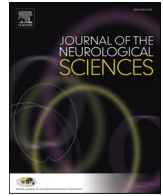




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Letter to the Editor

Reply to: Covid-19: Involvement of the nervous system. Identifying neurological predictors defining the course of the disease


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Dear Editor,

I read with interest the retrospective study by Zifko et al. [5] which provided excellent insight into the neurological predictors of the course of COVID-19 disease. One conclusion of this study was that the identified neurological symptoms of COVID-19 were not predicted by age of the participants. However, the authors did not account for the possibility that this conclusion may have been affected by the sample having not included patients under the age of 40 years.

Participation in this study was possible for patients over 18 years old who had been infected with COVID-19, conditional on their agreement to be interviewed. I am curious whether there may have been an element of non-response bias where older patients over 40 years were more likely to agree to be interviewed due to having experienced a greater severity of COVID-19 disease. The contrary may have been true for younger patients, making them less inclined to share their disease experience with the researchers if they felt COVID-19 had not significantly affected them, which may explain why patients under 40 years old were not recruited. The association of age with increasing severity of COVID-19 disease is supported by a review which links this association with higher levels of pro-inflammatory cytokines and comorbidities in older patients [4]. If non-response bias was present, the patients who were recruited may also have had varying COVID-19 disease symptoms compared to infected patients under 40 years, such as the occurrence of different neurological symptoms.

The discrepancy of neurological symptom occurrence between age groups is supported by studies such as by Lechien et al. [1], who found that older patients with COVID-19 infection were more likely to complain of neurological symptoms such as fatigue, versus younger patients who complained more frequently of symptoms such as anosmia. Unlike Zifko et al. [5], this study's sample included patients under 40 years. Therefore, had the authors included patients under 40 years, there may have been an observed association between age and the occurrence of different neurological symptoms which may have repeated similar evidence from other studies.

Furthermore, the severity of the identified neurological symptoms themselves was not measured by Zifko et al. [5]. This meant it could not have been explored whether age was associated with a greater severity of these symptoms. Meanwhile, other studies have explored the effect of age on COVID-19 neurological symptom severity. Firstly, Lee et al. [2]

found that anosmia was suffered for a greater duration in patients aged 20–39 years old compared to older patients who had been infected with COVID-19. On the other hand, older patients have been found to experience a greater degree of mood disturbance because of neurological disturbances related to COVID-19 compared to younger patients, which was a finding by one cross-sectional survey which found a positive association between standardised depression and anxiety questionnaires and age independent of other COVID-19 symptoms [3]. Therefore, neurological symptom severity may have been an important variable for the authors to address as they appear to vary by patients' age and exploring this may have been relevant for predicting the concerns of future patients with COVID-19 in clinical practice based on their age.

In conclusion, I urge that the authors of the above study, and future authors of studies of the neurological effects of COVID-19 infection, consider the varying disease experiences of adults of all ages. At the time of writing this letter, COVID-19 case numbers are rising across much of Europe, but with a higher prevalence of cases in younger patients compared to previous "waves" in countries such as the United Kingdom. This may reflect vaccination programmes having initially prioritised older patients. Therefore, it would seem imperative for studies to analyse how occurrence and severity of neurological symptoms may differ in younger age groups so that future COVID-19 infections which are likely to disproportionately affect them can be identified early by clinicians, and their main symptomatic concerns at presentation can be addressed.

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