MSJ Experimental Translational Clinical

Original Research Article

The association of upper respiratory infections with neuro-radiological course and attack rate of multiple sclerosis: Results from a large prospective cohort

Multiple Sclerosis Journal—Experimental, Translational and Clinical

July–September 2023, 1–7

DOI: 10.1177/20552173231196992

Moein Ghasemi, Dorreh Farazandeh, Behnam Amini, Mona Sedaghat, Anahita Najafi, Simin Khayatzadeh Kakhki, Pouya Torabi, Niloofar Jafarimehrabady, Ali Bitaraf, Houria Shariati, Golsa Gholampour, Saminnaz Kazemi, Abdorreza Naser Moghadasi and Maryam Vajihinejad

Abstract

Background: Although upper respiratory infections (URIs) are linked to multiple sclerosis (MS) attacks, SARS-COV2 has not been compared to URIs for attack rates.

Objectives: This study aimed to evaluate the attack rate and the results of neuroimaging in MS patients with URIs caused by COVID-19 and non-COVID-19 infections (NC-URI).

Methods: From May 2020 to April 2021, we followed 362 patients with relapsing-remitting MS in a prospective cohort design. Patients were monitored regularly every 12 weeks; an magnetic resonance imaging (MRI) scan was performed at enrollment and every time a relapse occurred. Poisson analysis was used to determine exacerbation rate ratios (RR) and the MRI parameters were tested using chi-square analysis.

Results: 347 patients with an average age of 38 and a female ratio of 86% were included. A RR of 2.24 ($p < 0.001$) was observed for exacerbations during the at-risk period (ARP). Attacks related to COVID-19 (RR = 2.13, $p = 0.001$) and NC-URIs (RR = 2.39, $p < 0.001$) were comparable regarding the increased risk of exacerbation ($p = 0.62$). Exacerbations within or outside the ARP did not significantly alter the number of baseline GAD-enhancing lesions ($p > 0.05$ for both).

Conclusion: COVID-19 has been shown to increase the risk of MS exacerbations, like other viral URIs.

Keywords: COVID-19, SARS-CoV-2, infection, multiple sclerosis, relapse, magnetic resonance imaging

Date received: 6 February 2023; accepted: 8 August 2023

Introduction

Multiple sclerosis (MS) is considered a multifactorial (mainly an immune-mediated) condition, which is characterized by dysregulation of the peripheral immune system that[1] results in demyelination and axonal injury in the central nervous system (CNS).[2,3] Relapse-remitting MS is the most common subtype of the disease and consists of mounting periodic attacks on the stable phase.[4] Several lines of evidence suggest that the immune system plays an integral and perhaps defining role in the development of MS[5]; alternative theories of MS pathogenesis state that a chronic viral infection may contribute to its pathogenesis.[6] It seems a foreign antigen, such as a virus or bacteria, provides an antigenic trigger for MS autoimmunity through molecular mimicry.[7] However, the cause of MS remains unknown.[8]

Most upper respiratory tract infections are viral in nature. According to previous studies, the risk of MS is increased after infection with infectious mononucleosis.[9,10] Other than these widely inspected viruses, some reports are suggesting an association between MS and other infections like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[6]

Moein Ghasemi and Dorreh Farazandeh contributed equally to the work as the first author.

Correspondence to:
Maryam Vajihinejad,
Department of Pathology, Shahid Sadoughi University of Medical Sciences, Daneshjoo Blvd., Yazd, Iran.
maryam.vajihinejadd@gmail.com

Moein Ghasemi, Dorreh Farazandeh, Behnam Amini,
Faculty of Medicine, Tehran

University of Medical Science, Tehran, Iran

Mona Sedaghat, Faculty of Medicine, Razi Educational and Therapeutic Psychiatric Center, University of Social Welfare and Rehabilitation, Tehran, Iran

Anahita Najafi, Simin Khayatzadeh Kakhki, Pouya Torabi, Faculty of Medicine, Tehran University of Medical Science, Tehran, Iran

Niloofar Jafarimehrabady, School of Medicine, University of Pavia, Pavia, Italy

Ali Bitaraf, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

Houria Shariati, Azad University of Medical Science, Tehran, Iran

Golsa Gholampour, Saminnaz Kazemi, Faculty of Medicine, Tehran University of Medical Science, Tehran, Iran

Abdorreza Naser Moghadasi, Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

Maryam Vajihinejad, Department of Pathology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Simultaneous involvement of two mechanisms has been proposed for this concurrence, first, an enhanced inflammatory response, which results in blood–brain barrier dysfunction and subsequent immune cell migration into the CNS, and the second is a direct neuroinvasion.[11–13]

MS attacks have been linked to upper respiratory infections (URIs); however, SARS-COV2 has not been compared to other URIs to determine whether attack rates differ.[14] This study aimed to evaluate the attack rate and the results of neuroimaging in MS patients with URI caused by COVID-19 and non-COVID-19 infections (NC-URI). We conduct a prospective, longitudinal investigation in a cohort of Iranian men and women in Sina Hospital and an additional outpatient clinic to assess MS during the COVID-19 pandemic.

Method

Patients

A prospective, longitudinal study design was used to follow a cohort of 362 patients aged between 20 and 65 years (from May 2020 to April 2021) and diagnosed with RRMS according to the 2017 McDonald criteria.[15] This study was conducted at the tertiary MS Center of Sina Hospital in Tehran based on the MS-COVID-19 registry system of Iran[16] (The Nationwide MS Registry of Iran [NMSRI] is a dynamic, follow-up-based registry[17]). We enrolled patients with (a) age between 20 and 65 years, (b) a definitive diagnosis of RRMS per the revised McDonald criteria[15] (by a neurologist ANM), and (c) the willingness to undergo a magnetic resonance imaging (MRI) scan upon initial evaluation. Exclusion criteria were as follows: (a) moribund patients that were not expected to survive to the end of the study, (b) the existence of a confounding underlying condition that would invalidate MS evaluation like other neurologic diseases, anoxic brain injury, or intracranial neurotrauma, and (c) inability to understand Persian. All patients gave written informed consent. The medical ethics committee of our hospital approved the study protocol (IR.AJAUMS.REC.1399.222).

Study design

The enrollment phase runs from May 2020 to July 2020. At baseline, the patients' basic demographics, Kurtzke's Expanded Disability Status Scale (EDSS), and functional system sub-scores were assessed by trained individuals, independent of their medical care. A study center staff member instructed the patients to call when they felt sick or experienced neurological impairment and visit the outpatient clinic every 12 weeks (specific dates were set for each patient). After a suspected infection or exacerbation, an additional outpatient clinic visit was scheduled within 3 days. In the case of suspected infection (worsening of cold symptoms, including nasal congestion, nasal discharge, fever, cough, myalgia, and headache). Nasal swab specimens were collected in duplicate to detect SARS-CoV-2 (COVID-19) by reverse transcriptase-polymerase chain reaction (RT-PCR). Patients kept a weekly diary to ensure that infections and neurological complaints were being reported to the clinician throughout the entire study period. Each patient was prospectively followed for 48 weeks (four outpatient visits at intervals of 12 weeks). Patients kept a weekly diary to ensure that infections and neurological complaints were being reported to the clinician throughout the entire study period. The data were analyzed using Sibley's definition of the at-risk period (ARP) for MS attacks, extending from 2 weeks before to 5 weeks after the URI.[18] We embedded the relapse/infection information with other questions to mask the specific hypothesis under investigation. Independent examiners, blind to the other factor, checked both relapses and infections. An illustration of the study design and follow-up strategies for enrolled participants is presented in Figure 1.

Definitions

An exacerbation of multiple sclerosis was defined as developing a new neurological symptom or worsening an existing symptom or symptoms attributable to multiple sclerosis lasting >24 h after a period of ≥30 days of improvement or stability.[19] Neurological deterioration only temporarily associated with a period of fever was not considered an exacerbation. Infections were defined as the onset of or definite worsening of cold symptoms, including nasal congestion, nasal discharge, fever, cough, myalgias, and headache. In the case of suspected infection, nasal swab specimens were collected in duplicate to detect SARS-CoV-2 (COVID-19) by RT-PCR. The PCR results of COVID-19 captured URIs in two categories: COVID-19 and NC-URIs. Symptoms of gastrointestinal or urinary tract infections were not included in this analysis. The state of COVID-19 vaccination was not assessed as a variable in this study because only 18 patients got the first dose of COVID-19 in the last 3 months of follow-up.

MRI protocol

An MRI scan was performed on all patients before the study; in case of exacerbation, an MRI scan was

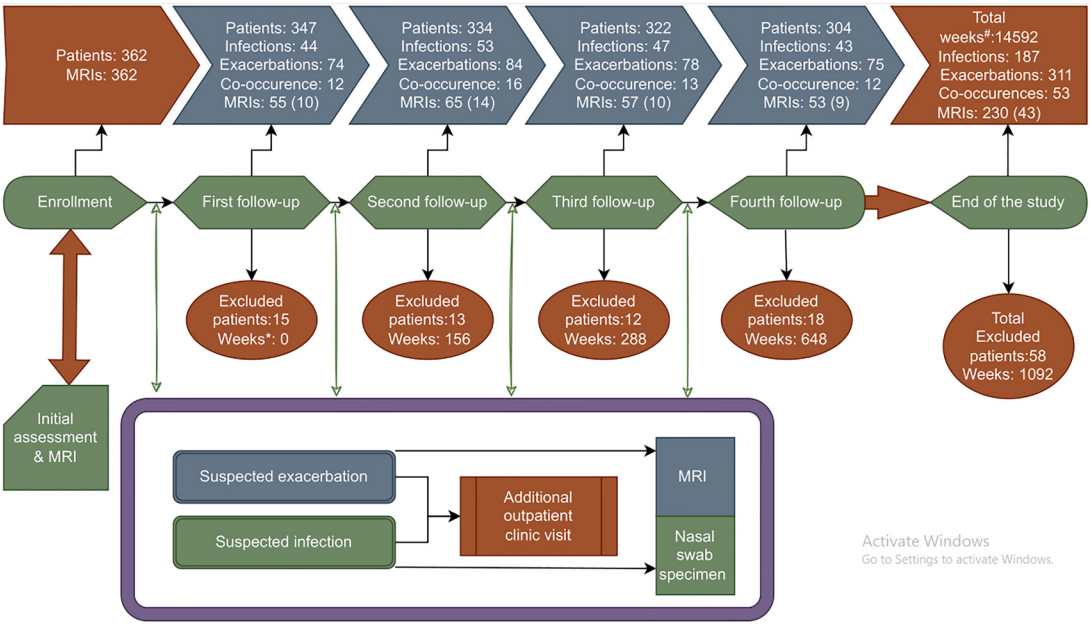

Figure 1. The study design and the follow-up strategy for the enrolled subjects. #Weeks of follow-up for patients who had remained in the study throughout. *Patients' follow-up weeks were determined based on the last stage they reached before their departure (If a patient left prior to their initial visit, they were omitted from the study and their follow-up weeks were not recorded).

performed 4 weeks after the onset of exacerbation. A 1.5 T MRI system (Philips NT, Best, The Netherlands) was used to obtain SE T1-weighted pre- and post-GAD-DTPA (diethylenetriaminepentaacetic acid) images (5 mm slices with 0.5 mm gap, TR [repetition time] = 450 ms, TE [echo time] = 15 ms, FOV [field of view] = 230 mm, matrix = 256 × 256); the dose of GAD-DTPA was 0.1 mmol/kg. The number of enhancing lesions and the estimated volumes of the enhancing tissue were measured in all scans performed.

Statistical methods

We used Sibley's "at-risk" period for MS attacks, which begins 2 weeks before a URI and ends 5 weeks afterward.[18] The ARP was determined for each patient, and the number of exacerbations occurring within and outside the ARP was counted. Exacerbation rates during and outside ARPs were compared using Poisson analysis and determined exacerbation rate ratios (RR). The MRI parameters were tested with chi-square analysis. The results are expressed as an odds ratio with 95% confidence intervals (95% CIs).

Results

Patient characteristics

Three hundred sixty-two patients were included (312 women and 50 men) in the enrollment phase. Fifteen patients withdrew after the intake visit (excluded from the study); 13 patients withdrew after the first regular visit; 12 after the second one, and 18 after the third visit. Three hundred and twelve of the subjects (86%) were female, similar to the general RRMS population. The average age was 38.3 years (range 20–65 years), and the average disease duration from diagnosis was 5.7 years (range 2–28 years). The average EDSS at entry was 1.9 (range 0–6.0), and the average number of exacerbations in the 2 years preceding enrollment was 1.8. A total of 301 patient-years (15,684 weeks) of follow-up were recorded, with an average follow-up of 45 weeks per patient. There was a total of 1307 visits to the outpatient clinic (approximately 3.7 visits per patient).

MS attacks and URIs

A total of 187 URIs was recorded in 122 patients, an average of 0.7 (range: 0–3) infections per year. A total of 57% of URIs were classified as COVID-19 and 43% as NC-URI. There were no statistically significant differences between exacerbations occurring during or outside the ARP according to age, gender, or DMT type. A total of 311 exacerbations occurred in 240 patients, resulting in an average exacerbation rate of 1.03 per patient per year (range: 0–4 per year). Fifty-three out of the total number of 311 exacerbations (17%) started during the ARP. These

exacerbations started on average 6 days after the clinical onset of infection, with only five exacerbations (9%) preceding the onset of infection.

Increased risk of exacerbation around the time of URIs

There was a higher rate of exacerbations during the infection period (Table 1). For this period, the exacerbation RR was 2.24 (95% CI: 1.7–5.3, $p < 0.001$, $\chi^2 = 16.8$). NC-URIs (RR = 2.39, 95% CI: 1.7–6.7, $p < 0.001$, $\chi^2 = 13.2$) or COVID-19 (RR = 2.13, 95% CI: 1.5–5.3, $p = 0.001$, $\chi^2 = 11.1$) infection have both resulted in an increased risk of exacerbation, but COVID-19's effect was not different from NC-URIs ($p = 0.62$, $\chi^2 = 0.23$).

Infection did not affect GAD enhancement

The average number of GAD-enhancing lesions per MRI was 0.52 at baseline. MRI scans were performed 4 weeks after clinically established exacerbations in 230 of the 311 cases. There were 22 and 23 scans taken after exacerbations that had been triggered by COVID-19-URIs and NC-URIs, respectively, while 188 scans were taken after exacerbations without URIs present. GAD-enhancing lesions were observed in 5 (25%) exacerbations triggered by COVID-19-URIs, 6 (26%) exacerbations triggered by NC-URIs, and 53 (28%) without URIs; none of which differed significantly from each other ($p > 0.05$).

Discussion

This prospective, longitudinal cohort study evaluated the attack rate and the results of neuroimaging in MS patients with URI caused by COVID-19 and NC-URI. Our research revealed higher rates of exacerbations during both COVID-19 URIs and NC-URIs. Our findings were comparable with the previous studies that have reported the association of different respiratory viral infections with MS attacks and exacerbations.[20–23] A recent study recorded a relative risk of 2.56 for exacerbations during ARP of COVID-19 over exacerbations outside ARP.[14] Nevertheless, another recent study revealed contradicting results that not only COVID-19 infection does not promote MS exacerbations but also can reduce the incidence risk of acute relapses.[24]

Although the presence of new GAD-enhancing lesions confirms exacerbations, their absence does not invalidate a clinical diagnosis of exacerbation. It has always been challenging for neurologists to diagnose infection-induced worsening of symptoms, even though the symptoms meet the criteria for exacerbation. During the course of our study, we attempted to minimize this diagnostic problem. In our study, newly detected GAD-enhancing lesions were comparable between exacerbations caused by URIs and those without URIs. Also, exacerbations reported by participants were considered pseudo-exacerbations if their neurological examination did not support an MS exacerbation. A prospective cohort study has documented that, while viral infections lead to an increased rate of MS relapse, these relapses are not accompanied by the formation of new GAD-enhancing lesions.[22] On the other hand, several studies suggest parasitical infections and microbial agents such as *Helicobacter pylori* might have protective effects against MS exacerbations and associated disability, and prevent the development of new enhancing lesions in MRI.[25–30]

Psychological stress is another possible contributing factor to the observed association between COVID-19 infection and MS exacerbations. Immunosuppressive therapies and fear of relapse have posed a great psychological burden on MS patients during the current pandemic, and as shown in previous studies, anxiety, and stressful events are associated with an increased relapse rate in the patients.[31,32] Increased blood–brain barrier (BBB) permeability during inflammation is considered an important step in MS relapse pathogenesis which is mitigated by the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[23] However, similar to a previous study, we did not observe any significant increase in gadolinium enhancement in MRI imaging of patients after COVID-19 infection, which contradicts the BBB penetration hypothesis.[22]

An increase in the inflammatory cytokines, alongside the activation of autoreactive T-cells during infections, plays an important role in MS exacerbation pathogenesis.[23] Several mechanisms contribute to the provoking factors of MS relapses. First antigen-presenting cells, including B cells, may activate CD4+ T cells in response to foreign and endogenous antigens, leading to inflammatory responses and tissue damage.[33] Second, the phenomenon that we know as "molecular mimicry" defines that sequence similarities among foreign and self-peptides could lead to the cross-activation of autoreactive T and B cells.[34] Third, epitope spreading, which is the induction of an autoimmune response against normally tolerated host antigens and epitopes as a consequence of the exposure of these antigens and epitopes during immune-mediated tissue inflammation.[35–37] Fourth, pathogens may trigger auto-reactive T and B cells bystander activation in autoimmune susceptible individuals.[22,38,39]

Table 1. Exacerbation rates for different upper respiratory tract infection (URI) conditions.

Condition	Follow-up weeks	Exacerbations	Annual exacerbation rate	Rate ratio (vs. absent-URIs)	p-value (χ^2)
No URIs	14,375	258	0.94	Reference	Reference
COVID-19 URIs	753	29	2.00	2.13 (1.5–5.3)	0.001 (11.1)
Non-COVID URIs	556	24	2.25	2.39 (1.7–6.7)	<0.001 (13.2)
Total URIs	1309	53	2.11	2.24 (1.7–5.3)	<0.001 (16.8)
Total	15,684	311	1.03	-	-

This study examined exacerbation rates for different URI conditions, including COVID-19 URIs, non-COVID URIs, and all URIs combined. The "No URIs" category represented exacerbation rates outside the ARP and served as a reference point for comparison. During the ARP, individuals with COVID-19 URIs experienced a significantly higher exacerbation rate compared to those without URIs. Over 753 weeks of follow-up, there were 29 exacerbations, resulting in an annual exacerbation rate of 2.00. The RR, comparing to the No URIs group, was 2.13 (95% CI: 1.5–5.3). Similarly, individuals with non-COVID URIs had a significantly higher exacerbation rate during the ARP. In 556 weeks of follow-up, there were 24 exacerbations, with an annual exacerbation rate of 2.25. The RR compared to the No URIs group was 2.39 (95% CI: 1.7–6.7). When considering all URIs, including both COVID-19 and non-COVID-19 cases, the exacerbation rate during the ARP remained significantly higher. Over 1309 weeks of follow-up, there were 53 exacerbations, resulting in an annual exacerbation rate of 2.11. The RR compared to the No URIs group was 2.24 (95% CI: 1.7–5.3). In the overall analysis combining all conditions, the total number of exacerbations and weeks of follow-up were considered. The annual exacerbation rate was calculated as 1.03. However, no RR or *p*-value was provided as it was not compared to the No URIs group. Follow-up weeks: The total number of weeks of follow-up for each condition. Exacerbations: The number of exacerbation events observed during the follow-up period. Annual exacerbation rate: The average number of exacerbations per year based on the follow-up period. RR: the exacerbation rate of each condition to the exacerbation rate of individuals without URIs (No URIs). The value in parentheses represents the 95% CI. *p*-value (χ^2): The *p*-value obtained from a χ^2 test, indicating the statistical significance of the difference in exacerbation rates between each condition and No URIs.CI: confidence interval; NC-URI: non-COVID-19 upper respiratory tract infection.

Our study has several limitations. First, we prospectively conducted this study, which is prone to distortions such as selection bias due to loss of follow-up or patients' informed refusal. Second, we did not evaluate the severity of upper respiratory tract infections and long intervals between regular examinations were another possible shortcoming. Third, since the method of infection diagnosis was based on clinical symptoms, patients with asymptomatic infections were possibly underdiagnosed. Fourth, due to false-negative RT-PCR results from upper respiratory specimens, we did not perform other characteristic laboratory or imaging findings that can further support the clinical diagnosis of COVID-19. In addition, there is a limitation that 230 of the 311 exacerbations were followed by an MRI. This lack of information may adversely affect our interpretation of the MRI results.

Our results could be considered preliminary evidence for the association between COVID-19 infection and MS exacerbations. These findings highlight the increased risks of the recent pandemic for the MS patient population and underscore the importance of appropriate protective measures to prevent further deterioration of the patient's disease and quality of life. Because of the controversy and the scarcity of studies regarding this subject, additional studies are required to be carried out to ascertain the reproducibility of our results and for a more robust conclusion. Further studies should consider using more diagnostic tests and more serological tests to distinguish URIs due to the overlap in clinical signs.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Anahita Najafi https://orcid.org/0000-0002-9191-9172
Maryam Vajihinejad https://orcid.org/0000-0003-2322-5731

References

1. Murúa SR, Farez MF and Quintana FJ. The immune response in multiple sclerosis. *Annu Rev Pathol: Mech Dis* 2022; 17: 121–139.
2. Gilden DH. Multiple sclerosis exacerbations and infection. *Lancet Neurol* 2002; 1: 45.
3. Donati D. Viral infections and multiple sclerosis. *Drug Discov Today Dis Models* 2020; 32: 27–33.
4. Pietrasik S, Dziedzic A, Miller E, et al. Circulating miRNAs as potential biomarkers distinguishing relapsing-remitting from secondary progressive multiple sclerosis. A review. *Int J Mol Sci* 2021; 22: 11887.
5. Bar-Or A and Li R. Cellular immunology of relapsing multiple sclerosis: interactions, checks, and balances. *Lancet Neurol* 2021; 20: 470–483.
6. Pignolo A, Aprile M, Gagliardo C, et al. Clinical onset and multiple sclerosis relapse after SARS-CoV-2 infection. *Neurol Int* 2021; 13: 695–700.
7. Tarlinton RE, Martynova E, Rizvanov AA, et al. Role of viruses in the pathogenesis of multiple sclerosis. *Viruses* 2020; 12: 43.
8. Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. *Handb Clin Neurol* 2014; 122: 231–266.
9. Handel AE, Williamson AJ, Disanto G, et al. An updated meta-analysis of risk of multiple sclerosis following infectious mononucleosis. *PLoS One* 2010; 5: e12496.
10. Bjornevik K, Cortese M, Healy BC, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science* 2022; 375: 296–301.
11. Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. *Immunity* 2020; 52: 910–941.
12. Dziedzic A, Saluk-Bijak J, Miller E, et al. The impact of SARS-CoV-2 infection on the development of neurodegeneration in multiple sclerosis. *Int J Mol Sci* 2021; 22: 1804.
13. Song E, Zhang C, Israelow B, et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain. *J Exp Med* 2021; 218: e20202135.
14. Barzegar M, Vaheb S, Mirmosayyeb O, et al. Can coronavirus disease 2019 (COVID-19) trigger exacerbation of multiple sclerosis? A retrospective study. *Mult Scler Relat Disord* 2021; 52: 102947.
15. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology* 2018; 17: 162–173.
16. Eskandarieh S, Sahraian MA and Naser Moghadasi A. Implementing coronavirus disease 2019 scale-up registry protocol in national multiple sclerosis registry system of Iran. *Current Journal of Neurology* 2021; 20.
17. Shahin S, Eskandarieh S, Moghadasi AN, et al. Multiple sclerosis national registry system in Iran: validity and reliability of a minimum data set. *Mult Scler Relat Disord* 2019; 33: 158–161.
18. Sibley WA, Bamford CR and Clark K. Clinical viral infections and multiple sclerosis. *Lancet* 1985; 325: 1313–1315.
19. Schumacher GA, Beebe G, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci* 1965; 122: 552–568.
20. Panitch HS. Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* 1994; 36: S25–S28.
21. Kriesel JD, White A, Hayden FG, et al. Multiple sclerosis attacks are associated with picornavirus infections. *Mult Scler* 2004; 10: 145–148.
22. Buljevac D, Flach HZ, Hop WCJ, et al. Prospective study on the relationship between infections and multiple sclerosis exacerbations. *Brain* 2002; 125: 952–960.
23. Marrodan M, Alessandro L, Farez MF, et al. The role of infections in multiple sclerosis. *Mult Scler* 2019; 25: 891–901.
24. Etemadifar M, Sedaghat N, Aghababaee A, et al. COVID-19 and the risk of relapse in multiple sclerosis patients: a fight with no bystander effect? *Mult Scler Relat Disord* 2021; 51: 102915.
25. Farrell R, Antony D, Wall GR, et al. Humoral immune response to EBV in multiple sclerosis is associated with disease activity on MRI. *Neurology* 2009; 73: 32–38.
26. Correale J, Fiol M and Gilmore W. The risk of relapses in multiple sclerosis during systemic infections. *Neurology* 2006; 67: 652–659.
27. Mohebi N, Mamarabadi M and Moghaddasi M. Relation of helicobacter pylori infection and multiple sclerosis in Iranian patients. *Neurol Int* 2013; 5: 31–33.
28. Correale J and Farez M. Association between parasite infection and immune responses in multiple sclerosis. *Ann Neurol* 2007; 61: 97–108.
29. Li W, Minohara M, Su JJ, et al. Helicobacter pylori infection is a potential protective factor against conventional multiple sclerosis in the Japanese population. *J Neuroimmunol* 2007; 184: 227–231.
30. Libbey JE, Cusick MF and Fujinami RS. Role of pathogens in multiple sclerosis. *Int Rev Immunol* 2014; 33: 266–283.
31. Potagas C, Mitsonis C, Watier L, et al. Influence of anxiety and reported stressful life events on relapses in multiple sclerosis: a prospective study. *Multiple Sclerosis Journal* 2008; 14: 1262–1268.
32. Stojanov A, Malobabic M, Milosevic V, et al. Psychological status of patients with relapsing-remitting multiple sclerosis during coronavirus disease-2019 outbreak. *Mult Scler Relat Disord* 2020; 45: 102407.

33. Wang J, Jelcic I, Mühlenbruch L, et al. HLA-DR15 molecules jointly shape an autoreactive T cell repertoire in multiple sclerosis. *Cell* 2020; 183: 1264–1281.e20.
34. Kohm AP, Fuller KG and Miller SD. Mimicking the way to autoimmunity: an evolving theory of sequence and structural homology. *Trends Microbiol* 2003; 11: 101–105.
35. Sfriso P, Ghirardello A, Botsios C, et al. Infections and autoimmunity: the multifaceted relationship. *J Leukoc Biol* 2010; 87: 385–395.
36. Tuohy VK and Kinkel RP. Epitope spreading: a mechanism for progression of autoimmune disease. *Arch Immunol Ther Exp (Warsz)* 2000; 48: 347–351.
37. Powell AM and Black MM. Epitope spreading: protection from pathogens, but propagation of autoimmunity? *Clin Exp Dermatol* 2001; 26: 427–433.
38. Berkovich RR. Acute multiple sclerosis relapse. *Continuum (Minneap Minn)* 2016; 22: 799–814.
39. Pacheco Y, Acosta-Ampudia Y, Monsalve DM, et al. Bystander activation and autoimmunity. *J Autoimmun* 2019; 103: 102301.