Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

which plays a key role in the pathogenesis of SARS-CoV-2 in lower airways [2].

Therefore, how can one explain that COPD patients are underrepresented in patients with SARS-CoV-2 infection?

We could hypothesize that the low prevalence of COPD patients in intensive care settings could be the consequence of pre-existing poor prognosis and decisions to limit the treatment to palliative care. Furthermore, patients with chronic respiratory diseases are likely to be more aware of viral epidemics and are more sensitive to containment and barrier actions than the general population. Another explication could come from COVID-19 pathophysiology.

Cell entry of SARS-CoV-2 is a multi-step process in which ACE-2 and the transmembrane protease serine 2 (TMPRSS2) for S protein priming play a crucial role. Considering a significant inverse relationship between ACE-2 gene expression and the severity of COPD [2], one hypothesis could be that COPD protects against SARS-CoV-2 through a TMPRSS2 inhibitor activity or by an a downregulation of the inflammatory pathway limiting severe forms of infection.

Interestingly, as reported by Halpin et al., inhaled corticosteroids, used by COPD patients can reduce the risk of viral infection. Indeed, budesonide was reported as a promising antiviral and anti-inflammatory drug candidate for the treatment of human rhinovirus infection [3]. *In vitro* experiments showed that inhaled formoterol alone or in combination with bronchodilators (i.e., glycopyrronium and budesonide) inhibited HCoV-229E replication partly by inhibiting receptor expression and/or endosomal function and modulated infection-induced inflammation. Inhaled corticosteroids also reduced the expression of transmembrane serine protease TMPRSS4 and TMPRSS11, which facilitates viral entry and proliferation in human bronchial epithelial cells *in vitro*. Therefore, inhaled corticosteroids in combination with bronchodilators could limit expression or activity of transmenbrane serine protease TMPRSS2 which facilitates SARS-CoV-2 entry in cells.

Surprisingly current smokers (i.e., a large part of COPD patients) could be protected against SARS-CoV-2 infection [4]. *In vivo* models support that chronic cigarette smoke exposure could downregulate ACE 2 expression in lungs via a mechanism dependent of Angiotensine II and Angiotensine II type 1 Receptor [5]. This result suggests a potential protector effect of nicotine against SARS-CoV-2 cell entry via a possible role of nicotinic acetylcholine receptors [4]. Whether cigarette smoking or nicotine do or do not provide a benefit effect warrants further studies.

Understanding why and how remains a challenge for researchers.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Disclosure of interest

The authors declare that they have no competing interest.

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C. Daubin [a,*]
A. Justet [b]
A. Vabret [c]
E. Bergot [b]
N. Terzi [d]

[a] *Department of Medical Intensive Care, CHU de Caen, 14000 Caen, France*
[b] *Department of Pulmonology & Thoracic Oncology, CHU de Caen, 14000 Caen, France*
[c] *Department of Virology, CHU de Caen, 14000 Caen, France*
[d] *Department of Medical Intensive Care, CHU de Grenoble-Alpes, 38000 Grenoble, France*

* Corresponding author.
E-mail address: daubin-c@chu-caen.fr (C. Daubin)

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First case of mild encephalopathy with reversible splenial lesion in SARS-CoV-2 infection

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Central nervous system damage has previously been described for coronaviruses [1]. Regarding SARS-CoV-2, various neurological manifestations have been reported in the literature involving both the central and the peripheral nervous systems [2,3]. A recent systematic review underlined the high rate of central nervous system involvement and neurological manifestations in SARS-CoV-2 infections [4], particularly in those involving severe infection.

Herein, we report the case of a patient infected by SARS-CoV-2 who developed an original neurological presentation defined as mild encephalopathy with reversible splenial lesion (MERS), which to our knowledge had never previously been described as occurring over the course of this infection.

A 47-year-old man from French-speaking Africa with no medical history or daily treatment was driven to our emergency department on April 8, 2020 due to onset of confusion over the previous 48 hours. He also reported that a febrile dry cough and headache had occurred during the previous 15 days. On admission, he presented normal temperature (37.5 °C), tachycardia (heart rate 107) and tachypnea (35 breaths per minute), slightly elevated blood pressure (150/84 mm Hg) and oxygen saturation upon arrival of

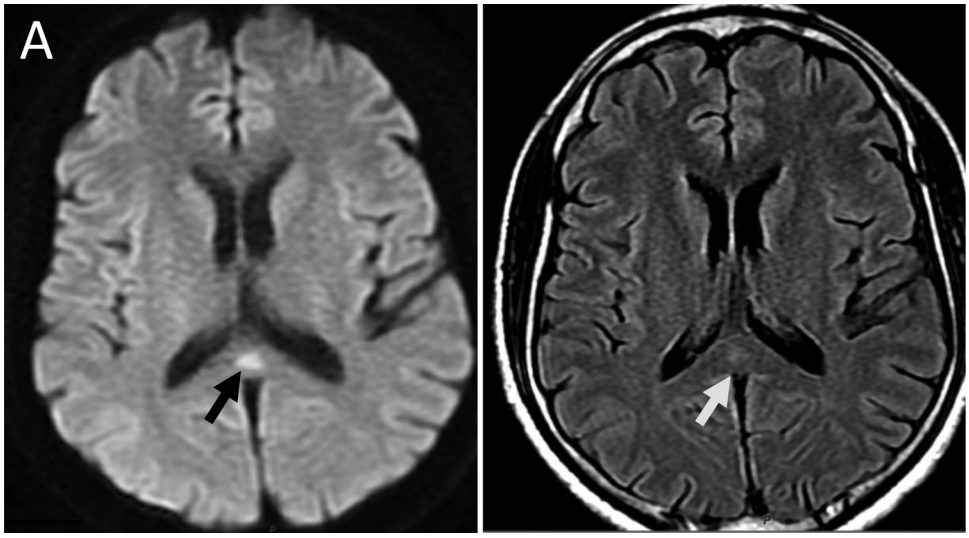

Fig. 1. Diffusion-weighted (left) and FLAIRT2-weighted (right) MR images showed a small ovoid lesion located in the center of the splenium of the corpus callosum (arrows).

94% in room air. Oxygen therapy was administered (2 liters per minute).

Neurological assessment revealed diffuse headache without meningism, several cognitive impairments, inattention without disorientation, psychomotor slowness, behavioral disorders, fabulations, false recognitions and anosognosia. In addition, the patient presented disinhibition, logorrhea, casual attitudes, and his Frontal Assessment Battery score was low (12/18). The remainder of his neurological and general examination was unremarkable. He did not have anosmia or ageusia.

Physiologically, he presented with lymphocytopenia (0.74×10^9 per L, N: 1.24–3.62;, highly elevated lactate dehydrogenase blood levels (638 U/L, N: 125–245) and markers of muscular damage, hepatic and renal dysfunction, elevated C Reactive Protein (171 mg/L; N < 6 mg) and moderate hyponatremia, but with no signs of cytokine release syndrome. A nasopharyngeal swab was carried out and was positive for SARS-CoV-2 nucleic acid, with a high viral load (cycle threshold value of 28). Given his respiratory symptoms, computerized tomography (CT) of the chest was performed and revealed moderate lung damage typical of SARS-CoV-2 pneumonia.

Due to his abnormal neurological assessment, the patient underwent brain magnetic resonance imaging (MRI), which revealed a small lesion with homogeneous diffusion restriction and hyperintensity on a fluid-attenuated inversion recovery (FLAIR) sequence within the corpus callosum splenium (Fig. 1). A perfusion MR sequence showed heterogeneous perfusion with mild posterior and left temporal hypoperfusion (Fig. 2). This was associated on MR angiography with narrowing of the distal and left intracerebral arteries. Electroencephalography revealed intermittent slow theta waves in the temporo-occipital left area, in good agreement with the MR hypoperfusion pattern. Cerebrospinal fluid (CSF) examination was normal for cell counts and for protein and glucose levels and was negative for SARS-CoV-2 and other common viruses.

The patient rapidly improved without any treatment for five days other than oxygen therapy. and left the hospital after 7 days.

Mild encephalopathy with reversible splenial lesion is a clinical–radiological syndrome having various clinical presentations but with a specific radiological picture of cytotoxic edema in the corpus callosum splenium.

Our patient showed several typical MERS-associated findings, including behavioral abnormalities, dysexecutive and memory disorder, benign course, EEG slowing and normal CSF [5]. His MR brain lesion fulfilled the criteria for the most common and mildest form of cytotoxic lesion of the corpus callosum [6]. The location in the center of the splenium, its ovoid pattern and lack of any mass effect or contrast enhancement clearly identified the lesion as a primary cytotoxic callosal lesion and excluded a corpus callosum lesion due to other causes such as ischemia, tumor or acute disseminated encephalomyelitis.

Numerous etiologies, such as viral and bacterial infection, as well as epilepsy, hyponatremia, altitude sickness with hypoxemia, and iatrogenic origins have been reported for MERS [6]. The still unproven pathomechanism of cytotoxic lesion of the corpus callosum may involve cytokine network dysregulation and altered cerebrovascular autoregulation. In our patient, there was no evidence of cytokine release syndrome, and rapid reversibility of the clinical encephalopathy did not support this hypothesis. He had no alcoholic intoxication, no treatment and no epilepsy on electroencephalography. His oxygen blood pressure was 75 mm Hg and while he had moderate hyponatremia, it was not enough to induce a drop in osmotic pressure.

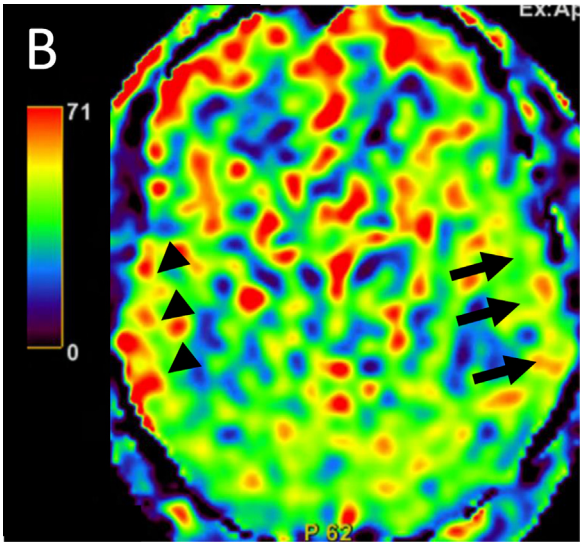

Fig. 2. Cerebral Blood Flow (CBF) map from an Arterial Spin Labelling perfusion MR sequence showed a slight hypoperfusion of the left temporal cortex (arrows) as compared with the right side (arrowheads).

The pathophysiology of this type of viral damage to the central nervous system remains unknown. Two hypotheses seem to prevail: neuron-to-neuron propagation, or vascular damage [7,8].

We now know that angiotensin-converting enzyme 2 (ACE2) is a SARS-CoV-2 receptor. ACE2 protein is also abundantly expressed in the arterial and venous endothelial and smooth muscle cells [8]. Vascular damage, with rupture of the blood-brain barrier, inflammation and edema, may be involved. The isolated and central lesion of the splenium and the spontaneous resolution might support the assumption of microvascular pathway alterations.

Another key to understanding the neurotropism of the virus could be neuron-to-neuron propagation, from the nasal cavity to the olfactory bulb [7,8]. In our case, the patient had no anosmia or ageusia, and the cerebrospinal fluid (CSF) was free of inflammatory cells and of viral RNA as indicated by RT-PCR. MR images showed no nonspecific change suggestive of encephalitis and no hypersignal on FLAIR T2-weighted images similar to the hypersignal recently reported in a young Japanese man with SARS-CoV-2 in CSF [9]. The rapid resolution of his neurologic symptoms pointed to a vascular etiology, rather than encephalitis. MR angiography also indicated a vascular rather than an encephalitic explanation of our patient's brain perfusion heterogeneity.

In conclusion, this case of encephalopathy suggests that SARS-CoV-2 potentially caused the observed brain injury. Physicians should pay attention to neurological or psychiatric symptoms among patients with SARS-CoV-2 infection and should therefore perform brain MRI. While the pathophysiology is currently unknown, this case might support the hypothesis of microvascular damage caused by the virus in the central nervous system, as has been shown in other tissues.

Contributions

Jeanne Chauffier designed the study, interpreted the data, and wrote the manuscript. Maya Husain investigated the patients and collected the data. Marie-Cécile Henry-Feugeas and Antoine Khalil interpreted the data and contributed to the writing of the manuscript. Nora Poey and Sylvie Lariven contributed to the writing of the manuscript. All the authors revised the manuscript and approved the final version.

Disclosure of interest

The authors declare that they have no competing interest.

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J. Chauffier [a,*]
N. Poey [a]
M. Husain [a]
T. de Broucker [c]
A. Khalil [b]
S. Lariven [a]
M.-C. Henry-Feugeas [b]

[a] *Department of Infectious and Tropical Diseases, Assistance Publique-Hôpitaux de Paris, Bichat-Claude-Bernard University Hospital, Paris, France*

[b] *Department of Radiology, Neuroradiology Unit, Assistance Publique-Hôpitaux de Paris, Bichat-Claude-Bernard University Hospital, Paris, France*

[c] *Department of Neurology, centre hospitalier de Saint-Denis, Saint-Denis, France*

* Corresponding author.
E-mail address: jeanne.chauffier@hotmail.fr
(J. Chauffier)

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Atypical pneumonia clusters

1. Introduction

Acute community acquired pneumonias are lower respiratory tract infections with highly heterogeneous clinical presentations in function of the responsible pathogen: virus, pyogenic bacteria, intracellular bacteria.

Microbiological diagnostic methods are constantly evolving in order to identify the responsible pathogen so as to appropriately treat the patient.

Detection by Polymerase Chain Reaction (PCR), be it specific or included in a pathogen panel (multiplex PCR), on a respiratory sample are rapid and easily accessible diagnostic tools, but their use and interpretation must be guided by the patient's medical history and context.

We will discuss 3 concomitant cases of atypical pneumonia (AP) from the same family admitted to the Amiens Teaching Hospital in order to illustrate that these new diagnostic methods should not be used to the detriment of pertinent patient history taking.

2. Case presentation

Three related patients (P1: son; P2: mother; P3: uncle) came to Emergency Room (ER) the same day suffering from fever, vomiting and diarrhea, during a time when there was no viral epidemic. The initial common clinical presentation also revealed dyspnea associated with a dry cough, requiring oxygen therapy. The symptomatology of the 3 patients can be found in Table 1 and the imagery in Fig. 1.