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.

Neuroimmunology Reports 1 (2021) 100008

Contents lists available at ScienceDirect

Neuroimmunology Reports

journal homepage: www.elsevier.com/locate/nerep

Case Report

A case report of multiple sclerosis after COVID-19 infection: causality or coincidence?

Ismail Ibrahim Ismail[a,*], Jasem Al-Hashel[a,b], Raed Alroughani[c], Samar Farouk Ahmed[a,d]

[a] Department of Neurology, Ibn Sina Hospital, Safat, Kuwait
[b] Health Sciences Centre, Kuwait University, Department of Medicine, Jabriya, Kuwait
[c] Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait
[d] Department of Neurology and Psychiatry, Minia University, Minia, Egypt

ARTICLE INFO

Keywords:
Demyelination
SARS-CoV-2
COVID-19
Multiple sclerosis
MRI

ABSTRACT

Introduction: Since the declaration of COVID-19 pandemic, several cases of demyelination of both peripheral and central nervous systems have been reported. The association of viral infection and the development of CNS demyelination has long been studied, and this link has recently been reported following SARS-CoV-2 infection as well.

Case report: We report a case of a 36-year-old male who developed CNS demyelinating disease, that fulfilled the diagnostic criteria of multiple sclerosis (MS), 2 months after laboratory-confirmed infection with SARS-CoV-2.

Conclusion: To our knowledge, this is the second published case report of MS in association with COVID-19 infection, and the first case from Middle East and North Africa (MENA) region, adding to the growing literature of a probable causal relationship between SARS-CoV-2 infection and the development of MS.

Introduction

Since the declaration of coronavirus disease 2019 (COVID-19) pandemic in March 2020, it has become increasingly evident that several neurological complications can occur in association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. It has been estimated that more than one-third of patients with COVID-19 developed neurological complications during the acute phase, and more than one-third developed neuropsychiatric complications 6 months after infection (Taquet et al., 2021 Apr 6).

In the setting of severe COVID-19 infection, a combination of systemic inflammation, hypercoagulability, and neuroinflammation may result in central nervous system (CNS) damage. As regards to demyelinating diseases, several cases of both central and peripheral nervous systems demyelination have been reported following COVID-19 infection. Viral infection has long been linked to the development of CNS demyelination, and this association has been reported following SARS-CoV-2 infection as well (Shalaby and Shehata, 2021).

Herein, we report a case of a 36-year-old male who presented with CNS demyelinating disease, that fulfilled the diagnostic criteria of multiple sclerosis (MS), 2 months after a laboratory-confirmed infection with SARS-CoV-2.

Case presentation

A 36-year-old right handed male, with history of idiopathic generalized epilepsy since the age of 10 years, presented to our neurology outpatient clinic with unsteady gait and sense of imbalance of a one-month duration in March 2021. His epilepsy was well-controlled, and he was maintained on levetiracetam 1 g per day. His latest magnetic resonance imaging (MRI) was in January 2020, and was normal (**Fig. 1**). In December 2020, he developed fever, cough, generalized body pain, and he tested positive for SARS-CoV-2 via a nasopharyngeal swab reverse transcription-polymerase chain reaction (RT-PCR). He had an uncomplicated course of illness, and was managed conservatively at home. In February 2021, he started to have gait instability, recurrent falls, incoordination and dizziness, in the absence of any other cognitive, bulbar, sensory, motor or sphincteric complaint. On examination, he was alert, conscious, and oriented with normal speech and higher mental functions. He had unsteady gait with inability for tandem walking. Cranial nerves assessment was normal, apart from bilateral gaze-evoked nystagmus. He had mild intention tremors and dysdiadochokinesia on the left side. Motor examination was of Medical Research Council (MRC) grade 5/5 in both upper limbs and right lower limb, and MRC grade 4/5 in

* Corresponding author.
E-mail addresses: dr.ismail.ibrahim2012@gmail.com (I.I. Ismail), jasemkumsa@hotmail.com (J. Al-Hashel), alroughani@gmail.com (R. Alroughani), samerelshayb@hotmail.com (S.F. Ahmed).

https://doi.org/10.1016/j.nerep.2021.100008
Received 8 May 2021; Accepted 7 August 2021

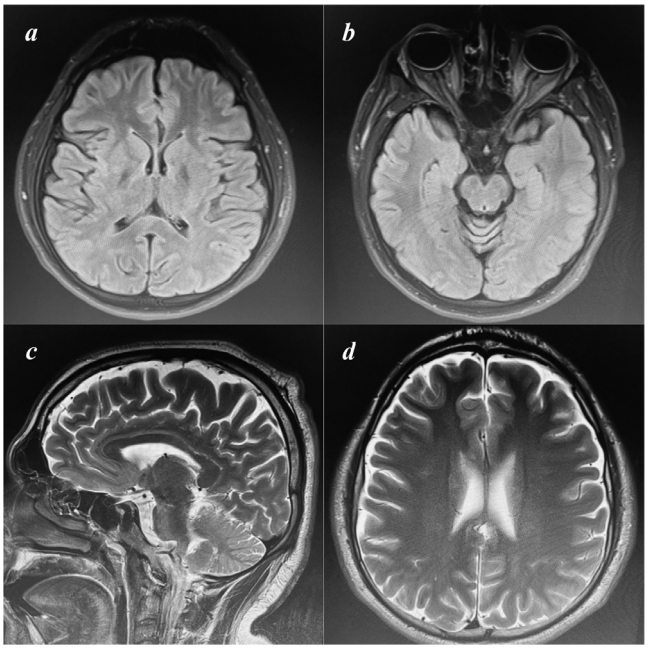

Fig. 1. Initial normal brain MRI of a 36-year-old male; (a,b) axial FLAIR, (c) sagittal, and (d) axial T2-weighted images.

left lower limb. Deep tendon reflexes were exaggerated (3+) all over the body. Sensory assessment showed reduced superficial sensation over the left side. Planter response was mute bilaterally. MRI of the brain with gadolinium showed multiple hyperintense white matter lesions involving the juxta-cortical and periventricular regions in both cerebral hemispheres, as well as the cerebellum, with no contrast-enhancement in any of the lesions, fulfilling the criteria of dissemination in space **(Fig. 2)**. Laboratory workup showed normal complete blood count; renal and liver functions; serum electrolytes; creatine kinase; inflammatory markers (erythrocyte sedimentation rate, C-reactive protein); serum vitamins B1, B6, B12, and folate; protein electrophoresis; immunoglobulin essay; and thyroid function. A panel for vasculitis and autoimmune antibodies including rheumatoid factor (RF), antinuclear antibody (ANA), anti-double-stranded DNA antibody (anti-dsDNA), extractable nuclear antigen (ENA) and antineutrophil cytoplasmic antibodies (ANCA) yielded negative results. Cerebrospinal fluid (CSF) analysis showed normal protein and glucose levels, no cells, and negative culture and sensitivity, and gram staining for bacterial infection. PCR screening for neurotropic viruses was negative in serum and CSF. Oligoclonal bands (OCB) were positive in CSF, fulfilling the criteria of dissemination in time. SARS-CoV-2 RNA was not tested in the CSF in our case due to delayed presentation. The patient was commenced on intravenous methylprednisolone 1000 mg per day for 3 days, with improvement regarding the gait, and limb weakness. The patient fulfilled the diagnostic criteria of multiple sclerosis (MS), and he was started on fingolimod 0.5 mg per day, as a disease-modifying therapy (DMT).

Discussion

We report a case of CNS demyelination following SARS-CoV-2 infection, that fulfilled the revised 2017 McDonald diagnostic criteria for MS. To our knowledge, this is the second published case report (Moore et al., 2021 Mar 1), and the first from Middle East and North Africa (MENA) region. Both cases presented with ataxia, showed positive OCBs in CSF, and multiple demyelinating lesions in the brain MRI, with normal spine. The concept of "*no better explanation*" posed a diagnostic challenge in both cases. MS pathogenesis could have been triggered by SARS-CoV-2, or this could be an exacerbation of a predetermined MS. However, the earlier normal MRI, and the onset of symptoms 2-months after COVID-19 infection, favors the probable causal relationship between viral infection and the development of MS.

It has been demonstrated that viral infection can induce an inflammatory response, activating myelin-specific T cells, which can accelerate the development of early or delayed virus-induced demyelination. Historically, SARS-CoV and MERS-CoV, which are genetically similar to SARS-CoV-2, has been associated with central demyelination in literature (Talbot et al., 2005). Several experimental studies revealed that murine coronavirus infection of susceptible mice has led to an inflammatory demyelination similar to MS, with coronavirus RNA sequences and its antigen detected in demyelinating lesions (Wu et al., 2020).

Several recent studies investigated the possible mechanisms of COVID-19 associated neurological complications. SARS-CoV-2 exhibits neurotropic properties and can cause direct neurological damage, through binding to angiotensin-converting enzyme-2 (ACE-2) receptors in CNS, or via blood circulation. Moreover, CNS damage appears to be mediated by an undesired immune reaction, leading to acute or delayed CNS demyelination (Lima et al., 2020). Accumulated evidence showed that SARS-CoV-2 and several proinflammatory cytokines, including IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, and IFN-γ, can cross the blood-brain-barrier, infecting macrophages, microglia, and astrocytes, which are the principal cells that mediate innate immunity in the CNS, thus creating a "perfect storm" for a pro-inflammatory state (Han et al., 2020). IL-6 is an important pro-inflammatory mediator that can induce an immune response in the nervous system, and plays a crucial role in regulating the immune response in MS. In EAE model of MS, IL-6 aggravates clinical manifestations, neuroinflammation, and demyelination, principally by promoting pathogenic T helper-17 cell generation in the peripheral lymphoid organs (Han et al., 2020). The levels of IL-6 were found to be correlated with the severity of COVID-19 symptoms, and this dysregulation can affect both innate and acquired immunity. Furthermore, most COVID-19 patients exhibit increased circulating levels of IL-17, which has a documented role in MS pathogenesis, based on the data from EAE model Petković and Castellano (2016).

In addition, Toll-like receptors (TLR), the main pattern recognition receptors in CNS, have played a significant role in the pathogenesis of both MS and COVID-19, mainly through recognition of viral particles, activation of the innate immune-system, and secretion of pro-inflammatory cytokines (Khanmohammadi and Rezaei, 2021 Jan 28).

A possible alternative explanation could be the production of antibodies against myelin triggered by the virus. This para-infectious or post-infectious etiology is reported in several cases of post-SARS-CoV-2 Guillain-Barre syndrome. SARS-CoV-2 may play a role in triggering MS, similar to the documented role of EBV (Kamel et al.).

Conclusion

We report a case of CNS demyelination following COVID-19 infection, that fulfilled the diagnostic criteria of MS. Our case adds to the growing field of research on the influence of SARS-CoV-2 on the nervous system, potentially triggering demyelination through an autoimmune CNS inflammatory process. Clinical and radiological monitoring is recommended in such cases, as the course of the demyelinating disease still seems unpredictable.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Authors' contributions

III, and SFA were involved with acquisition of data. III, RA, JYA and SFA treated the patient. III, and SFA wrote the initial manuscript.

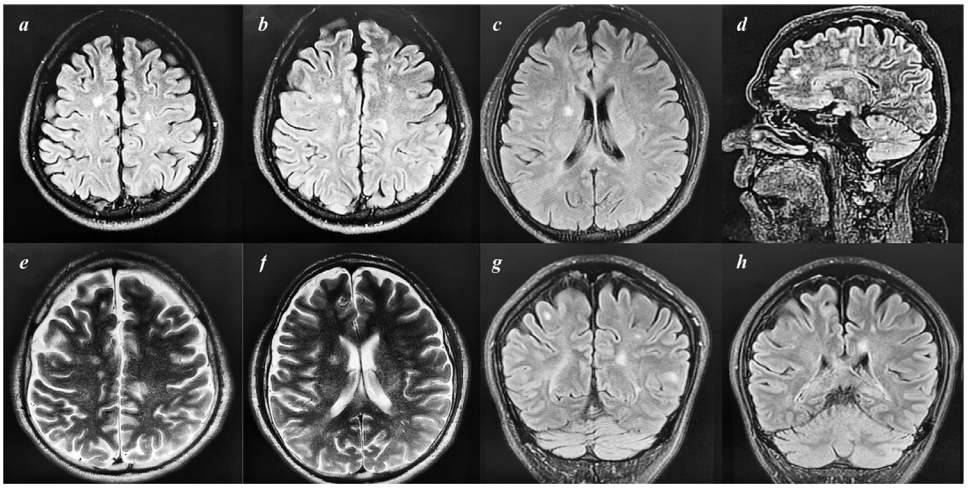

Fig. 2. Brain MRI done 2 months after COVID-19 infection; (a,b,c) axial FLAIR, (d) sagittal FLAIR, (e,f) axial T2-weighted, and (g,h) coronal FLAIR images, showing multiple white matter hyperintense lesions involving juxtacortical and periventricular regions in both cerebral hemispheres and the cerebellum.

III performed the literature review. All authors critically appraised and revised it. All authors read and approved the final manuscript.

Funding

No specific funding reported for this study.

Data availability

All data related to this case report are available on request to the corresponding author

Ethics approval

Approval was obtained from the Scientific Research Committee of Department of Neurology at Ibn Sina Hospital.

Informed consent

Informed consent was obtained from the patient.

Supplementary materials

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.nerep.2021.100008.

References

Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., Zhang, P., Liu, X., Gao, G., Liu, F., et al., 2020. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg. Microbes Infect. 9, 1123–1130.

Kamel WA, Ismail II, Al-Hashel JY. Guillain-barre syndrome following COVID-19 infection: first case report from kuwait and review of the literature. Dubai Medical Journal.:1-5.

Khanmohammadi, S, Rezaei, N., 2021. Role of toll-like receptors in the pathogenesis of COVID-19. Journal of Medical Virology.

Lima, M, Siokas, V, Aloizou, A-M, Liampas, I, Mentis, A-FA, Tsouris, Z, Papadimitriou, A, Mitsias, PD, Tsatsakis, A, Bogdanos, DP, Baloyannis, SJ, Dardiotis, E., 2020. Unraveling the possible routes of SARS-COV-2 invasion into the central nervous system. Curr Treat Options Neurol. 22 (11), 37. doi:10.1007/s11940-020-00647-z.

Moore, L, Ghannam, M, Manousakis, G., 2021. A first presentation of multiple sclerosis with concurrent COVID-19 infection. Eneurologicalsci 22, 100299.

Petković, F, Castellano, B., 2016. The role of interleukin-6 in central nervous system demyelination. Neural Regen Res 11 (12), 1922–1923. doi:10.4103/1673-5374.195273.

Shalaby, N.M., Shehata, H.S., 2021. Could SARS-CoV-2 herald a surge of multiple sclerosis? Egypt J Neurol Psychiatry Neurosurg 57, 22. doi:10.1186/s41983-021-00277-5.

Talbot, PJ, Boucher, A, Duquette, P, Gruslin, E., 2005. Coronaviruses and neuroantigens: myelin proteins, myelin genes. Chapter 7. Experimental models of multiple sclerosis 781–791.

Taquet, M, Geddes, JR, Husain, M, Luciano, S, Harrison, PJ., 2021 Apr 6. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. The Lancet Psychiatry.

Wu, Y, Xu, X, Chen, Z, et al., 2020. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun [Internet] 87, 18–22.