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Commentary

Can coronavirus disease 2019 (COVID-19) trigger exacerbation of multiple sclerosis? A retrospective study

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ABSTRACT

The effect of coronavirus disease (COVID-19) on the risk of relapse in multiple sclerosis (MS) have been unknown. In this retrospective study of 41 relapsing-remitting MS patients, number of relapses in pre-defined at risk-period (ARP) was compared with the previous two years. During the previous two years, a total of 32 attacks was reported, which 5 (15.6%) were during the at-risk period. After adjusting for age and sex, there was an increased risk of attack during ARP compared to the previous two years (RR: 2.566, 95%CI: 1.075-6.124, P=0.034). Our preliminary study suggested that COVID-19 can trigger exacerbation of MS.

1. Introduction

As understanding the clinical features and outcome of coronavirus disease (COVID-19) in multiple sclerosis (MS) patients improves, there is a lack of information regarding the effect of this infection on MS disease course. It is known that upper respiratory viral infection (URVI) increase the risk of relapses in MS patients (Buljevac et al., 2002; Edwards et al., 1998). However, there are currently no data to assess the effects of COVID-19 on the risk of relapse in MS. We aimed to examine the possible association between COVID-19 infection and relapse in patients with MS.

2. Method

This retrospective observational study was conducted in the outpatient MS clinic of Kashani Hospital affiliated to Isfahan University of Medical Sciences. All relapsing-remitting MS (RRMS) patients with a confirmed COVID-19 diagnosis based on reverse transcription-polymerase chain reaction (RT-PCR) who visited our outpatient MS clinic or contacted the center were included. Exclusion criteria were pregnancy and changes in disease-modifying therapy (DMT) within the previous two years.

Information on the number and timing of relapse in the past two years was extracted from the prospectively collected dataset (Mirmosayyeb et al., 2020). We also collected data on all patients via a telephone interviews. Relapse was defined as worsening of pre-existing symptoms or developing new symptoms, in the absence of fever, lasting at least 24h, after at least 30 days of improvement and stability (Thompson et al., 2018), and confirmed by presence of gadolinium enhancement on magnetic resonance imaging (MRI). At risk-period (ARP) was defined as a period including two weeks before until five weeks after COVID-19 onset (Sibley et al., 1985). Any attack in this period was considered related to the COVID-19.

We used Chi square test to compare relapse rate during ARP between patients required hospitalization due to COVID-19 and those didn't need. A generalized estimating equation (GEE) model with a Poisson distribution and a log link function was applied to compare the number of relapses during the at-risk period with the previous two years. The natural logarithm of person-time (week) is used as an offset. All statistical calculations were done using the SPSS 20.0 for Windows (SPSS, Chicago, IL, USA), and the $P<0.05$ was considered significant.

3. Result

A total of 41 RRMS patients with confirmed COVID-19 diagnosis were included in this study. The mean age was 35.10±9.20, and 31

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(75.6%) were female. The median disease duration and EDSS were 7.0 (5.0-10.7) and 0.0 (0.0-1.5), respectively. Nineteen (46.3%) patients received interferon, 9 (22.0%) were treated with teriflunomide, 8 (19.5%) with rituximab, 3 (7.3%) with fingolimod, and 2 (4.9%) were on dimethyl fumarate. Five patients were hospitalized due to COVID-19, but none required intensive care unit admission.

During the previous two years (4264 patient-weeks), a total of 32 attacks was reported in 22 (53.6%) patients, resulting in an annual average relapse rate of 0.32 (range 0-1). Out of 32 relapses, 5 (15.6%) were during the at-risk period (287 patient-weeks). These relapses occurred in 5 (12.2%) patients, and all started after the COVID-19 onset, with an average of 3.2 weeks (range 1-5). Two other patients reported neurological worsening after COVID-19 onset, but none met clinical relapse definition. One of five patients who experienced a relapse during ARP, required hospitalization due to COVID-19. No association between hospitalization for COVID-19 and risk of MS attack around the time of COVID-19 was found (P=0.853). After adjusting for age and sex, there was an increased risk of attack during ARP (RR: 2.566, 95%CI: 1.075-6.124, P=0.034) compared to the previous two years (Table 1).

Table 1
Attack rate during ARP and within past two years.

Period	Patient-weeks	Number of attacks	Attacks rate	RR (95% CI)	*P*-value
At-risk period	287	5	0.017	2.566 (1.075-6.124)	0.034
Not at-risk period	3977	27	0.007		

4. Discussion

In this small retrospective study, COVID-19 infection was shown to increase the risk of relapse in MS patients. Our findings are in line with previous observation that upper respiratory viral infections (Edwards et al., 1998; Kriesel et al., 2004), of which 10-30% are caused by coronaviruses (Paules et al., 2020), is associated with risk of MS relapse.

One of the putative mechanism underlying the observed association between COVID-19 and MS attacks could be expression of peripheral pro-inflammatory mediators such as interleukin (IL)-6, IL-7, IL-10, IL-17, granulocyte-colony stimulating factor, interferon (IFN)-γ, tumor necrosis factor (TNF)-α in COVID-19 infection (Vabret et al., 2020). High amounts of these factors can lead to blood-brain barrier dysfunction and facilitate the migration of monocytes, macrophages, and CD4+ and CD8+ T cells into the central nervous system (Dziedzic et al., 2021), which consequently can cause neurological worsening and MS exacerbation. Another possible mechanism is a direct invasion of the central nervous system (CNS) by SARS-COV-2 (Song et al., 2021).

Our study has some limitations including the small number of patients and retrospective nature of the study. We also had few patients with severe COVID-19 and the absence of information on the severity of relapse, and lack of information on presence of gadolinium enhancement on MRI in all patients are other limitations of this study.

In conclusion, this preliminary study suggested that COVID-19 can trigger exacerbation of MS. Further studies are needed to elucidate the possible relationship between COVID-19 and MS.

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Ethics approval

The regional bioethics committee of the Isfahan University of Medical Sciences approved the study (IR.MUI.MED.REC.1399.1045).

CRediT authorship contribution statement

Mahdi Barzegar: Conceptualization, Data curtion, Investigation, Methodology. **Saeed Vaheb:** Data curtion, Investigation, Project administration. **Omid Mirmosayyeb:** Data curtion, Investigation, Methodology, Project administration. **Alireza Afshari-Safavi:** Methodology, Conceptualization, Investigation, Project administration. **Nasim Nehzat:** Data curtion, Project administration. **Vahid Shaygannejad:** Conceptualization, Methodology, Project administration, Supervision.

Declaration of Competing Interest

Authors have no conflict of interest to declare

References

Buljevac, D., Flach, H., Hop, W., Hijdra, D., Laman, J., Savelkoul, H., van Der Meché, F., Van Doorn, P., Hintzen, R., 2002. Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain 125 (5), 952–960.
Dziedzic, A., Saluk-Bijak, J., Miller, E., Niemcewicz, M., Bijak, M., 2021. The impact of SARS-CoV-2 infection on the development of neurodegeneration in multiple sclerosis. Int. J. Mol. Sci. 22 (4), 1804.
Edwards, S., Zvartau, M., Clarke, H., Irving, W., Blumhardt, L., 1998. Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 64 (6), 736–741.
Kriesel, J.D., White, A., Hayden, F.G., Spruance, S., Petajan, J., 2004. Multiple sclerosis attacks are associated with picornavirus infections. Mult. Scler. J. 10 (2), 145–148.
Mirmosayyeb, O., Brand, S., Barzegar, M., Afshari-Safavi, A., Nehzat, N., Shaygannejad, V., Sadeghi Bahmani, D., 2020. Clinical characteristics and disability progression of early-and late-onset multiple sclerosis compared to adult-onset multiple sclerosis. J. Clin. Med. 9 (5), 1326.
Paules, C.I., Marston, H.D., Fauci, A.S., 2020. Coronavirus infections—more than just the common cold. JAMA 323 (8), 707–708.
Sibley, W., Bamford, C., Clark, K., 1985. Clinical viral infections and multiple sclerosis. Lancet 325 (8441), 1313–1315.
Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A.V., Skriabine, S., Lu, P., Weizman, O.-E., Liu, F., Dai, Y., 2021. Neuroinvasion of SARS-CoV-2 in human and mouse brain. J. Exp. Med. 218 (3), e20202135.
Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.
Vabret, N., Britton, G.J., Gruber, C., Hegde, S., Kim, J., Kuksin, M., Levantovsky, R., Malle, L., Moreira, A., Park, M.D., 2020. Immunology of COVID-19: current state of the science. Immunity 52 (2), 910–941.