NEUROLOGY AND COVID-19 IN 2020

The effects of the COVID-19 pandemic on people with dementia

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The COVID-19 pandemic has posed unique risks to people with Alzheimer disease and dementia. Research from 2020 has shown that these people have a relatively high risk of contracting severe COVID-19, and are also at risk of neuropsychiatric disturbances as a result of lockdown measures and social isolation.

The COVID-19 pandemic has had a unique impact on people with Alzheimer disease (AD) and other dementias. As research into this impact has accumulated throughout 2020, a clear picture has emerged that this population is particularly susceptible not just to SARS-CoV-2 infection and its effects, but also to the negative effects of the measures taken worldwide to control the spread of the virus.

> people with dementia are more likely to contract COVID-19 than people without dementia

Large-scale clinical data suggest that, even when old age and medical comorbidities such as hypertension and diabetes are taken into account, people with dementia are more likely to contract COVID-19 than people without dementia. Several reasons underlie the increased risk of SARS-CoV-2 infection in people with dementia, which are described in an important overview published in August[1]. First, cognitive impairment and neuropsychiatric symptoms make it challenging for individuals with dementia to understand and comply with safeguarding procedures, such as wearing masks and maintaining appropriate physical distancing[1]. Ignoring or forgetting warnings and an inability to follow self-quarantine measures increase the risk of infection.

In addition, most people who live in institutional settings (nursing or care homes), where rates of infection are disproportionately high worldwide[2], have dementia. Such living arrangements facilitate rapid transmission of the virus as residents and staff congregate and live within close proximity. Physical distancing is not feasible for residents who are dependent on staff to assist with basic activities of daily living (for example, toileting, bathing and eating). Furthermore, dementia-associated neuropsychiatric symptoms, such as agitation, intrusiveness or wandering, can also undermine safety protocols and increase the risk of infection among staff and other residents[1]. Accordingly, nursing and care homes have implemented increasingly severe lockdown measures, which further exacerbate pre-existing neuropsychiatric symptoms among residents with dementia[3].

As well as being at increased risk of contracting COVID-19, older adults with dementia are also more likely to have more severe disease consequences than those without dementia[4–7]. A large community cohort study conducted in the UK has shown that the risk of serious COVID-19 (defined as a requirement for hospitalization) was threefold higher for individuals with a diagnosis of dementia than for those without dementia[4]. The risk factors for dementia — age, obesity, cardiovascular disease, hypertension and diabetes mellitus — are also risk factors for SARS-CoV-2 infection[6] and for severe COVID-19. However, some evidence suggests that more specific mechanistic aspects of dementia and pre-existing brain pathology can increase the risk of neurological complications from COVID-19 (REF.[8]). In particular, a study of the UK Biobank cohort showed that the risk of COVID-19-related hospitalization was more than twofold higher among individuals who were homozygous for *APOE* ε4 than among individuals with the most common *APOE* ε3/ε3 genotype[8].

One possible mechanistic explanation for this association is that increased blood–brain barrier permeability associated with *APOE* ε4 leads to more extensive CNS inflammation in response to SARS-CoV-2 infection — in line with this hypothesis, *APOE* ε4 is known to exacerbate microglia-mediated neuroinflammation and subsequent neurodegeneration[9]. In addition, *APOE* ε4 is associated with increased cytokine production in response to inflammatory stimuli, which could intensify the already aggressive inflammatory response associated with COVID-19, resulting in a so-called cytokine storm[10]. The cytokine storm has been directly associated with lung injury, multi-organ failure and severe COVID-19 outcomes, including death[10].

> longer lockdown periods result in more severe neuropsychiatric symptoms

The restrictions that have been implemented in many countries to control the pandemic have also had important neuropsychiatric consequences for patients with dementia. In the population as a whole, forced social isolation has led to an increase in reported psychiatric symptoms (for example, stress, anxiety and depression) for all individuals; this relationship seems to be moderated by the loneliness associated with prolonged periods of lockdown[1,3,9]. In nursing and care homes, older adults are likely to experience additional distress owing to the absence of relatives who would normally visit them, as well as strict limitations on social activities and interactions with fellow residents. Data collected during the first half of 2020 show that such social isolation during the pandemic is associated with manifestation and/or exacerbation of neuropsychiatric symptoms even in cognitively healthy older adults[1,9].

Several studies — summarized in a review published in October[3] — have shown that, in older adults with dementia, psychiatric symptoms caused by social isolation are linked to more severe neuropsychiatric and behavioural disturbances[3]. Social isolation combined with confusion in care home residents with dementia might result in even greater agitation, boredom and loneliness than in residents without dementia, thereby leading to more severe neuropsychiatric symptoms. These neuropsychiatric symptoms seem to arise directly from social restrictions, as longer lockdown periods result in more severe neuropsychiatric symptoms[3]. Furthermore, some experts have suggested that behavioural complications that result from prolonged periods of lockdown in older adults with dementia could become chronic[3]. Some consequences

Key advances

- People with dementia are at high risk of SARS-CoV-2 infection because cognitive symptoms cause difficulty with following safeguarding procedures and living arrangements in care homes facilitate viral spread[1].
- Once infected, older adults with dementia are more likely to experience severe virus-related outcomes, including death, than are people without dementia[4].
- A homozygous *APOE* ε4 genotype is associated with an increased risk of hospitalization for COVID-19 (REF.[8]), possibly owing to exacerbated inflammation and cytokine production that leads to a cytokine storm.
- Older adults with dementia, especially those in care homes, are at high risk of worsening psychiatric symptoms and severe behavioural disturbances as a result of social isolation during the pandemic[3].

of neuropsychiatric disturbances, such as increased aggression and agitation, can be particularly challenging for carers and care home staff to manage.

In summary, the evidence to date indicates that older adults with dementia have a high risk of contracting COVID-19 and, once infected, have a high risk of disease-related morbidity and mortality. This population is often the first to go into, and the last to come out of, strict and prolonged periods of isolation to prevent SARS-CoV-2 infection, yet is at extremely high risk of worsening neuropsychiatric symptoms and severe behavioural disturbance as a direct result. Therefore, during and after the pandemic, implementation of caregiver support and the presence of skilled nursing home staff are essential to maintain social interaction and to provide extra support to older adults with dementia.

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https://doi.org/10.1038/s41582-020-00450-z

1. Mok, V. C. et al. Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future. *Alzheimers Dement.* **16**, 1571–1581 (2020).
2. Comas-Herrera, A. et al. Mortality associated with COVID-19 outbreaks in care homes: early international evidence. *LTCCOVID* https://ltccovid.org/2020/04/12/mortality-associated-with-covid-19-outbreaks-in-care-homes-early-international-evidence/ (2020).
3. Manca, R., De Marco, M. & Venneri, A. The impact of COVID-19 infection and enforced prolonged social isolation on neuropsychiatric symptoms in older adults with and without dementia: a review. *Front. Psychiatry* **11**, 1086 (2020).
4. Atkins, J. L. et al. Preexisting comorbidities predicting severe COVID-19 in older adults in the UK Biobank community cohort. *J. Gerontol. A Biol. Sci. Med. Sci.* **75**, 2224–2230 (2020).
5. Onder, G., Rezza, G. & Brusaferro, S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* **323**, 1775–1776 (2020).
6. Williamson, E. J. et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* **584**, 430–436 (2020).
7. Zhou, F. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **395**, 1054–1062 (2020).
8. Kuo, C.-L. et al. APOE e4 genotype predicts severe COVID-19 in the UK Biobank community cohort. *J. Gerontol. A Biol. Sci. Med. Sci.* **75**, 2231–2232 (2020).
9. Brown, E. E., Kumar, S., Rajji, T. K., Pollock, B. G. & Mulsant, B. H. Anticipating and Mitigating the Impact of COVID-19 Pandemic on Alzheimer's Disease and Related Dementias. *Am. J. Geriatr. Psychiatry* **28**, 712–721 (2020).
10. Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R. & Salem, R. The COVID-19 cytokine storm; what we know so far. *Front. Immunol.* **11**, 1446 (2020).

Competing interests

The authors declare no competing interests.