MRI Depicts Olfactory Bulbs and Cortical Involvement in COVID-19 Patients with Anosmia

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Abstract

Anosmia and ageusia are very common symptoms in SARS-CoV-2 infections. Here we present magnetic resonance imaging evidence of brain signal alterations in the olfactory bulbs and the piriform cortex, presumably caused by SARS-CoV-2.

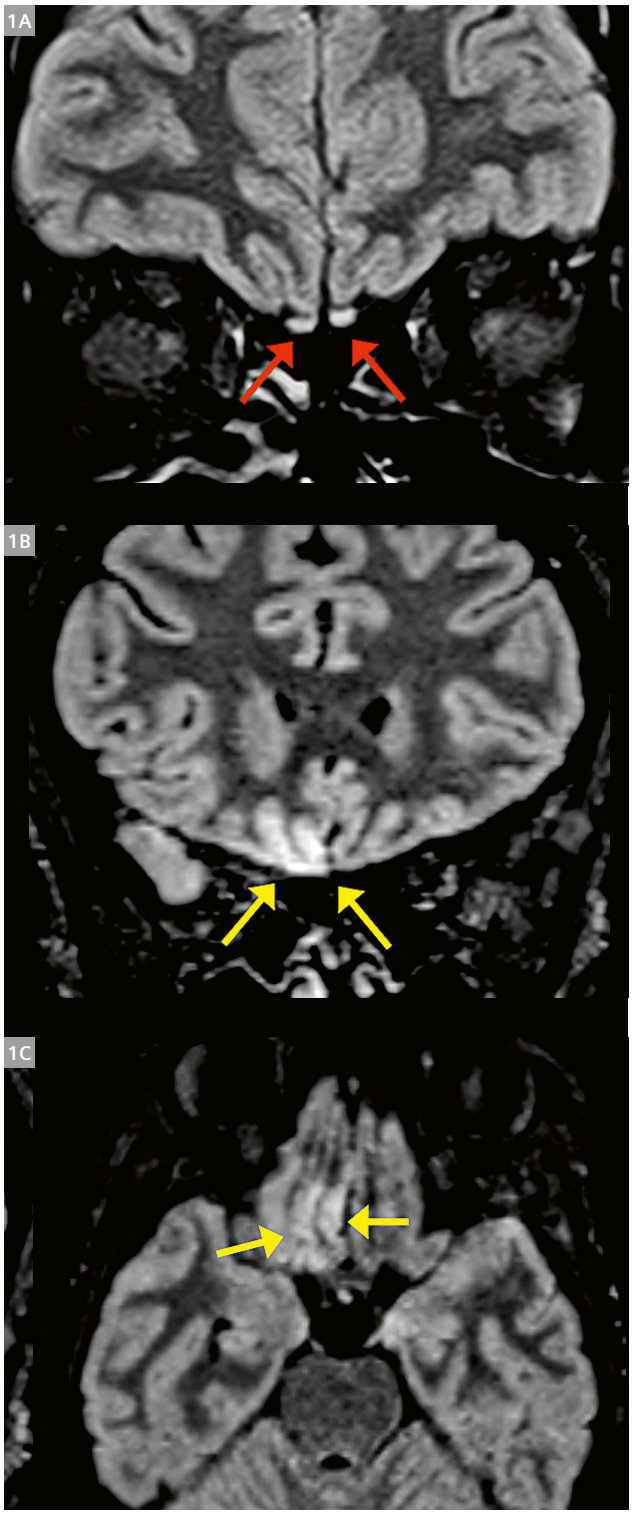
Key points

- In COVID-19 patients presenting with anosmia, T2-FLAIR hyperintensity can be depicted in the olfactory bulbs and anterior piriform cortex, suggesting possible viral invasion of the brain.
- The signal alteration is reduced when patients recover from the symptoms.
- Anosmia can be the predominant COVID-19 manifestation, and this should be taken into account when identifying and isolating infected patients in order to avoid disease spread.

The neurotropism of human coronaviruses has already been demonstrated in small animals [1]. In autoptic studies, the severe acute respiratory syndrome coronavirus (SARS-CoV), which was responsible for the SARS outbreak in 2002–2003, was found in the brain of infected patients [2]. It has been proposed that the neuroinvasive potential of the novel SARS-CoV-2 virus, which causes coronavirus disease 2019 (COVID-19), might be at least partially responsible for respiratory failure in COVID-19 patients [3]. In this paper, we will share magnetic resonance imaging (MRI) evidence of *in vivo* brain alteration presumably caused by SARS-CoV-2, and we will stress that anosmia can be the predominant symptom of COVID-19.

A 25-year-old female radiographer with no significant prior medical history who had been working in a COVID-19 ward presented with a mild dry cough that lasted for one day. This was followed by persistent and severe anosmia and ageusia. She was always nonfebrile. Three days later, a nasal fibroscopy was unremarkable, and non-contrast chest and maxillofacial computed tomography were negative. On the same day, a brain MRI was also performed, using a 1.5 Tesla scanner (MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany) equipped with a 20-channel phase array head and neck coil. On 2D and 3D fluid-attenuated inversion recovery (FLAIR) images, hyperintensity was evident in the bilateral olfactory bulbs (red arrows) and in the right rectus gyrus (yellow arrows). This signal alteration in the cortex of the brain area that is responsible for olfaction is highly suggestive of viral infection. Since many patients in the Italian outbreak complain of anosmia [4], a swab was performed and RT-PCR analysis was positive for COVID-19. In a follow-up MRI performed 28 days later, the signal alteration had almost completely disappeared and the patient had recovered from anosmia.

Similar but less-obvious MRI findings were depicted in a 39-year-old female COVID-19 patient who presented only with anosmia. In this case, the brain MRI was performed eight days after symptom onset. Furthermore, no brain abnormalities were seen in two other patients who presented with anosmia and underwent an MRI exam at 12 and 25 days from symptom onset, respectively.



1 **Brain MRI alterations in a COVID-19 patient presenting with anosmia (three days after symptom onset).**
Coronal 2D FLAIR **(1A, B)** and axial reformatted 3D FLAIR images showing hyperintensity in bilateral olfactory bulbs (red arrows) and in the right rectus gyrus (yellow arrows).

Here we report on human brain involvement in patients who tested positive for COVID-19. We show signal alterations that are consistent with viral brain invasion in regions that are congruent with the patients' symptoms. It should be noted that the posterior part of the gyrus rectus and medial orbital gyrus encompasses the so-called anterior piriform cortex, which receives input from the olfactory bulb through the lateral olfactory tract. The anterior piriform cortex and the posterior piriform cortex (the latter is located in the temporal lobe) are considered the most important olfactory cortical areas. Curiously, in humans, the anterior piriform cortex seems to play a crucial role in encoding the difference between groups of odors. In anosmic animals like the dolphin, this entry zone is so undeveloped and flat that Broca called the area the "olfactory desert" (*désert olfactif*) [5].

Although the presence of SARS-CoV-2 in the cortical FLAIR hyperintense areas is not demonstrated by the MR images, we believe that the congruence between the clinical manifestations in our patient (i.e., olfactory dysfunction) and the cortical brain MRI abnormalities is highly suggestive of possible viral invasion; similar focal abnormalities are definitely unusual and alternative diagnoses are very difficult to find, especially in the clinical setting of anosmia (for instance, anti-NMDAR encephalitis can cause transient FLAIR hyperintensities, but the clinical manifestations rule out this entity; status epilepticus may cause transient gyral edema with T2-FLAIR hyperintensity, but olfactory aura continua / simple partial status epilepticus is exceptional, typically originates from the mesial temporal lobe, and causes olfactory hallucinations but not loss of smell). By contrast, viral infections are commonly considered potential causes of transient or permanent sensorineural olfactory dysfunctions. In the presented cases, no analysis of cerebrospinal fluid (CSF) was performed; however, it should be noted that the clinical sensitivity of CSF analysis with molecular testing for intraparenchymal brain diseases remains undefined (with the exception of herpes simplex (HSV) encephalitis), negative results may not exclude infection, and in some cases cerebral biopsy may be necessary to confirm the diagnosis. Overall, we believe that the abovementioned MRI findings support the hypothesis that the SARS-CoV-2 virus can invade the brain. Based on the MRI findings, our hypothesis is that, following initial replication in the nasal mucosa, SARS-CoV-2 may, as is the case with other coronaviruses, spread from the olfactory epithelium to the olfactory bulb, and subsequently to the posterior gyrus rectus through the lateral olfactory tract [1, 2].

Overall, the presence of MRI abnormalities in the posterior part of the gyrus rectus could conceivably be related to the centripetal spreading of SARS-CoV-2 through the lateral olfactory tract, and the olfactory dysfunction experienced by our patient may have a sensorineural

origin. Our own and others' observations of normal brain imaging in subjects with COVID-19-related olfactory dysfunctions [6], and the disappearance of the MRI abnormalities in a follow-up study in one of our patients suggest that these imaging changes might not always be present in COVID-19, or are limited to the very early phase of the infection. Further, anosmia can be the predominant COVID-19 manifestation, and this should be taken into account when identifying and isolating infected patients in order to avoid disease spread.

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