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.

courses and educational activities on movement disorders sponsored by the Academy for Healthcare Learning, PeerView, Prime, QuantiaMD, WebMD–Medscape, Medicus, MedNet, Einstein, MedNet, Henry Stewart, American Academy of Neurology, Movement Disorders Society, and Vanderbilt University. The University of Florida and not MSO receives grants from Medtronic, AbbVie, Abbott, and Allergan. MSO has participated as a site principal investigator or co-investigator for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria. Research projects at MSO's institution, the University of Florida, receive device and drug donations from Medtronic, Abbott, Boston Scientific, and Neuropace. ERD is a medical adviser to and holds stock options in Grand Rounds, which provide a second opinion on the diagnosis and management of health-care conditions of employees generally of large corporations. ERD has also received honoraria for speaking at American Academy of Neurology courses; received compensation for consulting activities from 23andMe, Clintrex, GlaxoSmithKline, Lundbeck, MC10, MedAvante, Medico Legal services, US National Institute of Neurological Disorders and Stroke, Shire, Teva, and UCB; and research support from AMC Health, Burroughs Wellcome Fund, Davis Phinney Foundation, Duke University, GlaxoSmithKline, Great Lakes Neurotechnologies, Greater Rochester Health Foundation, Huntington Study Group, Michael J Fox Foundation, National Science Foundation, Patient-Centered Outcomes Research Institute, Prana Biotechnology, Raptor Pharmaceuticals, Roche, Saffra Foundation, and University of California Irvine. PC has received honoraria from serving on the scientific advisory board for Lundbeck, Teva, and Green Valley. PC has also received speaker fees from Roche, Lundbeck, Sanofi, Eisai, Green Valley, Luye, GlaxoSmithKline, Medtronic, and Boehringer-Ingelheim; and has received research support from Chinese Organisations for Scientific Research, and Michael J Fox Foundation. SKLD has received a research grant from the Parkinson Foundation. MSO, JA, and MM declare no competing interests.

*Bastiaan R Bloem, Emily J Henderson, E Ray Dorsey, Michael S Okun, Njideka Okubadejo, Piu Chan, John Andrejack, Sirwan K L Darweesh, Marten Munneke

bas.bloem@radboudumc.nl

Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Centre of Expertise for Parkinson and Movement Disorders, Radboud University Medical Centre, Nijmegen, Netherlands (BRB, SKLD, MM); Older People's Unit, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK (EJH); Department of Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK (EJH); Centre for Health and Technology, Department of Neurology, University of Rochester Medical Centre, Rochester, NY, USA (ERD); Norman Fixel Institute for Neurological Diseases, Department of Neurology, University of Florida, Gainesville, FL, USA (MSO); Neurology Unit, Department of Medicine, College of Medicine, University of Lagos, Lagos, Nigeria (NO); Department of Neurobiology, Neurology and Geriatrics, National Clinical Research Centre for Geriatric Disorders, Xuanwu Hospital of Capital Medical University, Beijing, China (PC); and Queens College, City University of New York, NY, USA (JA)

1 Bloem BR, Henderson EJ, Dorsey ER, et al. Integrated and patient-centred management of Parkinson's disease: a network model for reshaping chronic neurological care. *Lancet Neurol* 2020; **19:** 623–34.

2 Rompen L, de Vries NM, Munneke M, et al. Introduction of network-based healthcare at Kaiser Permanente. *J Parkinsons Dis* 2019; **10:** 207–12.

3 Eggers C, Dano R, Schill J, Fink GR, Hellmich M, Timmermann L. Patient-centered integrated healthcare improves quality of life in Parkinson's disease patients: a randomised controlled trial. *J Neurol* 2018; **265:** 764–73.

4 van Halteren AD, Munneke M, Smit E, Thomas S, Bloem BR, Darweesh SKL. Personalised care management for persons with Parkinson's disease. *J Parkinsons Dis* 2020; **10:** S11–20.

5 Bloem BR, Dorsey ER, Okun MS. The coronavirus disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. *JAMA Neurol* 2020; **77:** 927–28.

Provisional case definitions for COVID-19-associated neurological disease

In *The Lancet Neurology*, Mark Ellul and colleagues[1] propose case definitions for the association of COVID-19 with neurological diseases. We would like to discuss the practicality of their definitions and the potential causality behind the associations, through the example of Guillain-Barré syndrome. Guillain-Barré syndrome can be easily differentiated from neurovirulent neuropathies, such as West Nile virus-associated neuropathy, and there is surveillance on its incidence in several countries, which renders Guillain-Barré syndrome a good candidate for assessing the association between infection and neurological disease.

Neurological disease occurring in the 6-week interval after acute infection is considered evidence for autoimmune association. However, typical acute respiratory symptoms are not always indicators of acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; atypical presymptomatic or asymptomatic presentations of SARS-CoV-2 infection can occur before the onset of Guillain-Barré syndrome. Should we adopt the WHO-confirmed COVID-19 case definition[1] as the definition of SARS-CoV-2 infection? Moreover, should we use the screening date of a positive SARS-CoV-2 result as the onset of acute SARS-CoV-2 infection in all patients with Guillain-Barré syndrome without typical COVID-19 symptoms?

A possible association differs from a probable association in the evidence of other commonly associated causes. Although Ellul and colleagues[1] discuss evidence from other viruses as the cause of Guillain-Barré syndrome, influenza was not listed in their proposed case definitions for COVID-19-associated neurological disease. There is robust evidence on influenza-like illnesses as triggers for Guillain-Barré syndrome, and vaccination against influenza might reduce the risk of influenza-associated Guillain-Barré syndrome.[2] Early data showed a co-infection with influenza virus in about 50% of hospitalised patients with COVID-19.[3] Co-infection of SARS-CoV-2 also exists in influenza-like illness.[4] Therefore, influenza should be included among the possible causes of Guillain-Barré syndrome. Moreover, evaluation of the safety of a SARS-CoV-2 vaccine will face the same questions on whether Guillain-Barré syndrome is related to the infection itself or to the vaccine. Thus, information on the exact infectious agent is crucial for defining the adverse events of SARS-CoV-2 vaccines.

A pathogenic mechanism to link COVID-19 and Guillain-Barré syndrome has not yet been described. However, a molecular mimicry mechanism, autoimmune response against aberrant modification of nervous tissue by infection, and para-infectious immune dysfunction are common explanations for their potential association. We suggest that all these mechanisms should be investigated in COVID-19-related Guillain-Barré

syndrome. For example, molecular mimicry with heat shock proteins (HSPs) was reported as a potential pathogenic mechanism of Guillain-Barré syndrome after SARS-CoV-2 infection.[5] HSPs might also promote a superantigen response, which contributes to the para-infectious response.

To establish association and potential causality, researchers should endeavor to collect data from as many cases with COVID-19 as possible from whom SARS-CoV-2 is presumed as the single or joint cause, on the basis of accurate and timely diagnosis of SARS-CoV-2 infection.

We declare no competing interests.

*Hai-Feng Li, Hong-Jun Hao, Xiang-Jun Chen
drlhf@163.com

Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China (H-FL); Department of Neurology, Peking University, First Hospital, Beijing, China (H-JH); and Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China (X-JC)

1 Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020; **19:** 767–83.
2 Petráš M, Lesná IK, Dáňová J, Čelko AM. Is an increased risk of developing Guillain-Barré syndrome associated with seasonal influenza vaccination? A systematic review and meta-analysis. *Vaccines* (Basel) 2020; **8:** 150.
3 Yue H, Zhang M, Xing L, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. *J Med Virol* 2020; published online Jun 12. https://doi.org/10.1002/jmv.26163.
4 Kong WH, Li Y, Peng MW, et al. SARS-CoV-2 detection in patients with influenza-like illness. *Nat Microbiol* 2020; **5:** 675–78.
5 Lucchese G, Flöel A. SARS-CoV-2 and Guillain-Barré syndrome: molecular mimicry with human heat shock proteins as potential pathogenic mechanism. *Cell Stress Chaperones* 2020; **25:** 731–35.

Authors' reply

We read with interest the Correspondence by Hai-Feng Li and colleagues on our proposed definitions for COVID-19-associated neurological disease.[1] We thank the authors for recognising the importance of collecting cases together with accurate diagnostic evidence to elucidate disease mechanisms.

Any case criterion for a neurological syndrome associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection must incorporate a definition of acute SARS-CoV-2 infection, criteria for the diagnosis of the neurological syndrome itself, and an attempt to link the two in a temporal relationship, excluding other potential causes. The definition of acute SARS-CoV-2 infection must also reflect rapidly evolving diagnostic approaches.

In our proposed definition for SARS-CoV-2-associated Guillain-Barré syndrome, we selected a pragmatic definition of acute COVID-19 infection, reflecting the WHO definition of confirmed infection.[2] However, we accept that the timing of the infection onset is a challenge. A 6-week interval between viral symptoms onset and neurological disease is somewhat arbitrary, but from our knowledge of other infections triggering Guillain-Barré syndrome, a longer delay than this would cast the association into doubt. In patients without symptoms of SARS-CoV-2 infection but with positive RT-PCR or antibody testing, the true date of infection is even more difficult to elucidate.

We agree that it is important to exclude influenza as a potential trigger of Guillain-Barré syndrome, and viral symptoms might be difficult to distinguish. Epidemiological data can be informative, especially as the incidence of respiratory pathogens changes with the seasons around the world. RT-PCR testing for influenza and other respiratory viruses could be done alongside SARS-CoV-2 testing when possible. We advise caution in interpreting the results of studies using positive serum antibody testing for the diagnosis of influenza, which can be vulnerable to cross-reactivity and poor inherent test accuracy. Additionally, the study by Kong and colleagues[3] cited by Li and colleagues' Correspondence did not report co-infection, but rather early cases of COVID-19 in Wuhan, China, that were detected through the national influenza surveillance programme; existing influenza surveillance networks have been used for sentinel testing and to look for potential signs of community transmission worldwide, as supported by the WHO Global Influenza Surveillance and Response System. Furthermore, influenza-like illness is a syndromic definition and does not imply influenza to be the causative illness; its description aligns closely with the "acute respiratory infection" definition used to prompt testing for COVID-19 in earlier WHO and national guidelines.[4]

Our group has shown previously that, in patients with new neurological disease and evidence of more than one infection, there are additional challenges in thinking about causality, particularly when the results are from specimens collected outside the CNS.[5,6]

For the **WHO Global Influenza Surveillance and Response System** see https://www.who.int/influenza/gisrs_laboratory/en/

TS was an advisor for the GlaxoSmithKline ebola vaccine programme, chaired the Siemens diagnostics clinical advisory board and healthineers clinical advisory board, and also has a pending patent test for bacterial meningitis based on a blood test (GB 1606537.7; April 14, 2016). BS reports non-financial support from UK National Institute for Health Research through its Global Health Research Group on Brain Infections, outside the submitted work. All other authors declare no competing interests.

*Tom Solomon, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Mark A Ellul
tsolomon@liverpool.ac.uk

National Institute for Health Research Health Protection Research Unit in Emerging and Zoonotic Infections, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool L69 7BE, UK (TS, BS, SL, MAE); The Walton Centre National Health Service Foundation Trust, Liverpool, UK (TS, MAE); Queen Square Institute of Neurology, University College London, London, UK (LB); and Christian Medical College, Vellore, India (BS)

1 Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020; **19:** 767–83.
2 WHO. Surveillance case definitions for human infection with novel coronavirus (nCoV): interim guidance v1, January 2020. 2020. https://apps.who.int/iris/handle/10665/330376 (accessed Sept 17, 2020).
3 Kong WH, Li Y, Peng MW, et al. SARS-CoV-2 detection in patients with influenza-like illness. *Nat Microbiol* 2020; **5:** 675–78.
4 Fitzner J, Qasmieh S, Mounts AW, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. *Bull World Health Organ* 2018; **96:** 122–28.