Approaches to Understanding COVID-19 and its Neurological Associations

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There is an accumulating volume of research into neurological manifestations of coronavirus disease 2019 (COVID-19). However, inconsistent study designs, inadequate controls, poorly validated tests, and differing settings, interventions, and cultural norms weaken study quality and comparability, hence the understanding of the spectrum, burden, and pathophysiology of these complications. Therefore, a global COVID-19 Neuro Research Coalition, together with the World Health Organization, has reviewed reports of COVID-19 neurological complications and harmonized clinical measures for future research. This will facilitate well-designed studies using precise, consistent case definitions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and neurological complications, with standardized forms for pooled data analyses that nonspecialists can use, including those in low-income settings.

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to represent a serious global threat. After an apparent reduction in confirmed cases in several countries into the fall of 2020, likely owing to the introduction of control measures, numbers increased again sharply from the end of 2020 into early 2021, with 112,209,815 confirmed cases and 2,490,776 deaths as of February 25, 2021 (https://covid19.who.int/).

Neurological manifestations have been shown to be an important component of the disease spectrum during both the acute and post-acute phases of infection, but the prevalence of neurological symptoms, signs, or diseases varies significantly across studies with original data[1–3] and reviews.[4–9] This variability has been attributed to the purported mechanisms of action of SARS-CoV-2. There have been few reports of direct viral invasion of the central nervous system, as determined by virus detection in the cerebrospinal fluid, and the disease mechanisms for a wide range of other manifestations, including immune-mediated coagulopathy, endotheliopathy, vasculopathy, or vasculitis, are yet to be understood fully.[10–13]

However, variability in these published data might also reflect differences in the study populations, such as the methods of case ascertainment and definitions used, and in the use of inappropriate methods to infer causality.

In this Neurology Grand Rounds, we provide a critical appraisal of the association between SARS-CoV-2 and neurological symptoms, signs, or diseases, with the following aims: (1) to address the limitations of the current research data on the coronavirus disease 2019 (COVID-19) pandemic, with a focus on neurological manifestations from a methodological perspective; (2) to review the variable circumstances for data

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collection in different countries and socio-economic situations; and (3) to propose a globally coordinated approach for creating effective collaborations between researchers. This is required for future international investigations, in order to maximize added value and have the greatest impact on patient care and outcomes. Reviewing the range of potential neurological associations of SARS-CoV-2 or of their suggested clinical management is beyond the scope of this article and is covered well elsewhere.[3–9]

Neurological Manifestations: a Heterogeneous Picture

The diverse clinical manifestations of the COVID-19 outbreak led the medical community and societies at large to react differently in introducing preventative, diagnostic, and therapeutic measures. Although there have been many reports of neurological associations with SARS-CoV-2, there has not been much consistency in approach.[4] In many cases, these associated neurological manifestations have not been presented in the context of: (1) the origins of the investigated individuals and cohorts; (2) the limited subspecialty of clinicians reporting cases; (3) the variability of infection control measures within specific geographic areas; (4) the use of diagnostic tests with suboptimal sensitivity and specificity; (5) demographic, cultural, ethnic, health, and nutritional differences of the populations studied[14]; and (6) the lack of adequate control groups within the study design.[4,15,16] In addition, differing access to care owing to diverse health and social systems limits the inferences that can be made from study results, particularly between regions and countries and across specialties. All these limitations have negative effects on the generalizability of most published reports and, ultimately, on our knowledge of the spectrum of COVID-19 neurological complications, in addition to their pathophysiology and associated short- and long-term sequelae at a population level, which are crucial for the utilization of existing or new therapeutics and for planning service provision.

Problems Arising from Published Reports

Representativeness of Study Populations

With a few exceptions,[17–21] information on COVID-19 has been poorly representative of populations because it has been obtained from selected referral centers/regions and often from hospitalized patients, particularly patients admitted to intensive care units (ICUs).[1,22–25] In the absence of a well-defined population-level denominator, one cannot determine the extent of infection in controls, hence the strength of association between infection and neurological disease or who is at risk of such complications. Although there are some reports published from low- and middle-income countries (LMICs),[26–31] data are scarce, which leads to underrepresentation of these patients in our understanding of the spectrum of COVID-19 complications. Furthermore, the spectrum of the disease often reflects the most severely affected cases, such as those in ICUs. It is also worth noting that many of these reports were published while some patients were still in the hospital. Therefore, knowledge of the outcome and long-term impact of SARS-CoV-2 is lacking, although these studies are increasingly being undertaken. In the absence of these long-term follow-up data, the extent of morbidity and mortality occurring in the community will be poorly understood. Changes in exposure to the virus through new disease control measures and alterations in the structure of health-care systems have also impacted the epidemiology, even within the same country. More recently, we are also confronted with new mutations of SARS-CoV-2, which might contribute further to heterogeneous study populations. In addition, there are significant barriers to large population-based studies, which might render them particularly challenging during a pandemic, such as high costs, staff capacity limitations, and reduced participant travel to study sites which, in addition to other factors, such as fatigue, might exacerbate participant attrition. In Table, we demonstrate how the reported perception of the neurological burden might differ extensively according to variance in inclusion criteria, hence the study population. Therefore, only the investigation of well-defined case and control populations can provide an estimate of the true burden of neurological disorders associated with COVID-19.

Availability, Validity, and Reliability of Diagnostic Tests

Over the course of the pandemic, an increasing number of COVID-19 diagnostic tests, with varying levels of reliability, have been developed. These include tests reflecting current or recent SARS-CoV-2 infection, including RNA amplification using reverse transcriptase–polymerase chain reaction (RT-PCR) and also peri/post-infectious serological tests, which include enzyme-linked immunosorbent assays (ELISAs) and chemiluminescent immunoassays (CLIAs). ELISA is a method by which the antigenic substrate is immobilized on a plate and, when complexed with the antibody of interest in the patient sample and a reporter enzyme, the activity of the reporter enzyme can be used to determine the quantity of the antibody. CLIAs take a similar approach but use a chemiluminescent readout proportionate to the quality of (in the case of COVID-19) SARS-CoV-2 immunoglobulins.

In addition, lateral flow immunoassays (LFIAs) can be used to detect either SARS-CoV-2 antigens or serological responses. LFIAs are low-cost, potentially point-of-care tests take use an approach commonly adopted in home

TABLE. Variability of Incident Neurological Symptoms, Signs and Diseases in Coronavirus Disease 2019-Positive Patients by Selection Criteria

Symptom/ Disease	Minimum	Selection criteria	Maximum	Selection criteria
Headache	3.5%	Consecutive hospital patients aged ≥60 yr[32]	66%	Telephone questionnaire survey in COVID$^+$ patients[33]
Anosmia	5%	Search of neurological manifestations in a retrospective hospital series[1]	85.6%	COVID$^+$ patients seen in ENT consultation[34]
Ageusia	6%	Search of neurological manifestations in a retrospective hospital series[1]	88%	COVID$^+$ patients seen in ENT consultation[34]
Myalgia	2%	Consecutive hospital patients with brain/ spine imaging[35]	61%	Population-based survey in COVID$^+$ patients[36]
Altered mentation	2%	Retrospective cohort study of hospitalized patients with chest CT examination[37]	21%	Hospitalized patients with categorized neurological manifestations[38]
Stroke	0.5%	Retrospective hospital cohort[39]	77%	Retrospective neurology hospital series[24]
Seizures/ epilepsy	1%	Consecutive hospitalized patients[40]	9%	Patients seen in a COVID-19 dedicated hospital[31]

COVID$^+$ = coronavirus disease 2019 confirmed cases; CT = computed tomography; ENT = ear, nose, and throat.

pregnancy tests, in which the sample is placed in a device and flows laterally through an absorbent strip, and either SARS-CoV-2 antigens in the sample bind to conjugated antibodies or vice versa, which can then be visualized. The majority of serological tests widely available have focused on determining humoral immunity (ie, the detection of antibodies), but assays that can reliably reflect crucial aspects of cell-mediated immunity might be of greatest utility.[41]

In terms of reliability, although RT-PCR is routinely used, it has been associated with false-negative tests.[42,43] In addition, serological tests with reliable specificity have unfortunately been reported to have extremely variable sensitivity.[44] In a meta-analysis of 40 studies, the pooled sensitivity of ELISAs in the measurement of IgG or IgM was 84.3%, while LFIAs had 66.0% pooled sensitivity and CLIAs 97.8%.[45] In particular, antibody sensitivity was highest at least 3 weeks after symptom onset (69.9%) in comparison to the first week (50.3%). A high risk of selection bias was found in 98% of in-patient assessments, and high or unclear risk of bias owing to performance or interpretation of the serological test in 73%. Similar results were found in a Cochrane review that estimated the number of false diagnoses under different clinical assumptions relative to percentage prevalence.[46]

The use of many of these tests in clinical practice might be even more challenging in LMICs owing to a shortage of reagents and lack of well-equipped and well-staffed laboratories. In settings where both RT-PCR and serology are either not available or, when available, lack of quality assurance measures makes interpretation of results difficult, clinicians must take a pragmatic approach to determining a possible, probable, or definite diagnosis of COVID-19. This assessment should incorporate knowledge regarding community transmission of SARS-CoV-2, contact with cases, concomitant diseases (such as obesity, diabetes, cardiovascular disorders, or other noncommunicable diseases [including neurological disorders]), age, clinical features, and chest radiographs, especially if they show characteristic COVID-19 changes.

Methods for the Characterization of Neurological Complications

As with the underlying disease, the ascertainment of COVID-19 complications and the related treatment protocols must be based on valid and reliable diagnostic criteria.[17] In addition to accurate diagnostic tests, high inter-rater agreement on the diagnosis should be required across geographic areas and medical specialties. The latter depends on the accessibility of diagnostic tests and the background and experience of those involved in diagnoses. Physicians with neurological training are scarce in many LMICs, and access to neuroimaging facilities is often nonexistent. All these factors can impact data collection from diverse sources and investigators and might explain, at least in part, differences in the reported percentages of patients experiencing

complications across countries. This is particularly true for neurological manifestations. Although, for example, stroke and generalized tonic–clonic seizures can be diagnosed in a fairly easy manner, immune-mediated disorders (eg, cytokine release syndrome-associated encephalopathy) might be harder to identify.[47] The recent observation that ≤20% of antibodies against SARS-CoV-2 react with different organs, including the brain, also raises the possibility of secondary autoimmune encephalitis and other neurological complications.[48] A further challenge is presented in patient-reported symptoms, which might reflect cultural influences on the interpretation and reporting of one's complaints.[49–52]

Therefore, provisional clinical case definitions have been proposed by the World Health Organization (WHO) in an attempt to standardize criteria for the detection of neurological diseases.[4] With respect to the relationship between COVID-19 and these clinical case definitions, the terms "confirmed," "probable," and "suspected" were used for cases of meningitis, encephalitis, myelitis, or central nervous system vasculitis, and "probable association" or "possible association" for acute disseminated encephalomyelitis myelitis (ADEM), Guillain-Barré syndrome, and stroke.[4] However, these definitions of "associations" were based on the original publications from which the cases were reported, and the authors acknowledge that these are likely to require further refinement as more data emerge. Nevertheless, detailed and operationalizable clinical case definitions for each of the potential neurological complications/associations are being used within the neurological registries listed in Table S1.

Another emerging problem when establishing the causal link between COVID-19 and any accompanying manifestation or disease is the possibility of a chance association. This possibility cannot be excluded, particularly if the accompanying neurological disease is a common finding in the general population or if the purported infection-related complication is rare. Case reports might therefore be especially misleading unless supported by a thorough diagnostic work-up and subsequent larger series and case–control studies.

An additional complexity lies in the observation that some complications seem to be correlated with the severity of respiratory COVID-19 disease, whereas others seem independent of this. Detection of complications that arise in otherwise minimally symptomatic patients will be challenging for researchers, especially in resource-poor environments. In addition, some psychiatric manifestations might not be associated with the disease itself but with the overall social consequences of COVID-19 (eg, self-isolation, death of a loved one, or socio-economic factors). In this context, a bidirectional association is postulated, because survivors of COVID-19 are at increased risk of psychiatric sequelae, and psychiatric diseases are risk factors for COVID-19.[53]

Differing Diagnostic and Therapeutic Approaches across Countries

Diagnostic and therapeutic practices vary across countries, mostly reflecting different capacities for adherence to evidence-based guidelines, in addition to the availability and accessibility of reliable diagnostic and therapeutic services. This is particularly true in LMICs, where the ascertainment and management of neurological complications might be suboptimal owing to an insufficient number of services and specialists. In addition, the logistics of the delivery of medical care varies significantly, even between LMICs, with profound impacts on the numbers and types of patients who visit health facilities. For example, in some LMICs, people will seek assistance from local healers, thereby avoiding or delaying hospital care.[54] For these reasons, the clinical representation of neurological complications of COVID-19, as reported by medical professionals, might differ between and within countries depending on the selected population, which might have disproportionate representation from urban, better-educated, and more affluent individuals. Moreover, beliefs common in certain groups around the relative safety of hospitals might alter rates of visits to health-care facilities in both high-income countries (HICs) and LMICs.

Recent Developments

Disease Registries as Instruments for Standardized Data Collection on Neurological Disorders

Several neurological societies have developed registries for members to report neurological complications of COVID-19. These include, among others, ENERGY (European Academy of Neurology [EAN]),[55] GCS-NeuroCOVID (Neurocritical Care Society [NCS]),[56,57] the *Coro*Nerve Study (Association of British Neurologists, Royal College of Psychiatrists, British Paediatric Neurology Association, Neuroanaesthesia Critical Care Society, Intensive Care Society, and British Peripheral Nerve Society),[17,58] the Brain Infections Global COVID-Neuro Network,[59] and a number of other national neurological registries (including Italy,[60] Spain,[61] Germany,[62] and Mexico[63]). Table S1 illustrates the basic structure of some of these registries and the information that is collected from them. However, these data sources are limited to examining the burden of only those neurological disorders that have come to medical attention so far.[17,55] Therefore, many studies are now evaluating symptoms, neuroimaging, and biomarkers in community patients who have not been hospitalized,

including ENERGY and the newly created COVID-19 NeuroDatabank and NeuroBiobank.[64] However, the critical question remains: are community-level patients, for whom we have very limited data, neuroimaging, and biospecimens from the time period of their acute COVID-19/neurological insult, part of a spectrum together with those for whom we have comprehensive acute data, imaging, and biosamples to analyze, or are different underlying mechanistic processes responsible?

Nevertheless, many of these groups are now working to harmonize clinical and biomarker measures in an overarching analysis, which will provide information on both the regional and the global burden of neurological manifestations of the COVID-19 pandemic. Following a review of all published papers on neurological associations of COVID-19,[4] the Brain Infections Global COVID-Neuro Network has begun an individual patient data meta-analysis (https://braininfectionsglobal.tghn.org/covid-neuro-network/); data from this source will be pooled with the aforementioned datasets. The WFN Specialty Group on Environmental Neurology has also called for the creation of international COVID-19 neurological registries to collect and assemble data on acute, chronic, and long-latency effects of the infection on the nervous system.[65]

Global Platforms for Scientific and Technical Exchange: the WHO Global Forum on Neurology and COVID-19 and the Global COVID-19 Neuro Research Coalition

The WHO, within its newly founded Brain Health Unit, has created a Global Forum on Neurology and COVID-19 with an emphasis on 4 areas of importance: (1) acute clinical care, (2) surveillance, (3) long-term impact, and (4) provision of essential services. Its major aim is to convene experts within a common platform to generate discussion and facilitate knowledge exchange through the formation of a collaborative network of international stakeholders. The Forum will further strengthen opportunities and mechanisms for harmonization and has already developed a structured case report form, supported by clear case definitions, to standardize data collection during various phases of the disease. Additionally, to galvanize research around each of these 4 areas and underpin policy developments, a science-driven Global COVID-19 Neuro Research Coalition has been established by researchers, along with scientific associations and federations, with the following aims: (1) to bring together international researchers and their institutions to examine the association between COVID-19 and neurological diseases; (2) to promote partnership between HICs and LMICs; (3) to prioritize the work of the Coalition according to current and future, local and global needs; and (4) to bring global neurology to the forefront for decision-makers locally, nationally, and globally.[66]

Expected Short-Term and Long-Term Findings

By harmonizing case definitions and data items in existing registries and comparing various settings (in- and outpatient services, and HICs and LMICs) from which the data originated, a more complete picture of the spectrum of COVID-19 and its neurological associations can be formed in the short term. The demographic and clinical profile of registered patients can be compared and contrasted across countries. Using clinical settings as denominators, the incidence, prevalence, and at-risk populations for neurological manifestations can be determined. Data from these patients can also be used as a foundation for planning focused studies, and an international registry could provide a "trial-ready" infrastructure to facilitate the organization and conduction of randomized trials. The outcome of these combined efforts will undoubtedly have implications for patient care and morbidity associated with COVID-19 and offer insights for health policy-makers and rehabilitation practitioners in both HICs and LMICs.

An important clinical issue is also represented by post-acute COVID-19 symptoms, such as fatigue and disordered memory, sleep, and cognition, in addition to pain, headache, symptoms of dysautonomia, depression and anxiety, and potentially new-onset dementia.[67–71] Given that these neurological/neuropsychiatric disorders might persist long after the pandemic ends, it would be valuable to include them as a priority to study now and track them into the future. In addition, long-term surveillance programs should be activated to monitor the occurrence of immune-mediated neurological conditions (such as ADEM, Guillain-Barré syndrome, and autoimmune encephalitis) and to verify the proportion attributable to SARS-CoV-2.

Where Next

Poor knowledge of the underlying disease mechanisms driving both the spread of SARS-CoV-2 and, in particular, the complexity of the interactions between various viral and nonviral factors, is the most likely explanation for the present lack of understanding of the impacts of COVID-19 on the nervous system. Although it might be impossible pragmatically to design an impeccable study with strict control over all the factors implicated in defining the spectrum of the disease and its neurological complications, some basic indications can be given for planning and implementing high-quality investigations.

First, the representativeness of the study population must be considered in analysis and interpretation of findings. Hence, stringent diagnostic testing for SARS-CoV-2 in patients presenting with characteristic neurological

symptoms and signs must be encouraged, as in the WHO screening checklist,[72] and advocated for across geographic regions, especially including LMICs, where testing is often not readily available. This includes not only making the tests available at a multicountry institutional level (eg, Africa Centres for Disease Control and Prevention or WHO), but also ensuring that those tests reach areas where they are most needed. This requires sound governance and leadership at a national and subnational level in LMICs.

Overall, and irrespective of specific countries, in the absence of a population base, it is still possible to investigate representative cohorts, which should be drawn from the different clinical settings in which a patient is assessed (eg, including allied professionals who care for neurological patients, outpatient services, emergency rooms, ICU admissions). Crucially, this avoids selection bias from clinicians, who might report only patients from their own setting and subspecialty. In addition, such studies should ideally represent the entire geographic area that is under comparable containment measures rather than isolated hospitals or cities. For populations in remote areas of LMICs, mobile health methods using village-based lay reporters are being developed for the detection, characterization, and surveillance of neurological illnesses, which can also be applied to COVID-19-related complications.[73,74]

Second, future studies of neurological complications should be conducted using only well-validated diagnostic tests to overcome the major limitations of the present diagnostic evidence base. This can be accomplished by performing studies that satisfy the prerequisites of evidence-based diagnostic accuracy; in particular, specifying the purpose of the test, using consecutive sampling, and ensuring that reference tests are accurate, performed on all participants, and interpreted blind to the clinical presentation.[45]

Third, the ascertainment of COVID-19 complications in the acute phase or during follow-up should use accurate measures, valid and reliable case record forms, clinical case definitions, and standardized methods for the characterization of sequelae during follow-up, with the knowledge that this might be challenging in LMICs. To inform routine practice, additional investigations should focus on establishing and testing digital platforms available to report clinical criteria in LMICs. In addition, researchers in HICs using advanced techniques, such as fluid biomarkers or neuroimaging, should consider techniques that are applicable in LMICs.[75] The potential for presently unknown long-term and delayed-onset emergent neurological complications must also be recognized. Precise case definitions must be used to distinguish unrelated clinical conditions from those caused directly or indirectly by the virus or by an associated prophylaxis, treatment, or the broader psychosocial impact of the pandemic. Given that symptoms perceived by patients and/or physicians might not require immediate neurological consultation, follow-up visits (face-to-face or virtual) should be planned by those in charge of the initial consultation for a period of at least 12 months.

The WHO has produced standardized case report forms in collaboration with experts from the international scientific community and scientific societies (including the World Federation of Neurology) for both the acute period and the follow-up period, with key variables organized in continuously updated checklists and adaptations for different levels of care.[59] To guarantee the correct interpretation of these variables, a glossary is being prepared for all the terms used, with a definition of each term that can be interpreted clearly by clinicians, allied health professionals, and lay referents from HICs and LMICs alike (eg, patients and their caregivers). The identification of the variables is currently based on published reports and investigators' personal experience. An attempt is also being made to identify core variables, already present in the existing registries (see Table S1) that are easily collectable in LMICs during periods of high clinical demand, to facilitate the collection of the same data across countries in order to perform pooled studies and postpublication meta-analyses.

Fourth, to determine risk factors for the development of neurological manifestations attributable to SARS-CoV-2 during follow-up, well-defined case–control studies should be undertaken, recruiting matched COVID-19 control patients without neurological complications. Finally, careful neuropathophysiological and neuroimmunological studies, testing for biomarkers and immune correlates of brain disease, are needed to provide an anatomical basis for some of the neurological associations of the virus and gain a better understanding of the mechanisms potentially involved in SARS-CoV-2-related neuropathogenesis.

Conclusion

The identification of the complete spectrum of neurological manifestations in COVID-19, the study of the bidirectional association between these and underlying disease, the detection of environmental, genetic, and virological factors and the underlying neuropathophysiological host mechanisms will not only be useful for determining the overall burden of the disease, but are also required to address the both prevention and treatment of neurological complications of COVID-19. One of the crucially important rate-limiting steps in the advancement of our understanding of the effects of SARS-CoV-2 on the nervous system is the availability of standardized raw data from the scientific community. Sharing comprehensive,

anonymous, nonoverlapping datasets from well-designed cohort and case–control studies, applying a priori clinical case definitions for both infection and neurological complications, and, most importantly, identifying population-based data sources for both HICs and LMICs will be of immense value for us in mitigating the enormous impact of COVID-19 on the human brain.

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Author Contributions

E.B. contributed to the conception and design of the manuscript. E.B., B.D.M., T.S., and A.S.W. contributed to the interpretation of studies included in the manuscript. E.B., B.D.M., E.W., and A.S.W. contributed to drafting the text and preparing the figures. Members of the COVID-19 Neuro Research Coalition who contributed to revision of the text can be found in Table S2.

Potential Conflicts of Interest

Nothing to report.

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