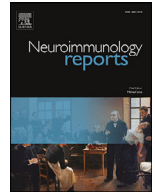




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



SARS-CoV2 infection as a potential trigger for severe relapse in a patient with multiple sclerosis who stopped disease modifying treatment due to COVID-19 pandemic

Michael Auer, Klaus Berek, Elena Fava, Anne Zinganell, Florian Deisenhammer, Harald Hegen^{#,*}, Franziska Di Pauli^{#,*}

Medical University of Innsbruck, Department of Neurology, Anichstraße 35, 6020 Innsbruck, Austria

ARTICLE INFO

Keywords:

Multiple sclerosis
Relapse
SARS-CoV-2
COVID-19
Disease modifying treatment

ABSTRACT

Background: During COVID-19 pandemic safety of disease modifying treatments (DMT) in patients with multiple sclerosis (MS) is still under debate. While there is no clear evidence for a higher risk of severe SARS-CoV-2 infection under DMT the risk of rebound of disease activity in case of stopping DMT is obvious.

Case report: We present the case of a 27-year-old patient with highly active relapsing remitting MS who interrupted DMT with alemtuzumab due to safety concerns and fear of COVID-19. Eventually, she developed COVID-19 disease and, concomitantly, a severe and disabling relapse requiring plasmapheresis.

Conclusion: This case raises the question whether SARS-CoV-2 might trigger disease reactivation as other viral infections were described to potentially trigger MS relapses. Furthermore, it reinforces the discussion on MS treatment during COVID-19 pandemic and shows the challenge of weighing up the elevated risk of COVID-19 and of severe MS relapse when interrupting an effective DMT.

Introduction

During COVID-19 pandemic treatment decisions in patients with multiple sclerosis (MS) are challenging and require weighing the risk of SARS-CoV-2 infection while on disease modifying treatment (DMT) against the risk of permanent disability due to MS relapses following interruption of DMT.

In recent months numerous studies of MS patients who experienced SARS-CoV-2 infection on DMT have been published (Sormani et al. 2021, Möhn et al. 2020). Overall, only a minority of MS patients can be considered at high risk of severe COVID-19 disease course (Bsteh et al. 2020), and most of DMTs do not seem to increase the risk of a severe SARS-CoV-2 infection. However, in particular for cell-depleting therapeutic agents there are no clear guidelines at the moment (Giovannoni et al. 2020, Amor et al. 2020).

So far, there are no data regarding MS relapses during or even caused by a SARS-CoV-2 infection.

Here we report the unfavorable course of a young MS patient who stopped treatment with alemtuzumab due to new warnings of severe

side-effects and the COVID-19 pandemic and, eventually, experienced SARS-CoV2 infection and, at the same time, a severely disabling relapse requiring corticosteroids and plasmapheresis.

Case report

A 27-year-old female patient with a history of insulin-dependent diabetes mellitus (DM) type I, arterial hypertension (aHT) and substituted hypothyroidism experienced first symptoms of MS in February 2019. She was admitted to hospital with dysarthria, ataxia and hypoesthesia of her right extremities and left face. The MRI scan showed numerous T2-lesions, about 25 of those with gadolinium-enhancement. Two courses of high-dose intravenous methylprednisolone (HDMP; in total 9 g followed by oral tapering) were administered and resulted in recovery of symptoms within several weeks. Due to the severe onset of MS, the patient received the first cycle of alemtuzumab in April 2019. During the following year no more relapses occurred and the Expanded Disability Status Scale (EDSS) remained stable at a score of 1.5 (exaggerated reflexes and mildly impaired fine motor skills).

* Corresponding authors at: Medical University of Innsbruck, Department of Neurology, Anichstraße 35, 6020 Innsbruck, Austria.

E-mail addresses: michael.auer@i-med.ac.at (M. Auer), k.berek@i-med.ac.at (K. Berek), elena.fava@tirol-kliniken.at (E. Fava), anne.zinganell@i-med.ac.at (A. Zinganell), florian.deisenhammer@tirol-kliniken.at (F. Deisenhammer), harald.hegen@i-med.ac.at, herald.hegen@i-med.ac.at (H. Hegen), franziska.di-pauli@i-med.ac.at (F. Di Pauli).

Authors contributed equally to this work

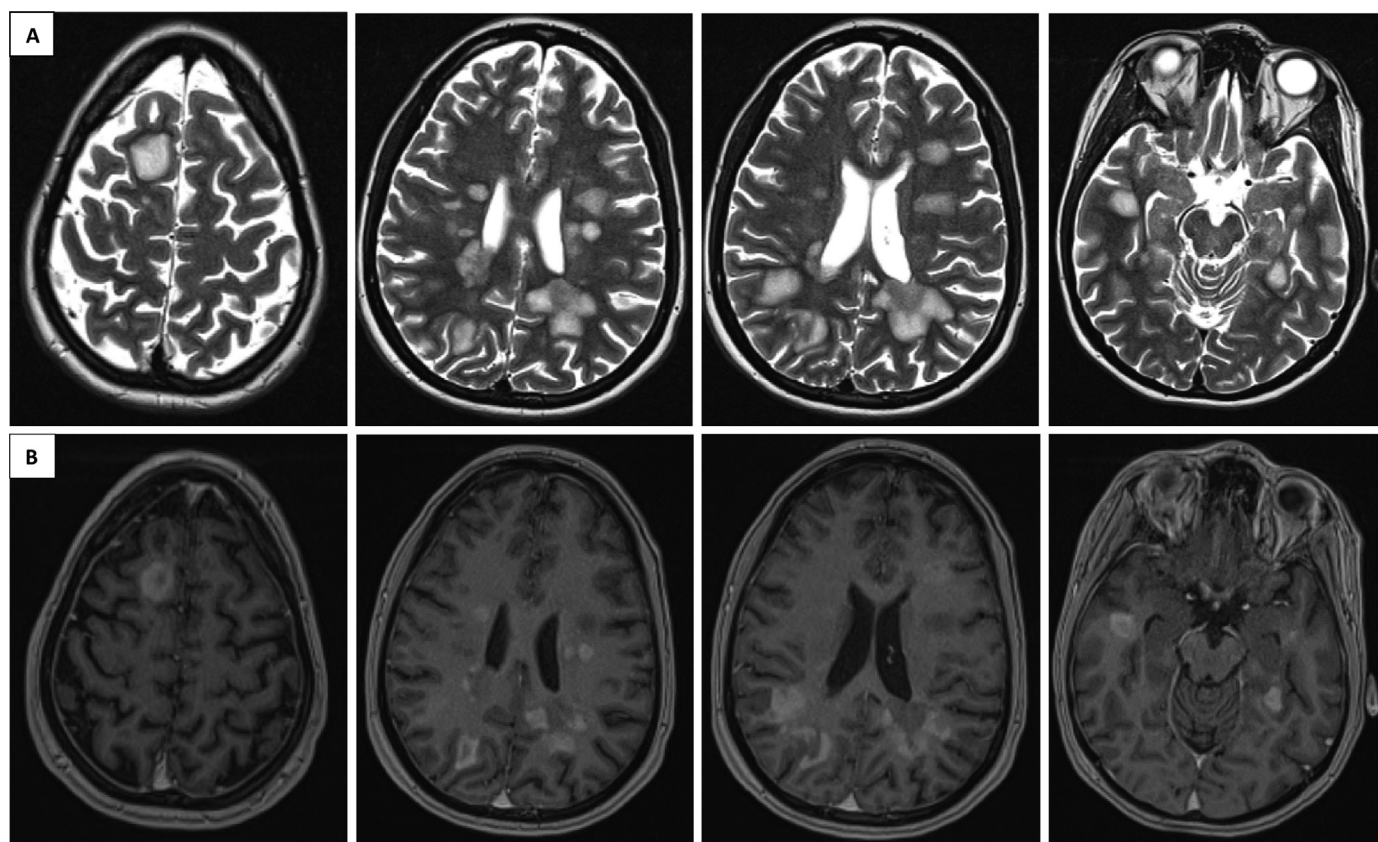


Fig. 1. Severe MS disease activity during SARS-CoV2-infection. MRI on January 30, 2021. Brain MRI during acute relapse shows (A) multiple, new hyperintense lesions on T2-weighted images with (B) gadolinium-enhancement on T1-weighted images.

The second cycle of alemtuzumab was planned for April 2020, but due to new side effect warnings, the risk factors of the patient with aHT and DM, a disease without evidence of activity, the first wave of the COVID-19 pandemic in Europe and the uncertainty about the potential elevated risk while on cell-depleting therapy, the treatment cycle was suspended.

On January 3rd, 2021 the patient was admitted to a local hospital due to diabetic ketoacidosis. At the same time, she suffered of sore throat and flu-like symptoms; and the treating physician described new neurologic symptoms including dysarthria and left sided hemianopsia. The brain MRI showed numerous new and contrast-enhancing lesions, so that a severe MS relapse was suspected. Progressive multifocal leukoencephalopathy or other infectious diseases of the central nervous system were excluded by cerebrospinal fluid analysis. The ketoacidosis was suspected secondary to the cognitive deficit in the context of the relapse and problems in handling the preexisting therapy with an insulin pump. On January 7, the patient was transferred to the intensive care unit of the Department of Neurology, University hospital of Innsbruck, Austria. Here, SARS-CoV-2-PCR was positive with a Cycle threshold value of 18, whereas three tests between January 3rd and 6 had been negative. At this time the flow cytometry revealed a decreased number of T-cells with a normal CD4/CD8 ratio while number of B-cells was within the normal range. In the X-ray of the chest a pneumonia was diagnosed and the patient developed fever up to 39°C. Therefore, treatment of COVID-19 pneumonia with remdesivir and dexamethasone was administered for five days. Due to severe diabetic ketoacidosis and COVID-19 pneumonia, treatment with HDMP had to be suspended.

Regarding the COVID-19 pneumonia the patient remained stable without need of oxygen inhalation. However, the neurologic status markedly worsened over these few days, so that the patient finally presented with a Balint syndrome (optic ataxia, ocular apraxia, visual

agnosia), dysarthria, left sided hemianopsia and severe cognitive impairment. After treatment of ketoacidosis and stabilization of COVID-19 pneumonia, on January 12, HDMP could be started and was given over seven days (6 g in total followed by oral tapering). Thereafter, the neurologic symptoms slightly improved over two weeks followed by another worsening including right sided hemiparesis and mild dysphagia. In the meantime, the patient had recovered from COVID-19 and was finally tested negative on January 28. Another cerebral MRI scan was performed on January 30 (Fig. 1). Due to the severe neurologic disability and progression of MRI lesions four cycles of plasmapheresis within five days were applied. Immediately thereafter, considering the negative anti-JC-virus antibody status, an immunomodulatory treatment with natalizumab was started.

Until the end of February 2021, the patient remained substantially disabled with an EDSS score of 6.0 and has not been able to return to her work or social life by now.

Discussion

This case shows the challenges of decision making in the therapy of MS patients during COVID-19 pandemic. Based on evidence to date, MS seems not to be an independent risk factor for SARS-CoV-2 infection or for a severe COVID-19 disease course. Similar to the general population, higher age, higher pre-existent disability and other comorbidities such as cardiac diseases or obesity were identified as risk factors for a severe COVID-19 disease course (Zheng et al. 2020, Salter et al. 2021). Even though it remains still unclear, whether DMT influences the risk for SARS-CoV-2 infection, there is some evidence that most DMTs do not seem to be associated with an increased risk of severe COVID-19 disease course (Sharifian-Dorche et al. 2021). Recent studies even described protective effects of some non-cell depleting agents such as interferon-beta,

glatiramer acetate, dimethyl fumarate and natalizumab while anti-CD20 antibodies were identified as potential risk factors for severe COVID-19 disease course (Reder et al. 2021, Salter et al. 2021).

Based on the mechanism of action of different DMTs, especially cell-depleting agents are thought to potentially increase the risk for viral infections. For alemtuzumab a higher prevalence of viral infections such as upper respiratory tract infections were found especially during the first months after each treatment cycle. Therefore, experts recommend to carefully consider the risk constellation in each patient, also considering a temporary delay of re-dosing (Giovannoni et al. 2020).

Some cases of SARS-CoV-2 infections in patients treated with alemtuzumab have been published, all of those showed mild disease courses. It was discussed that despite cell-depletion some immunocompetence may be obtained because the remaining lymphocytes are functional and the innate immune response is mostly preserved (Fernández-Díaz et al. 2020). One study even discussed that immune reconstitution induced by alemtuzumab may facilitate milder courses of COVID-19 (Matías-Guiu et al. 2020). A recent registry-based cross-sectional study of more than 1600 North American MS patients included nine alemtuzumab-treated patients and did not find this therapy to be associated with higher risk of severe disease course, while identifying disability, age, male sex, black race, cardiovascular comorbidities as well as corticosteroid treatment during the past two months and treatment with rituximab as potential risk factors for severe disease course (Salter et al. 2021).

Thus, the risk of severe SARS-CoV2 infection especially in young patients may be lower than the risk for severe relapses caused by treatment interruption.

So far, there is no literature available regarding SARS-CoV-2 as a potential trigger of MS relapses. However, viral infections in general and, more specifically, also upper respiratory tract infections such as adenovirus and influenza viruses were associated with an increased risk of MS relapses (Correale et al. 2006). Some authors speculate that nonspecific antigenic stimulation caused by viral infection could precipitate attacks of a demyelinating disease (Venkatesan and Johnson, 2014). Therefore, SARS-CoV-2 has to be considered as another potential viral trigger of MS relapses.

Thus, the risk association between COVID-19 and MS should be conversely discussed. SARS-CoV-2 could be a risk factor for worsening of MS and, therefore, continuous and sufficient treatment of MS at any time during the COVID-19 pandemic is essential for our patients.

Conclusion

Management of MS patients during the COVID-19 pandemic is challenging. First, insufficient therapy is critical especially in patients with active disease and the risk of disability due to severe relapses seems to outweigh the risk of a severe COVID-19 disease course. Secondly, SARS-CoV-2 might be a potential trigger of relapses in MS-patients. Reporting here the first case of concurrent COVID-19 disease and severe MS disease exacerbation does not prove causality, but it has to be further investigated.

Declaration of Competing interest

Michael Auer has participated in meetings sponsored by, received speaker honoraria or travel funding from Biogen, Novartis, Merck and Sanofi-Genzyme.

Klaus Berek has participated in meetings sponsored by and received travel funding from Roche and Biogen.

Elena Fava has participated in meetings sponsored by and received travel funding from Teva, Biogen.

Anne Zinganeli has participated in meetings sponsored by, received honoraria or travel funding from Biogen, Merck, Sanofi Genzyme, Teva and Roche.

Florian Deisenhammer has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Bayer, Biogen, Sanofi-Genzyme, Merck, Novartis and Roche.

Harald Hegen has participated in meetings sponsored by, received speaker honoraria or travel funding from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, Siemens, Teva, and received honoraria for acting as consultant for Biogen and Teva.

Franziska Di Pauli has received speaking honoraria from Biogen and Sanofi-Genzyme.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nerep.2021.100005.

References

- Amor, S, David Baker, D, Khoury, SJ, Schmierer, K, Giovannoni, G, 2020. SARS-CoV-2 and Multiple Sclerosis: Not All Immune Depleting DMTs are Equal or Bad. *Ann. Neurol.* 87 (6), 794–797. doi:10.1002/ana.25770.
- Bsteh, G, Bitschnau, C, Hegen, H, Auer, M, Di Pauli, F, Rommer, P, Deisenhammer, F, Berger, T., 2020 Sep 25. Multiple sclerosis and COVID-19: how many are at risk? *Eur. J. Neurol.* doi:10.1111/ene.14555.
- Correale, J, Fiol, M, Gilmore, W., August 22, 2006. The risk of relapses in multiple sclerosis during systemic infections. *Neurology* 67 (4). doi:10.1212/01.wnl.0000233834.09743.3b.
- Fernández-Díaz, E, Gracia-Gil, J, García-García, JG, Palao, M, Romero-Sánchez, CM, Segura, T., 2020. COVID-19 and multiple sclerosis: A description of two cases on alemtuzumab. *Mult. Scler. Relat. Disord.* 45, 102402. doi:10.1016/j.msard.2020.102402.
- Giovannoni, G, Hawkes, C, Lechner-Scott, J, Levy, M, Waubant, E, Golda, J., 2020 Apr; 39. The COVID-19 pandemic and the use of MS disease-modifying therapies. *Mult. Scler. Relat. Disord.*, 102073 doi:10.1016/j.msard.2020.102073.
- Matías-Guiu, J, Montero-Escribano, P, Pytel, V, Porta-Etessam, J, Matías-Guiu, JA., 2020. Potential COVID-19 infection in patients with severe multiple sclerosis treated with alemtuzumab. *Mult. Scler. Relat. Disord.* 44, 102297. doi:10.1016/j.msard.2020.102297.
- Möhn, N, Konen, FF, Pul, R, Kleinschnitz, C, Prüss, H, Witte, T, Stangel, M, Skripuletz, T, 2020 Dec 16. Experience in Multiple Sclerosis Patients with COVID-19 and Disease-Modifying Therapies: A Review of 873 Published Cases. *J. Clin. Med.* 9 (12), 4067. doi:10.3390/jcm9124067.
- Reder, AT, Centonze, D, Naylor, ML, Nagpal, A, Rajbhandari, R, Altincatal, A, Kim, M, Berdofe, A, Radhakrishnan, M, Jung, E, Sandrock, AW, Smirnakis, G, Popescu, C, De Moor, C, 2021. COVID-19 in Patients with Multiple Sclerosis: Associations with Disease-Modifying Therapies. *CNS Drugs* 35 (3), 317–330. doi:10.1007/s40263-021-00804-1.
- Salter, A, Fox, RJ, Newsome, SD, Halper, J, Li, DKB, Kanellis, P, Costello, K, Bebo, B, Rammohan, K, Cutter, GR, Cross, AH., 2021 Mar 19. Outcomes and Risk Factors Associated With SARS-CoV-2 Infection in a North American Registry of Patients With Multiple Sclerosis. *JAMA Neurol.*, e210688 doi:10.1001/jama.2021.0688.
- Sharifian-Dorche, M, Sahraian, MA, Fadda, G, Osheroova, M, Sharifian-Dorche, A, Karaminia, M, Saveriano, AW, La Piana, R, Antel, JPPaul Steven Giacomini PS, 2021 May; 50. COVID-19 and disease-modifying therapies in patients with demyelinating diseases of the central nervous system: A systematic review. *Mult. Scler. Relat. Disord.*, 102800. doi.org/10.1016/j.msard.2021.102800.
- Sormani, MP, De Rossi, N, Schiavetti, I, Carmisciano, L, Cordioli, C, Moiola, L, Radaelli, M, Immovilli, P, Capobianco, M, Trojano, M, Zaratini, P, Tedeschi, G, Comi, G, Battaglia, MA, Patti, F, Salvetti, M., 2021. Disease-Modifying Therapies and Coronavirus Disease 2019 Severity in Multiple Sclerosis. *Ann. Neurol.* doi:10.1002/ana.26028.
- Venkatesan, A, Johnson, RT., 2014. Infections and multiple sclerosis. *Handb. Clin. Neurol.* 122, 151–171. doi:10.1016/B978-0-444-52001-2.00007-8.
- Zheng, Z, Peng, F, Xu, B, Zhao, J, Liu, H, Peng, J, Li, Q, Jiang, C, Zhou, Y, Liu, S, Ye, C, Zhang, P, Xing, Y, Guo, H, Tang, W., 2020. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J. Infect.* 81 (2), e16–e25. doi:10.1016/j.jinf.2020.04.021.