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Anosmia in COVID-19 Associated with Injury to the Olfactory Bulbs Evident on MRI

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Abstract:

Patients with coronavirus infection disease 19 (COVID-19) may have symptoms of anosmia or partial loss of the sense of smell, often accompanied by changes in taste. We report 5 cases (3 with anosmia) of adult patients with COVID-19 in which injury to the olfactory bulbs was interpreted as microbleeding or abnormal enhancement on MRI. The patients had persistent headache (n=4) or motor deficit (n=1). This may be the mechanism by which the SARS-CoV-2 causes olfactory dysfunction.

Introduction

Coronavirus is a virus that has as main target the human respiratory system, but also has neuroinvasive capabilities and can spread from the respiratory tract to the CNS.[1-3] So, patients with coronavirus disease 19 (COVID-19) may present neurological symptomatology with repercussions on imaging exams[4-18] and were described association with ischemic infarct,[8, 9] hemorrhage,[11] acute hemorrhagic necrotizing encephalopathy,[10] cerebral venous thrombosis[13] and diffuse leukoencephalopathy with microhemorrhage[15].

Transmission from person to person occurs mainly by direct contact or by droplets spread by coughing or sneezing by an infected individual with virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[5, 19] Symptoms of COVID-19 usually appear after an incubation period of about five days. The most common symptoms are fever, cough, fatigue, headache and dyspnea.[5, 19, 20] In the most severe cases, patients may develop pneumonia, acute respiratory failure, distress syndrome and acute heart problems.[5, 19, 20]

Anosmia or partial loss of the sense of smell, usually accompanied by changes in taste, is a frequent complaint which helps in the diagnosis of COVID-19.[21-28] It is often a

transitory phenomenon, lasting but a few weeks.[21] However, the mechanism by which anosmia occurs has not yet been established.[29]

The hypothesis is that the virus enters into the central nervous system through the first neurons of the olfactory pathway, also named olfactory sensory neurons, located in the olfactory mucosa. The olfactory mucosa is a specialized neuroepithelium that is located in the highest portion of the nasal cavity, in direct contact with the external environment, below to cribriform plate.[1]. So, the virus crosses the cribriform plate to reach the olfactory bulbs where there are the second olfactory neurons.[1, 30]

There are recently only two reports which evaluated the olfactory bulb imaging and they are discordant[18 31]. The first letter showed bilateral inflammatory obstruction of the olfactory clefts that was confirmed on MRI of the nasal cavity, but no anomalies of the olfactory bulbs and tracts.[31] The second study reported a case with anosmia evaluated with 3D-CISS-T2-WI, which demonstrated severe enlargement and an abnormal high-signal intensity on T2 being interpreted as bilateral olfactory bulbs edema and also olfactory clefts mild edema.[18] The control MRI showed a reduction in the volume of the bulbs.[18]

To our knowledge, there is no other report evaluating the characteristics of the olfactory bulb specially using fat suppression T1 WI. There is not also any report evaluating and showing the presence of bleeding nor break of the blood-brain barrier in the olfactory bulbs and tracts as the possible pathophysiology of olfactory neuropathy associated with COVID-19.

Thus, in this study, the authors are demonstrating by MRI that one possible mechanism by which the SARS-CoV-2 causes olfactory dysfunction is by affecting intracranially the olfactory bulbs by a likely microvascular phenomenon.

Methods

This retrospective study was approved by the Institutional Review Board of the Ethics Committee of Universidade Federal de Pernambuco, Brazil. Informed consents were waived.

All scans were initially analyzed by the institution's own neuroradiologists. Subsequently, all images were reviewed independently by two neuroradiologists (MFVVA and OQCF, they were certificated by Ministry of Education and Culture of Brazil and the Brazilian College of Radiology), with 30 and 18 years, respectively, of neuroradiology experience, with no discordant results. An MRI was indicated mainly because of a persistent incapacitating headache.

The intensity of olfactory bulbs was defined as normal when the bulbs have the same cortex intensity, as typically seen in healthy controls. Abnormal olfactory bulb intensity is when the bulbs are more hyperintense than the cortex on T1WI and STIR.

After gadolinium injection on T1WI, enhancement of the olfactory bulbs is defined when they become more hyperintense in comparison with their intensity on pre-gadolinium T1WI. However, when there is only the post-gadolinium T1WI and the bulb is more hyperintense than the normal cortex, this represents olfactory bulb intensity abnormality and maybe an enhancement or microbleeding (methaemoglobin), as interpreted in the present study. Microbleeding (methaemoglobin) in the olfactory bulb is considered when there is hyperintense olfactory bulb, compared with the normal cortex or the normal contralateral bulb, on pre-gadolinium fat supression TIWI.

Brain MRI of patients with COVID-19 was evaluated from April 1, 2020 to May 18, 2020. Five patients were included in this study because their brain MRIs had their olfactory bulbs assessed appropriately with at least two sequences with thin slices exanimating the anterior cranial fossa. All five patients were evaluated with two coronal

sequences with thin slices: post-contrast fat suppression T1-WI and STIR. Only one patient had also thin slices pre-gadolinium fat suppression T1-WI.

The brain MRIs of the patients were performed on two 1.5 Tesla machines with the main technical parameters of the sequences described as follows. The coronal fat suppression T1WI (SPIR) parameters were respectively in both MRI machines: TR/TE = 561; 605/15; 9, matrix = 256; 288, FOV = 190; 150, thickness = 3 mm; 3.5 mm, slice orientation = coronal, bandwidth = 181; 96.6, time = 3.39 min; 4.49 min and NEX = 1; 3.

The coronal STIR had the following parameters in each MRI machine, respectively: TR/TE = 4,000; 2,650 /51; 90, TI = 180 matrix = 256; 224; FOV = 190; 150, thickness: 3; 3.45 mm, slice orientation: coronal, bandwidth = 190; 232.4, time = 2.46 min; 3.42 min and NEX = 1; 2.

Results

All five patients with COVID-19 (Table 1) had fever, headache and cough. The medical indications for realization of MRI were persistent headache (n=4) or motor deficit (n=1). All five cases had injury of the olfactory bulbs demonstrated by MRI (Figures 1 and 2).

The only patient who had pre-gadolinium fat suppression T1-WI (case 1) showed small hyperintensity in the left olfactory bulb (Figure 1 A) which remained hyperintense on post-gadolinium sequence (Figure 1 B) and also on STIR (Figure 1 C). This finding was suggestive of a small area of methemoglobin in the left olfactory bulb in this patient with anosmia.

In the four patients that did not have pre-gadolinium sequence, one patient that we did not have information about anosmia (Figure 2 A,; case 2) and two of them with anosmia (Figure 2 B-C; Cases 3 and 4)), showed hyperintensity suggestive of

enhancement of both olfactory bulbs following gadolinium injection. However, in the only patient with COVID-19 without clinical anosmia (case 5), there was a suggestive enhancement in the left olfactory bulb (Figure 2 D). The differential diagnosis in these cases is mainly with microbleeding (methaemoglobin) because the pre-gadolinium sequence was not performed. Coronal STIR of anterior cranial fossa did not show any abnormality in the olfactory bulbs in these four patients.

MRI of a healthy individual is used as a comparative control (Figure 2 E and F) to demonstrate that the normal olfactory bulbs do not enhance and are isointense to the cerebral cortex.

Discussion

This case series demonstrates abnormal intensity of the olfactory bulbs in 5 adult patients with COVID-19, three of whom had anosmia. In one patient (Case 1), the abnormal intensity can represent microbleeding (methemoglobin). However, in the other four patients, it could represent abnormal enhancement or microbleeding (methemoglobin) because they only had the sequence after injection of gadolinium fat suppression T1WI.

Previously, it was demonstrated, using an experimental mouse model, that the SARS-CoV could travel from the nose to the olfactory bulb.[32] Regarding the SAR-CoV infection, there was a time delay of about 60 hours from the time of nasal infection until the detection of the virus in the olfactory bulb.[1, 32]

The literature already has described that some other viruses can also use the olfactory nerve as a shortcut into the CNS, such as: influenza A virus, herpesviruses, poliovirus, paramyxoviruses, vesicular stomatitis virus, rabies virus, parainfluenza virus, adenoviruses, Japanese encephalitis virus, West Nile virus, chikungunya virus, La Crosse virus, mouse hepatitis virus, and bunya viruses. [30] "Viral infection of the CNS can lead

to damage from infection of nerve cells per se, from the immune response, or from a combination of both. Clinical consequences range from nervous dysfunction in the absence of histopathological changes to severe meningoencephalitis and neurodegenerative disease."[30] However, to our knowledge, we did not find any study evaluating and documenting the abnormalities such as microbleeding and/or enhancement in the olfactory bulbs by brain MRI occurring in these other kinds of viruses.

Probably, the impairment of olfactory function is much more frequent in COVID-19 since strictly speaking unilateral anosmia can be only detected through a detailed physical examination. The patient hardly perceives unilateral anosmia.

The importance of recognizing this hypersignal in olfactory bulbs on the thin slices of pre and/or post-gadolinium fat suppression T1WI, identified in this study, may help to suggest or support the etiological diagnosis of COVID-19 during and after this new pandemic.

Thus, we suggest, henceforth, to include in the routine brain MRI protocol at least a sequence with coronal thin slices pre and/or post-gadolinium fat suppression T1WI in the anterior fossa of the cranium. We suggest this because COVID-19 has a spectrum of clinical presentation of disease severity and cannot be suspected mainly after the epidemic. This will be more important in cases of refractory headache associated or not with other symptoms and signs such as fever and anosmia.

The weakness of this work is that it is a retrospective study with few cases, in which it was possible to evaluate the olfactory bulbs. Brain MRI scans of patients with COVID-19 have not been routinely scheduled to adequately evaluate the olfactory bulbs because other neurological complications were being investigated. The distortion at the air-tissue interface in fat suppression T1WI makes the findings somewhat difficult to interpret, but it seems that the images are true abnormal lesions along the olfactory bulbs.

Future prospective studies geared to evaluating the olfactory bulbs with a larger sample size will be needed to confirm our findings.

In conclusion, the authors demonstrated by MRI that one possible mechanism by which the SARS-CoV-2 causes olfactory dysfunction is by affecting intracranially the olfactory bulbs with development of microvascular phenomenon and injury, such as microbleeding and/ or blood-brain barrier breaking. This seems to be the first time that a neuroimaging study has documented this type of olfactory bulb injury in COVID-19 patients.

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Table 1- Demographic data of five patients with COVID-19 studied by brain MRI.

Patient #	age (years)/sex	Anosmia	Covid-19	Previous history of headache	Difficulty of breathing	Cough	Hospitalization	ICU	Anosmia	Headache	Other neurlogical symptoms	MRI indication	Encephalon MRI
1	25/woman	Yes	Confirmed	No	Yes	Yes	Yes	No	Yes	Yes	No	Persistent headache	Normal
2	40/man	Without information	Confirmed	No	No	Yes	Yes	No	Without information	Yes	Yes, leg motor deficit	Motor deficit	T2 hypersignal and diffusion in the corpus callosum splenium
3	34/woman	Yes	Confirmed	Migraine	Yes	Yes	Yes	No	Yes	Yes	No	Persistent headache	Normal
4	35/woman	Yes	Probable	Migraine	No	Yes	Yes	No	Yes	Yes	No	Persistent headache	Normal
5	43/woman	No	Confirmed	No	Yes	Yes	Yes	No	No	Yes	No	Persistent headache	Normal

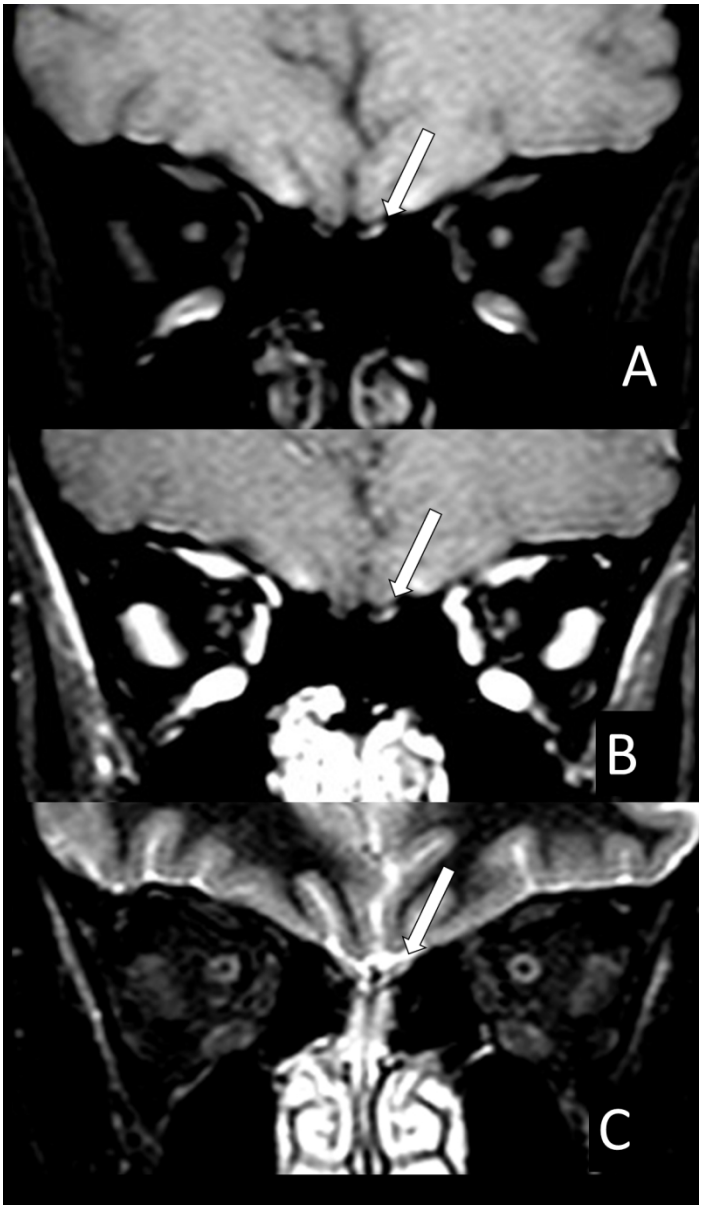

Figure 1 - Magnetic resonance imaging shows microbleeding (methaemoglobin) in the left olfactory bulb of patient (case 1) with COVID 19 and anosmia (A-C)- The left olfactory bulb (long arrows) has partial hyperintensity on pre-contrast fat suppression T1WI (A) and also in post-contrast fat suppression T1WI (B) and STIR (C).

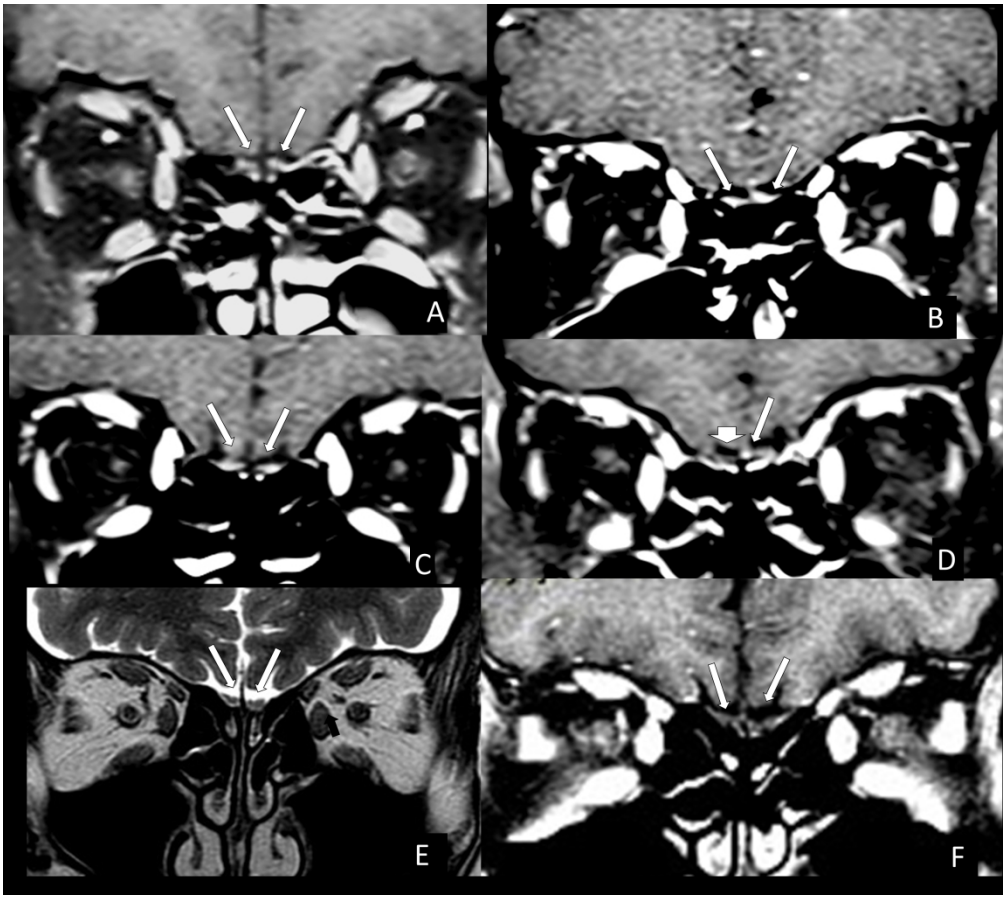

Figure 2 - The coronal postcontrast fat suppression T1WI shows hyperintensity suggestive of enhancement or methemoglobin in the olfactory bulbs of four patients with COVID 19 (A-D; Cases 2-5) compared with a normal patient with normal olfactory bulbs (E,F) – The coronal postcontrast fat suppression T1WI in three patients with COVID 19, (A-C; cases 2-4) shows that the both olfactory bulbs (long arrows) are small oval images which are hyperintense with contrast, having signal intensity higher than the intensity of the cortex. In figure D (case 5), the patient with COVID 19 shows hyperintensity only on the left bulb (long arrow), being the right olfactory bulb normal (short arrow). In the normal 60 years old male, the coronal T2WI (E) and the post-contrast fat suppression T1WI (F) demonstrate normal olfactory bulbs (long arrows) which are isointense to the cortex and for this reason being the olfactory bulbs normally hypointense on post gadolinium sequence (F).