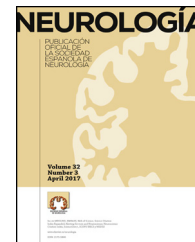




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## REVIEW ARTICLE

# Should we expect neurological symptoms in the SARS-CoV-2 epidemic?☆



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Received 27 March 2020; accepted 31 March 2020

**KEYWORDS**

Coronavirus;  
SARS-CoV;  
MERS-CoV;  
Multiple sclerosis;  
SARS-CoV-2;  
Mouse hepatitis virus;  
Neurological  
symptoms;  
Central nervous  
system

**Abstract**

**Introduction:** There is growing evidence that SARS-CoV-2 can gain access to the central nervous system (CNS). We revise the literature on coronavirus infection of the CNS associated with neurological diseases.

**Development:** Neurological symptoms were rarely reported in the SARS-CoV and MERS-CoV epidemics, although isolated cases were described. There are also reports of cases of neurological symptoms associated with CoV-OC43 and CoV-229E infection. The presence of neurological lesions, especially demyelinating lesions in the mouse hepatitis virus model, may explain the mechanisms by which coronaviruses enter the CNS, particularly those related with the immune response. This may explain the presence of coronavirus in patients with multiple sclerosis. We review the specific characteristics of SARS-CoV-2 and address the question of whether the high number of cases may be associated with greater CNS involvement.

**Conclusion:** Although neurological symptoms are not frequent in coronavirus epidemics, the high number of patients with SARS-CoV-2 infection may explain the presence of the virus in the CNS and increase the likelihood of early- or delayed-onset neurological symptoms. Follow-up of patients affected by the SARS-CoV-2 epidemic should include careful assessment of the CNS. © 2020 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**PALABRAS CLAVE**

Coronavirus;  
SARS-CoV;  
MERS-CoV;  
Esclerosis múltiple;  
SARS-CoV-2;

**¿Es esperable que haya cuadros neurológicos por la pandemia por SARS-CoV-2?****Resumen**

**Introducción:** Diversas evidencias sugieren que el SARS-CoV-2 puede penetrar en el sistema nervioso central (SNC). Los autores revisan los datos de la literatura sobre los hallazgos de coronavirus en el SNC asociado a enfermedades neurológicas.

☆ Please cite this article as: Matías-Guiu J, Gomez-Pinedo U, Montero-Escribano P, Gomez-Iglesias P, Porta-Etessam J, Matias-Guiu JA. ¿Es esperable que haya cuadros neurológicos por la pandemia por SARS-CoV-2? Neurología. 2020;35:170–175.

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Virus murino de la hepatitis;  
Síntomas neurológicos;  
Sistema nervioso central

*Desarrollo:* En las distintas epidemias con SARS-CoV y MERS-CoV la presencia de cuadros neurológicos es baja, pero se describen cuadros aislados de pacientes. También existen casos asociados a OC43-CoV y 229E-CoV. La existencia de lesiones neurológicas, especialmente desmielinizantes en el modelo MHV-CoV pueden explicar mecanismos de penetración de los CoV en el SNC y especialmente aquellos relacionados con la respuesta inmune, que puede justificar la existencia de CoV en pacientes con esclerosis múltiple. Los autores revisan aspectos diferenciales de SARS-CoV-2 y se plantean si debido al alto número de infectados, el virus puede afectar de forma mayor al SNC.

*Conclusión:* Aunque la presencia de síntomas neurológicos en las epidemias de CoV es baja, la mayor frecuencia de infectados por SARS-CoV-2 podría justificar el paso del virus y la posibilidad de clínica neurológica precoz o tardía con mayor incidencia. El seguimiento de los pacientes de la epidemia debe atender con cuidado a la evaluación del SNC.

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Human coronavirus (CoV) infection is associated with mild upper and lower respiratory tract symptoms, both in children and in adults. The 4 endemic human coronaviruses HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 are included among the known causes of common cold. HCoV-229E and HCoV-NL63 are classified as  $\alpha$ CoV, whereas HCoV-OC43 and HCoV-HKU1 are  $\beta$ CoV.<sup>1</sup> Two new  $\beta$ CoV, SARS-CoV and MERS-CoV, were recently discovered; these present a much more aggressive behaviour and have caused epidemics associated with extrapulmonary manifestations and high mortality rates. In 2003, SARS-CoV was identified as the cause of a severe respiratory syndrome first appearing in the Chinese province of Guangdong; in 2004, MERS-CoV caused an epidemic that mainly affected the Arabian Peninsula. On 31 December 2019, the World Health Organization reported a novel CoV (SARS-CoV-2) in patients with pneumonia in the city of Wuhan, in the Chinese province of Hubei; it subsequently spread rapidly through China and the rest of the world. The novel virus is classified as a  $\beta$ CoV and bears considerable similarity to SARS-CoV. SARS-CoV-2 infection has been declared a pandemic; it is associated with high mortality and has caused significant societal impact. The virus is expected to infect a large proportion of the world's population.

The central nervous system (CNS) is vulnerable to infection: many viruses can reach the brain, including herpesviruses,<sup>2</sup> arboviruses,<sup>3</sup> measles virus,<sup>4</sup> influenza virus, and HIV.<sup>2</sup> Coronaviruses may also infect the CNS,<sup>5,6</sup> which could lead to a high incidence of neurological symptoms. This article reviews the available evidence on the effects of human coronaviruses on the CNS.

## Neurological symptoms of coronavirus infection

It is an undisputed fact that coronaviruses can infect the CNS. CoV RNA has been detected in the CNS of patients with numerous neurological diseases.<sup>7,8</sup> CNS infection has caused

symptoms of encephalitis in children.<sup>9</sup> Cases of meningitis, Guillain-Barré syndrome, and other neuroimmune disorders have also been reported in the context of CoV infection.<sup>10–16</sup> HCoV-OC43 is considered the coronavirus with the greatest neuroinvasive potential, as it has been shown to invade, replicate, and remain in the mouse CNS, causing direct damage to neurons.<sup>17,18</sup> The virus has also been found to exploit axonal transport.<sup>19</sup> HCoV-OC43 can induce cell degeneration and death.<sup>20–22</sup> In humans, HCoV-OC43 has been detected in brain tissue from patients with a wide range of neurological diseases, including Alzheimer disease, Parkinson's disease, and multiple sclerosis, as well as in the brains of healthy individuals. Likewise, HCoV-229E has been associated with febrile seizures.<sup>23</sup> The literature also includes a report of an immunocompromised child who died due to HCoV-OC43-associated encephalitis.<sup>24</sup> Both HCoV-OC43 and HCoV-229E can infect innate immune cells.<sup>25,26</sup>

## MERS-CoV and SARS-CoV

MERS-CoV and SARS-CoV can cause severe lower respiratory tract infections, characterised by acute breathing difficulties and such extrapulmonary manifestations as diarrhoea, lymphocytopenia, hepatic and renal dysfunction, and multiple organ dysfunction syndrome, both in immunocompetent and immunocompromised individuals. The associated mortality rate is higher than 10%, although some cases are asymptomatic.<sup>27</sup> MERS-CoV and SARS-CoV have caused 2 epidemics, with a large number of people infected. Presence of neurological symptoms in these epidemics was rare according to the literature, although the available studies only analyse the initial phase of each epidemic. A retrospective study conducted in Saudi Arabia reported confusion in 25.7% of patients with Middle East respiratory syndrome (MERS), and seizures in 8.6%.<sup>28</sup> Only 4 cases of CNS involvement (acute disseminated encephalomyelitis, stroke, and encephalitis) and one case of critical illness polyneuropathy have been reported in the context of MERS.<sup>29,30</sup> Cases

of Guillain-Barré syndrome and delayed-onset peripheral neuropathy have also been reported, and one article even presents the timeline of neurological symptoms in a patient with MERS.<sup>31</sup> The literature also includes a case of MERS-CoV infection associated with intracerebral haemorrhage; according to the author, MERS-CoV infection was the only possible explanation for the stroke, with no other risk factors recorded.<sup>32</sup> An *in vitro* study has shown that certain cell lines, such as human neuronal cell lines, are particularly susceptible to MERS-CoV.<sup>33</sup> The delayed onset of neurological complications of MERS-CoV infection, the absence of the virus in cerebrospinal fluid, and the unclear association between MERS-CoV infection and Guillain-Barré syndrome suggest that the manifestations of MERS-CoV infection involve an immune component.<sup>34</sup> According to some authors, however, the failure to detect the virus in biological samples may be explained by methodological issues.<sup>35</sup> During the SARS-CoV outbreak of 2002–2003, reports of neurological symptoms were anecdotal.<sup>36,37</sup> Some patients developed axonal polyneuropathy a month after the onset of severe acute respiratory syndrome (SARS), and improved during follow-up. Other patients presented such neuromuscular disorders as myopathy and rhabdomyolysis.<sup>38,39</sup> SARS is associated with more severe symptoms than non-SARS viral respiratory tract infection.<sup>40</sup> Therefore, muscular disorders may be the result of the patients' critical situation rather than the virus itself. Stroke has also been reported in the context of SARS-CoV infection.<sup>41,42</sup>

## Coronaviruses and multiple sclerosis

CoV infection has been proposed as a contributing factor in the pathogenesis of multiple sclerosis (MS).<sup>43</sup> This hypothesis is supported by findings from several studies. Coronavirus-like particles have been detected in autopsied brain tissue from a patient with MS.<sup>44</sup> CoV isolates were identified in autopsied brain tissue from 2 patients with MS,<sup>45</sup> and other researchers have detected CoV RNA in brain tissue from patients with MS.<sup>46–48</sup> Another study reports intrathecal synthesis of antibodies to human CoV, which suggests CNS infection.<sup>49</sup> Human CoV RNA has also been detected in the cerebrospinal fluid of patients with MS.<sup>50</sup> Experimental studies have found that human CoV can infect neurons, astrocytes, and microglia in primary cultures,<sup>51</sup> as well as immortalised human microglial cells.<sup>52</sup> Interestingly, human CoV can also infect oligodendrocytic cell lines.<sup>53</sup> The hypothesis is further supported by the fact that viral upper respiratory tract infections, which may be associated with human coronaviruses, constitute an important trigger of MS relapses.<sup>54,55</sup>

## Mouse hepatitis virus

Mouse hepatitis virus (MHV) is a coronavirus that infects mice but not humans.<sup>56</sup> As it induces neurological disorders,<sup>57,58</sup> it constitutes an excellent experimental model for studying the effects of coronaviruses on the CNS. Neurotropic MHV strains can infect the CNS by intranasal or intravenous inoculation both in mice<sup>59</sup> and in primates.<sup>60</sup> Viral

entry through the blood-brain barrier has been associated with downregulation of interferon beta production in brain microvascular endothelial cells.<sup>61</sup> MHV infection causes acute encephalomyelitis associated with focal areas of demyelination; the role of the immune response during viral infection has been studied.<sup>62</sup> Microglial activation and inflammatory mediator expression in the CNS contribute to a local microenvironment that regulates viral replication, which may promote demyelination.<sup>63</sup> The demyelinating lesions associated with MHV infection suggest that this model may be useful in multiple sclerosis research.

## The SARS-CoV-2 epidemic and the hypothesis of the brain as a viral reservoir

Although SARS-CoV and SARS-CoV-2 are similar in many respects, they present genetic and structural differences.<sup>64</sup> The novel virus is characterised by the ease with which it spreads<sup>65</sup>; it is more contagious than SARS-CoV,<sup>66</sup> spreading through respiratory droplets and contact with infected individuals and objects. It can also be spread by asymptomatic infected individuals.<sup>67–69</sup> Several observational studies have analysed the symptoms of the disease, but few have addressed neurological symptoms, with the exception of headache and vestibular symptoms in observational studies<sup>70–75</sup> and a specific study of these symptoms in hospitalised patients,<sup>76</sup> and isolated case reports<sup>77</sup>. However, it has been suggested that the virus may affect the CNS, similarly to SARS-CoV, which was detected in the brains of some patients.<sup>78</sup> Clinical data reveal differential characteristics, including olfactory alterations and hallucinations; these symptoms have not been reported in patients with SARS-CoV or MERS-CoV infection. Several features of SARS-CoV-2 support the hypothesis of a particular affinity for the CNS.

The main structural differences between SARS-CoV and SARS-CoV-2 are observed in the fusion protein and in accessory proteins ORF3b and ORF8. The coronavirus genome encodes 4 main structural proteins, namely spike, envelope, membrane, and nucleocapsid proteins.<sup>79</sup> The viral surface glycoprotein (S) may induce neurodegeneration.<sup>80</sup> After infecting host cells, the viral genome is translated into 2 large precursor polyproteins, which are processed by ORF1a-encoded viral proteinases into 16 mature nonstructural proteins (nsp1–nsp16). Nonstructural proteins play an essential role in viral RNA replication and transcription,<sup>81</sup> whereas ORF3b has been associated with the immune response.<sup>82</sup> As occurs with SARS-CoV, the SARS-CoV-2 spike glycoprotein S1 subunit receptor-binding domain binds to ACE2 receptors, the site of viral entry into the host cell; this has given rise to the possibility of creating an experimental model of SARS-CoV-2 infection.<sup>83</sup> Interestingly, the ACE2 receptor is widely expressed in the brain,<sup>84</sup> which supports the hypothesis that CNS involvement may be common in the SARS-CoV-2 epidemic.<sup>85</sup> *In vitro* studies report a positive correlation between ACE2 expression and SARS-CoV infection.<sup>86</sup> Viruses can enter the CNS via the haematogenous route (in which the virus infects the endothelial cells of the blood-brain barrier) or the neuronal route. It is unlikely that SARS-CoV-2 is able to cross the blood-brain barrier<sup>87</sup> due to its large size; the

most likely entry route is through the olfactory or trigeminal nerves. Thus, the high incidence of olfactory alterations in SARS-CoV-2-infected individuals may indicate viral entry into the CNS. Findings from studies of the MHV model and the detection of CoV in patients' brains suggest that the virus may remain in the host's CNS for long periods of time without causing neurological symptoms and that the brain may be a viral reservoir.<sup>88</sup>

## Conclusions

Coronaviruses can enter the CNS, where they may either damage CNS cells or remain latent. Although neurological symptoms are not frequent, they may indicate viral entry into the CNS, which may cause early- or delayed-onset neurological symptoms. Follow-up of patients with SARS-CoV-2 infection should include careful assessment of the CNS.

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