EAN consensus statement for management of patients with neurological diseases during the COVID-19 pandemic

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Background and purpose: The recent SARS-CoV-2 pandemic has posed multiple challenges to the practice of clinical neurology including recognition of emerging neurological complications and management of coexistent neurological diseases. In a fast-evolving pandemic, evidence-based studies are lacking in many areas. This paper presents European Academy of Neurology (EAN) expert consensus statements to guide neurologists caring for patients with COVID-19.

Methods: A refined Delphi methodology was applied. In round 1, statements were provided by EAN scientific panels (SPs). In round 2, these statements were circulated to SP members not involved in writing them, asking for agreement/disagreement. Items with agreement >70% were retained for round 3, in which SP co-chairs rated importance on a five-point Likert scale. Results were graded by importance and reported as consensus statements.

Results: In round one, 70 statements were provided by 23 SPs. In round two, 259/1061 SP member responses were received. Fifty-nine statements obtained >70% agreement and were retained. In round three, responses were received from 55 co-chairs of 29 SPs. Whilst general recommendations related to prevention of COVID-19 transmission had high levels of

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agreement and importance, opinion was more varied concerning statements related to therapy.

Conclusion: This is the first structured consensus statement on good clinical practice in patients with neurological disease during the COVID-19 pandemic that provides immediate guidance for neurologists. In this fast-evolving pandemic, a rapid response using refined Delphi methodology is possible, but guidance may be subject to change as further evidence emerges.

Introduction

In December 2019, a new viral disease causing respiratory symptoms was described in the Wuhan area in China [1]. Severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2) was identified causing coronavirus disease 2019 (COVID-19). On 11th March, the World Health Organization declared the COVID-19 outbreak a pandemic, after the disease had spread across the world to 114 countries at the time [2]. With the high number of infected people stressing global healthcare systems, capacity in both primary and hospital care settings were overwhelmed. It quickly emerged that a substantial proportion of COVID-19 patients presented with neurological symptoms, suggesting either direct neurotropism or secondary effects of the virus on the central and peripheral nervous system [3–5]. Lockdown measures ensued in many countries across Europe and beyond to contain viral spread, including social distancing and interruption of elective healthcare services. These measures changed lives for the majority of people with specific impact on those living with chronic neurological diseases.

With little to no evidence-based information on the new disease available as the pandemic rapidly escalated, the European Academy of Neurology (EAN) started to publish expert advice to guide clinical practice for neurologists during the pandemic on their EANcore COVID-19 website. With this paper, the first consensus statement on neurological care and COVID-19 is presented.

Method for reaching consensus

The EAN has expert groups organized into 29 scientific panels (SPs) covering almost all neurological specialist areas. SPs consist of neurologists and trainees with special interest in that field and comprise representatives of each European national neurological society (up to 47), and a variable number of individual members, residents, research fellows and patient representatives. The SPs are usually led by two elected co-chairs and a management group, including up to three elected members of the SP, a representative of the EAN residents and research fellow section and, where applicable, a representative of any subspecialty society holding a memorandum of understanding with EAN.

Refined Delphi process

A refined Delphi process through three rounds of surveying members of the EAN SPs was conducted to generate a structured consensus statement.

In the first round, on 31 March 2020, all 29 SPs were invited to submit expert advice on good clinical practice in patients with neurological disease during the COVID-19 pandemic. Twenty-three submissions were received by 17 April 2020, written by SP co-chairs or up to five members of the SP management group. All SP expert statements are available at the following link: https://www.eanpages.org/category/academic_scientific/scientific_panels_report/. The statements provided by the 23 SPs were retrospectively regarded as round 1.

For the second round, the items of those expert advice were entered into a survey questionnaire with a five-point Likert scale to determine the level of agreement (strongly agree/agree/neutral/disagree/strongly disagree). This questionnaire was sent to all members of the SPs who were not involved in writing the original statements. The recommendations were displayed in random order to the participants to avoid sequence bias. Answers were recorded anonymously but a core set of demographic data was obtained in the first section of the questionnaire (Table S1). Items voted 'strongly agree' or 'agree' by ≥70% of members were selected to proceed to the next round. The other items were removed from the process at this stage.

In round 3, all remaining items were again entered into a survey questionnaire with a five-point Likert scale and submitted only to the co-chairs of each SP, asking to rate importance of the statement (absolutely essential/very important/average importance/little importance/no importance at all). Between 5

(absolutely essential) and 1 (no importance at all) points were recorded for each item and an average for each item was calculated and reported as an importance score. Demographic data were again collated using the same questions as in round 2 and anonymized responses were provided.

Results

In the first round, 23 SP reports from 29 SPs (response rate 79%) were received. From these statements, single items were extracted and, after removal of duplicates, 70 statements were listed in a single document for the questionnaire applied for the second round.

In the second round, 1061 potential respondents were approached. 259 (24%) responded within the required period of 1 week. Overall, responses were received from 35 countries (out of 47 EAN institutional member countries). The nationalities with the highest number of respondents were Italy (14%), Germany (8%), Austria (7%) and Greece (6%). Sixty-six percent of respondents were male and 34% female. The median age of respondents was 51 years (range 26–75 years). Twelve per cent of respondents were continuously, 49% occasionally involved in the care of patients with COVID-19; 39% reported no involvement at all. Respondents represented all 29 SPs with the most common subspecialties being multiple sclerosis (26%), stroke (24%), neuroimmunology (17%), clinical neurophysiology (16%) and movement disorders (15%).

Fifty-nine items received agreement from 70% or more of respondents. Eleven recommendations did not reach this level of combined agreement and were excluded from round 3 (Table S2).

The third-round questionnaire was sent to 55 SP co-chairs, 48 of whom responded within the required time period of 1 week (87% response rate). 70.8% of respondents were male and 29.2% female. Median age of respondents was 51 years (range 34–73 years). 75% of respondents reported involvement in the care of COVID-19 patients and 18.8% continuous involvement. The most commonly specified subspecialties were multiple sclerosis (20.8%), movement disorders (20.8%), stroke (18.7%), amyotrophic lateral sclerosis and frontotemporal dementia (14.6%), clinical neurophysiology (12.5%), epilepsy (12.5%), neuroimmunology (12.5%), muscle and neuromuscular junction disorders (12.5%) and dementia and cognitive disorders (12.5%).

Consensus statements

The 59 agreed items were divided into general or neurology specific advice. Statements on general measures mostly echo the general recommendations of hygiene and social distancing, or general advice on disease management but not specific to COVID-19 (Table S3).

Neurology and COVID-19 specific recommendations were divided into the following sections:

- Organization of care (Table 1)
- Management and therapy of neurological symptoms (Table 2)
- Management and therapy of neurological complications (Table 3)
- Considerations for patients with chronic neurological conditions (Table 4)

General recommendations and recommendations on organization of care, with only few exceptions, received the highest levels of agreement (>90%) (Tables S3 and 1). Agreement on management and therapy of neurological symptoms and syndromes ranged from 70% to 88% (Table 2). Agreement on management and therapy of neurological COVID-19 complications ranged from 78% to 94% (Table 3), whereas agreement on recommendations for patients with chronic neurological conditions during the COVID-19 pandemic ranged from 75% to 97% (Table 4). Agreement around pharmacological treatments for specific immune-mediated diseases was generally lower compared to more general therapeutic approaches. The importance score reflected mostly agreement from round 2.

Discussion

With this consensus statement, the EAN provides neurologists with structured recommendations based on broad consensus for good clinical practice in the care of patients with neurological diseases during the COVID-19 pandemic. Recommendations are wide-ranging; some statements refer to neurological involvement in patients suffering from COVID-19, and the guidance includes advice on changes in service provision and prevention of infection amongst clinicians and other staff. Therefore, they may guide development of local standard operating procedures and help to convince healthcare providers on the importance of continuing supportive care in patients with chronic and acute neurological diseases.

To the best of our knowledge, this is the first consensus statement on COVID-19 produced by structured design, involving experts in several subfields of neurology. Other neurological societies have presented a guidance based on expert advice derived from individual or committee experience [6,7] but without a structured method of agreement on items and covering only specific aspects of neurology care [8–14].

Table 1 Recommendations on organization of care during the COVID-19 pandemic

Recommendation	Importance score	Per cent agreement
During endovascular treatment for acute stroke patients, special conditions to prevent potential exposure/contamination with SARS-CoV-2 should be applied without delaying treatment	4.66	96%
Adequate supply of medication and ventilatory support equipment for a period of prolonged isolation must be ensured	4.42	94%
In the case of respiratory decompensation in patients with neuromuscular disorders, e.g. amyotrophic lateral sclerosis (ALS), on home ventilatory support or with initial respiratory symptoms, the patient or caregiver should contact the homecare/palliative team/caring ALS centre and inform the physician who regularly cares for the patient	4.39	96%
Special hygienic conditions (according to contamination prevention guidelines) must be prepared if electroencephalographic (EEG) and electromyographic (EMG) investigations are necessary	4.34	98%
Whilst performing neurophysiology investigations, technicians should adhere to the rules being followed by the intensive care unit (ICU) healthcare staff, including droplet and airborne precautions	4.3	95%
Specialist consultations should be provided over the telephone or where available via teleconsultation. This may help to identify those patients who need a face to face appointment	4.26	94%
Neurologists must be included in the care of COVID-19 patients, even in the early stages and in the ICU to detect neurological symptoms and disorders	4.16	73%
Taking into account the shortage of personal protective equipment, and the potential risk of infecting both healthcare staff and patients, departments are encouraged to postpone all elective EEG and EMG investigations unless urgent and likely to change management significantly. However, these decisions should be managed according to local policies and guidelines	4.12	84%
Patients with neuromuscular disorders particularly affecting respiratory function (e.g. ALS) should be confined to their homes to prevent becoming infected since the impact of respiratory infections is expected to be more serious than in the general population	3.93	92%
If applicable, a principal carer should be identified: one principal carer should coordinate care provided to the patient. This carer should remain with the patient in self/social isolation	3.88	80%
Walking aids or wheelchairs, as well as other surfaces, should be disinfected with detergents or products containing alcohol. This should also include the entrance area, where clothes from the outside are gathered	3.86	90%
If applicable, a back-up carer should be identified for each patient, limiting external contacts to avoid the risk of spreading the infection	3.59	89%
Consider prolonging follow-up magnetic resonance imaging appointments in asymptomatic, long-term survivors of less malignant brain tumours, e.g. meningiomas and schwannomas	3.5	77%

Some subspecialty societies have issued structured expert recommendations, which were open for discussion on their respective websites and approved by the board [15,16]. The EAN consensus recommendation method incorporates progressive evaluation of agreement and importance of each item in three phases, involving an escalation of expertise across rounds. It is proposed that this structured refined Delphi process results in a broad and robust consensus statement with a high level of transparency. The breadth of expertise is illustrated by our second round on agreement, with involvement of 259 participants representing many different countries, national neurological societies, neurological subspecialties and patient representatives.

It is important to note that some of our statements refer to experiences during the peak of the first wave when high numbers of patients were suffering from COVID-19. Once the first wave has passed, the applicability of self-isolation and other infection control measures may be re-evaluated, according to the local prevalence of infection and official regulations. However, it should be borne in mind that many of the statements here refer to patients with neurological disorders that may confer a particular vulnerability to complications of COVID-19, and so they may remain relevant for some time. It is unclear at the time of writing whether the pandemic will evolve into a second wave. If so, it may be necessary to readapt our clinical practice and consensus statements to address rapidly changing circumstances, considering both varying national and regional recommendations and variation in infection and building on progress to date.

There are limitations of these consensus recommendations. First, the call for statements from SPs was designated in round 1 retrospectively, and prospective declaration may stimulate a higher response rate. However, our response rate of 79% within 18 days is already high. Secondly, the short response periods of a week for rounds 2 and 3 may have reduced response rates. This might be true especially for round 2 which had a low response rate of 24%. However, it was still possible to obtain responses from 259 specialists

Table 2 Recommendations on therapy of neurological symptoms/syndromes during the COVID-19 pandemic

Recommendation	Importance score	Per cent agreement
Common neurological diseases requiring intensive care unit admission (e.g. traumatic brain injury, ischaemic stroke, haemorrhagic stroke, status epilepticus, neuro-immunological diseases and many others) have to be managed as usual, independent of COVID-19 infection status	4.55	86%
Before starting a cell-depleting therapy (e.g. ocrelizumab, rituximab, alemtuzumab, cladribine), the risk of immune suppression and susceptibility to infections up to several weeks after treatment initiation must be considered. It may be advisable to delay initiation of cell-depleting therapies until the peak of the pandemic is over in the region. For occasional patients, the risk of not starting the cell-depleting therapy may outweigh the risk of severe COVID-19 infection and this has to be discussed with the patient in detail	4.02	83%
Intravenous corticosteroid pulse therapies that are provided in the absence of a clear clinical indication or justification should be avoided	4	87%
For therapies with immune-depleting properties or primary immune suppressive agents (e.g. ocrelizumab, rituximab, cladribine, alemtuzumab, mitoxantrone) in the first weeks after initiation, there could be an increased risk of infections. In older patients and patients with comorbidity (cardiovascular, pulmonary), treatment initiation should be delayed (if disease activity allows)	3.98	83%
There is currently no evidence to suggest that intravenous immunoglobulin (IVIG) or plasma exchange (Plex) carry any additional risk in catching COVID-19. Plex and IVIG should be reserved for patients with acute exacerbation of neurological disease indications	3.82	75%
For patients with ongoing therapies with immune-depleting properties or primary immune suppressive agents (e.g. ocrelizumab, rituximab, cladribine, alemtuzumab, mitoxantrone), timing of retreatment with immune-depleting therapies should be revised by the consultant and delay in treatment is recommended if possible or alternative options considered	3.82	70%
Paracetamol should preferably be used for antipyretic or analgesic treatment if no contraindications	3.55	86%
Conditions such as orthostatic hypotension or postural orthostatic tachycardia syndrome may occur in patients recovering from COVID-19 infections resulting from viral illnesses due to gastrointestinal fluid loss, prolonged bed rest and deconditioning of the cardiovascular and viscero-sensory systems	3.55	77%
Ibuprofen for antipyretic or analgesic use might be considered if deemed necessary and in the absence of alternatives (see European Medicines Agency advice)	3.41	72%
There is currently no evidence to support the assumption that inhibition of complement using the monoclonal antibody eculizumab increases susceptibility to COVID-19 infection or its outcome	3.33	70%

across the full range of neurological specialties, supporting broad-based consensus, and the round 3 response rate of 87% remained high. Thirdly, in rounds 2 and 3, no further additions were allowed. This was felt necessary in order to archive a consensus statement in a short period of time. The time pressure inherent in crisis response dictated various aspects of methodology, as rapid action was considered the first priority to support neurologists dealing with the pandemic. It is argued that this limitation may be considered acceptable in these circumstances and given that the first round was created by more than 50 authors. Hence, this is a recommendation based on expert advice. It does not report evidence-based guidance, as would be expected in EAN guidelines. A further limitation of this study is that statements might be interpreted in different ways. For example, the statement 'Common neurological diseases requiring intensive care unit admission have to be managed as usual, independent of COVID 19 infection' was considered ambiguous upon review, but was intended to indicate that usual standards of care in critically ill patients must not be compromised. Finally, the fast-moving nature of the pandemic means that updates are likely to be required as new research results emerge. Therefore, the validity of the single statements within this consensus recommendation has to be reviewed as time and knowledge about the disease evolve. One example may be the recent announcement of the beneficial effect of dexamethasone in patients with active COVID-19 [17]. In our recommendations, careful use of intravenous steroid pulse therapy for treatment of neurological diseases is referred to. Although dexamethasone may prove beneficial in active COVID-19 disease [17], little knowledge exists at present if high dose steroids in neurologically affected individuals may increase risk of infection with SARS-CoV-2. Another important example is the diagnostic statement 'Neurologists must be included in the care of COVID-19 patients, even in the early stages and in the intensive care unit to detect neurological symptoms and disorders'. This was agreed by 73% of respondents in round 2, and assigned a mean importance score of 4.12 in round 3, indicating that SP co-chairs felt this to be very important to absolutely essential at the time of the questionnaire. Given subsequent emerging data on neurological involvement in acute COVID-19 [5,18–20], it may be that agreement

Table 3 Recommendations on overall management of neurological COVID-19 complications

Recommendation	Importance score	Per cent agreement
Severe neurological complications can occur in COVID-19 patients during hospitalization, such as seizures, encephalopathy, encephalitis and cerebrovascular events including ischaemic stroke or intracerebral haemorrhage	4.35	85%
During the stay in critical care, prolonged intensive care unit (ICU) admission may cause development of multifactorial encephalopathy, critical illness neuropathy and myopathy	4.3	94%
In ICU, survivors must be evaluated and followed for cognitive impairment, psychiatric and/or physical disability which is commonly referred to as the post ICU-care syndrome	4.16	86%
In order to understand the biology of the disease, neuropathological examination should be requested in deceased patients with suspected neuro-invasive SARS-CoV-2 infection to assess for lower brainstem and medullary involvement	4.12	81%
There may be a higher risk of subacute neurological complications, including Guillain–Barré syndrome and other autoimmune diseases such as necrotizing encephalitis	4.09	78%

Table 4 Recommendations for patients with chronic neurological conditions during the COVID-19 pandemic

Recommendation	Importance score	Per cent agreement
Patients on immunosuppressive medication should practice extra vigilant social distancing, including avoiding public gatherings/crowds and avoiding crowded public transport	4.47	94%
Patient information should stress the importance of maintaining concordance with and supply of prescribed medication	4.45	97%
In any case of acute signs of infection, immune therapies must not be initiated or continued; in particular, immune-depleting agents should be delayed until symptoms have disappeared	4.2	84%
Extra focus should be put on symptoms of infection as persons with dementia may not report these	4.12	88%
Sphingosine-1-phosphate-receptor-modulators (fingolimod, siponimod) in general are associated with increased risk of respiratory infections, but cessation of therapy is associated with significant risk of disease activity returning in multiple sclerosis patients (including rebound activity). Patients should be specifically advised to confine contacts and minimize risks of infection	4.07	86%
Patients receiving plasma exchange or intravenous immunoglobulin as maintenance therapy should continue these if necessary, but extra precautions may need to be taken because of the need for travel to and from a healthcare facility	4.02	75%
Huntington's and Parkinson's disease patients may be particularly vulnerable to respiratory infections or pneumonia due to limited respiratory capacity related to reduced mobility of their thoracic cage. Therefore, it is important to be vigilant in counselling patients to undertake all precautions for reducing exposure risk	3.93	94%
New treatment options for COVID-19 include antiviral, immunomodulatory and immunosuppressive drugs, which may have drug–drug interactions with antiepileptic drugs (AEDs). Hence, dose adjustments of AEDs or COVID-19 treatment might be necessary	3.91	84%
Certain infusion therapies (e.g. natalizumab, rituximab, ocrelizumab, alemtuzumab) may require travel to infusion centres and it is strongly recommended that this decision be made based on regional incidence of COVID-19 and risk/benefit balance for the individual patient	3.86	92%

and importance on this topic would be even higher if repeated now. Similarly, although the European Medicines Agency had already issued a statement on use of ibuprofen in COVID-19 as mentioned in our statement, further publications over recent weeks have strengthened the evidence base that ibuprofen appears safe [21]. Knowledge on use of immunomodulatory treatment is growing and expert advice already differs from the consensus statements published here [22-24]. However, it has to be stressed that expert statements differ from consensus or guidelines and represent a different perspective and level of evidence. Furthermore, in an emergency situation such as the current pandemic, evidence is sparse. Hence, expert recommendations are more feasible in timeframes necessary to address the need of physicians and patients. Nevertheless, it will remain mandatory to produce more formalized fully evidence-based structured guidance during the subsequent course of the pandemic. Online platforms such as the EANcore COVID-19 area of ean.org allow more rapid updates in this context, as further evidence emerges.

It is believed that the main strength of this paper is the broad-based multi-specialty input approach used

to produce consensus recommendations rapidly in a crisis situation, whilst maintaining a scientifically rigorous methodology. This methodology could be applied in future to similar situations if necessary, when a new medical condition is rapidly evolving and guidance is needed for doctors in any specialty coming to terms with new circumstances and challenges. This would include a possible second wave of COVID-19. In fact, being prepared for such situations is recommended by identifying potential groups for rounds 2 and 3 and by installing the necessary technical provision to be able to act quickly. Within this infrastructure, expert opinion can be rapidly and transparently assessed using the refined Delphi methodology. This approach enabled the EAN-COVID-19 task force to produce these pan-European consensus-based statements which seek to guide harmonization of high-quality healthcare across Europe in the face of current challenges. It is hoped that this document helps both leaders and individual clinicians to adapt to the crisis for the benefit of our patients with neurological disorders.

Disclosure of conflicts of interest

Dr von Oertzen is web editor in chief of the European Academy of Neurology (EAN), co-chair of the EAN scientific panel for epilepsy. Dr M. Leone was associate editor of the *European Journal of Neurology* up to 2019. He is chair of the Guideline Production Group of the European Academy of Neurology. Pille Taba is co-chair of the Infectious Diseases Panel of the European Academy of Neurology.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Structure of demographic data collected in questionnaires of rounds 2 and 3

Table S2. Recommendations eliminated in the second round

Table S3. General recommendations ordered by descending average importance score

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