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.

COVID-19 and selective vulnerability to Parkinson's disease

The current COVID-19 pandemic provides a unique opportunity to investigate the hypothesis that viral infections can precipitate neurodegeneration. Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), a pathogenic homolog of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), invades the brain through ACE2,[1] and SARS-CoV-2 might be neurotropic too. SARS-CoV-2 also enters cells via the ACE2 receptor,[1] which is widely expressed in the CNS, including in the striatum,[2] where the virus might precipitate or accelerate neurodegeneration.[3,4] SARS-CoV-2 might infiltrate the CNS directly through the olfactory or vagus nerves, or haematogenously. This infection could, in turn, prompt cytotoxic aggregation of proteins, including α-synuclein. This hypothesis is supported by evidence in animal models that viral infections can trigger α-synucleinopathies in the CNS.[5]

We suspect that neuronal populations are not equally susceptible to degeneration, and that dopaminergic neurons are selectively vulnerable because of their intrinsic properties. For instance, high bioenergetic demands from highly arborised axons, and impaired proteostasis resulting from large axon size, can promote α-synuclein aggregation and result in selective vulnerability to non-cell autonomous factors that promote α-synuclein seeding, such as neuroinflammation and environmental neurotoxins.

α-Synuclein could function as a native antiviral factor within neurons, as shown by an increased neuronal expression of α-synuclein following acute West Nile virus infection.[6] West Nile virus and SARS-CoV-1 are both enveloped, single-stranded, positive sense RNA viruses with analogous viral entry and replication mechanisms.[1,6] Therefore, similar α-synuclein upregulation might occur with SARS-CoV-2 infection. The consequences of this pathological process could be further exacerbated by a peripheral inflammatory response, as occurs in COVID-19. A rodent model of peripheral H5N1 influenza infection showed persistent CNS microglial activation and abnormal α-synuclein phosphorylation, associated with a loss of dopaminergic neurons in the substantia nigra pars compacta.[7] We postulate that antiviral α-synuclein accumulation following SARS-CoV-2 infection might compound pre-existing cell-autonomous vulnerability and lead to α-synuclein propagation and widespread neurodegeneration. Prospective longitudinal studies in survivors of COVID-19 can help to support this hypothesis.

SARS-CoV-2 infection might also interfere with α-synuclein clearance. Other neurotropic viruses, such as H1N1 influenza, can obstruct protein clearance to maintain optimal viral protein levels, rendering infected host cells unable to counterbalance α-synuclein accumulation.[8] SARS-CoV-2 proteins are capable of binding human protein trafficking molecules.[9] One such protein in particular, ORF8, is specifically involved in endoplasmic reticulum regulation.[9] If SARS-CoV-2 can impair proteostasis through ORF8 binding and cause dysregulated endoplasmic reticulum protein trafficking, then α-synuclein could aggregate uncontrollably.

Finally, the bioenergetic stress of SARS-CoV-2 neuroinvasion might be insurmountable for certain neuronal populations. Nigrostriatal dopaminergic neurons display high cellular energy requirements to fuel elevated basal oxidative phosphorylation in the mitochondria, high axon terminal density, and extensive axonal arborisation. Considering this large metabolic energy use, if additional cellular energy reserves are unavailable, the cellular stress of COVID-19 infection might drive these vulnerable neurons over the threshold of neurodegeneration.

AJS reports personal fees from AbbVie, Voyager, and Neurocrine Biosciences, outside of the submitted work. He is paid a stipend as Editor-in-Chief of the journal *Movement Disorders*. All other authors declare no competing interests.

*Alexandra Pavel, Danielle K Murray, *A Jon Stoessl*
jstoessl@mail.ubc.ca

Division of Neurology, Pacific Parkinson's Research Centre, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC V6T2B5, Canada

1 Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 2008; **82:** 7264–75.
2 Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol* 2007; **292**: R373–81.
3 Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A. SARS-CoV-2: at the crossroad between aging and neurodegeneration. *Mov Disord* 2020; **35:** 716–20.
4 Victorino DB, Guimaraes-Marques M, Nejm M, Scorza FA, Scorza CA. COVID-19 and Parkinson's disease: are we dealing with short-term impacts or something worse? *J Parkinsons Dis* 2020; published online May 7. https://doi.org/10.3233/JPD-202073.
5 Tulisiak CT, Mercado G, Peelaerts W, Brundin L, Brundin P. Can infections trigger alpha-synucleinopathies? *Prog Mol Biol Transl Sci* 2019; **168:** 299–322.
6 Beatman EL, Massey A, Shives KD, et al. Alpha-synuclein expression restricts RNA viral infections in the brain. *J Virol* 2015; **90:** 2767–82.
7 Jang H, Boltz D, Sturm-Ramirez K, et al. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. *Proc Natl Acad Sci USA* 2009; **106:** 14063–68.
8 Marreiros R, Müller-Schiffmann A, Trossbach SV, et al. Disruption of cellular proteostasis by H1N1 influenza A virus causes α-synuclein aggregation. *Proc Natl Acad Sci USA* 2020; **117:** 6741–51.
9 Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583:** 459–68.

COVID-19 in older people with cognitive impairment in Latin America

The COVID-19 pandemic in Latin America and Caribbean countries (LACs) has failed to capture the attention

Figure: **An elderly man walks through a district in Lima, Peru, that is heavily infected with COVID-19**
Alejandro, who is 83 years old and has arthrosis, using his walker through a crowded market in San Juan de Lurigancho, a heavily COVID-19-infected district in Lima, Peru. Alejandro lives alone and goes out to get food and medicines. He has symptoms associated with depression and cognitive decline but has no access to neurological care. Photo and testimony courtesy of Alexander Kornhuber and Maritza Pintado Caipa.

and attract the resources necessary to control it. The wrenching choice between public health and economic welfare that has polarised political debate in the USA and Europe is starker in LACs, where older people and people with dementia are especially susceptible. We want to raise awareness about this grave situation.

The population in LACs tripled between 1950 and 2000. Although LAC populations are still young compared with the USA and western Europe, the rate of ageing is among the highest in the world.[1] This pattern of ageing is seen in nearly every country in the region,[2] with a shift in dependant populations from young children to older relatives.[2] Conditions such as obesity, hypertension, diabetes, and elevated cholesterol, which increase the risk of mortality from COVID-19, have become more prevalent.

For more on the **LAC-CD** see http://lac-cd.org/en/home/

See **Online** for appendix

The first patient with confirmed COVID-19 was diagnosed in February, 2020 (a 61-year-old man in São Paulo, Brazil). In a few weeks, Brazil surged into the top ranks of the most affected countries. Peru quickly closed its borders in March, 2020, and imposed rigorous quarantine measures. However, 4 months later, Peru now has the second highest number of confirmed cases in LACs. Chile, which also implemented control measures, is third highest among LACs. The public health conditions in these countries are complex and pose unique challenges; one underlying explanation for the surge in cases might be a large informal economy, in which workers need to leave their house every day to clean other households or to stand, for instance, at crowded traffic corners to sell their goods or shine shoes. According to the World Economic Forum, about 55% of all workers in LACs toil in the informal economy,[3] which amounts to nearly 140 million people. Physical distancing in the informal economy can be tantamount to starvation.

Other explanations point to economic inequality and inadequate public health systems[4] but fail to mention the near absence of long-term care facilities and programmes for the cognitively impaired. Dementia care differs from standard medical care in that caring for dementia must involve support for daily activities. Few long-term care centres exist in LACs. Millions populate densely packed favelas or barrios, in which large families often share a single room, and many find moving a grandparent to a nursing home inconceivable. However, older people cannot be quarantined within crowded living quarters, where they can be exposed to young asymptomatic carriers, and older people who live alone struggle to access care without risking contact with infected individuals (figure). Extended families that ordinarily create a protective environment and provide informal care[5] can engender environments that increase mental health problems and domestic abuse.[6]

The situation with professional health workers provides little solace. Weak health-care systems have contributed to the already enormous toll in mortality in health-care workers. For instance, with 20% of over 11 000 health workers in Mexico ill with COVID-19—one of the highest rates in the world—hospital staffing is exiguous.[7] Many hospitals in LACs have inadequate protective equipment and there is scarce support for health-care workers who become sick.[8]

Barriers to telemedicine, such as restricted internet access, cause additional complications,[4] with around 40% of hospitals not providing remote consultations.[8] Certainly, LACs are far from uniform, and some cities with stronger health systems and resources might be able to meet the needs of people with dementia better than others. Here, we put forth an urgent plea for an international coalition to address issues related to dementia care in LACs. Regional cooperation and shared experience cannot be ignored in these difficult times. Brain health diplomacy, potentially led by multiregional non-governmental organisations devoted to dementia, in partnership with local institutions should coordinate an action plan.

We thank Alzheimer's Association, the Global Brain Health Institute, the Tau Consortium, the National Institutes of Health and National Institute on Aging, Inter-American Development Bank, and the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat). We also thank Margherita Melloni for her insightful revision of an early version of this manuscript. The contents of this publication are solely the responsibility of the authors and do not represent the official views of these institutions. AI is partly supported by grants from CONICET, CONICYT and FONDECYT Regular (1170010 and 1171200), FONCYT-PICT (2017-1818 and 2017-1820), ANID and FONDAP (15150012), the INECO Foundation, the Inter-American Development Bank, the Global Brain Health Institute (ALZ UK-20-639295), National Institutes of Health and National Institute on Aging (R01 AG057234), and the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat). KSK declares no competing interests. This Comment was written on behalf of the Latin America and the Caribbean Consortium on Dementia (LAC-CD); see the appendix (pp 1–2) for the full Consortium author list.

**Agustin Ibanez, Kenneth S Kosik, for the Latin America and the Caribbean Consortium on Dementia (LAC-CD)*
agustin.ibanez@gbhi.org

Global Brain Health Institute (GBHI), University of California San Francisco, San Francisco, CA, USA (AI); and Neuroscience Research Institute and Department of Molecular, Cellular, and Developmental Biology, University of California Santa Barbara, Santa Barbara, CA, USA (KSK)

1 Caruso Bloeck M, Galiani S, Ibarrarán P. Long-term care in Latin America and the Caribbean? Theory and policy considerations. August, 2017. Washington DC: Inter-American Development Bank, Social Protection and Health Division. https://publications.iadb.org/publications/english/document/Long-Term-Care-in-Latin-America-and-the-Caribbean-Theory-and-Policy-Considerations.pdf (accessed June 1, 2020).

2 Ritchie H, Roser M. Age Structure. September, 2019. https://ourworldindata.org/age-structure (accessed June 1, 2020).

3 Kraemer-Mbula E, Wunsch-Vincent S (eds). The informal economy in developing nations. Cambridge, UK: Cambridge University Press, 2016.

4 Burki T. COVID-19 in Latin America. *Lancet Infect Dis* 2020; **20:** 547–48.

5 Parra MA, Baez S, Allegri R, et al. Dementia in Latin America: assessing the present and envisioning the future. *Neurology* 2018; **90:** 222–31.

6 Llibre-Guerra JJ, Jiménez-Velázquez IZ, Llibre-Rodriguez JJ, Acosta D. The impact of COVID-19 on mental health in the Hispanic Caribbean region. *Int Psychogeriatr* 2020; published online May 8. https://doi.org/10.1017/S1041610220000848.

7 Kitroeff N, Villegas P. 'It's not the virus': Mexico's broken hospitals become killers, too. May 28, 2020. https://www.nytimes.com/2020/05/28/world/americas/virus-mexico-doctors.html (accessed June 1, 2020).

8 Delgado D, Wyss Quintana F, Perez G, et al. Personal safety during the COVID-19 pandemic: realities and perspectives of healthcare workers in Latin America. *Int J Environ Res Public Health* 2020; **17:** 2798.