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Original article

Sars-Cov-2 infection related inflammatory and demyelinating disease; a brief case series

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ABSTRACT

Background: Since March 2020, during the Coronavirus disease 2019 (COVID-19) pandemic, it has been observed that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has neurological involvement with various clinical tables.

Methods: We present 3 new cases admitted to our clinic with various neurological findings which were affected by SARS-CoV-2.

Results: Imaging studies have shown that inflammatory/demyelinating lesions appeared in different areas of the central nervous system which were accepted as an atypical demyelinating spectrum associated with Covid 19.

Conclusions: With increasing experience, it has been suggested that SARS-CoV-2 may also have a neurotrophic effect. The spectrum of neurological involvement is also expanding as the pandemic continues. These 3 cases suggest that the virus plays a role in the clinical onset of the inflammatory/demyelinating disease.

1. Introduction

Coronavirus disease 2019 (COVID-19) is typically manifested by fever and respiratory symptoms caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although SARS-CoV-2 is a respiratory infection agent, it has been shown to be able to involve other systems, including the nervous system. To date, various neurological syndromes have been reported, such as encephalitis, cerebrovascular diseases and peripheral neuropathy cases, which may be associated with SARS-CoV-2 (Ellul et al., 2020). In terms of demyelinating diseases, there have been limited number of case reports with acute disseminated encephalomyelitis (ADEM), myelitis and also atypical demyelinating event thought to be related to this virus (Zanin et al., 2020; Palao et al., 2020; Zhang et al., 2020; Zhao et al., 2020). Most recently, a case diagnosed with multiple sclerosis (MS) after an optic neuritis (ON) attack associated with COVID-19 infection has been published (Zoghi et al., 2020). Here we describe 3 new cases that have developed inflammatory / demyelinating lesions which were suspected to be associated with SARS-CoV-2.

2. Case 1

A 28-year-old male patient was admitted to the emergency service

with left hemiparesis and hemihypoesthesia, which he noticed when he woke up in the morning. There was no feature in his medical history and did not describe oral or genital ulcer. Neurological examination revealed 4/5 hemiparesis and globally limb hyperreflexia. His blood test had normal hemogram, biochemistry, sedimentation, C-reactive protein (CRP), procalcitonin, fibrinogen, D-dimer but ferritin level was mildly elevated (356 ng/mL, > 336).

Chest CT scan shows multiple ground-glass opacity areas and nasopharyngeal swab a realtime polymerase chain reaction (RT-PCR) test resulted positively for SARS-CoV-2, compatible with COVID-19. Brain magnetic resonance imaging (MRI) showed hyperintense nodular lesions on T2-weighted fluid-attenuated inversion recovery (FLAIR) in both centrum semiovale adjacent to the lateral ventricles with diffusion restriction and contrast enhancement, which were considered as an inflammatory process (Fig. 1A-F). There were no lesion in cortical/juxtacortical, posterior fossa and medulla spinalis. Visual evoked potential (VEP) and fundus evaluation, autoimmune panel, Cranial MR-angiography, transthoracic echo were all normal for the differential diagnosis of ischemic/vasculitic and demyelinating disease.

Lumbar puncture was performed; cerebrospinal fluid (CSF) opening pressure was 24 cm water, and CSF analysis showed slightly increased protein levels (36,8 mg/dL, >35) and no cell. Oligoclonal bands (OCB) resulted in type 1, with normal IgG-index. Although the patient had no

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respiratory symptoms and all vital parameters (blood pressure, pulse, respiratory rate, fever) were normal, hydroxychloroquine 400 mg / day was started for 5 days. After management of the infection, intravenous methylprednisolone (IVMP) treatment was given to the patient for 5 days and neurological deficits were fully recovered.

3. Case 2

An 18-year-old woman presented to the neurology outpatient clinic with a 10 days history of headache and a 3 days history of blurring of vision on the left eye. There was no feature in her medical history had not previously experienced any neurological symptoms. An examination showed visual acuity of finger movement from 40 cm and a left afferent pupillary defect with central scotoma. Fundoscopic examination showed papillitis in the left eye. In addition, there were signs of pyramidal tract dysfunction seen as global limb hyperreflexia. Orbital MRI confirmed a left-sided optic nerve lesion on T2 weighted images (Fig. 2A-B). Brain MRI showed multiple T2-FLAIR hyperintense lesions, located in supratentorial, posterior fossa and corpus callosum without gadolinium enhancement which were considered as inactive demyelinating plaques (Fig. 2C-F). Cervical spine MRI revealed a non-contrasting T2-hyperintense lesion at C4 level. Visual evoked potential (VEP) results showed no response in the left eye, whereas only latency prolongation (P121) was observed on the right eye. Laboratory results showed the presence of oligoclonal IgG bands in the CSF as type 2 with elevated IgG-index (0.75). The autoimmune and serological studies in blood and CSF ruled out other aetiology. Anti-IgG-NMO-AQP4 were not identified in serum samples. Anti-Myelin oligodendrocyte glycoprotein (MOG)

antibodies was not available in our laboratory. Serological tests for tuberculosis, borreliosis, lyme, syphilis, and HIV remained negative. SARS-CoV-2 PCR analysis of nasopharyngeal exudate and immunological testing was IgG was negative whereas positive for IgM, suspicious for a possible active infection. Her chest CT was normal and she was referred to infectious diseases clinics. Treatment was not recommended as she was asymptomatic and had no systemic involvement. Because her vision was nearly counting fingers on her right eye, she was started on IVMP and despite completion to 10 days, recovery was only achieved by 70%.

4. Case 3

A 48-year-old man admitted to the emergency department with complaints of arthralgia, weakness and cough and he was hospitalized. Chest CT scan was compatible with viral pneumonia and nasopharyngeal swab RT-PCR testing for SARS-CoV-2 returned positive (Fig. 3A). The patient was given hydroxychloroquine 400 mg/day+favipiravir 1200mg/day treatment with the diagnosis of Covid-19. On the 10th day of his hospitalization he was consulted to our neurology department with right hemiparesia that developed 1 day ago. Neurological examination revealed frust hemiparesis, globally limb hyperreflexia and Babinski's sign positive on the right side.

Brain MRI showed T2- FLAIR hyperintense lesions in corpus callosum and right cerebellum adjacent to the fourth ventricle, both with contrast fixation and diffusion restriction (Fig. 3B-G). The MRI of the whole spinal cord was normal. CSF analysis showed a mild pleocytosis (24- lymphocyte) without atypical cell, normal glucose, and increased

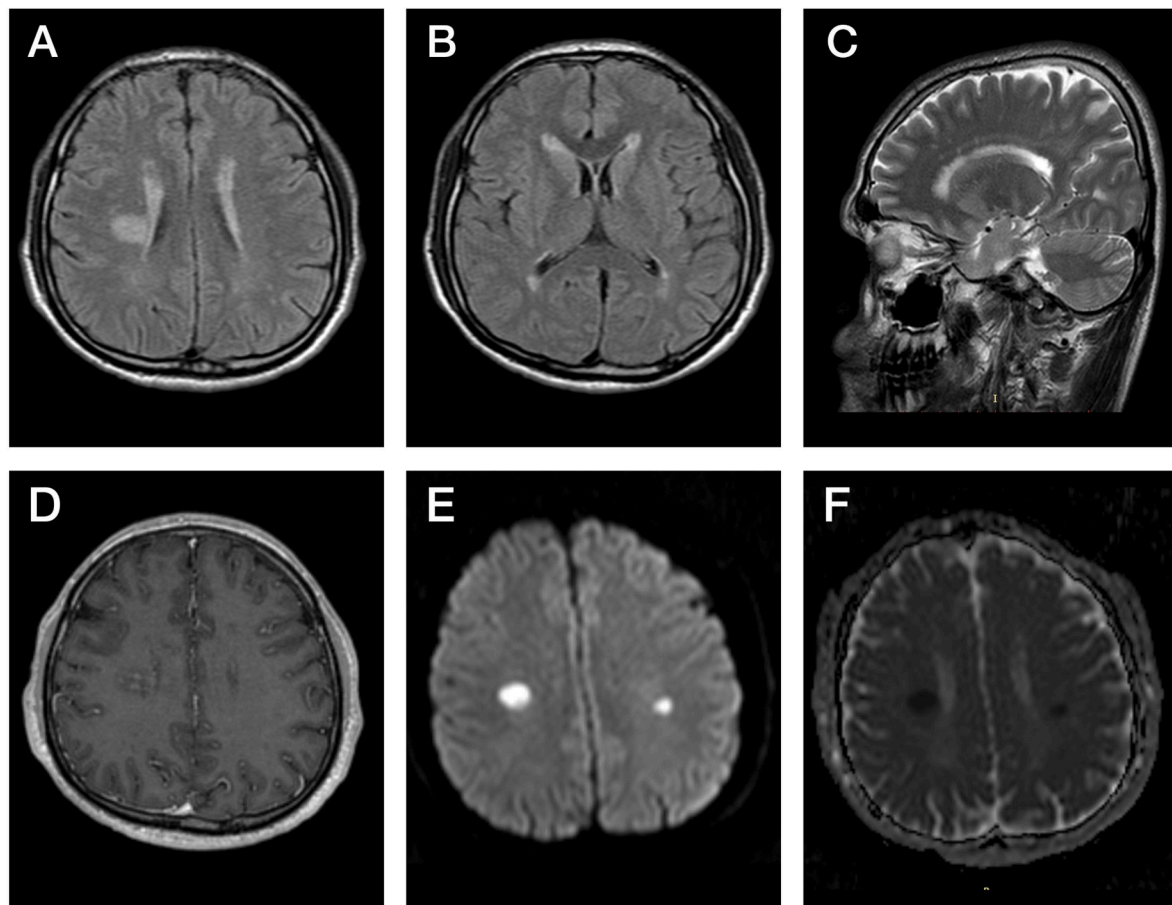


Fig. 1. Brain MRI showed hyperintense nodular lesions on T2-FLAIR in both centrum semiovale adjacent to the lateral ventricles (A). In sagittal section; hyperintense, millimetric lesions perpendicular to the corpus callosum were observed on T2-weighted images. (B). The lesions were heterogeneously slightly contrasted on contrast-enhanced series (D) and diffusion restriction was observed with ADC response (E and F).

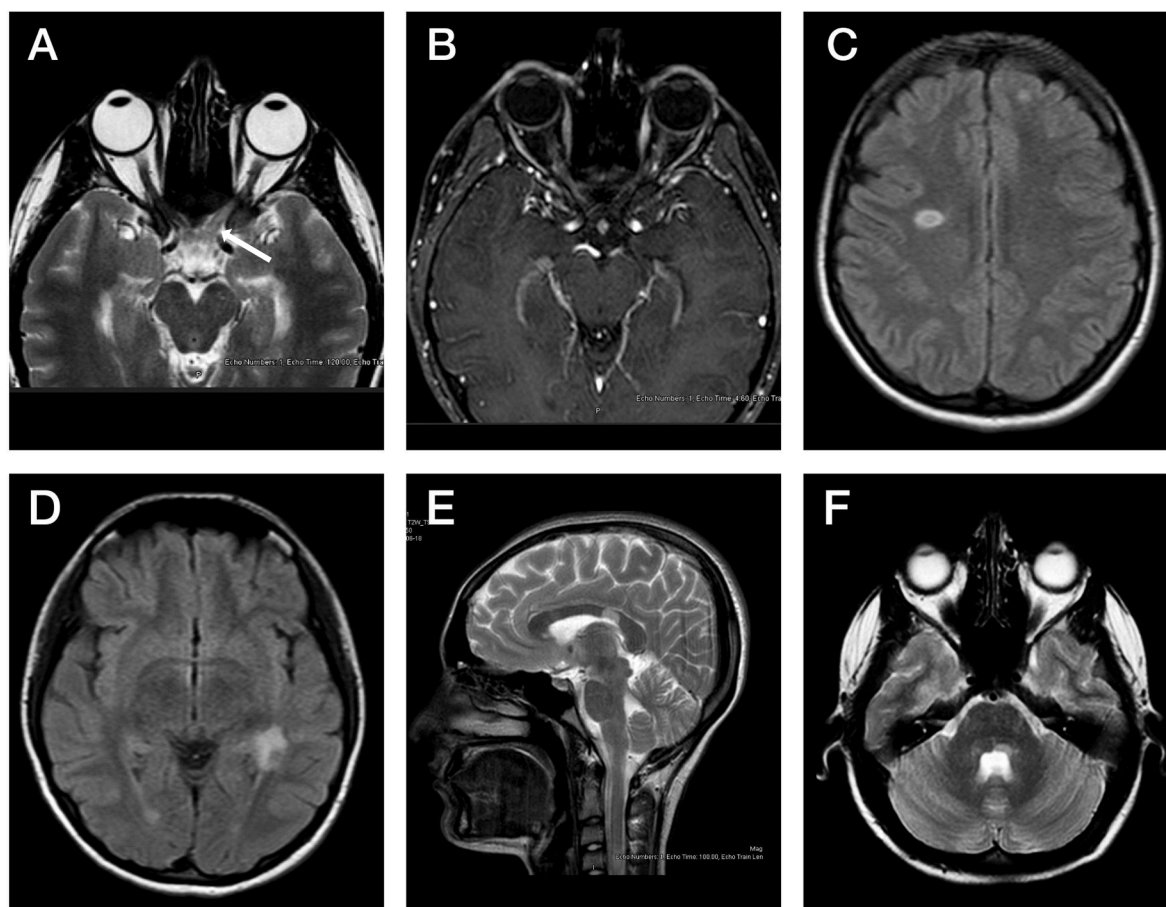


Fig. 2. Orbital MRI confirmed the lesion in the intracranial part of the optic nerve on the left side, on T2-weighted images (A), without contrast enhancement (B). Brain MRI showed multiple inactive demyelinating plaques on T2-FLAIR (C-F).

protein levels (100 mg/dL, >35). OCB was type 1 but elevated IgG index (0,76, >0,66) was detected. Anti-IgG-NMO-AQP4 were not identified in serum samples. Autoimmune-panel was positive for antinuclear antibody (ANA) (1:160), without fulfilling the criteria of systemic lupus erythematosus. It was decided to follow the patient with acetylsalicylic acid 100 treatment in consideration of a possible vascular event. Neurological deficit completely resolved within 2 weeks. Control MRI after 2 months revealed that the lesions regressed spontaneously and contrast enhancement was no longer observed (Fig. 3H-I). LP was repeated; and cells counts returned to normal (3-lymphocyte) with a decrease in protein level (43 mg/dL).

5. Discussion

There is increasing evidence for neurological manifestations that might be associated with COVID-19 (Ellul et al., 2020). The spectrum of neurological involvement is also expanding as the pandemic continues. Up to date, some of the human coronaviruses (HCoV) strains have been shown to have neurotropic effect as they can spread from the respiratory tract to the central nervous system (CNS) (Desforgues et al., 2019). When it comes to the novel coronavirus, there is little evidence to date to suggest that SARS-CoV2 might invade neural cells (Liu et al., 2020). In this case series, we suggest that the virus might play a role in the clinical onset of the inflammatory demyelinating diseases. The responsible mechanism leading to this involvement may not be directly related to the virus itself, but rather may play a triggering role in autoimmune processes in susceptible individuals as previously suggested for other viral agents such as Epstein Barr Virus (EBV) (Donati, 2020).

The World Health Organization (WHO) has established provisional

case definitions for meningitis, encephalitis, myelitis or CNS vasculitis associated with SARS-CoV-2 (WHO 2020). Accordingly, it is accepted as a confirmed case only under one of the following conditions: 1) SARS-CoV-2 is detected in CSF or brain tissue 2) if there are intrathecal antibodies specific to SARS-CoV-2.

If there is evidence of SARS-CoV-2 in respiratory or other non-CNS sample, or SARS-CoV-2 specific antibodies detected in serum indicating acute infection; it is considered as possible case. All 3 patients we share here are considered to be possible cases of COVID-19 related neurological disease. In patients 1 and 3, the SARS-CoV-2 PCR positivity was accompanied by radiological evidence of infection, but in patient 2, only Ig M seropositivity was detected although she was asymptomatic in terms of infection. Relating to only one positive seromarker compatible with coronavirus infection the question of a possible false positivity of the test rises. However, the patient might also be asymptomatic relating to COVID-19 disease. Suhandynata et al showed that viral specific IgM and IgG had a very low false positive rate in a longitudinal study of 54 PCR-confirmed COVID-19 patients (Suhandynata et al., 2020). In their study, the positive predictive values (PPV) was demonstrated for IgM, IgG, and IgG/IgM panel; 94.4%, 89.4%, and 85.6%, respectively. In such cases, as in our case 2, even if there is a possibility of false positivity, it will still be necessary to carefully evaluate the patient in terms of COVID-19 disease while the pandemic continues. In our patients, it was not possible to check SARS-CoV-2 PCR in the CSF. In cases of neurological involvement, positivity of SARS-CoV-2 PCR in the CSF has been rarely reported in the literature (1).

Neurological involvement was severe in all cases of COVID-19 associated demyelinating disease that were shared in the literature, and treatments varying from IVMP to plasmapheresis were given

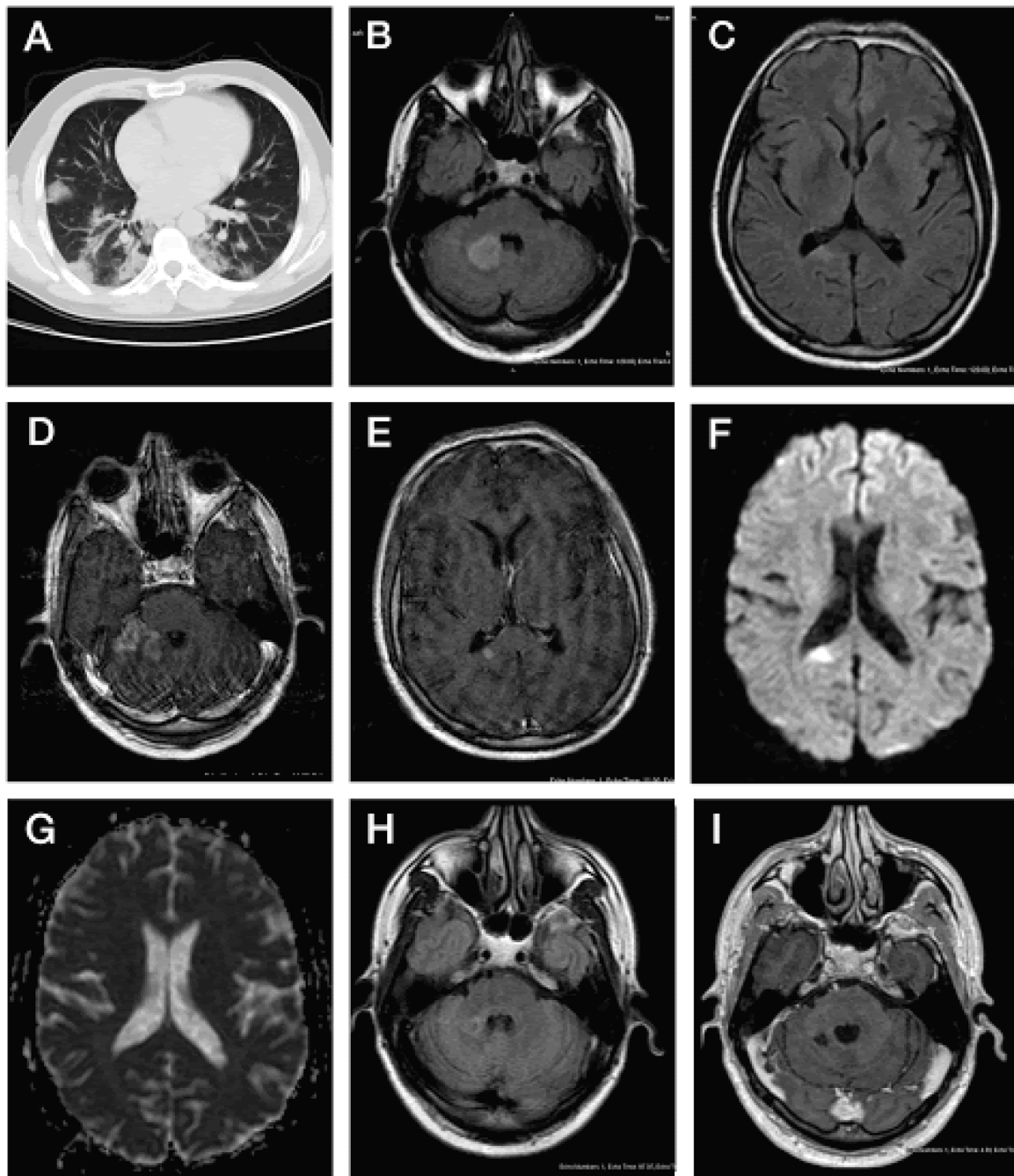


Fig. 3. Chest CT shows bilateral multiple ground-glass opacity (A). Brain MRI with contrast showed T2-FLAIR hyperintense lesions in the right cerebellar hemisphere and middle cerebellar peduncle adjacent to the fourth ventricle (B). At the supratentorial level there was a lesion adjacent to the lateral ventricle in the right half of the corpus callosum splenium (C). Both of lesions were with contrast fixation, more prominent in peripheral parts (D-E). Both of lesions were hyperintense on diffusion-weighted imaging (DWI) without apparent diffusion coefficient (ADC) response (F-G). Control MRI after 2 months revealed that the lesions regressed spontaneously (H) and contrast enhancement was no longer observed (I).

according to the severity of the disease. On the other hand, these patients also received treatments for infection (Zanin et al., 2020; Palao et al., 2020). In our cases, patient 2 had a severe ON which is rare for idiopathic retrobulbar optic neuritis however the other patients showed full recovery.

Uptodate there is a dilemma relating to how to treat COVID-19 disease and each institution has a protocol for managing the infection. In our patients our approach is primarily focused on keeping the infection under control. The first patient was asymptomatic but had radiological lung involvement, so he was treated with hydroxychloroquine monotherapy before IVMP. The second patient had no symptoms and no

systemic involvement, so IVMP treatment was started immediately due to severe vision loss. In the third patient, the infection clinic was serious and antiviral and antibiotic therapy were given together. IVMP was not given because the neurological symptoms were mild. Our ON patient was filling the MS criteria, so immunomodulatory treatment was started, with glatiramer acetate. It is wondering whether the other 2 patients will stay as a single attack or will they be multiphasic. Further long-term studies relating to the pathophysiology of COVID-19 are warranted.

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CRediT authorship contribution statement

Nurhan Kaya Tutar: Writing – review & editing. **Sami Omerhoca:** Visualization, Investigation. **Eda Coban:** Conceptualization. **Nilufer Kale:** Supervision.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

- Desforgues, M., Le Coupanec, A., Dubeau, P., Bourgoign, A., Lajoie, L., Dubé, M., Talbot, P.J., 2019. Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? *Viruses* 12 (1), 14. <https://doi.org/10.3390/v120100148>.
- Donati, D., 2020. Viral infections and multiple sclerosis. *Drug Discovery Today: Disease Models*. <https://doi.org/10.1016/j.ddmod.2020.02.00310>.
- Ellul, M.A., Benjamin, L., Singh, B., Lant, S., Michael, B.D., Easton, A., Kneen, R., Defres, S., Sejvar, J., Solomon, T., 2020. Neurological associations of COVID-19. *The Lancet Neurology*. [https://doi.org/10.1016/S1474-4422\(20\)30221-0](https://doi.org/10.1016/S1474-4422(20)30221-0).
- Liu, J., Tan, B., Wu, S., Gui, Y., Suo, J., Li, Y., 2020. Evidence of central nervous system infection and neuroinvasive routes, as well as neurological involvement in the lethality of SARS-CoV-2 infection. *Journal of Medical Virology*. <https://doi.org/10.1002/jmv.265709>.
- Palao, M., Fernández-Díaz, E., Gracia-Gil, J., Romero-Sánchez, C.M., Díaz-Maroto, I., Segura, T., 2020. Multiple Sclerosis following SARS-CoV-2 infection. *Multiple Sclerosis and Related Disorders* 102377. <https://doi.org/10.1016/j.msard.2020.1023776>.
- Suhandynata, R.T., Hoffman, M.A., Kelner, M.J., McLawhon, R.W., Reed, S.L., Fitzgerald, R.L., 2020. Longitudinal Monitoring of SARS-CoV-2 IgM and IgG Seropositivity to Detect COVID-19. *The Journal of Applied Laboratory Medicine*. <https://doi.org/10.1093/jalm/jfaa079>.
- WHO, 2020. Coronavirus disease 2019 (COVID-19): Situation report, 61. *World Health Organization, Geneva*.
- Zanin, L., Saraceno, G., Panciani, P.P., et al., 2020. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochir (Wien)*. <https://doi.org/10.1007/s00701-020-04374-x> published online May 4.
- Zhang, T., Rodricks, M.B., & Hirsh, E. (2020). COVID-19-associated acute disseminated encephalomyelitis: A case report. *medRxiv* <https://doi.org/2020.04.16.20068148> (preprint).
- Zhao, K., Huang, J., Dai, D., Feng, Y., Liu, L., & Nie, S. (2020). Acute myelitis after SARS-CoV-2 infection: A case report. *medRxiv* 10.1101/2020.03.16.20035105.
- Zoghi, A., Ramezani, M., Roozbeh, M., Darzam, I.A., Sahraian, M.A., 2020. A case of possible atypical demyelinating event of the central nervous system following COVID-19. *Multiple Sclerosis and Related Disorders*, 102324. <https://doi.org/10.1016/j.msard.2020.1023247>.