Acute and late neurological complications of COVID19:

The quest for evidence

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Sir,

There is inevitable uncertainty when a new disease strikes and understanding the full spectrum of COVID-19 neurological complications is no exception. Neurologists in endemic areas are diligently working to understand the impact of COVID-19 on the nervous system. To date, more than 100 articles have been published on the neurological aspects of COVID-19 but there are insufficient high-quality cohort studies or case series to elucidate the full picture. We, therefore, read with interest, in this Journal, the case-series of potential acute neurological complications of COVID-19 in individuals seen at a tertiary neurological referral centre in the UK during the peak of the recent outbreak (Paterson *et al.*, 2020). Forty-three clinical cases were described in detail including history, examination and extensive investigations. The authors are to be commended for their care and diligence. This case-series adds to our knowledge about the potential spectrum of neurological features but, as noted by the authors, leaves many questions unanswered. Table 1 lists selected reports of neurological interest and complications.

First, there is uncertainty about the actual incidence, prevalence and scale of neurological complications as the denominator is not known at this stage (Herman et al., 2020). Of note, proportionally more cases of neurological complications of SARS-CoV-2 have been reported, than with two other coronaviruses, SARS-CoV and MERS-CoV, at similar stages of the disease trajectory. This may be due to the scale of COVID-19, compared to the numbers of SARS and MERS cases. One multicentre Chinese study suggested that the incidence of COVID-19 neurological complications could be less than 5% (Xiong et al., 2020). A national reporting database from the UK described 114

cases with confirmed neurological or neuropsychiatric complications (Varatharaj et al., 2020). With nearly 300,000 cases of COVID-19 in the UK this is likely to be a significant underestimate, because of reporting bias. Realistic epidemiological estimation will only be possible with well-designed national or international studies that take into account difference across populations and healthcare settings. This is challenging given there are confounders such as genetic predisposition, viral evolution and local preventative measures.

Secondly, the causality of neurological impairments needs to be carefully evaluated (Ellul *et al.,* 2020). Evidence of a direct viral insult to the CNS is lacking. Most CSF examinations failed to detect the virus (Destras *et al.,* 2020; Moriguchi *et al.*, 2020). No post-mortem examination to date has found direct evidence of the virus in the brain (Bian and the Covid-Pathology Team, 2020; Solomon *et al.,* 2020), concurring with the findings in the recent case-series in this Journal (Paterson *et al.*, 2020). A much higher incidence of ischemic strokes was, however, noted among people with COVID-19 compared to those with influenza (Merkler *et al.,* 2020). Studies are needed to ascertain if there are unique COVID-19 related factors that increase stroke risk compared to other viral infections. In the longer term, it is not certain whether there will be an increase of immune-mediated neurological diseases such as acute demyelinating encephalomyelitis (ADEM)-like and Guillain-Barre Syndrome (Toscano *et al.,* 2020), consequent to COVID-19, akin to the increased incidence of narcolepsy seen after the H1N1-pandemic (Partinen *et al.*, 2014). Close long-term follow-up of well-defined cohorts of people who recovered from COVID-19 are required to clarify this.

Thirdly, the clinical spectrum in this case-series, is in accord with reports from China, Spain and the UK (Mao *et al.*, 2020; Romero-Sanchez *et al.*, 2020; Varatharaj *et al.*, 2020; Xiong *et al.*, 2020). Impairment of consciousness and stroke were the most common features in all series but ADEM-like illness was not previously reported, which may reflect a local ascertainment bias. It is not possible to compare rates of peripheral neurological disorders between the different reports due to differences in the definitions used. The current case-series suggests that seizures were rare, with or without a prior history of epilepsy (Lu *et al.*, 2020).

The full spectrum of neurological complications is worthy of further investigation, by larger well-designed studies. There are also likely differences in the clinical spectrum of neurological impairments according to age, such as a predominance of cerebrovascular complications in older people (Varatharaj et al., 2020; Xiong et al., 2020).

Neurological complications of children with COVID-19 are less well established. Early reports suggested children were spared from COVID-19 and, if infected, developed less severe illness, but increasing numbers of paediatric cases developing severe systemic inflammatory response requiring hospitalization are being reported. A recent report described four children presenting with a distinct neurological syndrome associated with lesions in the splenium of the corpus callosum evident on neuroimaging (Abdel-Mannan et al., 2020). Further work is needed to determine whether a unique or more prominent pattern of neurological complications exists in different age groups.

Fourthly, the knowledge of COVID-19 related sequelae will contribute to the

design of appropriate rehabilitation pathways. The need for pulmonary rehabilitation is well established (Liu *et al.*, 2020) while the physical consequences of COVID-19 are less well described. Admission to intensive care unit with prolonged immobilization, pronation cycles and mechanical ventilation with curarization, may trigger neurological complications. Prolonged physical inactivity due to admission to less intensive wards or home confinement may play a role on cognitive and motor dysfunction, especially in the elderly (Carda *et al.*, 2020). At present, there are around 90 registered ongoing studies (https://clinicalstudies.info.nih.gov; https://clinicaltrials.gov; https://www.clinicaltrialsregister.eu) on rehabilitation in COVID-19, with tentative protocols based on the partial knowledge of medium and long term sequelae.

Future studies need to have an adequate sample size, be prospective, have an estimate of the denominator, and use consistent terms and definitions, include detailed history, including existing comorbidities, and have standardised examinations and investigations.

To date, there are no reports of specific subacute or chronic complications post-COVID-19 infection but some are predictable such as cognitive impairment in survivors of mechanical ventilation or encephalopathy. We need to remain vigilant to post-COVID-19 neurological symptoms, with well-designed follow-up studies and surveillance which may be achieved by linkage to national health databases.

To accelerate knowledge building on COVID-19, we call for an international, collaborative, and open-access registry to follow prospectively large numbers of individuals who recover from COVID-19. Most COVID-19 reports are from China,

Europe and the US and little is known in terms of neurological complications in other regions where the pandemic is now raging such as Africa, India and Latin America. Data sharing and international collaboration are particularly important and beneficial, when considering the gaps in research capabilities in countries with limited resources.

There is strength in numbers and sustained effort is needed to understand and optimize treatment of the neurological sequelae of this disease that has changed the world since its denouement in December 2019.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests in relation to this commentary.

Reference

Abdel-Mannan O, Eyre M, Lobel U, Bamford A, Eltze C, Hameed B, *et al.* Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA neurology 2020.

Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, *et al.* Characteristics of ischaemic stroke associated with COVID-19. Journal of neurology, neurosurgery, and psychiatry 2020.

Bian X-W, the Covid-Pathology Team. Autopsy of COVID-19 victims in China. National Science Review 2020.

Carda S, Invernizzi M, Bavikatte G, Bensmail D, Bianchi F, Deltombe T, *et al.* COVID-19 pandemic. What should PRM specialists do? A clinician's perspective. Eur J Phys Rehabil Med 2020.

Coolen T, Lolli V, Sadeghi N, Rovai A, Trotta N, Taccone FS, *et al.* Early postmortem brain MRI findings in COVID-19 non-survivors. Neurology 2020.

Destras G, Bal A, Escuret V, Morfin F, Lina B, Josset L, *et al.* Systematic SARS-CoV-

2 screening in cerebrospinal fluid during the COVID-19 pandemic. The Lancet Microbe 2020.

Ellul M, Varatharaj A, Nicholson TR, Pollak TA, Thomas N, Easton A, *et al.* Defining causality in COVID-19 and neurological disorders. Journal of Neurology, Neurosurgery & Psychiatry 2020: jnnp-2020-323667.

Galanopoulou AS, Ferastraoaru V, Correa DJ, Cherian K, Duberstein S, Gursky J, *et al.* EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: A small case series preliminary report. Epilepsia Open 2020; 5(2): 314-24.

Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, *et al.* Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020.

Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, *et al.* Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection. Radiology 2020: 201697.

Kremer S, Lersy F, de Seze J, Ferre JC, Maamar A, Carsin-Nicol B, *et al.* Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology 2020: 202222.

Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Clin Pract 2020; 39: 101166.

Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, *et al.* New-onset acute symptomatic seizure and risk factors in Corona Virus Disease 2019: A Retrospective Multicenter Study. Epilepsia 2020.

Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al.* Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA neurology 2020.

Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, *et al.* Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza. JAMA neurology 2020.

Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, *et al.* A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2020; 94: 55-8.

Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, *et al.* Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 2020; 382(20): e60.

Partinen M, Kornum BR, Plazzi G, Jennum P, Julkunen I, Vaarala O. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. The Lancet Neurology 2014; 13(6): 600-13.

Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, *et al.* The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain : a journal of neurology 2020.

Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, Sanchez-Larsen A, Layos-Romero A, Garcia-Garcia J, *et al.* Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology 2020.

Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, *et al.* Neuropathological Features of Covid-19. The New England journal of medicine 2020: NEJMc2019373.

Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, *et al.* Guillain-Barre Syndrome Associated with SARS-CoV-2. N Engl J Med 2020; 382(26): 2574-6.

Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, *et al.* Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 2020.

Xiong W, Mu J, Guo J, Lu L, Liu D, Luo J, *et al.* New onset neurologic events in people with COVID-19 infection in three regions in China. Neurology 2020.