REVIEW ARTICLE

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

J. Matías-Guiu∗, U. Gomez-Pinedo, P. Montero-Escribano, P. Gomez-Iglesias, J. Porta-Etessam, J.A. Matías-Guiu

Servicio de Neurología, Instituto de Neurociencias, Hospital Clínico San Carlos, San Carlos, IdISSC, Madrid, Spain

Received 27 March 2020; accepted 31 March 2020

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/).

¿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, Matías-Guiu JA. ¿Es esperable que haya cuadros neurológicos por la pandemia por SARS-CoV-2? Neurología. 2020;35:170–175.

∗ Corresponding author.
E-mail address: neurol.hcsc@salud.madrid.org (J. Matías-Guiu).

2173-5808/© 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/).
**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.

© 2020 Sociedad Española de Neurología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

---

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 αCoV, whereas HCoV-OC43 and HCoV-HKU1 are βCoV.1 Two new βCoV, 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 βCoV 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,2 arboviruses,3 measles virus,4 influenza virus, and HIV.2 Coronaviruses may also infect the CNS,5,6 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.1,8 CNS infection has caused symptoms of encephalitis in children.9 Cases of meningitis, Guillain-Barré syndrome, and other neuroimmune disorders have also been reported in the context of CoV infection.10—16 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.17,18 The virus has also been found to exploit axonal transport.19 HCoV-OC43 can induce cell degeneration and death.20—22 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.23 The literature also includes a report of an immunocompromised child who died due to HCoV-OC43—associated encephalitis.24 Both HCoV-OC43 and HCoV-229E can infect innate immune cells.25,26

**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.27 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%.28 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.29,30
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.\textsuperscript{31} 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.\textsuperscript{32} An in vitro study has shown that certain cell lines, such as human neuronal cell lines, are particularly susceptible to MERS-CoV.\textsuperscript{33} 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.\textsuperscript{34} According to some authors, however, the failure to detect the virus in biological samples may be explained by methodological issues.\textsuperscript{35} During the SARS-CoV outbreak of 2002–2003, reports of neurological symptoms were anecdotal.\textsuperscript{36,37} 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.\textsuperscript{38,39} SARS is associated with more severe symptoms than non-SARS viral respiratory tract infection.\textsuperscript{40} 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.\textsuperscript{41,42}

**Coronaviruses and multiple sclerosis**

CoV infection has been proposed as a contributing factor in the pathogenesis of multiple sclerosis (MS).\textsuperscript{43} This hypothesis is supported by findings from several studies. Coronavirus-like particles have been detected in autopsied brain tissue from a patient with MS.\textsuperscript{44} CoV isolates were identified in autopsied brain tissue from 2 patients with MS,\textsuperscript{45} and other researchers have detected CoV RNA in brain tissue from patients with MS.\textsuperscript{46–48} Another study reports intrathecal synthesis of antibodies to human CoV, which suggests CNS infection.\textsuperscript{49} Human CoV RNA has also been detected in the cerebrospinal fluid of patients with MS.\textsuperscript{50} Experimental studies have found that human CoV can infect neurons, astrocytes, and microglia in primary cultures,\textsuperscript{51} as well as immortalised human microglial cells.\textsuperscript{52} Interestingly, human CoV can also infect oligodendrocytic cell lines.\textsuperscript{53} 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.\textsuperscript{54,55}

**Mouse hepatitis virus**

Mouse hepatitis virus (MHV) is a coronavirus that infects mice but not humans.\textsuperscript{56} As it induces neurological disorders,\textsuperscript{57,58} 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\textsuperscript{59} and in primates.\textsuperscript{60} Viral entry through the blood-brain barrier has been associated with downregulation of interferon beta production in brain microvascular endothelial cells.\textsuperscript{61} MHV infection causes acute encephalomyelitis associated with focal areas of demyelination; the role of the immune response during viral infection has been studied.\textsuperscript{62} Microglial activation and inflammatory mediator expression in the CNS contribute to a local microenvironment that regulates viral replication, which may promote demyelination.\textsuperscript{63} 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.\textsuperscript{64} The novel virus is characterised by the ease with which it spreads\textsuperscript{65}; it is more contagious than SARS-CoV\textsuperscript{66} spreading through respiratory droplets and contact with infected individuals and objects. It can also be spread by asymptomatic infected individuals.\textsuperscript{67–69} 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\textsuperscript{70–72} and a specific study of these symptoms in hospitalised patients,\textsuperscript{76} and isolated case reports\textsuperscript{77}. 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.\textsuperscript{57} 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.\textsuperscript{73} The viral surface glycoprotein (S) may induce neurodegeneration.\textsuperscript{80} 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,\textsuperscript{81} whereas ORF3b has been associated with the immune response.\textsuperscript{82} 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.\textsuperscript{83} Interestingly, the ACE2 receptor is widely expressed in the brain,\textsuperscript{84} which supports the hypothesis that CNS involvement may be common in the SARS-CoV-2 epidemic.\textsuperscript{85} In vitro studies report a positive correlation between ACE2 expression and SARS-CoV infection.\textsuperscript{86} 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\textsuperscript{87} 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.  

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.

References

1. Corman VM, Muth D, Niemeyer D, Drosten C. Hosts and sources of endemic human coronaviruses. Adv Virus Res. 2018;100:163–88.  
2. Xu J, Ikezu T. The comorbidity of HIV-associated neurocognitive disorders and Alzheimer’s disease: a foreseeable medical challenge in post-HAART era. J Neuroimmune Pharmacol. 2009;4:200–12.  
3. Brask J, Chauhan A, Hill RH, Ljunggren HG, Kristensson K. Effects on synaptic activity in cultured hippocampal neurons by influenza A viral proteins. J Neurovirol. 2005;11:395–402.  
4. Katayama Y, Hotta H, Nishimura A, Tatsuno Y, Homma M. Detection of measles virus nucleoprotein mRNA in autopsied brain tissues. J Gen Virol. 1995;76:3201–4.  
5. Desforges M, le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. Virus Res. 2014;194:145–58.  
6. Bohmwald K, Gávež NMS, Rios M, Kalergis AM. Neurologic alterations due to respiratory virus infections. Front Cell Neurosci. 2018;12:386.  
7. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory coronaviruses. J Virol. 2000;74:8913–21.  
8. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson’s disease. Mov Disord. 1992;7:153–8.  
9. Li Y, Li H, Fan R, Wen B, Zhang J, Cao X, et al. Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. Intervirology. 2016;59:163–9.  
10. Yeh EA, Collins A, Cohen ME, Duffner PK, Faden H. Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. Pediatrics. 2004;113:e73–6.  
11. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis. 2004;10:342–4.  
12. Turgay C, Emine T, Ozlem K, Muhammet SP, Haydar AT. A rare cause of acute flaccid paralysis: human coronaviruses. J Pediatr Neurosci. 2015;10:280–1.  
13. Sharma K, Tengsupakul S, Sanchez O, Phaitas R, Maertens P. Guillain-Barre syndrome with unilateral peripheral facial and bulbar palsy in a child: a case report. SAGE Open Med Case Rep. 2019;7, http://dx.doi.org/10.1177/2050313X19838750.  
14. Aligathani H, Subahi A, Shirah B. Neurological complications of middle east respiratory syndrome coronavirus: a report of two cases and review of the literature. Case Rep Neurol Med. 2016;2016, http://dx.doi.org/10.1155/2016/3502683, 3502683.  
15. Yeh EA, Collins A, Cohen ME, Duffner PK, Faden H. Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. Pediatrics. 2004;113:e73–6, http://dx.doi.org/10.1542/peds.113.1.e73.  
16. McGavern DB, Kang SS. Illuminating viral infections in the nervous system. Nat Rev Immunol. 2011;11:318–29, http://dx.doi.org/10.1038/nri2971.  
17. Jacomy H, Talbot PJ. Vacuolating encephalitis in mice infected by human coronavirus OC43. Virology. 2003;315:20–33, http://dx.doi.org/10.1016/S0042-6822(03)00323-4.  
18. Jacomy H, Fragoso G, Almazan G, Mushynski WE, Talbot PJ. Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/C mice. Virology. 2006;349:335–46, http://dx.doi.org/10.1016/j.virol.2006.01.049.  
19. Dubé M, le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol. 2018;92:e00404–18, http://dx.doi.org/10.1128/JVI.00404-18.  
20. Favreau DJ, Desforges M, St-Jean JR, Talbot PJ. A human coronavirus OC43 variant harboring persistence-associated mutations in the S glycoprotein differentially induces the unfolded protein response in human neurons as compared to wild-type virus. Virology. 2009;395:255–67, http://dx.doi.org/10.1016/j.virol.2009.09.026.  
21. Favreau DJ, Meessen-Pinard M, Desforges M, Talbot PJ. Human coronavirus-induced neuronal programmed cell death is cyclophilin D dependent and potentially caspase dispensable. J Virol. 2012;86:81–93, http://dx.doi.org/10.1128/JVI.00622-11.  
22. Meessen-Pinard M, le Coupanec A, Desforges M, Talbot PJ. Pivotal role of receptor-interacting protein kinase 1 and mixed lineage kinase domain-like in neuronal cell death induced by the human neuroinvasive coronavirus OC43. J Virol. 2016;91, http://dx.doi.org/10.1128/JVI.01513-1.  
23. Harman KB, Calik M, Karal Y, Isikay S, Kokac O, Ozcelik A, et al. Viral etiological causes of febrile seizures for respiratory pathogens (EFES Study). Hum Vaccin Immunother. 2019;15:496–502, http://dx.doi.org/10.1080/21645515.2018.1526588.  
24. Morfopoulou S, Brown JR, Davies GS, Anderson G, Virasami A, Qasim W, et al. Human coronavirus OC43 associated with fatal encephalitis. N Engl J Med. 2007;357:497–8, http://dx.doi.org/10.1056/NEJMct1509458.  
25. Collins AR. Human macrophages are susceptible to coronavirus OC43. Adv Exp Med Biol. 1998;440:635–9.  
26. Patterson S, Macnaughton M. R. Replication of human respiratory coronavirus strain 229E in human macrophages. J Gen Virol. 1982;60:307–14.  
27. WHO Mers-Cov Research Group. State of knowledge and data gaps of Middle East respiratory syndrome coronavirus (MERS-CoV) in humans. PLoS Curr. 2012;5, http://dx.doi.org/10.1371/currents.outbreaks.0bf719e352e7478f8ad85fa30127dd8b.  
28. Saad M, Omran AS, Baig K, Bahloul A, Elzein F, Matin MA, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis. 2014;29:301–6.  

http://dx.doi.org/10.1016/S0042-6822(03)00323-4.
29. Arabi YM, Harthi A, Hussein J, Bouchama A, Johani S, Hajeer AH, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome coronavirus (MERS-CoV). Infection. 2015;43:495–501.

30. Algahtani H, Subahi A, Shirah B. Neurological complications of Middle East respiratory syndrome coronavirus: a report of two cases and review of the literature. Case Rep Neurol Med. 2016;2016, 3502683.

31. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological complications during treatment of middle east respiratory syndrome. J Clin Neurol. 2017;13:227–33, http://dx.doi.org/10.3988/jcn.2017.13.3.227.

32. Al-Hameed FM. Spontaneous intracranial hemorrhage in a patient with Middle East respiratory syndrome corona virus. Saudi Med J. 2017;38:196–200, http://dx.doi.org/10.15537/smj.2017.2.16255.8.

33. Chan JF, Chan KH, Choi GK, To KK, Tse H, Cai JP, et al. Differential cell line susceptibility to the emerging novel human betacoronavirus 2c EMC/2012: implications for disease pathogenesis and clinical manifestation. J Infect Dis. 2013;207:1743–52.

34. Talbot PJ, Arnold D, Antel JP. Virus-induced autoimmune reactions in the CNS. Curr Top Microbiol Immunol. 2001;253:247–71.

35. Leland DS, Ginocchio CC. Role of cell culture for virus detection in the age of technology. Clin Microbiol Rev. 2007;20:49–78, http://dx.doi.org/10.1128/CMR.00002-06.

36. Stainsby B, Howitt S, Parr J. Neuromusculoskeletal disorders following SARS: a case series. J Can Chiropr Assoc. 2011;55:32–9.

37. Chao CC. Peripheral nerve disease in SARS: report of a case. Neurology. 2003;61:1820–1.

38. Tsai LK, Hsieh ST, Chao CC, Chen YC, Lin YH, Chang SC, et al. Neuromuscular disorders in severe acute respiratory syndrome. Arch Neurol. 2004;61:1669–73.

39. Leung TW, Wong KS, Hui AC, To KK, Lai ST, Ng WF, et al. Myopathic changes associated with severe acute respiratory syndrome. Arch Neurol. 2005;62:1113–7.

40. Rainer TH, Lee N, Ip M, Galvani AP, Antonio GE, Wong KT, et al. Features discriminating SARS from other severe viral respiratory tract infections. Eur J Clin Microbiol Infect Dis. 2007;26:121–9.

41. Umapathi T, Kor AC, Venketasubramanian N, Lim CC, Pang BC, Yeo TT, et al. Large artery ischemic stroke in severe acute respiratory syndrome (SARS). J Neurol. 2004;251:1227–31.

42. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan. 2005;14:113–9. Abstract.

43. Talbot PJ. Virus-induced autoimmunity in multiple sclerosis: the coronavirus paradigm. Adv Clin Neurosci. 1997;7:215–33.

44. Tanaka R, Iwasaki Y, Koprowski H. Intracerebral virus-like particles in brain of a multiple sclerosis patient. J Neurol Sci. 1976;28:121–6.

45. Burks JS, DeVald BL, Jankovsky LD, Gerdes J, C. Two coronaviruses isolated from central nervous system tissue of two multiple sclerosis patients. Science. 1980;209:933–4.

46. Murray RS, Brown B, Brian D, Cabirac GF. Detection of coronavirus RNA and antigen in multiple sclerosis brain. Ann Neurol. 1992;31:525–33.

47. Stewart JN, Mounir S, Talbot PJ. Human coronavirus gene expression in the brains of multiple sclerosis patients. Virology. 1992;191:502–5.

48. Dessau RB, Lisby G, Frederiksen JL. Coronaviruses in brain tissue from patients with multiple sclerosis. Acta Neuropathol. 2001;101:601–4.

49. Salmi A, Ziola B, Hovi T, Reunanen M. Antibodies to coronaviruses OC43 and 229E in multiple sclerosis patients. Neurology. 1982;32:292–5.

50. Cristallo A, Gambero F, Bramonti G, Ferrante P, Battaglia M, Cereda PM. Human coronavirus polyadenylated RNA sequences in cerebrospinal fluid from multiple sclerosis patients. Microbiologia. 1997;2:105–14.

51. Bonavía A, Arbour N, Yong VW, Talbot PJ. Infection of primary cultures of human neural cells by human coronaviruses 229E and OC43. J Virol. 1997;71:800–6.

52. Arbour N, Côté G, Lachance C, Tardieu M, Cashman NR, Talbot PJ. Acute and persistent infection of human neural cell lines by human coronavirus OC43. J Virol. 1999;73:3338–50.

53. Arbour N, Ékandé S, Côté G, Lachance C, Chagnon F, Tardieu M, et al. Persistent infection of human oligodendrocytic and neuroglial cell lines by human coronavirus 229E. J Virol. 1999;73:3326–37.

54. Andersen O, Lyngner PE, Bergstrom T, Andersson M, Vahlne A. Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. J Neurol. 1993;240:417–22.

55. Sibley WA, Bamford CR, Clark K. Clinical viral infections and multiple sclerosis. Lancet. 1985;1:1313–5.

56. Barthold SW, Smith AL. Viremic dissemination of mouse hepatitis-virus-JHM following intranasal inoculation of mice. Arch Virol. 1992;122:35–44.

57. Buchmeier MJ, Dalziel RG, Koolen MJ, Lampert PW. Molecular determinants of CNS virulence of MVM-4. Adv Exp Med Biol. 1987;218:287–95, http://dx.doi.org/10.1007/978-1-4684-1280-2_38.

58. Hosking MP, Lane TE. The pathogenesis of murine coronavirus infection of the central nervous system. Crit Rev Immunol. 2010;30:119–30, http://dx.doi.org/10.1615/CritRevImmunol.v30.i2.20.

59. Lavi E, Fishman PS, Highkin MK, Weiss SR. Limbic encephalitis after inhalation of a murine coronavirus. Lab Invest. 1988;58:31–6.

60. Cabirac GF, Soike KF, Zhang JY, Hoel K, Butunoi C, Cai YG, et al. Entry of coronavirus into primate CNS following peripheral infection. Microb Pathog. 1994;16:349–57.

61. Bleau C, Filliol A, Samson M, Lamontagne L. Brain invasion by mouse hepatitis virus depends on impairment of tight junctions and beta interferon production in brain microvascular endothelial cells. J Virol. 2015;89:9896–908, http://dx.doi.org/10.1128/JVI.01501-15.

62. Savarin C, Bergmann CC. Fine tuning the cytokine storm by IFN and IL-10 following neurotropic coronavirus encephalomyelitis. Front Immunol. 2018;9:3022, http://dx.doi.org/10.3389/fimmu.2018.03022.

63. Chatterjee D, Addya S, Khan RS, Kenyon LC, Choe A, Cohrs RJ, et al. Mouse hepatitis virus infection upregulates genes involved in innate immune responses. PLoS One. 2014;9:e111351, http://dx.doi.org/10.1371/journal.pone.0111351.

64. Ceccarelli M, Berretta M, Venanzi Rullo E, Nunnari G, Capocarpo B. Differences and similarities between Severe Acute Respiratory Syndrome (SARS)-Coronavirus (CoV) and SARS-CoV-2 would a rose by another name smell as sweet? Eur Rev Med Pharmacol Sci. 2020;24:2781–3, http://dx.doi.org/10.26355/eurrev_202003_20551.

65. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in wuhan china, of novel coronavirus-infected pneumonia. Engl J Med. 2020, http://dx.doi.org/10.1056/NEJMoa2001316.

66. Chen J. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. Microbes Infect. 2020, http://dx.doi.org/10.1016/j.micinf.2020.01.004.

67. Lai CC, Shih TP, Ko WC, Tang HJ, Hsieh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020;105924, http://dx.doi.org/10.1016/j.ijantimicag.2020.105924.

68. Perrella A, Carannante N, Berretta M, Rinaldi M, Maturo N, Rinaldi L. Novel Coronavirus 2019 (Sars-CoV2): a global
Should we expect neurological symptoms in the SARS-CoV-2 epidemic?

---

69. Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect. 2020;9:386–9.

70. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–13. http://dx.doi.org/10.1016/S0140-6736(20)30211-7.

71. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506. http://dx.doi.org/10.1016/S0140-6736(20)30183-5.

72. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020. http://dx.doi.org/10.1001/jama.2020.1585.

73. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368:606. http://dx.doi.org/10.1136/bmj.m606.

74. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020. http://dx.doi.org/10.1097/CMA.0000000000000744.

75. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. http://dx.doi.org/10.1016/S2213-2600(20)30079-5.

76. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. BMJ. doi:10.1101/2020.02.22.20026500.

77. Filatov A, Sharma P, Hindi F, Espinosa P. Neurological complications of coronavirus disease (COVID-19): encephalopathy. Cureus. 2020;12:e7352. http://dx.doi.org/10.7759/cureus.7352.

78. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020. http://dx.doi.org/10.1002/jmv.25728.

79. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23.

80. Desforges M, Le Coupene A, Brison E, Meessen-Pinard M, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neuroviral agents in humans. Adv Exp Med Biol. 2014;807:75–96, http://dx.doi.org/10.1007/978-981-32-1777-6_6.

81. Narayanan K, Ramirez SJ, Lokugamage KG, Makino S. Coronavirus nonstructural protein 1: common and distinct functions in the regulation of host and viral gene expression. Virus Res. 2015;202:89–100.

82. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020;9:221–36. http://dx.doi.org/10.1080/22221751.2020.1719902.

83. Chan JF, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC, et al. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin Infect Dis. 2020;325, http://dx.doi.org/10.1093/cid/ciaa325.

84. Li W, Sui J, Huang IC, Kuhn JH, Radosztsky SR, Marasco WA, et al. The S proteins of human coronavirus NL63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ACE2. Virology. 2007;367:367–74, http://dx.doi.org/10.1016/j.virol.2007.04.035.

85. Baig AM, Khaierq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution host-virus interaction, and proposed neurotrophic mechanisms. C5 Chem Neurosci. 2020, http://dx.doi.org/10.1021/acschemneuro.0c00122.

86. Hofmann H, Geier M, Marzi A, Krumbiegel M, Peipp M, Fey GH, et al. Susceptibility to SARS coronavirus S protein-driven infection correlates with expression of angiotensin converting enzyme 2 and infection can be blocked by soluble receptor. Biochem Biophys Res Commun. 2004;319:1216–21, http://dx.doi.org/10.1016/j.bbrc.2004.05.114.

87. Joob B, Wiwanitkit V. Neurologic syndrome due to MERS: is there a possibility that the virus can cross the blood-brain barrier to cause a neurological problem? Ann Trop Med Public Health. 2015;8:231, http://dx.doi.org/10.4103/1755-6783.162654.

88. Sorensen O, Coulter-Mackie MB, Puchalski S, Dales S. In vivo and in vitro models of demyelinating disease. IX. Progression of JHM virus infection in the central nervous system of the rat during overt and asymptomatic phases. Virology. 1984;137:347–57.