



## Original article

## Multiple sclerosis following SARS-CoV-2 infection

M. Palao\*, E. Fernández-Díaz, J. Gracia-Gil, C.M. Romero-Sánchez, I. Díaz-Maroto, T. Segura

Neurology Department, Complejo Hospitalario Universitario de Albacete, Castilla-La Mancha, Spain

## ARTICLE INFO

## Keywords:

COVID-19

SARS-CoV-2

MHV-59

Demyelinating disease

Optic neuritis

## ABSTRACT

SARS-CoV-2 infection can produce neurological features. The most common are headache, anosmia and dysgeusia but patients may also develop other central nervous system (CNS) injuries.

We present a patient affected by Covid-19 who initially consulted for decreased visual acuity. The MRI showed inflammation in the right optic nerve and demyelinating lesions in the CNS.

We speculate that an immune mechanism induced by SARS-CoV-2, which can activate lymphocytes and an inflammatory response, plays a role in the clinical onset of the disease. This pathogen may be associated with either the triggering or the exacerbation of inflammatory/demyelinating disease.

## 1. Introduction

At the end of 2019, the first case of SARS-CoV-2 virus infection was reported in Wuhan (China) with a subsequent worldwide expansion due to a high rate of infectivity, becoming a pandemic with more than 4 million patients affected to date (COVID-19 Map - Johns Hopkins Coronavirus Resource Center 2020). It is a viral infection with a wide spectrum of severity and prognosis. Although the respiratory system is principally involved, the infection can also produce complications in other anatomical locations. Currently, there is little information regarding the neurological manifestations associated with COVID-19 (Romero-Sánchez et al., 2020).

With respect to demyelinating diseases, several cases of peripheral nervous system involvement in the form of Guillain-Barré syndrome have been reported (Alberti et al., 2020; Zhao et al., 2020). However, available information about demyelinating complications of the central nervous system (CNS) is limited with only one report of acute disseminated encephalomyelitis (ADEM) in a severe COVID-19 patient being published to date (Zanin et al., 2020) and a single case of meningo-encephalitis (Moriguchi et al., 2020), the latter with the presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) confirmed by PCR. As viral infections have been linked to the development of demyelinating diseases (Donati, 2020) it would be interesting to know if this relationship also exists in the case of SARS-CoV-2.

We present a case of first presentation of demyelinating disease in the form of optic neuritis **following SARS-CoV-2 infection**. This case was included and partially described in a previously published registry of neurological complications of COVID-19<sup>2</sup> and here we fully discuss all the clinical and radiological details.

## 2. Case report

Our patient is a 29-year-old woman, with a medical history of asthma and rhinoconjunctivitis. She consulted on April 14th for a 10-day history of decreased visual acuity in the right eye. At the beginning, she presented with an upper altitudinal defect, followed by further worsening in both visual field defect and visual acuity. This was associated with continuous retro-ocular pain exacerbated by eye movements as well as colour desaturation. She had not previously experienced any neurological symptoms.

At the time of her assessment, she was living with her father who had confirmed SARS CoV2 infection. Symptoms had started 2–3 weeks earlier with the patient complaining of anosmia and dysgeusia associated with asthenia and proximal myalgias in her limbs which disappeared within a week.

On neurological examination, she presented with a visual acuity of 20/200 and a relative afferent pupillary defect in her right eye. Fundoscopic examination showed papillitis in the right eye. In addition, there were signs of pyramidal tract dysfunction seen as hyperreflexia in the lower limbs with a right-sided predominance, ipsilateral ankle clonus, right mute plantar response and bilateral Hoffmann's sign.

Orbital MRI (Fig. 1) confirmed a right-sided optic nerve lesion with significant contrast enhancement. Brain MRI (Fig. 2) showed sparse supratentorial periventricular demyelinating lesions, only one of them with gadolinium enhancement indicating activity. No infratentorial or cortical/juxtacortical lesions were detected. The MRI of the whole spinal cord was normal.

Laboratory results showed the presence of oligoclonal IgG bands in the CSF. Anti-IgG-NMO-AQP4 and anti-MOG antibodies were not

\* Corresponding author at: Neurology Department, Complejo Hospitalario Universitario de Albacete, Hermanos Falco, 37, 02008 Albacete, Spain.

E-mail address: [mariapalaorico@gmail.com](mailto:mariapalaorico@gmail.com) (M. Palao).

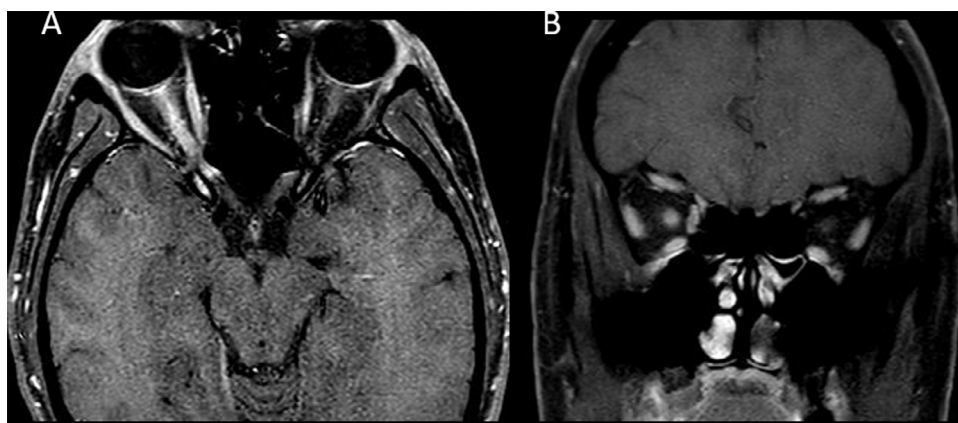


Fig. 1. Orbital MRI (A. axial B. coronal) contrast-enhanced T1 showing a right-sided optic nerve lesion with significant contrast enhancement.

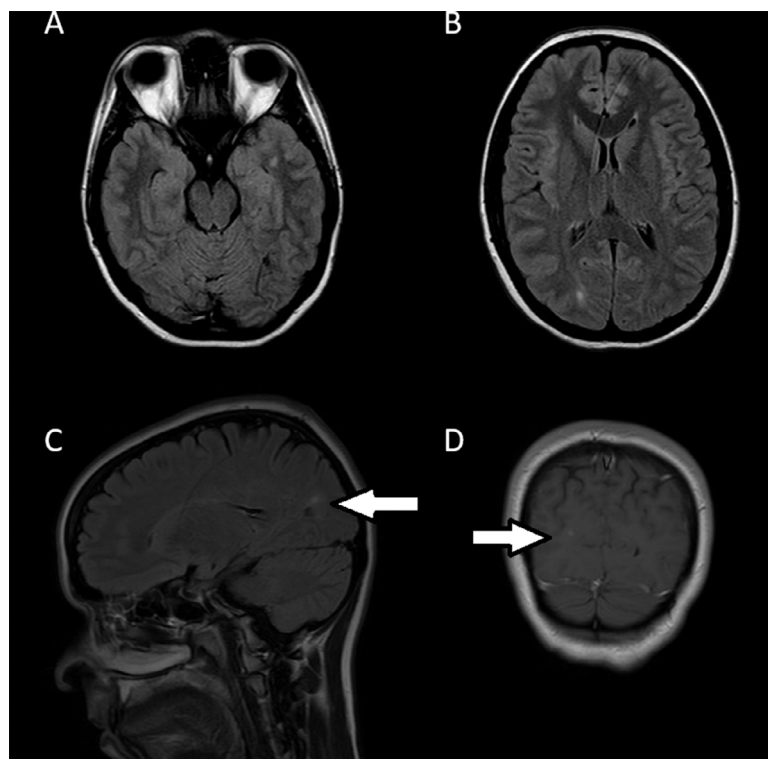


Fig. 2. Brain MRI, FLAIR (A, B, C) and contrast-enhanced T1 (D) sequences showing supratentorial periventricular demyelinating lesions in left temporal (A) and right occipital lobe (B, C) with gadolinium enhancement (D).

identified in serum samples. SARS-CoV-2 PCR analysis of nasopharyngeal exudate and CSF was negative whereas immunological testing was positive for both IgM and IgG, compatible with past infection. The autoimmune and serological studies in blood and CSF ruled out other aetiologies.

The patient was treated with three intravenous pulses of methylprednisolone at a daily dose of 1 g, followed by a tapering oral regimen with progressive improvement of ocular pain and visual acuity. On discharge the patient was able to distinguish letters in near vision optotype at 20/30.

### 3. Discussion

We report a first presentation of CNS demyelinating disease shortly after COVID-19 disease. To date, there is little evidence previously described in the literature (Zanin et al., 2020). In our case, the patient presented symptoms attributed to COVID-19 infection (anosmia and

dysgeusia) prior to the visual manifestations. The brief temporal gap leads us to consider the existence of a causal relationship.

There is plenty of evidence to support the association between viral infections and the development of demyelinating diseases. For example, Epstein-Barr virus infection is considered an important risk factor for the development of multiple sclerosis (Donati, 2020). Other viruses that cause common infections in humans like varicella-zoster, influenza or adenovirus are associated with more frequent and severe relapses in patients with MS (Andersen et al., 1993; McKay et al., 2017). Indeed, some studies show that viral respiratory tract infections may be linked to most of the exacerbations of MS (Marrodan et al., 2019).

If we focus on the coronavirus (CoV) family, there is clear evidence of its neurotropic character. In previous epidemics caused by other coronaviruses the presence of human CoV in the brain tissue of patients with MS, as well as its RNA has been demonstrated (Murray et al., 1992). In addition, the presence of intrathecal synthesis of human anti-CoV antibodies in CSF obtained from MS patients has also been

observed (Matías-Guiu et al., 2020). Further evidence is provided by an animal model of coronavirus, MHV-59 (mouse hepatitis virus), which has been previously used for the creation of viral-induced inflammation models. When inoculated intracranially, it can induce meningitis, acute focal encephalitis and most importantly, optic neuritis (Shindler et al., 2008). Such demyelination does not seem to be produced as a result of direct infection by the virus itself, but rather by the activated T-lymphocytes being responsible for the damage, through activation of the microglia and inflammatory mediators (Savarin and Bergmann, 2017). Immunopathological mechanisms for demyelination include autoimmunity, direct immune cytotoxicity, and indirect damage (Houtman and Fleming, 1996). The proposed mechanism by which these viruses access the CNS are either through haematogenic spread or via the neurogenic pathway (Desforges et al., 2014). In addition, it has been postulated that the virus can spread locally through the cribiform plate of the ethmoid bone where it is believed to cause the olfactory symptoms (Matías-Guiu et al., 2020).

Since our patient met the criteria for multiple sclerosis diagnosis and exhibited non-enhancing periventricular lesions, we assume that the pathogenic process had already started prior to COVID-19 disease, due to genetic or previous environmental factors. In this case, SARS-CoV-2 may have acted as a precipitating factor rather than multiple sclerosis being a direct consequence of the infection. However, we cannot rule out the possibility of the result for the SARS-CoV-2 PCR in CSF being a false negative because the test has not been properly validated and its sensitivity is unknown.

Our own experience along with the animal models described earlier, reinforce the idea of SARS-CoV-2, as with other viral infections, being a trigger of neurological autoimmunity. Further evidence derived from both experimental and clinical studies are warranted.

### Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

### CRedit authorship contribution statement

**M. Palao:** Conceptualization, Methodology, Investigation, Writing - original draft, Visualization. **E. Fernández-Díaz:** Conceptualization, Investigation, Supervision, Writing - review & editing. **J. Gracia-Gil:** Conceptualization, Methodology, Investigation, Writing - review & editing. **C.M. Romero-Sánchez:** Conceptualization, Methodology, Investigation, Writing - review & editing. **I. Díaz-Maroto:** Conceptualization, Methodology, Investigation, Writing - review & editing. **T. Segura:** Conceptualization, Supervision, Writing - review & editing.

### Declaration of Competing Interest

The author declared no potential conflicts of interest with respect to

the research, authorship, and/or publication of this articles.

### Acknowledgments

We thank Dr. J Ahmad MD. For the expert advice in the translation process. We also want to thank our patients for the patience and trust they are showing us during this difficult time of COVID-19 pandemic. We also want to acknowledge the work and dedication of all our colleagues in the hospital.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

### References

- COVID-19 Map - Johns Hopkins Coronavirus Resource Center. <https://coronavirus.jhu.edu/map.html> (accessed May 10, 2020).
- Romero-Sánchez, C.M., Díaz-Maroto, I., Fernández-Díaz, E., et al., 2020. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOV registry. *Neurology*. <https://doi.org/10.1212/WNL.0000000000009937>. published online June 1.
- Alberti, P., Beretta, S., Piatti, M., et al., 2020. Guillain-Barré syndrome related to COVID-19 infection. *Neurol. - Neuroimmunol. Neuroinflammation* 7, e741.
- Zanin, L., Saraceno, G., Panciani, P.P., et al., 2020. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochir. (Wien)* 162 (7), 1–4.
- Zhao, H., Shen, D., Zhou, H., Liu, J., Chen, S., 2020. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* 19, 383–384.
- Moriguchi, T., Harii, N., Goto, J., et al., 2020. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int. J. Infect. Dis.* 94, 55–58.
- Donati, D., 2020. Viral infections and multiple sclerosis. *Drug Discov. Today Dis. Models*. <https://doi.org/10.1016/J.DDMOD.2020.02.003>. [Epub ahead of print].
- Andersen, O., Lygner, P.E., Bergström, T., Andersson, M., Vabne, A., 1993. Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. *J. Neurol.* 240, 417–422.
- McKay, K.A., Jahanfar, S., Duggan, T., Tkachuk, S., Tremlett, H., 2017. Factors associated with onset, relapses or progression in multiple sclerosis: a systematic review. *Neurotoxicology* 61, 189–212.
- Marrodan, M., Alessandro, L., Farez, M.F., Correale, J., 2019. The role of infections in multiple sclerosis. *Mult. Scler.* J. 25, 891–901.
- Murray, R.S., Brown, B., Brain, D., Cabirac, G.F., 1992. Detection of coronavirus RNA and antigen in multiple sclerosis brain. *Ann. Neurol.* 31, 525–533.
- Matías-Guiu, J., Gomez-Pinedo, U., Montero-Escribano, P., Gomez-Iglesias, P., Portales-Estessam, J., Matías-Guiu, J.A., 2020. Should we expect neurological symptoms in the SARS-CoV-2 epidemic? *Neurologia* 35, 170–175.
- Shindler, K.S., Kenyon, L.C., Dutt, M., Hingley, S.T., Das, S.J., 2008. Experimental optic neuritis induced by a demyelinating strain of mouse hepatitis virus. *J. Virol.* 82, 8882–8886.
- Savarin, C., Bergmann, C.C., 2017. Viral-induced suppression of self-reactive T cells: lessons from neurotropic coronavirus-induced demyelination. *J. Neuroimmunol.* 308, 12–16.
- Houtman, J.J., Fleming, J.O., 1996. Pathogenesis of mouse hepatitis virus-induced demyelination. *J. Neurovirol.* 2, 361–376.
- Desforges, M., Le Coupanec, A., Stodola, J.K., Meessen-Pinard, M., Talbot, P.J., 2014. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res.* 194, 145–158.