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## Commentary

## Could Sars-Cov2 affect MS progression?

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## ABSTRACT

A long-term neurologic sequela arising from COVID-19 infection in multiple sclerosis (MS) patients could be related both to the increase of cytokines and the activation of NLRP3 inflammasome by the Sars-CoV2. These two mechanisms may cause a worsening of MS several months after the resolution of the infection.

## Dear Editor,

Are patients with multiple sclerosis (MS) at higher risk of worsening their demyelination disease after contracting Sars-CoV2?

COVID-19 increases circulating pro-inflammatory cytokines levels (cytokines storm), modifies production of IFN-1, triggers proliferation of macrophages and induces vascular damage both in symptomatic and asymptomatic patients (Li et al., 2020). We speculate that this intense immune-stimulation and systemic stress due to the SARS-COV2 infection, in MS patients with a hyper-reactive immune system, could be responsible for a higher frequency of MS relapses and long-term disease progression, even after successful recovery from COVID-19 (Merad and Martin, 2020).

Several factors may create a high-risk environment for people with MS. At first, Soares and colleagues demonstrated genetic variant which influence the activation of inflammasomes (Soares et al., 2019). The authors have identified specific genetic variant in NLRP3 and NLRC4 inflammasomes which could influence the response to the disease modifying therapy (DMT) and the severity of MS.

Van den Berg and colleagues have shown that SARS-CoV2 activates directly the NLRP3, which function is fundamental to mount a proper adaptive immune response against the virus. The variation in patients' response to the viral infection could be attributed to the inability to downregulate NLRP3 inflammasome activation; patients with a dysfunctional immune system can demonstrate a dysregulated NLRP3 inflammasome activity resulting in severe COVID-19 presentation with tissue damage and cytokine storm (van den Berg and Te Velde, 2020).

Freeman and Swartz confirmed that the Sars-Cov2-related

inflammation is associated with an intense, rapid stimulation of the innate immune response that triggers activation of the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome pathway and generates a release of proinflammatory cytokines, particularly IL-6 and IL-1 $\beta$  (Freeman and Swartz, 2020).

Soares confirmed that the activation of NLRP3 inflammasome and the consequent increased IL-1 $\beta$  and IL-18 production, represents a risk factor for the development of MS and progression to severe forms of the disease (Soares et al., 2019).

The inflammasomes are multiprotein complexes of the innate immune response involved in the processing of caspase-1, the activation of pro-inflammatory cytokines interleukin (IL)–1 $\beta$  and IL-18 as well as the cell death-mediated mechanism of pyroptosis and the activation of the adaptive immune response (Govindarajan et al., 2020). Interestingly, inflammasome activation antagonizes type I interferon production and type I interferon can antagonize inflammasome activation (Guarda et al., 2011). Recently Zhang et al. (2020), have shown how important is the role of IFN-1 in COVID-19 especially in the modulation of massive macrophage production.

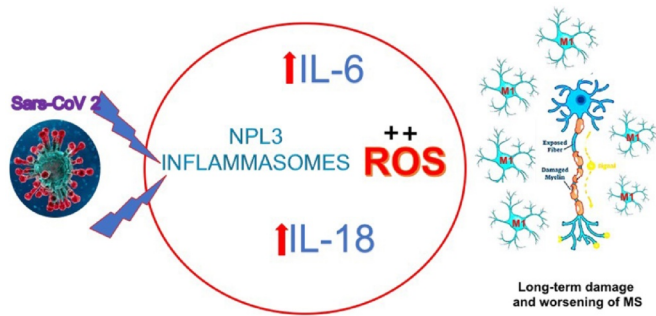
The role of IFN-1 in modulation of the immune response, could explain the fact that MS patients who are being treated with DMT rarely present with a severe form of COVID-19 (Sormani et al., 2020). However, studies are still preliminary and several controversies exist (Thakolwiboon et al., 2020).

Regardless of the role of IFN-1, the over-activity of inflammasomes should be considered a potential negative factor that could impact long-term MS outcomes (Boziki et al., 2020).

We speculate that the activation of NLRP3 inflammasome may

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**Fig. 1.** The image summarizes the mechanisms which could be responsible of the worsening of multiple sclerosis (MS) progression, despite MS patients rarely incur in severe form of COVID-19.

stimulate microglia and macrophages through the production of inflammatory cytokines (Goleva et al., 2018) and by the increase of circulating reactive oxygen species (ROS) (Tschopp and Schroder, 2010) be responsible of the massive production of M1 (bad) microglia (Di Stadio and Angelini, 2019).

Another plausible mechanism, which may explain the higher risk of clinical deterioration in people with MS is that COVID-19 induces an extreme oxidative stress with subsequent increase of circulating ROS. This increase may be persistent for several months and might activate the M1 (bad) microglia (Di Stadio and Angelini, 2019). The latter is responsible for neurological deterioration in MS patients as recently showed by Goleva et al. (2018) (Fig. 1).

Considering the above changes, should an increase in the relapse rate and/or an increase in disability be expected in MS patients post-COVID-19? Are clinical outcomes dependent on the relative levels of inflammasome vs type I interferon activity in MS patients? May the unfriendly environment, characterized by excessive chronic inflammation, impacts disability progression and neurodegeneration?

To answer this question, it is necessary to study a large population of COVID-19-infected MS patients over time to further investigate the role of SARS-CoV2 in the progression, severity and quality of life of people with MS.

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none of the authors declares conflict of interests.

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