Encephalitic syndrome and anosmia in COVID-19: Do these clinical presentations really reflect SARS-CoV-2 neurotropism? A theory based on the review of 25 COVID-19 cases

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Abstract
Since the discovery of coronavirus disease 2019 (COVID-19), a disease caused by the new coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathology showed different faces. There is an increasing number of cases described as (meningo)encephalitis although evidence often lacks. Anosmia, another atypical form of COVID-19, has been considered as testimony of the potential of neuroinvasiveness of SARS-CoV-2, though this hypothesis remains highly speculative. We did a review of the cases reported as brain injury caused by SARS-CoV-2. Over 98 papers found, 21 were analyzed. Only four publications provided evidence of the presence of SARS-CoV-2 within the central nervous system (CNS). When facing acute neurological abnormalities during an infectious episode it is often difficult to disentangle neurological symptoms induced by the brain infection and those due to the impact of host immune response on the CNS. Cytokines release can disturb neural cells functioning and can have in the most severe cases vascular and cytotoxic effects. An inappropriate immune response can lead to the production of auto-antibodies directed toward CNS components. In the case of proven SARS-CoV-2 brain invasion, the main hypothesis found in the literature focus on a neural pathway, especially the direct route via the nasal cavity, although the virus is likely to reach the CNS using other routes. Our ability to come up with hypotheses about the mechanisms by which the virus might interact with the CNS may help to keep in mind that all neurological symptoms observed during COVID-19 do not always rely on CNS viral invasion.

KEYWORDS
anosmia, central nervous system, COVID-19, encephalitis, meningitis, SARS-CoV-2

1 | INTRODUCTION
Coronavirus disease 2019 (COVID-19) is a pathology induced by a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Two clinical presentations are classified as atypical forms of COVID-19: confusion syndrome and anosmia. They are often considered as both resulting from nervous system damage, the first one being linked to a direct central nervous system (CNS) involvement and the second one to a peripheral nervous system damage.

There is an increasing number of cases reporting as SARS-CoV-2 (meningo) encephalitis. Nevertheless, evidence is often lacking. Encephalitis can lead to diverse neurological symptoms (confusion, seizure, focal signs, and coma) that reflect brain injury. Meningitis is
characterized by a neck stiffness and the presence of a cerebrospinal fluid (CSF) pleocytosis, without any parenchymal involvement. A sustained inflammatory response originating outside the brain can also lead to vascular and cells damage without any viral proliferation within the CNS (acute encephalopathy). Many pathogens including coronaviruses can induce an auto-immune response directed toward the CNS after the resolution of an infection (acute disseminated encephalomyelitis [ADEM]). It is often difficult to distinguish encephalitis, meningitis, and neurological symptoms induced by metabolic, vascular, or auto-immune disorders occurring during or after a severe infection.

We reviewed all COVID-19 cases reporting a brain damage (except the ones related to ischemic stroke in the context of a severe infection) and we proposed the mechanisms by which SARS-CoV-2 could impair the CNS. It is urgent to clarify the different ways SARS-CoV-2 may interact with the CNS to distinguish the severe cases (i.e., SARS-COV-2 encephalitis) from the ones related to a transient impact of SARS-CoV-2 infection on the CNS.

1.1 | Case reports

Among 98 records identified from Pubmed database (the search terms “central nervous system,” “CNS,” “neurological,” “encephalitis,” “meningitis,” “meningoencephalitis,” “meningo-encephalitis,” “seizure,” “seizures,” “confusion,” “encephalopathy,” “COVID,” “SARS,” and “coronavirus” were used between 1st of December 2019 and 26th of May 2020), 85 titles and abstracts were screened (13 duplicates) with no language restrictions. Sixty-four were excluded because they were not relevant to the topic covered in this paper. Twenty-one articles reported as SARS-CoV-2 brain injury were fully read, corresponding to 25 cases.

When performed (n = 10), the SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) in the CNS was positive only in four patients (40%). Among those four cases, comorbidities have been reported in two of them (50% vs 33% of the patients with a negative RT-PCR in the CNS), the virus was systematically found in the upper respiratory tract (the test was performed simultaneously in the CNS and in the nasopharynx only for two patients, and no other body compartment has been tested), and they all displayed a severe form except one (75% vs 33% of the patients with a negative RT-PCR), with one death and no recovery at the day of the publication for the other three severe cases.

Most of patients were males (n = 17, 68%) and reported comorbidities (n = 13, 52%). Alteration in mental status/confusion were the most reported neurological symptoms (n = 22, 88%). The neurological symptoms were concomitant with respiratory symptoms (n = 7, 28%) or appeared in the context of a worsening of initial respiratory symptoms (n = 7, 28%). Cerebral magnetic resonance imagery (MRI) performed in twelve patients revealed abnormalities in 50% of cases and showed inflammatory lesions that brain computed tomography (CT) failed to reveal (cases 25 and 914). Among the fourteen lumbar punctures performed, 50% were normal (no pleocytosis and no elevation of proteins level). A lymphocytic pleocytosis was found in five cases (36%). An elevation of proteins level in the CSF was reported only in two cases (14%). When performed (n = 8) SARS-CoV-2 RT-PCR on CSF samples were positive only in two cases (25%). Finally, almost half of the patients (n = 11, 44%) had a severe infection (intensive care unit, mechanical ventilation, death) with recovery in the majority of cases (n = 15/24, 62.5%) (Table 1).

1.2 | The indirect impact of SARS-CoV-2 on the CNS

Although many authors presented their cases as SARS-CoV-2 (meningo) encephalitis, this diagnosis remains speculative without any evidence of the virus within the CNS. The neurological symptoms observed in the infant (case 5) and the child (case 715) reported in Table 1 with fast and total recovery are in favor of a moderated effect of cytokines on the brain. This mechanism has been recently proposed to explain aseptic CSF pleocytosis commonly observed in infants during urinary tract infections. The apparition of neurological impairments after the resolution of respiratory symptoms observed in three patients in this paper (cases 10, 16, 19 and 24) are highly suggestive of ADEM.

1.3 | Possible mechanisms of SARS-CoV-2 brain invasion

Based on post-mortem data available about the brain of healthy people and patients with neurological diseases, we now know that CNS brain invasion by coronaviruses might probably occur more frequently than expected. Animal studies have shown that coronaviruses are able to reach the CNS via peripheral nerves. Based on these data and the neurological symptoms found in COVID-19 some have postulated that SARS-CoV-2 might have neurotropic properties. As a matter of fact, the presence of a virus within the CNS involves two concepts: the virus capacity to reach the CNS (neuroinvasiveness) and the virus capacity to proliferate efficiently within the CNS (neurovirulence). Neuroinvasiveness can be achieved by viruses able at using the machinery of neurons be transported within a neuron as seen in the case of herpes viruses. Viruses can also be present in the CNS using other pathways such as the bloodstream. In this case the virus does not need any particular affinity for neurons (neurotropism) (Figure 1).

1.3.1 | SARS-CoV-2 CNS invasion via the hematogenous route

Virus can take advantage of the increased local blood vessels permeability and epithelium disruption induced by a sustained inflammatory response to reach the bloodstream. Unlike primary viremia that occurs silently during the early stage of an infection, this secondary viremia occurs later and during a sustained viral
| Case | Authors | Sex (M/F), age (y or d) | Country | Comorbidities | Neurological symptoms | CNS samples | Brain abnormalities | Brain MRI | Outcome | Neurological diagnosis proposed by the authors |
|------|---------|-------------------------|---------|---------------|----------------------|-------------|---------------------|----------|---------|-----------------------------------------------|
| 1    | Filatov et al | M, 74 y USA | Parkinson, CVD, COPD | C | Altered mental status | n | ND | ND | Yes | aN | n | ND | Poor prognosis | Encephalopathy |
| 2    | Moriguchi et al | M, 24 y Japan | Ac | Unconsciousness, seizures, meningitis | Lymphocytic pleocytosis | + | Yes | ND | n | Encephalitis | Poor prognosis | Meningitis |
| 3    | Poyiadji et al | F, 55 y USA | C | Altered mental status | Traumatic | ND | ND | ND | Hemorrhagic lesions | ANE |
| 4    | Duong et al, updated by Hung et al | F, 41 y USA | Diabetes, obesity | I | Disorientation, hallucinations, seizures, meningitis | Lymphocytic pleocytosis | + | No | aN | n | ND | Recovery | Meningitis |
| 5    | Chacón-Aguilar et al | M, 26 d Spain | No | C | Hypertonia, seizures, irritability | n | ND | ND | No | n | ND | Recovery |
| 6    | Ye et al, Yin et al | M, 64 y China | No | Ac | Altered consciousness, pyramidal syndrome, meningitis | n | ND | Neg | No | ND | n | ND | Recovery | Encephalitis |
| 7    | MoAbee et al | M, 11 y USA | No | I | Seizures | Pleocytosis | ND | ND | No | aN | n | ND | Spontaneous recovery | Encephalitis |
| 8    | Paniz-Mondolfi et al | M, 74 y USA | Parkinson | C | Confusion, agitation, aggressivity | ND | Viral particles coming in/out of the endothelial wall and inside neural cell bodies | + (brain tissue) | Neg (CSF) | Yes | ND | aNR | ND | Death | Encephalitis |
| 9    | Zanin et al | F, 54 Italy | Brain artery aneurysm | Ac | Unconsciousness, seizures | Yes (before) | ND | Neg | Yes | aN | n | Multifocal hyperintense lesions | Recovery | Encephalitis or ADEM |
| 10   | Pellittero and Ferrer-Bergua | F, 30 Spain | No | Ar | Vestibular syndrome | Yes (before) | ND | ND | ND | No | ND | n | Fast recovery | |
| Case | Authors | Sex (M/F), age (y or d) | Country | Comorbidities | Neurological symptoms | CNS samples | SARS-CoV-2 RT-PCR in CSF or brain sample | Severity (ICU/MV/death) | Brain abnormalities | Neurological diagnosis proposed by the authors |
|------|---------|--------------------------|---------|---------------|----------------------|-------------|------------------------------------------|-------------------------|----------------------|-----------------------------------------------|
| 11   | Franceschi et al | M, 48 y | USA | Obesity | Ac | Altered mental status | ND | ND | ND | Yes | ND | Edema, hemorrhage | Recovery | PRES |
| 12   | Franceschi et al | F, 67 y | USA | CVD, asthma, diabetes | I | Altered consciousness, confusion | ND | ND | ND | No | ND | Edema | Recovery | PRES |
| 13   | Sohal and Mos-sammam | M, 72 y | USA | CVD, diabetes, chronic kidney disease on hemodialysis | C | Altered mental status, seizures | ND | ND | ND | Yes | aN | aNR | ND | Death | Encephalitis |
| 14   | Chaumont et al | M, 67 y | France | No | C | Ac | Lymphocytic pleocytosis | ND | No | aN | ND | n | Partial recovery | Meningoencephalitis |
| 15   | Bernard-Valnet et al | F, 64 y | Switzerland | Ac | Disorientation, focal signs, seizures, hallucinations, psychotic symptoms | Lymphocytic pleocytosis | ND | Neg | aN | ND | n | Recovery | Meningoencephalitis |
| 16   | Bernard-Valnet et al | F, 67 y | Switzerland | Ar | Confusion, aggressivity, focal signs | Lymphocytic pleocytosis | ND | Neg | No | ND | n | Recovery | Meningoencephalitis |
| 17   | Beach et al | M, 76 y | USA | Major neurological disorder, CVD | I | Altered mental status | ND | ND | ND | No | ND | aNR | ND | Partial recovery | Encephalopathy |
| 18   | Beach et al | M, 70 y | USA | Dementia with Lewy bodies, CVD | B | Altered mental status | ND | ND | ND | No | ND | aNR | ND | Partial recovery | Encephalopathy |
TABLE 1 (Continued)

| Case | Authors         | Sex (M/F), age (y or d) | Country       | Comorbidities                                                                 | Neurological symptoms          | CNS samples | SARS-CoV-2 RT-PCR in CSF or brain sample | Brain abnormalities | Severe (ICU/MV/death) | Outcome                  | Neurological diagnosis proposed by the authors |
|------|----------------|-------------------------|---------------|-------------------------------------------------------------------------------|-------------------------------|-------------|-------------------------------------------|---------------------|------------------------|-------------------------|-----------------------------------------------|
| 19   | Beach et al    | M, 68 y                 | USA           | Schizophrenia, chronic kidney disease                                        | Altered mental status (after fall), akinetic mutism | DS          | ND                                        | ND                  | NS                     | Recovery                  | Encephalopathy                |
| 20   | Beach et al    | F, 87 y                 | USA           | Dementia, CVD, COPD, diabetes                                                 | Altered in consciousness, altered mental status, agitation, mydriasis | DS          | ND                                        | ND                  | ND                     | Death                    | Encephalopathy                |
| 21   | Zayet et al    | M, 68 y                 | France        | Obesity                                                                       | Altered consciousness, confusion | DS          | ND                                        | ND                  | ND                     | Recovery                  | Encephalopathy                |
| 22   | Zayet et al    | M, 39 y                 | France        | No                                                                           | Unconsciousness, focal sign    | DS          | ND                                        | ND                  | ND                     | Recovery                  | Encephalopathy                |
| 23   | Al-olama et al | M, 36 y                 | United Arab Emirates | No                                                                           | Unconsciousness, seizures     | DS          | ND                                        | ND                  | ND                     | Stated Meningoencephalitis complicated with hematoma |
| 24   | Fasano et al   | M, 54 y                 | USA           | Controlled HIV                                                                | Confusion, seizures, agitation | DS          | ND                                        | ND                  | ND                     | Recovery                  | Encephalopathy                |
| 25   | Haddad et al   | M, 41 y                 | USA           | Controlled HIV                                                                | Confusion, seizures, agitation | DS          | ND                                        | ND                  | ND                     | Recovery                  | Encephalopathy                |

Note: F–55 y: for case 3, the authors did not precise the patient’s age and wrote: "A female airline worker in her late fifties."
Abbreviations: ADEM, acute disseminated encephalomyelitis; aN, abnormalities; aNR, abnormalities not related to COVID-19; ANE, acute necrotizing encephalopathy; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid; CT, computed tomography; CVD, cardiovascular disease; EEG, electroencephalogram; Hyperprot, elevation of proteins level in CSF (>100 mg/dL); ICU, intensive care unit; mHyperprot, moderated elevation of proteins level in CSF (50–100 mg/dL); MRI, magnetic resonance imagery; MV, mechanical ventilation; n, normal; ND, not done; Neg, negative SARS-CoV-2 RT-PCR; PRES, posterior reversible encephalopathy syndrome; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

aWhen anosmia was not explicitly investigated; ? when the patient’s mental status did not allow to investigate anosmia; () to precise if anosmia appeared before or was concomitant with neurological symptoms.
bOnset of neurological symptoms: Ac for apparition of neurological symptoms after respiratory symptoms while those are still present, Ar for apparition of neurological symptoms after respiratory symptoms resolution, B for apparition of neurological symptoms before respiratory symptoms, I for isolated neurological symptoms, and C for concomitant respiratory and neurological symptoms.
1A. PRIMARY VIREMIA

During a viral infection, a small amount of virus can reach the bloodstream. As lymphatic vessels drain into the circulatory system, virus particles can freely reach the bloodstream via this way. Taking advantage from the disruption of the blood-brain-barrier (BBB) caused by the inflammation or using ACE-2 receptors present at the surface of BBB endothelial cells, SARS-CoV-2 could then enter the CSF (2A), without any proliferation within the brain parenchyma (3A). In this case symptoms would be limited to a meningeal syndrome.

1B. SHORTCUT PATHWAY FROM NASAL CAVITY TO OB

When SARS-CoV-2 enters the nasal cavity it could reach the CNS via two routes. 2Bi: It could “passively” reach the CSF via the OECs that have an open connection with the CSF; the CNS immune response should prevent spread of SARS-CoV-2 into the brain parenchyma (3A). 2Bii: SARS-CoV-2 could also invade ORNs with the assumption that ACE-2 is present in those cells; in this case the virus would use a nerve pathway by being transported retrogradely from ORNs to the OB and could continue to spread through chains of connected neurons to reach the brain (3B), which might result in possible irreversible damage to the CNS. 1C. The secondary viremia: during a sustained viral replication due to the host inability to clear the viral proliferation a large amount of virus is produced and the respiratory epithelium can be disrupted, allowing the virus to reach the bloodstream. The virus could then cross the endothelial barrier by taking advantage from the disruption of the BBB caused by the inflammation or using ACE-2 receptors present at the surface of BBB endothelial cells (2C). The ineffective immune response leads to a viral proliferation within the brain parenchyma leading to neural cells damages and severe neurological symptoms (3C). ACE-2, angiotensin converting enzyme II; CNS, central nervous system; CoM, comorbidities; CSF, cerebrospinal fluid; NE, nasal epithelium; OB, olfactory bulb; OEC, olfactory ensheathing cell; ORN, olfactory receptor neuron.
replication due to the host inability to clear the viral infection. After having reached the bloodstream the virus can use three ways to enter the brain: invading the endothelial cells of the blood-brain-barrier (BBB) (Figure 1, 1C/2C/3C), crossing the epithelial cells of the blood-CSF barrier in the choroid plexus, or using the immune cells ("Trojan horse") which are naturally able to migrate across the BBB during inflammation. To our knowledge the only human cases of proven coronavirus brain invasion associated with neurological symptoms have been described for SARS-CoV. The three reported patients with SARS-CoV encephalitis all had a relative alteration of their immune system, all displayed severe pneumonia, and SARS-CoV was found in other body compartments. Gu et al’s study which investigated eight autopsies of patients who died from a severe form of SARS-CoV infection showed that the virus was systematically found in the brain. Interestingly all patients had other organs impairment. All those cases are more in favor of a SARS-CoV spread from an hematogenous dissemination.

It has been shown that SARS-CoV can infect and replicate within peripheral blood mononuclear cells (PBMCs), although the viral replication was limited. The capacity of SARS-CoV-2 to infect and to replicate within PBMCs, which can cross the BBB ("Trojan horse"), remains unknown. The viral gene expression of SARS-CoV-2 in patients PBMCs has not been reported yet. According to these preliminary data the "Trojan horse" mechanism does not appear to contribute to SARS-CoV-2 brain invasion.

SARS-CoV-2 invades human via angiotensin converting enzyme II (ACE-2). It has been shown that in the human brain ACE2 protein might be present only in the endothelial and the smooth muscle cells present in brain arteries and veins. The autopsy performed on case 8 confirmed the possibility of a brain access pathway via the endothelial cells of the BBB. Interestingly this patient had a history of Parkinson disease. Based on the fact that ACE2 expression is modulated by intrinsic factors such as hypertension or ischemic injuries, it is possible that history of neurovascular injuries create favorable local conditions for allowing SARS-CoV-2 brain proliferation. In this hypothesis, SARS-CoV-2 might not be a neurotropic virus per se but rather an opportunist neuropathogène that proliferates within brain parenchyma only in the case of severe SARS-CoV-2 infection and in patients with neuropathological disorders or immunosuppressed conditions.

1.3.2 SARS-CoV-2 meningitis

Similarly to enteroviruses which are the principal causal agents of meningitis whereas rarely involved in encephalitis, the presence of SARS-CoV-2 within the CSF does not mean that it is able to invade the brain and cause encephalitis. In the nasal epithelium olfactory receptor neurons (ORNs) are surrounded by the olfactory ensheathing cells that have an open connection with the CSF surrounding the olfactory bulbs: those cells create a direct channel between the nasal cavity and the CNS for particles or pathogens up to 100 nm (Figure 1, 1B/2Bi/3A). Also, viral particles could be found in the CSF due to the anatomical connection recently highlighted between the CNS lymphatic system and the nasal lymphatic vessels or via of the lymphatic vessels of the head and the neck that drain into the circulatory system (Figure 1, 1A/2A/3A). Thus SARS-CoV-2 will be present within the CNS without any neurotropic ability. The presence of SARS-CoV-2 within the CSF might induce a local immune response aimed at limiting viral proliferation in immunocompetent patients. This might result in a meningitis that can resolve spontaneously without sequela. This clinical presentation may be complicated with encephalopathy due to the transient effect of cytokines on brain functioning, as seen in case 4 in this review.

1.3.3 The shortcut olfactory route: anosmia and encephalitis

Anosmia has been mainly reported in pauci-symptomatic patients, although we cannot rule out that this symptom would be unnoticed in severe patients. It has been shown in animal studies that the fast apoptosis of ORNs prevents anterograde transport of respiratory virus into the CNS. Anosmia might rather reflect an efficient innate immune response that leads to ORNs apoptosis via indirect and still unknown mechanisms, and that thus prevents SARS-CoV-2 from reaching the CNS. In this case one may expect that a brain invasion occurring via the nasal pathway would only occur in patients with an inefficient local immune response.

The first case of proven SARS-CoV-2 meningoencephalitis (case 2) has been seen as reflected SARS-CoV-2 potential to be transferred from the nasal cavity to the CNS via an anterograde trans-synaptic route (Figure 1, 1B/2Bi/3B). In fact, the patient showed mainly MRI lesions within a region connected with the olfactory bulbs and a pan-paranasal sinusitis. The human olfactory mucosa directly connects the outside world to the CNS via its ORNs: the axons of these bipolar cells cross the cribriform plate of the ethmoid bone that separates the nasal and cranial cavities, and end in the olfactory bulbs. The hypothesis on a shortcut pathway from nasal cavity to the CNS comes from studies conducted in animals. They showed that an intranasal inoculation of coronaviruses led to the spread of viruses into the CNS without evidence of proliferation within the lower respiratory tract. Nevertheless, it has been shown that ACE2 might be absent or rare in ORNs, which make the hypothesis of a nerve pathway from those cells less probable than another one which is more likely to be investigated in the future. Moreover, observations in animal models do not necessarily reflect how a virus behaves in human. In those experimental studies, viral strains are sometimes selected for their neurotropic properties and large amounts of virus are sometimes required to induce CNS disease after peripheral inoculation.

Another question is raised by the discrepancy between the existence of this putative effective pathway and the relative rarity of SARS-CoV-2 encephalitis. After a primary infection herpes simplex virus (HSV) almost systematically reaches the peripheral nervous system, although HSV encephalitis (HSE) remains rare. Studies conducted in animals and in familial cases of HSE strongly
suggest the major roles of host innate immune response and viral factors (strain, route of inoculation, amount of virus) in limiting or promoting HSV access to the CNS.\textsuperscript{45} We can postulate that SARS-CoV-2 encephalitis would occur only in patients with a higher susceptibility to SARS-CoV-2 (higher density of ACE2 in the ORNs, relative deficit in CNS innate immune response) or in the case of a more virulent strain of SARS-CoV-2 able to reach the CNS directly from the olfactory route. Contrary to meningoencephalitis observed during a secondary viremia in patients with comorbidities and with a severe infection, an encephalitis that would occur via a nerve pathway could be observed in young people without comorbidities, as for the two proven cases of (meningo)encephalitis in this review (cases 2\textsuperscript{5} and 23\textsuperscript{2}). According to this hypothesis neurological symptoms might be isolated or may precede low respiratory tract symptoms. More importantly, the diagnosis could be missed if the lumbar puncture is performed too early after the onset of neurological symptoms, as observed in HSE.\textsuperscript{46}

2 \hspace{1em} CONCLUSION

This paper highlights the fact that in most cases the neurological symptoms reported in the literature were more related to the indirect impact of SARS-CoV-2 on brain rather than to a parenchymal invasion. COVID-19 pandemic should not eclipse other neurological infections: \textit{Streptococcus pneumoniae} and enteroviruses remain the principal cause of meningoencephalitis.\textsuperscript{38} This review also highlighted the necessity to perform a brain MRI as this imagery is superior to CT in highlighting parenchymal lesions linked to meningoencephalitis or vasculitis complications.\textsuperscript{47} In patients with severe neurological symptoms, multiple samples should be performed (in different body compartments but also repeatedly) and the viral genomic sequences compared when possible.

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