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Editors Welcome

Is multiple sclerosis a risk factor for infections?

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During the current COVID-19 pandemic, the infection risk for each individual is determining their ability to work, interact with their partners, children and parents. Many of us have changed our treatment practices for MS and related diseases out of fear of a potentially lethal infection, but what do we know about the risk of infection in a patient who is not taking disease modifying treatments (DMTs)?

We used to advise our patients that they have an overactive immune system that attacks the protective layer of their nerve cells in the brain. But is the rest of the immune system of an MS patient intact and able to fight infections and cancers the way a normal immune system does?

The article from Persson et al. in this volume (Persson et al., 2020) adds to the increasing evidence based on large data analysis, that people with MS have a higher risk of infections than the general population. In this study they examined a large US cohort derived from the Department of Defense healthcare system and a large UK cohort from general practice registries. This allowed them to compare 8695 MS cases in the US with 86,934 in the general population matched for age, sex and geography. Similarly, they contrasted 6932 MS cases from the UK to 68,526 in the general population. People with MS from the US and UK had significantly higher rates of any transmissible disease at 76% and 25% respectively. Infections leading to hospitalization were more than doubled in both cohorts. All types of infection were increased: viral, fungal, pneumonia and influenza but also opportunistic ones. The infection rate seemed to be higher in the US than in the UK. This could be due to differences in data collection for each cohort, but the authors also queried if this is because of prescription of immunosuppressive medication being higher in the US than in the UK. Unfortunately, in the UK cohort DMTs were not recorded. Therefore, they compared patients on monoclonal antibody treatment to all other cases in the US cohort and found that the risk of any infection was actually lower in the cohort treated with monocloncal antibodies compared to the remaining cohort, but infections leading to hospitalization seemed to occur more frequently in the cohort on monocloncal antibodies.

These findings are similar to another recent study (Ghaderi et al., 2019) which based their analysis on a nationwide data collection on influenza infections in Norway: infection related hospitalizations were 3–5 times higher in people with MS than the general public. The finding that MS patients are more likely to be hospitalized is not that surprising given that any infection, especially when fever occurs, can lead to a worsening of preexisting MS symptoms. So, frequency of hospital admissions is not necessarily giving us the answer to whether MS itself or its treatment is predisposing patients to infections. Interestingly, the rate of community acquired pneumonia is 3.6 times higher in MS than the general population (Vinogradova et al., 2009) - higher than in patients with diabetes mellitus, stroke and even patients on immunosuppressive therapies!

A study from British Columbia examined 6793 MS cases of which 1716 were exposed to DMTs (Wijnands et al., 2018). There was no difference in the risk of infection between not taking DMT and being on injectable treatment like beta-interferon or glatiramer acetate. Oral DMTs and natalizumab increased by 50% the risk of infection related physician claims but not hospitalizations; hospitalization risk correlated better with level of disability. This study was unable to outline which treatment is most risky but a Swedish registry study had much more detailed data on their patients (Luna et al., 2019) and was able to compare 6421 MS patients to 42 645 matched cases from the general population. 3260 of these MS patients were on rituximab, 1588 on natalizumab, 1535 on fingolimod and 2217 on injectables. While the study from British Columbia could not find any significant difference in infection risk between people on no treatment and those on immune modulators like beta-interferon and glatiramer acetate, this Swedish cohort had an incidence ratio of any infection of 8.9 in MS cases versus 5.2 in the general population. Infections occurred almost twice as often in people with MS than in the general population. 11% of the general population took any sick leave in the preceding year, 23% of patients on injectables and 30% of patients on rituximab, fingolimod or natalizumab. Interestingly, after adjusting for clinical parameters the higher rate of any infections only remained significant for rituximab.

In Persson's study (Persson et al., 2020) the greatest danger was for urinary tract infection where females were at higher risk than males. This should not surprise any clinician. The most commonly treated infection by MS specialists is not herpes (simplex or zoster), whose incidence is increased with some of the DMTs, but rather urinary tract infection. This results from bladder dysfunction which is extremely common in MS and often not appropriately treated. The other more

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prevalent infection is aspiration pneumonia. Again, many of our patients suffer from swallowing difficulties. A symptom that often escapes the attention of both doctor and patient.

Infections can worsen residual MS symptoms, especially in patients with higher disability. Perhaps clinicians are just more easily alerted and paying closer attention to treating infections in the MS population, in particular in those on immunosuppressive therapies?

It is not clear yet whether patients with MS are more likely to get infected with coronavirus although early data from Italian, Swedish and French registries are not supportive of this claim (https://iwims.world/iwims-global-scientific-meetings). What we do know is that when infected, MS patients with poor outcome are those older with severe disability, most of whom are not even on disease-modifying treatment.

Finally, there is the question of reversed causality. Could the apparent higher incidence of infection in MS be inflated by the presence of prior relapse (suspected or not) which would then promote infection. Furthermore, as mentioned above, patient vigilance is likely increased in MS whether or not DMTs are being administered. Thus, intercurrent infection will be detected more frequently due to heightened awareness. Although the authors do allude to the possibility of selective recall bias it is unclear whether both of these important variables have been taken into account sufficiently in these studies.

Before we undo our recent success in preventing disability due to MS using effective therapies, out of fear of infection, we should look closely at the reasons for infections in this population.

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