Neurology and COVID-19

Scientific brief

29 September 2021

World Health Organization

Introduction

The predominant acute presentations of COVID-19 are respiratory, but neurological manifestations have been recognized as an important component of the disease, even in cases without respiratory symptoms *(2-5)*. The neurological manifestations associated with COVID-19 range from mild to critical, affect adults and children and can present both during and after acute COVID-19 infection. Reported neurological signs, symptoms or syndromes in the acute phase include headache, dizziness, impaired taste or smell, delirium, agitation, stroke, seizures, coma, meningoencephalitis and Guillain-Barré syndrome *(6, 7)*. Consequences in the post-acute phase are also emerging, as either persisting or newly developing signs and symptoms (post-COVID-19 condition); these include headache, problems with smell or taste, cognitive impairment, confusion, fatigue, difficulty concentrating, sleep disturbances and neuropsychiatric symptoms *(8, 9)*.

COVID-19 disproportionately affects people with pre-existing neurological disorders. Chronic neurological disorders were found to be independently associated with increased mortality in hospitalized COVID-19 patients (hazard ratio [HR]: 2.13; 95% confidence interval [CI]: 1.38–3.28) *(10)*. Individuals with pre-existing neurological conditions have been affected by disruptions to routine care, delayed care because of concerns about infectious risks and disruptions to supply chains for medicines and resultant stock-outs *(11)*.

This scientific brief provides a comprehensive overview of the relationship between neurology and COVID-19 and covers what is currently known about:

- the acute neurological manifestations of COVID-19
- the neurological sequelae associated with post-COVID-19 condition
- the risk of infection, severe illness and mortality from COVID-19 for people with pre-existing neurological conditions
- the extent of disruptions to neurological services caused by the pandemic and mitigation strategies to address these disruptions
- emerging evidence for neurological complications following COVID-19 vaccination.

The target audience for this document includes health care providers, researchers, policy-makers and other stakeholders interested in the evidence relating to neurology and COVID-19. The aim is to increase awareness and recognition of the associated neurological aspects of COVID-19 to improve care and mitigation responses, particularly in low-resource settings.

Methods

This scientific brief is based on the evidence that emerged from systematic or rapid reviews and meta-analyses commissioned by WHO *(14)*;[1] WHO pulse surveys *(15)*; WHO's rapid assessment on services for mental, neurological and substance use (MNS) disorders *(16)* and other relevant publications.

[1] Beghi E, Giussani G, Westenberg E, Allegri R, Garcia-Azorin D, Guekht A, Acute and Post-Acute Neurological Manifestations of COVID-19**:** Present findings, critical appraisal, and future directions. Manuscript in preparation, 2021.; Chomba M, Schiess N, Seeher K, Akpalu A, Baila J, Boruah AP et al. Pre-existing neurological conditions and COVID-19 risk. A commissioned rapid review.(https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3907265); and Misra S, Kolappa K, Prasad M, Radhakrishnan D, Thakur KT, Solomon T. et al. Frequency of neurological manifestations in COVID-19: a systematic review and meta-analysis of 350 studies (https://www.medrxiv.org/content/10.1101/2021.04.20.21255780v1)

Review of the evidence

Acute neurological manifestations of COVID-19

To assess the types and frequencies of reported neurological manifestations associated with COVID-19, WHO assisted with a systematic review and meta-analysis involving data from 145 721 patients with acute COVID-19 infections derived from 350 case series *(17)*. COVID-19 infection was confirmed by real-time reverse-transcription polymerase chain reaction (RT-PCR) detection, high-throughput sequencing, SARS-CoV-2 viral culture in throat swab specimens, SARS-CoV-2 antibody detection in blood samples or SARS-CoV-2 viral culture in throat swab specimens. Most patients (*n*=129 786, 89%) included in the review were hospitalized.

A total of 23 acute neurological symptoms (Table 1) and 14 neurological diagnoses (Table 2) were reported in the literature. Up to one third (*n*=48 059) of COVID-19 patients experienced some type of neurological manifestation, and 1 in 50 developed a stroke. In COVID-19 patients aged over 60 years, the most frequent neurological manifestation was acute confusion/delirium (pooled prevalence: 34%; 95% CI: 23–46%).

Table 1. Pooled prevalence of neurological symptoms included in the meta-analysis *(17)*

Variables	Number of studies	Pooled events	Pooled sample size	Pooled prevalence (%)	95% CI (%)
Corticospinal tract signs[a]	2	128	198	65	58–71
Agitation	3	145	468	45	3–93
Fatigue	169	14 121	45 766	32	30–35
Myalgia or fatigue	22	619	2 246	31	25–37
Taste impairment	38	2934	12 631	21	15–29
Myalgia	207	12 183	59 821	20	18–23
Smell impairment	51	4 647	30 925	19	13–25
Smell or taste impairment	14	518	3 100	18	10–28
Headache	202	8 609	51 969	13	12–15
Headache and dizziness	9	676	3 520	12	8–17
Acute confusion/ delirium	19	2 318	23 921	11	7–16
Disturbance of consciousness	25	693	15 129	7	5–10
Dizziness	46	809	13 473	7	5–8
Tinnitus	5	30	884	5	1–10
Vision impairment	10	126	2 904	4	1–9
Hearing impairment	6	20	819	3	1–5
Sensory impairment	4	23	1 082	2	1–5
Cognitive impairment	3	22	1 131	2	0–5
Cranial nerve palsy	3	7	463	2	0–8
Hemiplegia/ paresis	2	5	467	2	0–10
Neuralgia	7	41	3 183	1	0–3
Seizure	15	127	15 467	1	0–2
Ataxia	5	25	2 266	1	0–2

CI: confidence interval.
[a] Corticospinal tract signs are diffuse hyperreflexia, ankle clonus and bilateral extensor plantar reflexes.

For all ages, the likelihood of experiencing acute confusion/delirium, stroke, seizure and movement disorders increased with increasing severity of COVID-19, but these associations were not statistically significant. Smell and taste impairments were significantly associated with non-severe COVID-19 (odds ratio [OR]: 0.44; 95% CI: 0.28–0.68 and OR: 0.62; 95% CI: 0.42–0.91, respectively). In COVID-19 patients aged over 60 years, the presence of any neurological manifestations was associated with significantly increased mortality (OR: 1.80; 95% CI: 1.11–2.91).

Table 2. Pooled prevalence of neurological diagnoses included in the meta-analysis *(17)*

Variables	Number of studies	Pooled events	Pooled sample size	Pooled prevalence (%)	95% CI
Neuropsychiatric disorders	3	243	1 293	24	2–61
Skeletal muscle injury[a]	4	111	1 545	5	1–12
Myopathy[b]	3	55	5 736	2	0–4
Stroke	29	664	43 024	2	1–2
Ischaemic stroke/TIA	29	527	43 024	1	1–2
Movement disorder	5	48	6 581	1	0–1
CIN/ polyneuropathy	5	48	7 251	1	0–2
Status epilepticus	2	2	282	1	0–5
Haemorrhagic stroke	21	133	36 972	0.31	0.15–0.50
Encephalitis	4	8	4 658	0.30	0–1
Guillain-Barré syndrome	4	22	7 403	0.28	0–1
Parainfectious radiculitis	2	2	858	0.23	0–1
Cerebral venous thrombosis	2	4	14 573	0.12	0–2
PRES	3	6	4 311	0.12	0.02–0.27

CIN: critical illness myopathy; PRES: posterior reversible encephalopathy syndrome; TIA: transient ischaemic attack.
[a] Includes significant creatinine kinase elevation and rhabdomyolysis.
[b] Includes CIN, PRES and TIA.

Limitations

The overall risk of bias was assessed as being low for most studies (*n*=296, 85%) but studies with higher risk of bias yielded higher prevalence estimates. Also, for most outcomes the meta-analyses yielded a high degree of heterogeneity, indicating substantial clinical or methodological diversity, which in some instances rendered the pooling of data inappropriate.

There are gaps in the evidence for non-hospitalized patient cohorts because their data are rarely reported in the literature. The evidence gaps have implications for incidence, prevalence, duration and severity. Similarly, the timing of the onset of signs or symptoms is often not reported. Limitations in study design of included case series precluded the comparison between acute neurological manifestations caused by COVID-19 and the incidence of such manifestations in the general population. Finally, in the absence of well-designed cohort studies, there are insufficient data to definitively assert causality between these symptoms and COVID-19.

Neurological sequelae associated with post-COVID-19 condition

Complications following acute viral illnesses are well described *(18, 19)*. Soon after the advent of the COVID-19 pandemic, longitudinal cohort studies started to assess long-term sequelae of COVID-19, including neurological manifestations. At the same time, patients began to connect with each other and report on prolonged symptoms of COVID-19. In response, WHO commissioned a rapid review of 28 published population-based, cohort or case-control studies[2]. The review established specific new-onset neurological symptoms, signs or diagnoses occurring after the acute phase of COVID-19 that can be interpreted as complications of COVID-19; assessed specific neurological symptoms, signs or diagnoses that persist after the acute phase of COVID-19; and determined factors associated with these post-acute neurological manifestations.

Of the 28 studies, only two followed patients for up to 6 months. Pooling of information was not possible for methodological reasons. In a retrospective cohort of 1733 COVID-19 patients discharged from hospital, 19.6% (*n*=340) reported neurological manifestations after a median follow-up of 186 days *(9)*. The complaints most commonly reported were fatigue or muscle weakness (63%; 1038/1655) and sleep difficulties (26%; 437/1655). Anxiety and depression were reported by 23% (367/1617) of patients and difficulty walking by 24% (103/423). The second prospective study followed 61 hospitalized COVID-19 patients with and without history of admission to an intensive care unit (ICU) *(20)*.

[2] Beghi E, Giussani G, Westenberg E, Allegri R, Garcia-Azorin D, Guekht A, Acute and Post-Acute Neurological Manifestations of COVID-19: Present findings, critical appraisal, and future directions. Manuscript in preparation, 2021.

Common complaints at discharge included amnestic dysfunction (30%; 18/61), dysexecutive syndrome (33%; 20/61), ataxia (11%, 7/61), and tetraparesis (18%; 11/61) *(20)*.

Limitations

The evidence for long-term or newly emerging neurological complications after COVID-19 is limited, particularly in asymptomatic or non-hospitalized patients. Similarly, little is known about neurological sequelae in paediatric patients with conditions related to COVID-19, including multisystem inflammatory syndrome (MIS-C). Data from low- and middle-income countries are scarce, particularly in the post-acute phase. This has led to underreporting of neurological findings in the context of COVID-19 with reference to geography, ethnicity and sociocultural environment.

Methodological issues and study design flaws further reduce the strength of the current evidence because some studies have included in the control group asymptomatic patients who were not screened with molecular or serological tests to confirm or exclude SARS-CoV-2 infection. Screening methods and diagnostic protocols vary across studies, depending on the background of the local investigators, the diagnostic approach, the number and type of contacts during follow-up and, not least, attrition and patient compliance. In addition, studies were done under surge conditions, which led to incomplete diagnostic assessment.

The current understanding of neurological sequelae associated with post-COVID-19 condition is based mainly on patient reports; clinically relevant manifestations; and greater attention towards symptoms, signs and diseases that have been illustrated in previous reports By contrast, information is limited on signs that can be documented only through testing, imaging or biochemical or pathological investigations.

Pre-existing neurological conditions and COVID-19

A range of pre-existing noncommunicable diseases (NCDs) are associated with an increased risk of severe outcomes in COVID-19 *(21)*. These include several neurological conditions such as stroke and dementia. People with certain pre-existing neurological conditions are more vulnerable to SARS-CoV-2 infection, experience exacerbations of their pre-existing disease *(22)* and have higher risks of severe outcomes and death *(10, 23)*. To synthesize the growing evidence on this topic, WHO commissioned a rapid review of 26 articles from 12 countries across three continents, with a total of 379 947 COVID-19 patients, to establish the risk of infection, severe illness and mortality from COVID-19 for people with pre-existing neurological conditions.[3]

The rapid review found that certain pre-existing neurological diseases are associated with severity of COVID-19.[4] The most prevalent were cerebrovascular disease and dementia/neurodegenerative diseases (pooled OR: 1.99; 95% CI: 1.81–2.18). Mortality was high among people with pre-existing neurological conditions (pooled OR: 1.74; 95% CI: 1.56–1.94).

Limitations

Risk of bias was deemed high for most articles, and the overall quality of studies using GRADE (Grading of Recommendations Assessment, Development and Evaluations) methodology was low; hence, the value of the current evidence is limited. Most studies on the relationship between SARS-CoV-2 and pre-existing neurological conditions are based on retrospective cohorts or case series, with few data from prospective studies. Future research will benefit greatly from the use of standardized definitions and reporting for comorbidities, neurological symptoms or diagnoses. Use of standardized case report forms – such as those published by WHO *(25, 26)* – can also contribute to the accuracy and reliability of data.

Disruptions to essential neurological services caused by the COVID-19 pandemic and mitigation strategies

Interruption of routine treatment and care, as well as supply chains for medications during the COVID-19 pandemic, present significant challenges for people with neurological conditions *(11)*. According to the latest WHO *Pulse survey on continuity of essential health services during the COVID-19 pandemic (27)*, 45% of 121 countries for which information was available still reported disruptions to services for MNS disorders in the first quarter of 2021. Likewise,

[3] Chomba M, Schiess N, Seeher K, Akpalu A, Baila J, Boruah AP et al. Pre-existing neurological conditions and COVID-19 risk. A commissioned rapid review. (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3907265)
[4] Ibid.

disruptions to rehabilitation services, a crucial aspect of neurological care, continue to be reported by 53% (of 89 countries). With respect to neurology-specific services, WHO's rapid assessment of services for MNS disorders during the COVID-19 pandemic in mid-2020 *(16)* revealed that one in three of 98 countries closed down neurology inpatient units at least partly during the pandemic. Regarding service provision, surgeries for neurological disorders were disrupted in two-thirds of 130 countries for which information was available, and the management of emergency conditions such as status epilepticus was at least partially disrupted in 35% of the same 130 countries.

To better understand the extent of service disruption, its causes and mitigation strategies for neurological disorders in the context of COVID-19, WHO commissioned a rapid review of 369 articles, providing data on 210 419 patients from 105 countries *(14)*.

Studies that investigated the extent of service disruption (*n*=188) described it as mild (*n*=40, 21%), moderate (*n*=131, 70%) or severe (*n*=10, 5%). The most frequently described reasons for service disruption across 240 studies were travel restrictions related to lockdown (*n*=196, 82%), closure of services or consultations as per health authority directive (*n*=157, 65%) and reduced outpatient volume due to patients not presenting (*n*=135, 56%). A total of 224 studies reported on mitigation strategies, with the most frequently reported strategies being telemedicine and other teleconsultation formats (*n*=184, 82%), novel dispensing approaches for medicines (*n*=116, 52%) and redirection of patients (*n*=95, 42%).

Limitations

To date, most of the data on service disruption have been derived from high- and middle-income countries, with information from low-income countries lacking. Similarly, evidence of the effectiveness and acceptability of mitigation strategies to patients remains limited. In addition, the current published literature seems biased towards certain settings or types of services (e.g. outpatient, emergency or inpatient care). There are few reports on other areas that are crucial for treating people with chronic neurological conditions (e.g. neurorehabilitation). Going forward, more systematic evaluations and reporting of disruption of the whole spectrum of neurological services can provide a more comprehensive picture.

Neurological complications following COVID-19 vaccination

There is a low risk following COVID-19 vaccination of neurological complications including Bell's palsy *(28)*, cerebral venous sinus thrombosis (CVST) and possibly Guillain-Barré syndrome *(29)*. However, the risk of such complications is substantially lower than the risks associated with infection with SARS-CoV-2 *(30, 31)*. Since March 2021, cases of thromboses associated with thrombocytopenia have been reported in patients vaccinated with the Oxford-AstraZeneca ChAdOx1-S and Johnson & Johnson (J&J) Janssen Ad26.COV2.S COVID-19 vaccines. Evaluation of the cases by national and international bodies concluded that there was a plausible causal link between these two adenovirus-vectored vaccines and CVST *(32-34)*, based on the temporal association with vaccination and an increased incidence when compared with expected baseline rates of CVST *(35-42)*. WHO has provided guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination against COVID-19 *(43)*.

Overall knowledge gaps

Current evidence suggests that SARS-CoV-2 can affect the nervous system. Multiple and probably overlapping mechanisms have been proposed for the neurological manifestations; they include hypoxia, cytokine storm, post-infectious autoimmune responses, hypercoagulability, neurologic complications of severe systemic illness and potential direct neurotropism. Questions remain regarding the characteristics, timing and severity of neurological manifestations of COVID-19, including the pathophysiological mechanisms through which SARS-CoV-2 affects the nervous system. As more data emerge, associations of specific neurological disorders with COVID-19 will be further clarified – as has been seen, for example, with Guillain-Barré syndrome *(29)*. Prospective data, as well as biomarker and neuropathological studies, are needed on the short- and long-term neurological sequelae.

Existing reports on the association between COVID-19 and most neurological manifestations are flawed by selection and information bias, and available data reflect the spectrum of neurological manifestations in patients with the more severe COVID-19 cases. Neurological signs or symptoms occurring during the acute phase of COVID-19 infection cannot easily be disentangled from those with onset in the post-acute phase, and follow-up data are scarce, particularly for subclinical findings such as cognitive impairment.

Other gaps in the literature include a lack of clarity on the interplay between pre-existing neurological disease and other underlying comorbidities such as hypertension and diabetes. Studies in this area were hospital-based and biased to people with more severe symptoms, making the findings difficult to generalize to people based in the community or having only mild symptoms. Understanding the impact of neurological conditions requires the inclusion of diverse populations from a variety of social backgrounds.

Guidance is also needed for studies evaluating the disruption or the efficacy of mitigation strategies for care. Efforts should be made to harmonize the methods in this area of research and to enhance the comparability between studies and over time. In addition, funding for and progress in neurological research and training have been affected by the pandemic, owing to the temporary suspension of research projects or postponement or cancellation of fellowships, which need to be re-established as soon as possible *(44)*.

Implications for further research

Well-designed case–control and cohort studies are needed to understand which patients are most vulnerable to neurological manifestations in the acute and post COVID-19 condition and to understand causality related to COVID-19. Series of patients with neurological conditions need to be compared to patients without neurological conditions. Use of case report forms (CRFs) such as WHO's post-COVID-19 condition CRF *(45)* is encouraged to standardize data collection. Future research directions should include more "bottom-up" evidence-gathering efforts; for example, international surveys of neurological associations such as one recently undertaken by the European Federation of Neurological Associations (EFNA) with support from members of the WHO *Neurology and COVID-19 Global Forum (46)*.

Conclusion

A wide spectrum of acute and post-acute neurological manifestations associated with COVID-19 have been reported across the globe. Clinicians and health care workers should be aware of such presentations and complications *even in the absence of respiratory symptoms.* Disruptions in access to essential neurological services and availability of essential medications for people with pre-existing neurological conditions can be detrimental; hence, mitigation strategies such as remote technology and telemedicine alternatives should be judiciously employed. The COVID-19 pandemic continues to have an impact on neurological health, service delivery, research and training while widening existing disparities worldwide. Recognizing and addressing these factors will provide opportunities to improve neurological care worldwide.

Plans for updating

WHO continues to monitor the situation closely for any changes that may affect this scientific brief. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief will expire 1 year after the date of publication.

Acknowledgements

Contributors

In response to the ongoing global pandemic and increasing reports of neurological manifestations in COVID-19, the World Health Organization (WHO) established the Neurology and COVID-19 Global Forum in June 2020. This collaborative network of international stakeholders currently includes more than 70 clinicians, researchers and technical experts from 25 countries. The forum focuses on COVID-19 neurological surveillance, acute clinical care, follow-up, long-term impact and the provision of essential services. The development of this scientific brief has benefited from this wide range of expertise and from collaborations with other neurology and COVID-19 groups *(12, 13)*. External reviewers of this document included members of this Global Forum.

External reviewers: Ricardo Allegri (Universidad de Buenos Aires, Argentina), Ettore Beghi (Istituto di Ricerche Famacologiche Mario Negri IRCCS Milano, Italy), Chahnez Charfi Triki (Hedi Chaker Hospital, Tunisia), Mashina Chomba (University Teaching Hospitals, Zambia), Sherry Chou (University of Pittsburgh, United States of America [USA]), David Garcia-Azorin (Hospital Clinico Universitario Valladolid, Spain), Alla Guekht (Moscow Research and Clinical Center for Neuropsychiatry, Russian Federation), Kameshwar Prasad (All India Institute of Medical Sciences, India), Deanna Saylor (University Teaching Hospitals, Zambia), Tom Solomon (University of Liverpool, United Kingdom of Great Britain and Northern Ireland), Kiran Thakur (Columbia University, USA) and Andrea Winkler (Technical University of Munich, Germany).

WHO: Neerja Chowdhary, Tarun Dua, , Kavitha Kolappa, Nicoline Schiess, Katrin Seeher (Brain health unit, Department of Mental Health and Substance Use), Janet Diaz (Lead, Clinical Management Response COVID-19, Health Care Readiness), Jill Farrington (Regional Medical Officer, Cardiovascular Diseases and Diabetes) Wouter de Groote (Rehabilitation Programme, SDR Unit, Non-communicable Disease Department) and Yuka Sumi (Department of maternal, newborn, child and adolescent health and ageing).

Declaration of interests

All external reviewers were asked to complete the WHO declaration of interest form and underwent review by internet and bibliographic database. None had conflicts of interest requiring a management plan.

Plans for updating

WHO continues to monitor the situation closely for any changes that may affect this scientific brief. Should any factors change, WHO will issue a further update. Otherwise, this scientific brief document will expire 1 year after the date of publication.

Related WHO publications

COVID-19 clinical management: living guidance ***(47)***. This guidance document is intended for clinicians caring for COVID-19 patients during all phases of their disease (i.e. from screening to discharge). This update has been expanded to meet the needs of front-line clinicians. It promotes a multidisciplinary approach to care for patients with COVID-19, including those with mild, moderate, severe or critical disease.

Expanding our understanding of post-COVID-19 condition: report of a WHO webinar – 9 February 2021 ***(47)***. There has been an increase in the number and scope of research activities on post-COVID-19 condition by public health agencies, academics, patient-led research groups and other stakeholders. Currently, progress in diagnosis, treatment and management has been limited by a lack of consensus on the clinical case definition and limited understanding of the clinical characterization during the recovery period and associated pathophysiology. With the goal of advancing this field by bringing together stakeholders from around the world, WHO organized this and other webinars to expand the knowledge of the post-COVID-19 condition.

Policy brief: COVID-19 and the need for action on mental health ***(48)***. This United Nations (UN) policy brief outlines the impact of the pandemic on mental health, including a box specifically highlighting the links between COVID-19 and neurology. Implementation of recommended actions by national decision-makers will help to minimize and address the mental and brain health consequences of this pandemic.

The impact of COVID-19 on mental, neurological and substance use services ***(16)***. This report of a survey completed by 130 countries during the period June–August 2020 established for the first time the extent of disruption to mental, neurological and substance use services; the types of services that have been disrupted; and how countries are adapting to overcome these challenges.

Maintaining essential health services: operational guidance for the COVID-19 context interim guidance ***(49)***. This document recommends practical actions that countries can take at national, subregional and local levels to reorganize and safely maintain access to high-quality, essential health services in the pandemic context. It also outlines sample indicators for monitoring essential health services and describes considerations on when to stop and restart services as COVID-19 transmission recedes and surges.

Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19) ***(43)***. CVST is a neurological condition and is a common presentation of TTS. TTS has emerged as a new adverse event following immunization in individuals vaccinated with COVID-19 non-replicant adenovirus-vectored vaccines (AstraZeneca COVID-19 ChAdOx-1 vaccine and J&J Janssen COVID-19 Ad26.COV2-S vaccine). WHO has issued this interim emergency guidance to increase awareness about TTS in the context of COVID-19 vaccination, and to assist health care providers with the assessment and management of potential TTS cases.

References

1 WHO coronavirus disease (COVID-19) dashboard [website]. Geneva: World Health Organization; 2021 (https://covid19.who.int/).

2 Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N et al. Delirium in COVID-19: A case series and exploration of potential mechanisms for central nervous system involvement. Gen Hosp Psychiatry. 2020;65:47–53.

3 Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19(9):767–83.

4 Fridman S, Bres Bullrich M, Jimenez-Ruiz A, Costantini P, Shah P, Just C et al. Stroke risk, phenotypes, and death in COVID-19: systematic review and newly reported cases. Neurology. 2020;95(24):e3373–e85.

5 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. New Eng J Med. 2020;382(20):e60.

6 Favas TT, Dev P, Chaurasia RN, Chakravarty K, Mishra R, Joshi D et al. Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. Neurol Sci. 2020;41(12):3437–70.

7 Abdullahi A, Candan SA, Abba MA, Bello AH, Alshehri MA, Afamefuna Victor E et al. Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. Front Neurol. 2020;11:687.

8 Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network – United States, March–June 2020. MMWR. 2020;69(30):993–8.

9 Huang C, Huang L, Wang Y, Li X, Ren L, Gu X et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220–32.

10 García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, Talavera B et al. Neurological comorbidity is a predictor of death in COVID-19 disease: a cohort study on 576 patients. Front Neurol. 2020;11:781.

11 Antonini A. Health care for chronic neurological patients after COVID-19. Lancet Neurol. 2020;19(7):562–3.

12 Winkler AS, Knauss S, Schmutzhard E, Leonardi M, Padovani A, Abd-Allah F et al. A call for a global COVID-19 neuro research coalition. Lancet Neurol. 2020;19(6):482–4.

13 Helbok R, Chou SH, Beghi E, Mainali S, Frontera J, Robertson C et al. NeuroCOVID: it's time to join forces globally. Lancet Neurol. 2020;19(10):805–6.

14 García-Azorín D, Seeher KM, Newton CR, Okubadejo NU, Pilotto A, Saylor D et al. Disruptions of neurological services, its causes and mitigation strategies during COVID-19: a global review. J Neurooncol. 2021:1–14.

15 Pulse survey on continuity of essential health services during the COVID-19 pandemic. Interim report. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS_continuity-survey-2020.1).

16 The impact of COVID-19 on mental, neurological and substance use services: results of a rapid assessment. WHO. 5 October 2020. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/978924012455).

17 Misra S, Kolappa K, Prasad M, Radhakrishnan D, Thakur KT, Solomon T et al. Frequency of neurological manifestations in COVID-19: a systematic review and meta-analysis of 350 studies (submitted for publication). medRxiv. 2021:2021.04.20.21255780 (https://www.medrxiv.org/content/medrxiv/early/2021/04/23/2021.04.20.21255780.full.pdf).

18 Dos Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, de Oliveira WK et al. Zika virus and the Guillain-Barré syndrome – case series from seven countries. New England Journal of Medicine. 2016;375(16):1598–601 (https://pubmed.ncbi.nlm.nih.gov/27579558/).

19 Honigsbaum M, Krishnan L. Taking pandemic sequelae seriously: from the Russian influenza to COVID-19 long-haulers. Lancet. 2020;396(10260):1389–91.

20 Nersesjan V, Amiri M, Lebech AM, Roed C, Mens H, Russell L et al. Central and peripheral nervous system complications of COVID-19: a prospective tertiary center cohort with 3-month follow-up. J Neurooncol. 2021:1–19.

21 Addressing noncommunicable diseases in the COVID-19 response. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/bitstream/handle/10665/331923/NCD-COVID-19-eng.pdf?sequence=1&isAllowed=y).

22 Kubota T, Kuroda N. Exacerbation of neurological symptoms and COVID-19 severity in patients with preexisting neurological disorders and COVID-19: a systematic review. Clin Neurol Neurosurg. 2020:106349.

23 Kim SW, Kim SM, Kim YK, Kim JY, Lee YM, Kim BO et al. Clinical characteristics and outcomes of COVID-19 cohort patients in Daegu Metropolitan City outbreak in 2020. J Korean Med Sci. 2021;36(1):e12.

24 Comas-Herrera A, Zalakain J, Lemmon E, Henderson D, Litwin C, Hsu AT et al. Mortality associated with COVID-19 outbreaks in care homes: early international evidence. LTC responses to COVID-19. 21 May. International Long-Term Care Policy Network; 2020 (https://ltccovid.org/2020/04/12/mortality-associated-with-covid-19-outbreaks-in-care-homes-early-international-evidence/).

25 Global COVID-19 clinical platform: rapid core case report form (CRF). Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-Clinical_CRF-2020.4).

26 Global COVID-19 clinical platform case report form (CRF) for post COVID condition (Post COVID-19 CRF). Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/global-covid-19-clinical-platform-case-report-form-(crf)-for-post-covid-conditions-(post-covid-19-crf-)).

27 Second round of the national pulse survey on continuity of essential health services during the COVID-19 pandemic. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS-continuity-survey-2021.1).

28 Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. Lancet Infect Dis. 2021;21(4):450–2.

29 Keddie S, Pakpoor J, Mousele C, Pipis M, Machado PM, Foster M et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain. 2021;144(2):682–93.

30 Bourdette D, Killestein J. Quelling public fears about Guillain-Barre syndrome and COVID-19 vaccination. Neurology. 2021.

31 Lunn MP, Cornblath DR, Jacobs BC, Querol L, van Doorn PA, Hughes RA et al. COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations. Brain. 2021;144(2):357–60.

32 European Medicines Agency. COVID-19 vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 2021 (https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood).

33 European Medicines Agency. COVID-19 vaccine safety update VAXZEVRIA AstraZeneca AB (14 April 2021 update). 2021 (https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-14-april-2021_en.pdf).

34 European Medicines Agency. COVID-19 vaccine safety update VAXZEVRIA AstraZeneca AB (29 March 2021 update). 2021 (https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-29-march-2021_en.pdf).

35 Castelli GP, Pognani C, Sozzi C, Franchini M, Vivona L. Cerebral venous sinus thrombosis associated with thrombocytopenia post-vaccination for COVID-19. Crit Care. 2021;25(1):137.

36 D'Agostino V, Caranci F, Negro A, Piscitelli V, Tuccillo B, Fasano F et al. A rare case of cerebral venous thrombosis and disseminated intravascular coagulation temporally associated to the COVID-19 vaccine administration. J Per Med. 2021;11(4):285.

37 Franchini M, Testa S, Pezzo M, Glingani C, Caruso B, Terenziani I et al. Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination. Thromb Res. 2021;202:182–3.

38 Mehta PR, Apap Mangion S, Benger M, Stanton BR, Czuprynska J, Arya R et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination – A report of two UK cases. Brain Behav Immun. 2021;95:514–7.

39 Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. New Eng J Med. 2021;384(20):1964–5.

40 Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. New Eng J Med. 2021;384(22):2124–30.

41 See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2 to April 21, 2021. JAMA. 2021;325(24):2448–56.

42 Wolf ME, Luz B, Niehaus L, Bhogal P, Bäzner H, Henkes H. Thrombocytopenia and intracranial venous sinus thrombosis after "COVID-19 vaccine AstraZeneca" exposure. J Clin Med. 2021;10(8):1599.

43 Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19). Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/WHO-2019-nCoV-TTS-2021.1).

44 Cuffaro L, Carvalho V, Di Liberto G, Klinglehoefer L, Sauerbier A, Garcia-Azorin D et al. Neurology training and research in the COVID-19 pandemic: a survey of the resident and research fellow section of the European Academy of Neurology. Eur J Neurol. 2020.

45 Global COVID-19 Clinical Data Platform for clinical characterization and management of hospitalized patients with suspected or confirmed COVID-19 [website]. Geneva: World Health Organization; 2021 (https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/data-platform).

46 Triki CC, Leonardi M, Mallouli SZ, Cacciatore M, Karlshoej KC, Magnani FG et al. Global survey on disruption and mitigation of neurological services during COVID-19: the perspective of global international neurological patients and scientific associations. J Neurooncol. 2021:1–13.

47 Clinical management of COVID-19. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/clinical-management-of-covid-19).

48 United Nations. Policy brief: COVID-19 and the need for action on mental health. 2020 (https://unsdg.un.org/sites/default/files/2020-05/UN-Policy-Brief-COVID-19-and-mental-health.pdf).

49 Maintaining essential health services: operational guidance for the COVID-19 context interim guidance. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-essential-health-services-2020.1).

WHO reference number: WHO/2019-nCoV/Sci_Brief/Neurology/2021.1