	Yes	No	44.2	48.4	3	Yes	No	43.8	56.6	10
19	47	M	No	No	27.5	22.3	0	No	No	28.8	23.7	5
20	42	M	No	No	30.8	40.7	1	No	No	41.5	38.6	6

Abbreviations: OB = olfactory bulbs; OC = olfactory clefts; OFL = olfactory function loss; SARS-CoV2 = severe acute respiratory syndrome coronavirus 2.

Olfactory functional assessment

For healthy controls, the mean olfactory score was 9.4 ± 0.7 (range 8–10).

For patients with SARS-CoV2 infection, the mean delay between the onset of OFL and olfactory tests was 5.9 ± 3.2 days (range 1–13 days). At the time of the first consultation, the mean VOS was 1.6 ± 1.9 (range 0–6), while the mean olfactory score was 2.8 ± 2.7 (range 0–8). There were 5 patients with a score of 0 and 15 patients with a score <8. There was a significant difference in the mean olfactory score between healthy controls and patients with SARS-CoV2 infection ($p <$ 0.001).

At the 1-month follow-up, the mean VOS and the mean olfactory score had improved to 7.4 ± 2.6 (range 1–10) and 8.3 ± 1.9 (range 4–10), respectively (figure 2). Four patients had recovered a normal olfactory function with a visual olfactory score of 10, and 4 patients had almost recovered with a score

of 9. There was a significant difference in the mean olfactory score between the initial test and the second test performed at the 1-month follow-up in patients with SARS-CoV2 infection ($p <$ 0.01).
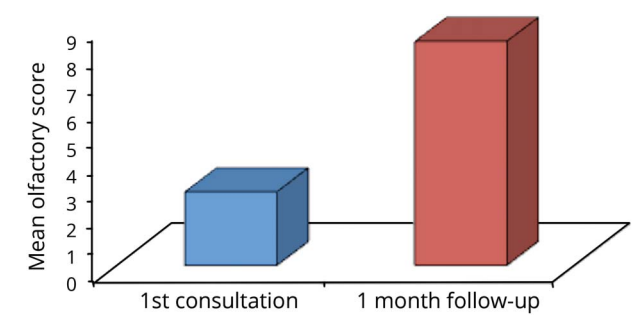
Imaging data

The mean delay between the initial onset of OFL and MRI was 5.9 ± 3.2 days (range 1–13 days).

Obstruction of the OC

In healthy controls, complete obstruction of the OC was never observed. The interrater agreement for OC obstruction was 1.

In patients with SARS-CoV2 infection, complete obstruction of the OC was observed in 19 of 20 patients (1 right-side, 1 left-side, 17 bilateral) on the first MRI. One patient had no OC obstruction. In this patient, the MRI was performed 11 days after the onset of OFL. There was a significant difference

in OC obstruction between patients with SARS-CoV2 infection and controls ($p < 0.001$). The interrater agreement for OC obstruction was 0.9.

At the 1-month follow-up, 12 of 19 patients with initial obstruction of the OC had recovered a normal patency of the OC. Altogether, a complete obstruction of the OC was still observed at the 1-month follow-up in only 7 of 20 patients (3 right-side, 3 left-side, 1 bilateral) (figures 3–5). Of these 7 patients with persistent obstruction of the OC, 5 of 6 patients with unilateral OC obstruction had an olfactory test score ≥8, 1 patient with unilateral OC obstruction had an olfactory test score of 4, and the only patient with bilateral OC obstruction had an olfactory score of 5. The interrater agreement for OC obstruction was 0.77.

There was a significant decrease in OC obstruction between the first and second MRIs ($p = 0.004$). We also found a significant correlation between the degree of OC obstruction and the severity of the olfactory score ($p = 0.004$). All patients except one, with bilateral patent OC on the second MRI, had recovered an olfactory score ≥8. At the 1-month follow-up, among the 4 SARS-CoV2–infected patients with OFL (score <8), 2 patients had OC obstruction (1 right-side, 1 bilateral) and 2 patients had no obstruction of the OC.

OB volume

In healthy controls, the mean OB volume was 37.5 ± 13.2 mm^3 on the right side and 36.4 ± 13.7 mm^3 on the left side.

In patients with SARS-CoV2 infection, the mean OB volume on the first MRI was 37.7 ± 9.9 mm^3 on the right side and 40.2 ± 8.8 mm^3 on the left side. There was no significant difference in OB volume between patients with COVID-19 and healthy controls ($p = 0.33$).

At the 1-month follow-up, the mean OB volume was 38.1 ± 9.5 mm^3 on the right side and $38.2.2 \pm 11.8$ mm^3 on the left side. There was no significant difference in OB volume between the first and second MRIs ($p = 0.97$ on the right side, $p = 0.53$ on the left side).

Discussion

In this study, we report the olfactory functional test results and MRI findings in 20 patients with SARS-CoV2 infection associated with OFL at the first stage of the disease and at the 1-month follow-up.

The debate is still ongoing as to what extent the loss of smell in SARS-CoV2 infection is caused by congestion in the OC and/or direct damage to the olfactory sensory neurons, causing structural changes in the OB and pathways.

Here, at the early stage of the symptoms (<15 days), we observed a complete obstruction of the OC in 95% of patients with SARS-CoV2 infection, which was likely to cause an impairment of the olfactory function by preventing odorant molecules from reaching the olfactory epithelium. Even if the origin of the OC obstruction remains uncertain, it has already been reported in patients with OFL after a severe nasopharyngeal infection.[20] Only 1 of our patients had a slight diffuse mucosa hyperplasia, which was also observed in 1 healthy control. We believe that our patient corresponds to the definition of Biacabe et al.,[21] who described patients with isolated obstructed OC with clear sinuses or with a mild disease severity. Indeed, obstruction of the OC has also been reported in patients with chronic rhinosinusitis and sinonasal polyposis.[21]

At the 1-month follow-up, the OC obstruction was no longer present in 12 of 19 patients (63%), and most of these patients had recovered from their olfactory loss, as evaluated with the VOS and 5-odorant molecules test. Indeed, SARS-CoV2 infects cells through interactions between its S protein and the ACE2 protein on target cells.[14,15] It has been reported that cells from the human nasal respiratory and support cells from the olfactory epithelium express ACE2 protein.[22] Since that report, several others have hypothesized that this inflammatory obstruction of the OC might be the result of the interaction between SARS-CoV2 and ACE2 protein expressed by the olfactory epithelium.[23]

OC = olfactory clefts.
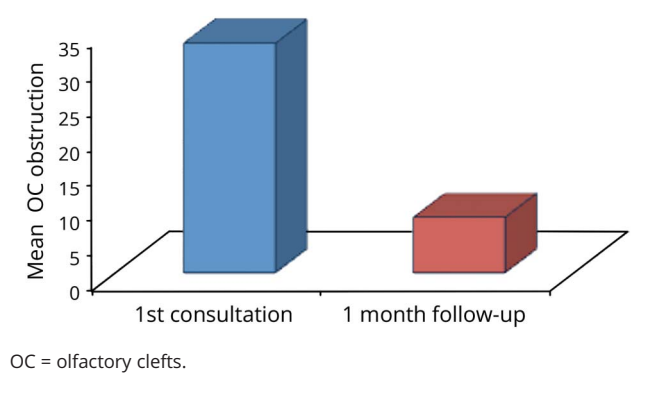
Figure 4 Patient 11: 38-year-old woman with severe acute respiratory syndrome coronavirus 2 infection
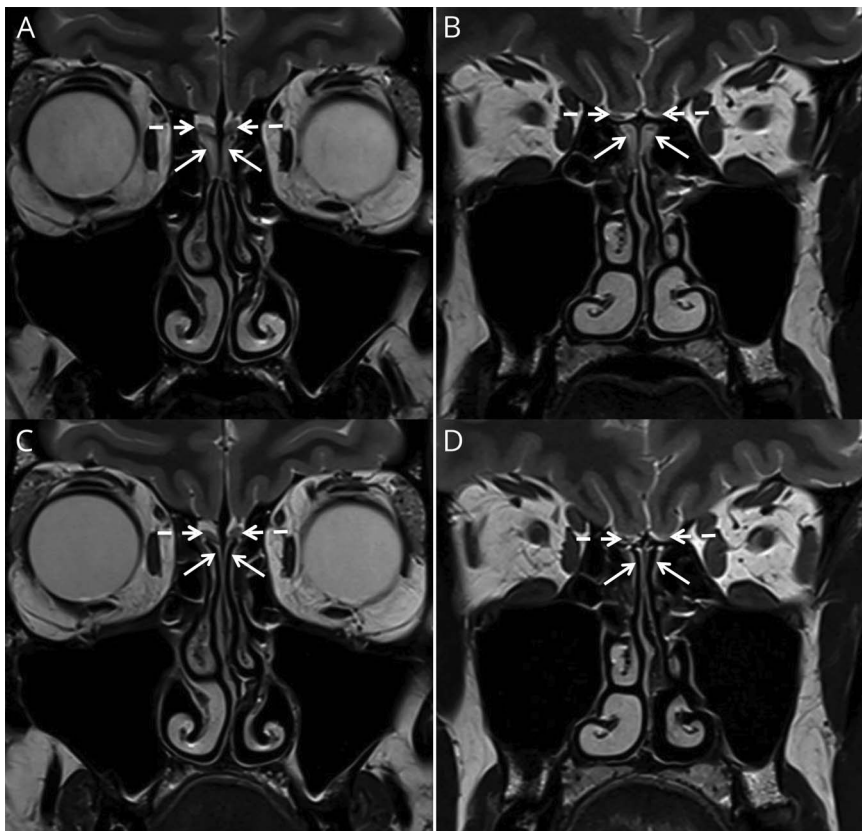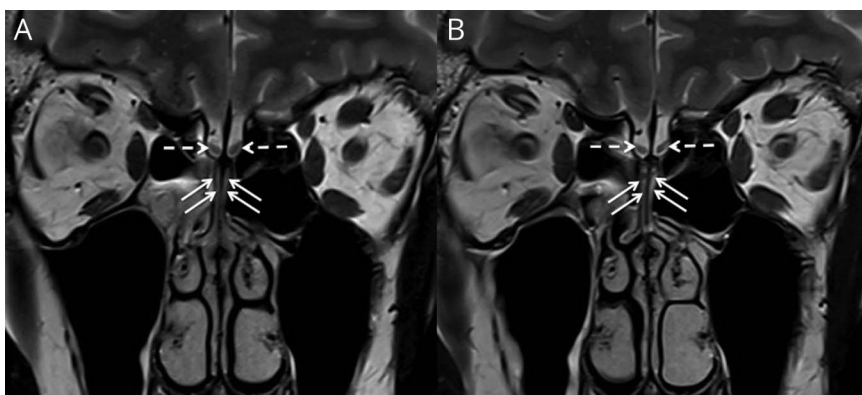

Coronal section of the olfactory clefts (OC) and bulbs on MRI on 2D T2-weighted sequences. (A and B) On the first MRI, the olfactory bulbs (white dotted arrow) are normal (right 38.1 mm³, left 42.1 mm³), while a bilateral inflammatory obstruction (white arrow) of the OC is observed below the olfactory bulbs (A, white dotted arrow) and olfactory tracts (B, white dotted arrow). (C and D) At the 1-month follow-up, the volume of the olfactory bulbs (white dotted arrow) remains normal (right 29.2 mm³, left 39.3 mm³), and no inflammatory obstruction of the OC is observed within the (A) anterior and (B) posterior parts of the OC. The olfactory score at the first consultation and the 1-month follow-up was 0 and 10, respectively.

However, some scientific peers have questioned the inflammatory OC obstruction observed on MRI as the cause of the OFL because most patients did not appear to exhibit significant nasal congestion.[24] In our opinion, the lack of this symptom seems conceivable because only 10% of inhaled air actually reaches the OC during normal resting breath.[25]

It has also been suggested that SARS-CoV2 could invade the brain via the cribriform plate close to the OB and the olfactory epithelium, causing some structural changes in the OB. Recently, in a single case report, Laurendon et al.[12] described MRI findings in a patient with SARS-CoV2 infection associated with a complete anosmia. MRI showed a bilateral obstruction of the OC, in addition to a severe enlargement and

Figure 5 Patient 8: 53 year-old man with severe acute respiratory syndrome coronavirus 2 infection

Coronal section of the olfactory clefts and bulbs on MRI on 2D T2-weighted sequences. (A and B) On the first MRI, the olfactory bulbs (white dotted arrow) are normal (right 33.2 mm³, left 39.1 mm³), while a bilateral inflammatory obstruction (white arrow) of the olfactory clefts is observed. (C and D) At the 1-month follow-up, the volume of the olfactory bulbs (white dotted arrow) remains normal (right 38.2 mm³, left 41.9 mm³), but an inflammatory obstruction of the OC (white arrow) is still observed. The olfactory score at the first consultation and the 1-month follow-up was 0 and 5, respectively.

an abnormal high-signal intensity of the OB. A second MRI was performed 20 days after the initial onset of anosmia and showed a complete resolution of the OC obstruction and enlargement of the OB. Although we found a significant decrease in OC obstruction after 1 month of follow-up, we did not find the same results concerning OB changes. However a decreased neural activity in the olfactory pathways, despite normal morphology of the OB, seems conceivable. Galougahi et al.[26] have reported a reduced metabolic activity in the orbitofrontal cortex in a patient with SARS-CoV2 infection and anosmia. Three of our patients without persistent OC obstruction still had loss of smell at the 1-month follow-up. One could hypothesize that the impairment of the neural function in the central olfactory pathways could occur secondarily after the initial OC obstruction. Moreover, in a recent single case, Politi et al.[27] described a patient with SARS-CoV2 infection and anosmia that present a transient cortical fluid-attenuated inversion recovery (FLAIR) hyperintensity in the gyrus rectus and in the OB that might have result from invasion of SARS-CoV2 to the brain through the olfactory pathway.

Our study has several potential therapeutic implications. Preventing definitive anosmia in patients with SARS-CoV2 infection is crucial, considering that patients with OFL are at risk of nutritional deficits, depression, and injury due to the incapability to smell dangerous odors.[28]

The diagnosis of isolated OC obstruction is usually made in patients with a long history of OFL, and it is not possible to treat the potential initial cause of the disease, namely virus-induced inflammation of the OC. In these patients, most treatments actually do not work.[20] Jankowski et al.[29] have reported the results of surgical OC dilation in patients with dysosmia secondary to constitutional stenosis of the OC. The context is quite different in SARS-CoV2–infected patients, and this surgical option probably should not be considered first.

Our study has some limitations. First, our sample size was relatively small, which might explain some nonsignificant results. Second, because of its duration (40 odorants) and accessibility, the olfactory evaluations could not have been performed as usual with the University of Pennsylvanian Smell identification Test as a result of the sanitary crisis.[30] Therefore, a visual scale and a test based on the forced choice method were chosen to assess the olfactory function.[19] Nevertheless, given that many patients with COVID-19 are probably well aware of the association with the loss of smell, this could certainly affect the self-reporting VOS scores. In addition, a complete anosmia could not be confirmed because our quantitative test evaluates only 5 odorant molecules. Another limitation was the lack of fibroscopic examination with a standardized and validated scoring of the OC because of the sanitary situation.[31]

In addition, because 3D-FLAIR sequences were not performed in all patients (fewer than half of these patients),

we could not exclude an impairment of the OB, on the basis solely of the measure of their volume. Indeed, Yao et al.[32] have reported that the volume of the OB is decreased in patients with postinfectious olfactory loss and is inversely related to the duration of olfactory loss. However, cerebral and OB anomalies on 3D-FLAIR sequences have been reported in only 2 case reports.

Further prospective studies with follow-up are warranted to evaluate the prognostic value of this obstruction and the impairment of the central olfactory pathways.

This study evaluated the OC as well as the olfactory function in a cohort of patients with SARS-CoV2 infection presenting with OFL. Our results indicate that OFL and OC obstruction are present at the early stage of the disease and that both improved at the 1-month follow-up. These findings support the hypothesis that OFL in SARS-CoV2–infected patients is caused, at least in part, by reversible inflammatory changes in the OC.

Appendix Authors

Name	Location	Contribution
Michael Eliezer, MD	AP-HP Lariboisière Hospital, Paris, France	Design and conceptualized study; analyzed the data; acquisition of data; drafted the manuscript for intellectual content
Anne-Laurel Hamel, MD	AP-HP Lariboisière Hospital, Paris, France	Analyzed the data; Acquisition of data; revised the manuscript for intellectual content
Emmanuel Houdart, MD, PhD	AP-HP Lariboisière Hospital, Paris VII University, France	Analyzed the data; Revised the manuscript for intellectual content
Philippe Herman, MD, PhD	AP-HP, Lariboisière Hospital, Paris VII University, France	Revised the manuscript for intellectual content
Juliette Housset, MD	AP-HP, Lariboisière Hospital, Paris, France	Acquisition of data
Clement Jourdaine, MD	AP-HP, Lariboisière Hospital, Paris, France	Interpreted the data; statistical analysis
Corinne Eloit, MD	AP-HP, Lariboisière Hospital, Paris, France	Revised the manuscript for intellectual content

Continued

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