ORIGINAL ARTICLE

The European Academy of Neurology COVID-19 registry (ENERGY): an international instrument for surveillance of neurological complications in patients with COVID-19

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Abstract

The COVID-19 pandemic is a global public health issue. Neurological complications have been reported in up to one-third of affected cases, but their distribution varies significantly in terms of prevalence, incidence and phenotypical characteristics. Variability can be mostly explained by the differing sources of cases (hospital vs. community-based), the accuracy of the diagnostic approach and the interpretation of the patients' complaints. Moreover, after recovering, patients can still experience neurological symptoms. To obtain a more precise picture of the neurological manifestations and outcome of the COVID-19 infection, an international registry (ENERGY) has been created by the European Academy of Neurology in collaboration with European national neurological societies and the Neurocritical Care Society and Research Network. ENERGY can be implemented as a stand-alone instrument for patients with suspected or confirmed COVID-19 *and* neurological findings or as an addendum to an existing registry not targeting neurological symptoms. Data are also collected to study the impact of neurological symptoms and neurological complications on outcomes. The variables included in the registry have been selected in the interests of most countries, to favour pooling with data from other sources and to facilitate data collection even in resource-poor countries. Included are adults with suspected or confirmed COVID-19 infection, ascertained through neurological consultation, and providing informed consent. Key demographic and clinical findings are collected at registration. Patients are followed up to 12 months in search of incident neurological manifestations. As of 19 August, 254 centres from 69 countries and four continents have made requests to join the study.

KEYWORDS

COVID-19, SARS-CoV-2, neurological diseases, complications, outcome, registry, EAN

HISTORICAL BACKGROUND AND RATIONALE

The present pandemic attributed to SARS-CoV-2 virus has become a global public health problem (https://covid19.who.int). This highly contagious coronavirus (more than 21 million people resulting positive, as of 17 August), is responsible in humans for different expressions of infection severity and involvement of organs/systems, including the nervous system [1]. Neurotropism is a common feature of coronaviruses [2] and can be due to a direct action on the nervous tissue and/or to an indirect action through the activation of cytokine cascade and immune-mediated mechanisms [3–5]. Additionally,

neurological symptoms can occur as a complication secondary to systemic illnesses or from the exacerbation of pre-existing neurological conditions. Neurological manifestations include symptoms reflecting the overall severity of the disease (as documented by encephalitis and encephalopathy) or more specific syndromic entities (e.g., stroke or Guillain–Barré syndrome) that might be the result of the peculiar mechanisms of action of the virus [6].

Neurological manifestations have been reported in about one-third of adult and elderly cases, as indicated in the first clinical series from Wuhan, China [7]. Children have also been shown to be affected, although to a lesser extent [8]. Data are mostly driven by case reports and small series that are illustrated in a comprehensive review [9]. Headache, myalgia, anosmia, fatigue/sleepiness are the most frequently reported symptoms [10]. Amongst severe manifestations, altered mental status [11], stroke [12,13] and peripheral nerve involvement [14] can be the most frequent. Mild complaints and subclinical findings are not uncommon and might indicate that neurological findings are more common than expected and are underdiagnosed unless accurate screening methods are adopted. This suggests that an active search might be followed by even higher numbers. Moreover, it is becoming evident that several symptoms persist after recovering from COVID-19 infection [15]. This new evidence suggests further and careful surveillance and monitoring.

In published reports, the distribution of neurological symptoms, signs and diseases varied significantly in terms of prevalence, incidence and phenotypical characteristics. This variability can be mostly explained by the differing sources of cases (hospital vs. community-based), the accuracy of the diagnostic approach, and the subjective interpretation of the patients' complaints by the attending physicians. Thus, a standardized approach is needed to provide a clearer outline of the spectrum of neurological disorders comparing the main clinical aspects of COVID-19 disease in different countries and verifying whether differences, if any, can be attributed to differences in environmental and genetic factors. The approach also allows for the evaluation of the severity of illness across resource settings to examine the role of critical illness or prolonged hospitalization on symptoms and draw conclusions regarding causality between viral infection and neurological manifestations. A registry represents the ideal instrument for this purpose.

A REGISTRY AS AN INSTRUMENT FOR A STANDARDIZED DATA COLLECTION

Registries are the instruments used to detect and define the spectrum of a given disease in population-based samples or in specific settings. The demographic and clinical characteristics of the individuals to be included in a registry are pre-defined. The source(s) of cases is(are) identified. Each patient is assigned a unique identifier. The diagnosis, and any other factor deemed important for the description of a registered case, is defined using commonly accepted and unanimously applied criteria. The data are collected in compliance with these pre-assigned criteria. To preserve the representativeness of the sample, *all* patients eligible for inclusion and releasing an informed consent are registered. If a follow-up is required, patients are assessed at specific time points for the identification of any incident complication. Attrition can be minimized through an active and accurate search of the individuals qualifying for inclusion and, where a follow-up is needed, to be invited at follow-up visits.

PLANNING AND DEVELOPMENT OF A EUROPEAN REGISTRY

The European Academy of Neurology (EAN) has been active since the start of the COVID-19 outbreak with a number of activities to promote knowledge, research and international collaborations [10]. Starting in April 2020, a Task Force was assembled, including clinicians and epidemiologists from various countries (the authors of the present report). One of the projects of this Task Force was to develop a European registry.

Objectives of a European COVID-19 registry

The overall aim of a European COVID-19 registry is to provide epidemiological data on the spectrum of neurological symptoms and signs in patients with COVID-19 infection reported by neurologists or other key referents in outpatient services, emergency rooms or hospital departments. The registry can be implemented as a stand-alone instrument for patients with suspected or confirmed COVID-19 *and* neurological findings or as an addendum to an existing registry not targeting neurological signs and symptoms. More specific primary objectives are (1) to evaluate the prevalence of neurological manifestations in patients with suspected or confirmed COVID-19 disease; and (2) to assess the general characteristics of these neurological manifestations. Secondary objectives are (1) to gain epidemiological data on neurological manifestations of the COVID-19 infection in different countries in Europe and, where available, in non-European countries; and (2) to study the impact of neurological symptoms and neurological complications on outcomes.

An accurate search was made of existing national registries and databases to identify the variables most commonly collected, with a threefold purpose: (1) to select the data considered of primary interest by most countries; (2) to favour data pooling and meta-analyses on common variables from differing sources; and (3) to focus on variables that could be easily collected even in resource-poor countries. The variables identified were critically appraised and only those on which there was full agreement were retained. For each variable, a definition was provided resulting from widely accepted criteria or, where not available, fully agreed by the group. The collection of the data was kept to a minimum to prevent attrition and loss of data due to the constraints posed by the outbreak.

Patients to be registered

A patient was eligible for inclusion provided that all the following criteria were satisfied: (1) age 18 years or older; (2) symptoms suggesting confirmed COVID-19 infection; (3) case ascertainment through neurological consultation; and (4) patient's informed consent (according to the requirements of local regulatory agencies).

Study conduct

All neurologist members of the EAN or its affiliated national societies are entitled to participate and register all consecutive patients fulfilling the inclusion criteria of patients they are asked to visit. No additional investigations were needed beside a detailed neurological examination and a list of the most common variables recorded in the pandemic. To expand the numbers of patients to be registered, data collection will be both prospective and retrospective. A number of general symptoms and signs of infection, a list of prominent comorbidities and a number of neurological diseases, selected amongst those identified in previous series and case reports and accompanied by proper definitions, have been included in a semi-structured case report form (Table 1). All registered patients with neurological symptoms are asked to be followed for 12 months, with telephone calls at 6 and 12 months to verify the vital status, the functional abilities and identify neurological symptoms, signs or diagnoses that might have occurred after the acute phase of the disease. The neurologist (or a designated partner of the local study team) is required to be in charge of the follow-up.
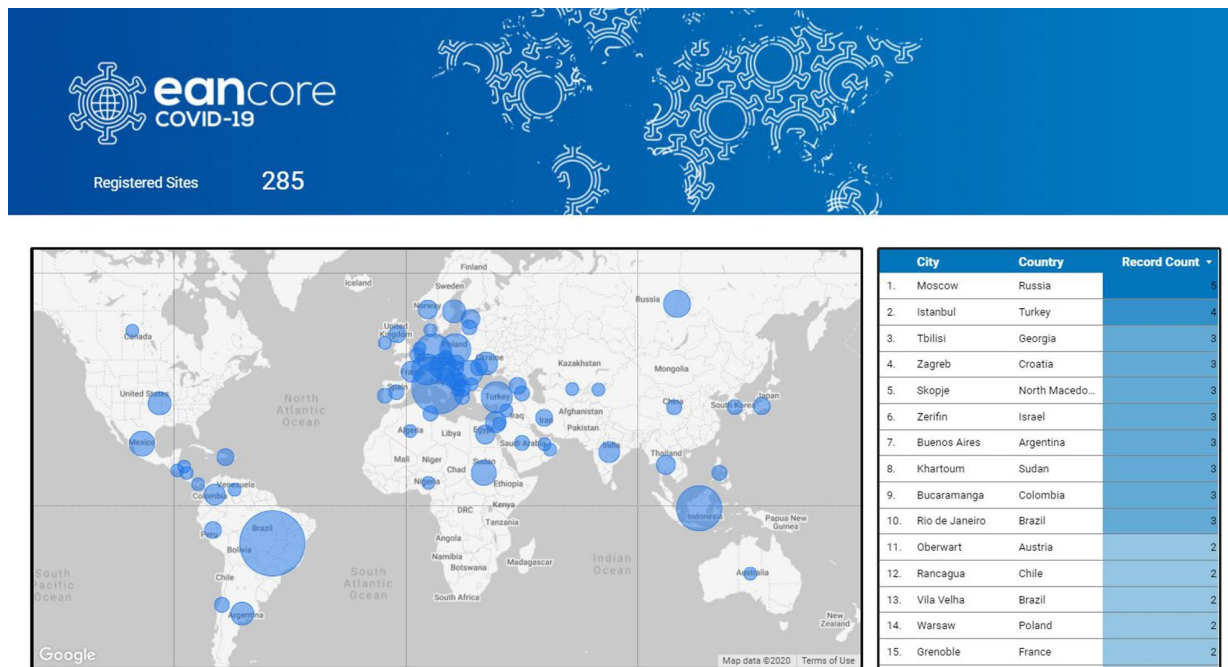
Statistical analysis plan

Statistical analyses will be performed in conformity with two separate plans. The first plan refers to countries adhering to the EAN registry. The plan includes descriptive statistics to be performed on all variables collected in the registry. Inferential statistics are also included using conventional univariate and multivariate methods. Cross-tabulations were pre-planned to correlate each symptom, sign and neurological diagnosis to demographics and the other clinical variables, including comorbidities and the main complications of infection. These data will be presented in the entire sample and for each country separately. The neurological diagnoses made at the time of the infection will be contrasted to the status at last observation (recovered, alive with functional impairment, dead). Multivariate analyses will also be performed using logistic regression models with status at last observation (alive/dead) as the dependent variable and neurological diagnoses as the independent variables, adjusting for demographics, comorbidities, setting and country. Follow-up data will be analysed in survivors with Kaplan–Meier curves using the occurrence of a neurological diagnosis as the outcome variable and demographics and comorbidities as prognostic predictors. Comparisons will be tested with the log-rank test and independent prognostic predictors will be assessed using Cox hazard models, adjusting for setting and country. Retrospective and prospective data will be analysed separately and compared. The modality for data collection (retrospective vs. prospective) will also be included in multivariable analysis models. The significance will be set at the 5% level ($p = 0.05$).

A separate plan (still to be discussed with partners in charge of independent data collections and willing to share their data) will

TABLE 1 List of variables included in the registry

General and demographic	Site of visit, source of contagion, results of testing (where available), year of birth, sex, height, weight, smoking, duration of infection
History	Arterial hypertension, diabetes, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic bronchial/pulmonary disease, anaemia, cancer, immune-mediated disease, other non-neurological (specify), neurological disease
General COVID-19 complications	Dyspnoea, pneumonia, cardiovascular disease, renal insufficiency/dialysis, coagulation disorder/disseminated intravascular coagulopathy, septic shock, extracorporeal membrane oxygenation, other (specify)
Admission	Hospital, intensive care unit (mechanical ventilation)
New neurological manifestations	Date of onset, headache, hyposmia/hypogeusia, dysautonomia, vertigo, myalgia, sleep disturbances, excessive daytime sleepiness/hypersomnia, cognitive impairment, dysexecutive syndrome, hyperactive delirium, hypoactive delirium/acute encephalopathy, stupor/coma, syncope, seizures/status epilepticus, meningitis/encephalitis, stroke, movement disorders, ataxia, spinal cord disorder, peripheral neuropathy, other (specify)
Diagnostic tests	CSF, CT/MRI
Outcome	Modified Rankin Scale at discharge; if death, date, autopsy
6-month follow-up	Modified Rankin Scale, new neurological manifestations; if death, date, autopsy
12-month follow-up	Modified Rankin Scale, new neurological manifestations; if death, date, autopsy

FIGURE 1 Map of Europe including the location of the centres participating in the European Academy of Neurology registry [Colour figure can be viewed at wileyonlinelibrary.com]

consider two options: (1) inclusion of anonymized individual patient data; (2) a meta-analysis of aggregated data.

Sample size calculation

The primary end-points of the EAN registry are to determine the prevalence of neurological manifestations in COVID-19 patients. The hypotheses tested by this registry are exploratory; hence a sample size calculation was not performed.

Implementation of the registry

When the protocol (Annex 1) and the case report form (Annex 2) were in final form, an extensive correspondence was started with the national societies affiliated to the EAN and with individual members. The goal was to advertise the registry and encourage countries and individuals to use this instrument. As of 17 August 2020, a total of 254 centres from four continents declared their willingness to participate. A heatmap of the participating sites is illustrated in Figure 1. The profile of each centre will be provided through the completion of an ad hoc form (Annex 3) that will also include the setting where the patient was registered.

Whilst the EAN registry was distributed to the participating sites, a discussion was started with countries using their own registries in Europe with the intent to organize data sharing (individual patient data) or pooling (meta-analysis).

In parallel, an intensive collaboration was also started with the Global Consortium Study of Neurological Dysfunction in COVID-19 (GCS-NeuroCOVID), centrally coordinated through the University of Pittsburgh in the United States. Endorsed by the Neurocritical Care Society and the Neurocritical Care Research Network, at the end of March 2020 the GCS-NeuroCOVID investigators designed and implemented Tier-1, basic pragmatic cohort studies to determine neurological manifestations of COVID-19 and their prevalence amongst the hospitalized COVID-19 patient population. This will be followed by a Tier-2 study which will further characterize main phenotypes of neurological manifestations of COVID-19 along with evaluation of long-term outcome, and an experimental/translational Tier-3 study to investigate potential disease mechanisms and biomarkers [16,17]. The GCS-NeuroCOVID consortium also developed a paediatrics study arm to examine neurological features of COVID-19 across the full lifespan. Currently, GCS-NeuroCOVID consortium has 123 adult and 96 paediatric sites representing all continents.

The similarities in scientific aims and the complementary global outreach of the two large consortia (EAN and GCS-NeuroCOVID) generated an ideal opportunity for global collaboration. The two consortia plan to combine data in a general analysis which will provide important information on the global and regional burden of neurological manifestations of the COVID-19 pandemic. A Memorandum of Understanding outlining the terms of this collaboration was established and jointly signed by leaders of the EAN, the Neurocritical Care Society and the Neurocritical Care Research Network. This collaboration led to the planning of joint activities aimed at promoting harmonization of data collection, to be extended to children and adolescents, and to include a more detailed search of data during follow-up.

At the same time, the World Health Organization promoted a global forum aimed at identifying the most important issues to

be investigated at a global level, in terms of improved knowledge of the spectrum of COVID-19 infection and its neurological acute and late complications, and the detection of failures in the provision of care. Representatives from both the EAN and the GCS-NeuroCOVID consortium investigators serve on this important mission.

Expected short-term and long-term findings

The activation of the EAN registry and its interaction with several other surveillance systems in and outside Europe will provide a number of short-term and long-term findings. In the short term, a more complete picture will be offered of the spectrum of the disease and its neurological complications, comparing the various settings where the patients were registered. The demographic and clinical profile of registered patients will be compared across European countries to detect similarities and differences. Demographic and clinical characteristics of patients from countries with differing proportions of affected individuals and COVID-related deaths will also be compared. Using the settings for denominators, prevalence and incidence of neurological signs and diseases will also be calculated, separating the neurological manifestations of the infection from well-defined syndromic entities. Registered data will also be used to plan focused studies and the established registry can serve as a critical infrastructure to facilitate global research in future unanticipated events.

CONFLICTS OF INTEREST
None declared.

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

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APPENDIX 1

EAN NEURO-COVID TASK FORCE

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ANNEX 1

STUDY PROTOCOL

CORE SCIENTIFIC COMMITTEE

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Michael Crean. Press & Communication, European Academy of Neurology, Vienna, Austria

ADVISORY COMMITTEE

All members of the EAN Covid-19 Task Force

ENLARGED SCIENTIFIC COMMITTEE

Two representatives from Italy, Spain and Portugal; one representative from any other participating country.

DATA MANAGEMENT

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TABLE OF CHANGES

Date	Page/Section	Description of Change
July 29	Pg. 6/procedure section	Sentence added which allows for inclusion of retrospective patient data
September 7	Pg. …	Secondary objectives: Added "… and non-European countries"
	Pg. …	Methodology: "Included will be all COVID-19 patients whom the neurologists have been asked to visit or are available in the local registries and fulfilled the inclusion criteria. Both retrospective and prospective cases are eligible for inclusion."
	Pg. …	CRF: Added "Final COVID-19 status"
September 19	Pg. 8	Information on data sharing with third countries.

BACKGROUND & RATIONALE

An unexpected outbreak caused by COVID-19 virus is devastating the world population and the global economy. Europe is at present the continent with the highest number of affected individuals and deaths. Despite the exponential increase in the number of infections, information available on the full spectrum of the disease is still

insufficient. Recent reports strongly suggest that COVID-19 infection spreads to organs other than the respiratory system, including the central and peripheral nervous system. The involvement of the nervous system can be due to a direct action of the virus on the nervous tissue and/or to an indirect action through the activation of immune-mediated mechanisms. Moreover, the need for prolonged intensive care management in severe COVID-19 patients leads to well-known adverse effects on the central and peripheral nervous system, including post Intensive Care Unit (ICU) syndrome and ICU acquired weakness.

At present, information available on the involvement of the nervous system during this outbreak is based on case reports and retrospective clinical series. These sources are open to selection bias, although there are indicators that neurological complications in COVID-19 patients are associated with a worse outcome. In addition, both differences in the dissemination of the infection across Europe and variability of measures adopted to contrast the outbreak prevent a correct surveillance of the clinical characteristics of the infection, including the occurrence of neurological disorders.

Currently available information can provide a picture of the rich spectrum of symptoms, signs, and diagnoses associated with COVID-19 infection. However, in the light of the wide differences in timing and severity of the outbreak across Europe, it is impossible to define the association between the impairment of neurological functions and the outcome of the infection. Consequently, to adopt adequate preventing measures without a systematic collection of the information in a well-defined cohort of patients is very challenging. Only a registry can shed some light on the burden and general characteristics of neurological complications of the COVID-19 outbreak and the association of these complications with the demographic and clinical features of the affected individuals.

OBJECTIVES

The main objective of this international Registry is to provide epidemiological data on neurological manifestations (symptoms/signs and diagnoses) in patients with COVID-19 infection reported by neurologists in outpatient services, emergency rooms, and hospital departments. The EAN registry can be implemented as *stand-alone* registry for COVID-19 patients or as *an addendum* to an existing registry not targeting neurologic signs and symptoms.

1. **Primary objectives** are:
   a. To evaluate the prevalence of neurological manifestations in patients with *confirmed*COVID-19 disease
   b. To assess the general characteristics of the neurological manifestations.
2. Secondary objectives are:
   a. To collect epidemiologic data on neurological manifestations of the COVID-19 infection in European and non-European countries
   b. To evaluate the prevalence of neurological manifestations in patients with suspected COVID-19 disease

   c. To study the outcome of neurological manifestations in COVID-19 patients (including the incidence of new neurological manifestations)
   d. To evaluate the incidence of neurological manifestations during follow-up.

WORKING HYPOTHESES

1. Neurological manifestations are relatively common in COVID-19 patients
2. There may be variability in neurological manifestations among different countries
3. Neurological manifestations and complications contribute to worse outcome in confirmed COVID-19 patients.

PROMOTER
The Registry is promoted and endorsed by the European Academy of Neurology (EAN).

PARTICIPANTS TO THE REGISTRY
National Neurological Societies or divisions of Neurology from individual academic centres can apply to participate to the ENERGY Consortium.

STUDY DESIGN

Methodology
Neurologists are asked to implement this study protocol in their institution/clinic, to assess and record demographic and other data, neurologic symptoms and signs according to the annexed electronic Case Record Form (eCRF) in confirmed and suspected COVID-19 patients. Included will be all COVID-19 patients whom the neurologists have been asked to visit or are available in the local registries and fulfilled the inclusion criteria. Both retrospective and prospective cases are eligible for inclusion.

The minimum requirement is to register COVID-19 patients with neurological symptoms and/or signs and/or defined neurological disorders (see inclusion criteria). However, the inclusion of ALL patients with confirmed COVID-19 infection is encouraged to provide the numbers for the calculation of the fraction of the affected population attributable to neurological disorders and the comparison of the overall spectrum of the disease in people with and without neurological manifestations. In centres accepting to include all COVID-19 patients, another physician may be assigned as the person in charge of registration.

Patients
Inclusion criteria
For all COVID-19 patients
- Age 18 or older
- Symptoms suggesting COVID-19 infection OR confirmed COVID-19 infection
- Provided informed consent (according to the requirements of local regulatory agencies).

For COVID-19 patients with neurological signs, symptoms and/or defined neurological disorders

- Age 18 or older
- Symptoms suggesting COVID-19 infection OR confirmed COVID-19 infection
- Neurological evaluation/consultation
- Provided informed consent (according to the requirements of local regulatory agencies).

Exclusion criteria

- Symptoms suggesting other (pulmonary/systemic) infection than COVID-19 AND other confirmed infection.

Procedure

Patients' inclusion can be performed prospectively, at the time of the visit or at patient's discharge, whichever is most convenient; or retrospectively, provided that all inclusion criteria are satisfied. Visits can be performed anywhere in the context of health care facilities (outpatient services, emergency rooms, hospital departments). If at the time of the visit, the clinical picture of the patient is incomplete, the neurologist is invited to contact the caring physician upon discharge to complete the e-CRF. The collection of the data will be kept to a minimum to prevent attrition and loss of data due to the constraints posed by the outbreak. No additional investigations are needed besides a detailed neurological examination and common variables recorded in this pandemic. The registration of the patients will continue until the end of the outbreak.

All registered patients with neurological symptoms will be followed up to 12 months, with telephone calls at 6 and 12 months, to verify clinical conditions, functional abilities, and identify neurological manifestations that might have occurred after the acute phase of the disease. The neurologist (or a designated partner of the local study team) will oversee the follow-up.

A guide is annexed to this protocol to define each variable and facilitate data collection in the e-CRF.

Statistical analysis plan

Descriptive statistics will be performed on all variables collected in the registry. Inferential statistics will include univariate and multivariate analyses. Cross-tabulations will be performed for each symptom, sign and neurological diagnosis against demographics and the other clinical variables, including comorbidities and the main complications of infection. These data will be presented in the entire sample and for each country separately. The neurological diagnoses made at the time of the infection will be contrasted to the status at last observation (recovered, alive with functional impairment, dead). The prevalence of neurological symptoms, signs and diagnoses will be calculated using the number of neurological consultations as denominator and symptoms/signs and, separately, neurological diagnoses as a group. Multivariate analyses will be also performed using logistic regression models with status at last observation (alive with or without functional impairment/dead) as the dependent variable

and neurological diagnoses as the independent variables, adjusting for demographics, comorbidities, centre and country. Follow-up data will be analysed in survivors with Kaplan-Meier curves using the occurrence of a neurological diagnosis as the outcome variable and demographics and comorbidities as prognostic predictors. Comparisons will be tested with Log-rank and independent prognostic predictors will be assessed using Cox's hazard models, adjusting for centre and country. The significance will be set at the 5% level ($p = 0.05$).

Sample size calculation. The primary endpoints of this registry are to determine the prevalence and the general characteristics of neurological manifestations in COVID 19 patients. The hypotheses of this registry are exploratory; hence a sample size calculation has not been performed.

BENEFIT AND RISK RATIO

ENERGY will not interfere with the diagnostic and therapeutic decisions made by the attending physicians for the management of the disease. There may be a benefit for patients undergoing neurological examination by early identification of neurological symptoms and signs which may result in a specific treatment. Therefore, the detection of complications may lead to a better management of patients included in this registry.

Consecutive data collection will result in a better understanding of neurological disease manifestations and complications in suspected and confirmed COVID-19 positive patients. This will be important for an early identification of core neurological symptoms during the pandemic.

COLLECTION OF DATA

Routinely captured data will be collected in a web-based eCRF (REDCap) and stored in a password- protected database not accessible directly from the internet. The password is provided to every participating site. Each centre will be assigned a numeric code generated by the central database. The data will be securely stored at the Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Austria contracted by the EAN central office. All procedures will comply with the EU Regulation 2016/679 (DSGVO, engl. GDPR) on the protection of natural persons regarding personal data processing and movement.

ETHICAL STANDARDS

The Principal Investigators (PIs) will ensure that the study is conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

ETHICS COMMITTEE

The protocol will be submitted by the PI to the local ethics committees (ECs). Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the survey. Only individual data collected after the patient's informed consent will be used. Every eligible patient will be assigned an anonymized code.

DATA CONFIDENTIALITY

Participants' and centres' confidentiality is strictly held in trust by the participating investigators. All medical or administrative staff with an access to the data is subject to a duty of confidentiality and data protection. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidentiality agreement protocols.

The study sponsor (European Academy of Neurology) and representatives of local authorities may inspect all documents and records required to be maintained by the local investigator for the participants in this registry. Research data of the registry, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Managers and the Statisticians of the registry. For this purpose, data will be de-identified and anonymized at input into the eCRF by the local centres/PIs. Individual participants and their research data will be identified by a unique identification number. The eCRF system used by clinical sites and by research staff will be secured and password protected. In the situation when a centre would be temporary not able to access the eCRF or complete it, a paper-based CRF will be available on demand. To keep administration and data correctness on a high level, this possibility should only rarely be used. These records will be entered in the eCRF at the EAN central office in collaboration with the research staff of the Medical University of Innsbruck and the Mario Negri Institute of Milan.

DATA SHARING & OWNERSHIP

Where ENERGY is an addendum to other registries or databases, formal collaborations can be activated with European and international organisations to share common variables in the intent to provide a broad European and even worldwide picture and favour comparisons. For countries with independent registries/databases and that wish to share their data but are unwilling to use this registry, data will be compared in aggregate using pre-specified statistical plans. The data collected by individual centres will be accessible to these centres without restriction. All participants should be registered as active members of the EAN Neuro-COVID Registry Consortium.

The data collected can be also used to test scientific hypotheses forwarded by any active member. However, these hypotheses should be illustrated in ad-hoc protocols to be submitted for approval to the Registry Core Scientific Committee. The scientific reports should be published on behalf of the EAN and the affiliated neurological societies.

Participating sites will be informed of any data sharing agreement with organisations in countries not associated to the European Union.

PUBLICATION, AND AUTHORSHIP

Data will be made available to the scientific community by means of abstract or scientific papers submitted to peer-reviewed journals. Authorship of the main manuscript will follow the ICMJE recommendations that base authorship on the following four criteria:

- Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work,

AND

- Drafting the work or revising it critically for important intellectual content, AND
- Final approval of the version to be published, AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A writing committee composed by the Core Scientific Committee will draft the work and will be authors of the manuscript. All publications will be made in the name of ENERGY Consortium. All those who satisfy the criteria for authorship will be listed as authors. Each centre will be mentioned at least by the name of one author and listed "on behalf of the ENERGY consortium" in the main publications in PubMed. Additional authors will be listed based on the contribution of each site to the registry. Each author's contribution within the Consortium will be specified.

CASE RECORD FORM

Centre ID
Patient's code
Site of visit

- Hospital
- Emergency room
- Outpatient service
- Other (spec)

  Year of birth
  Sex
  Height
  Weight
  Smoking (no/yes)
  Source of contagion

- Occupation
- Family member
- Social
- Travel
- Other (specify)

  Date of first symptoms of infection
  Final COVID-19 status Comorbidities in history (no/yes)
  If yes, check all that apply
- Arterial hypertension
- Diabetes
- Cardiovascular disease
- Chronic kidney disease
- Chronic liver disease
- Chronic bronchial/pulmonary disease
- Anemia
- Cancer
- Immune-mediated disease
- Other non-neurological (specify)

Neurological disease Premorbid Modified Rankin Scale

Relevant COVID-19 complications (not present in history) (No/Yes) If yes, check all that apply

- Dyspnea
- Pneumonia
- Cardiovascular disease
- Renal insufficiency/dialysis
- Coagulation disorder/disseminated intravascular coagulopathy
- Septic shock
- Extracorporeal membrane oxygenation
- Other (specify)
  Hospital admission (no/yes)
  ICU admission (no/yes)
  Mechanical ventilation (No/Yes)

New neurological symptoms/signs/diagnoses (no/yes)

If yes:

  Date of onset of neurological symptoms/signs
  Check all that apply and state if related/unrelated to COVID-19

- Headache
- Hyposmia/hypogeusia
- Dysautonomia
- Vertigo
- Myalgia
- Sleep disturbances
- Excessive daytime sleepiness/hypersomnia
- Cognitive impairment
- Dysexecutive syndrome
- Hyperactive delirium
- Hypoactive delirium/acute encephalopathy
- Stupor/coma
- Syncope

- Seizures/status epilepticus
- Meningitis/Encephalitis
- Stroke
- Movement disorders
- Ataxia
- Spinal cord disorder
- Peripheral neuropathy
- Other (specify)

Diagnostic tests
- CSF (No/Yes)
- CT/MRI (No/Yes)

Outcome
- Modified Rankin Scale at discharge
- If patient died, date of death
- If death, autopsy (No/Yes)

Follow-up

6 months
- Modified Rankin Scale
- Occurrence of new neurological issues (No/Yes)
- If yes, date of onset and specification
- If patient died, date of death
- If death, autopsy (No/Yes)

12 months

- Modified Rankin Scale
- Occurrence of new neurological issues (No/Yes)
- If yes, date of onset and specification
- If patient died, date of death
- If death, autopsy (No/Yes)

ANNEX 2

CASE REPORT FORM

Ean NEuro-covid ReGistrY (ENERGY)

Patient Number	_____ (automatically generated patientcounter)
Data entry is	⬡ prospective ⬡ retrospective

Identification

Username	_____ (automatically filled out user ID)
Site of visit	⬡ Hospital (Ward/ICU) ⬡ Emergency Room ⬡ Outpatient service ⬡ Other, specify (Where is the patient seen by neurologist)
If site of visit is other, please specify	_____
Reason for neurological assessment	⬡ Consulation ⬡ Other, specify
If reason is other, please specify	_____
Date of registration	_____ (Date in which the patient was first seen by neurologist (MM/DD/YYYY))
Date of admission	_____ (If hospitalized, date of patient admission (MM/DD/YYYY))

Demographics & History

Year of birth	_____ ((YYYY, 4-digits))
Biological sex	⬡ Male ⬡ Female ⬡ Intersex ⬡ Unknown
Patient's height	_____ ((in cm, 3-digits))

Patient's weight	
	((in kg, 3-digits))

Current smoker	◯ Yes ◯ No ◯ Unknown

Source of COVID-19 contact	◯ Occupation
	◯ Family member
	◯ Social
	◯ Travel
	◯ Unkown
	◯ Other, specify
	(Where was the most probable exposure)

If source is other, please specify	

Date of COVID-19 symptom onset	
(If the exact day is unkown, enter 01 as day and check the next question!)	(Date when the patient started noticing first symptoms (MM/DD/YYYY))
	☐ I don't know the exact day

Final COVID-19 status (final diagnosis)	☐ Suspected
	☐ Confirmed
	☐ PCR negative
	☐ PCR positive (oropharyngeal AND/OR serum AND/OR CSF)
	☐ Antibodies positive
	☐ Other, specify
	(If patient first tested negative and then turned positive, please code as positive. (Multiselect))

If final status is other, please specify	

Comorbidities in history

Any comorbidity with impact on patients perceived health? If yes, specify in the next questions	◯ Yes ◯ No ◯ Unkown

Arterial hypertension	◯ Yes ◯ No ◯ Unknown
	(History of hypertension or taking anti-hypertensive medications prior to admission)

Diabetes	◯ Type 1
	◯ Type 2
	◯ Unkown
	◯ No
	◯ Other, specify
	(History of diabetes (types 1 or 2) or taking antidiabetic medications)

If diabetes is other, please specify	

	Yes	No	Unknown
Cardiovascular Disease	○	○	○
Chronic kidney disease	○	○	○
Chronic liver disease	○	○	○
Chronic pulmonary disease	○	○	○
Anemia	○	○	○
Cancer	○	○	○
Immunosuppressed state	○	○	○

Cardiovascular Disease: History of cardiovascular disease (myocardial infarction; chronic heart failure, coronary artery disease, peripheral artery disease or taking cardiovascular drugs)   Chronic kidney disease: History of any disease affecting renal function (includes undergoing dialysis)   Chronic liver disease: History of any disease affecting liver function   Chronic pulmonary disease: History of any disease affecting lung function (includes chronic obstructive pulmonary disease, asthma)   Anemia: History of decrease in whole-blood Hb concentration requiring treatment   Cancer: Any neoplasm with impact on patient's health   Immunosuppressed state: Pre-existing immunosuppressed state (taking immunosuppresants/chemotherapy, chronic steroids, hematologic malignancy, HIV, other immunodeficiency syndrome)

Other non-neurological comorbidities	○ Yes, specify ○ No ○ Unknown (Any other non-neurological disease with impact on patient's health)
If any other non-neurological comorbidities is yes, please specify	_____
Premorbid modified Rankin Scale score (mRS)	_____ (mRS score (0 - 5, 1-digit))
Another complication	○ Yes, specify ○ No ○ Unknown (Did the patient develop another complication)
Any neurological disease with impact on patient's health	☐ Dementia ☐ Parkinson's disease ☐ Stroke: ICH, ischemic stroke, TIA ☐ Multiple sclerosis ☐ Motor neuron disease ☐ Neuromuscular disorder ☐ Neuropathy ☐ Other, specify ☐ No ☐ Unkown ((Check all that apply, multiselect))
If another complication is yes, please specify	_____
If any other neurological disease, please specify	_____

Complications: Any complications requiring medical intervention and/or hospitalization
  Dyspnea: Shortness of breath not explained by an overt pulmonary disease (e.g. pneumonia, ARDS)
  Pneumonia: Did the patient develop clinical or radiographic evidence of pneumonia
  Cardiovascular: Did the patient develop cardiovascular complications (including myocardial infarction)
  Renal insufficiency/dialysis: Did the patient develop acute kidney injury requiring dialysis/continuous renal replacement therapy (CRRT)
  Coagulation disorder/disseminated intravascular coagulation: Did the patient develop any coagulation disorder/disseminated intravascular coagulation
  Refractory shock: Did the patient experience refractory shock while hospitalized
  Extra-Corporeal Membrane Oxygenation (ECMO): Did the patient require ECMO therapy while hospitalized
  Mechanical ventilation: Did the patient receive mechanical ventilation

	Yes	No	Unknown
Renal insufficiency/dialysis	○	○	○
Coagulation disorder /Disseminated intravascular coagulation	○	○	○
Refractory shock	○	○	○
Extra-Corporeal Membrane Oxygenation (ECMO)	○	○	○
Mechanical ventilation	○	○	○

New Neurological Findings

Neurological findings at visit   ○ Yes   ○ No
                                        (Did the patient have any neurological complaint)

Neurological findings date

 (If the exact day is unkown, enter 01 as day and check the next question!)   _____
                                                                                     (Date of patient developed the first neurological signs and symptoms (DD/MM/YYYY))

                                        ☐ I don't know the exact day

	Yes, not COVID assoc	Yes, likely COVID assoc	No	Unknown
Headache	○	○	○	○
Hyposmia/Hypogeusia	○	○	○	○
Dysautonomia	○	○	○	○
Vertigo	○	○	○	○
Myalgia	○	○	○	○
Sleep disturbances	○	○	○	○
Sleepiness/Hypersomnia	○	○	○	○
Cognitive impairment	○	○	○	○
Dysexecutive syndrome	○	○	○	○
Hyperactive delirium	○	○	○	○
Hypoactive delirium/acute encephalopathy	○	○	○	○

Stupor/coma	○	○	○	○
Syncope	○	○	○	○
Seizures/status epilepticus	○	○	○	○
Meningitis/encephalitis	○	○	○	○
Stroke	○	○	○	○

Headache: Did the patient develop new on set headache before or or during hospitalization for COVID 19 (self report or family report)
  Hyposmia/Hypogeusia: Did patient have abnormal smell or taste before or during hospitalization/clinical visit for COVID-19 (self-reported or family reported)
  Dysautonomia: Did the patient exhibit signs/symptoms of dysautonomia
  Vertigo: Did the patient report about dizziness with the feeling that (s)he or the objects around are moving when they are not
  Myalgia: Did patient develop/complain about myalgia
  Sleep disturbances: Did the patient complain/exhibit a disturbance of sleep or a non-restorative sleep
  Sleepiness/Hypersomnia: Did patient develop excessive daytime sleepiness (involuntary napping, daily) and/or hypersomnia (>10 hours sleep/24h)
  Cognitive impairment: Did the patient develop any symptoms of higher functions impairment (amnesia, aphasia, apraxia, agnosia, etc)
  Dysexecutive syndrome: Does the patient present inattention, disorientation, poorly organized movements in response to command in off-sedation
  Hyperactive delirium: Did the patient develop delirium (acute mental disturbance characterized by confused thinking and disrupted attention often accompanied by impaired speech or hallucinations)
  Hypoactive delirium/acute encephalopathy: Did patient develop new onset altered mental status before or during hospitalization for COVID 19, EXCLUDING direct medication effect or hypotension (MAP < 60 mmHg)
  Stupor/coma: Did patient develop stupor or coma (no speech, absent purposeful movements/reaction to painful stimuli, no eye opening or only for a short time even after painful stimuli)
  Syncope: Did the patient exhibit transient loss of consciousness due to an insufficient blood flow to the brain
  Seizures/status epilepticus: Did the patient present with transient or prolonged disruption of the brain's electrical activity accompanied by altered consciousness and/or other neurological and behavioural manifestations
  Meningitis/encephalitis: Did patient have meningitis or encephalitis (confirmed by CSF findings)
  Stroke: Is the patient exhibiting signs of acute stroke (confirmed by neuroimaging)

Does the patient present any of new observed movement disorders

	Yes, not COVID assoc	Yes, likely COVID assoc	No	Unknown
Tremor	○	○	○	○
Chorea	○	○	○	○
Dystonia	○	○	○	○
Myoclonus	○	○	○	○
Dyskinesia	○	○	○	○
Parkinsonism	○	○	○	○
	Yes, not COVID assoc	Yes, likely COVID assoc	No	Unknown
Ataxia	○	○	○	○
Spinal cord disorder	○	○	○	○
Peripheral neuropathy	○	○	○	○

Ataxia: Did patient have ataxia (lack of voluntary coordination of muscle movements that can include gait abnormality, speech changes, and abnormalities in eye movements)
  Spinal cord disorder: Did patient show signs of myelopathy or evidence of myelitis (confirmed by CSF)
  Peripheral neuropathy: Any type of impairment of peripheral nervous system

Other new neurological findings	○ Yes - not COVID assoc ○ No ○ Yes - likely COVID assoc ○ Unknown (Did the patient develop other new neurological symptoms or signs)
If other findings is yes, please specify	

Additional Diagnostic Tools

CSF performed	○ Yes ○ No ○ Unknown (Did the patient undergo a lumbar puncture)
If abnormal, please specify	○ Yes - not COVID assoc ○ No ○ Yes - likely COVID assoc ○ Unknown
CT/MRI	○ Yes ○ No ○ Findings assoc. with neuro disease ○ Unknown (Did the patient undergo neuroimaging)
If abnormal, please specify	○ Yes - not COVID assoc ○ No ○ Yes - likely COVID assoc ○ Unknown

Outcome

	Yes	No	Unknown
Was the patient admitted to the hospital?	○	○	○
Was the patient admitted to the ICU?	○	○	○

Status at discharge/visit	
Modified Rankin Scale score (mRS) (Discharge/visit)	(mRS score at discharge (0 - 6, 1-digit))
If (mRS=6): Date of death	((MM/DD/YYYY))
If (mRS=6): Autopsy performed	○ Yes ○ No ○ Unknown
If (mRS=0-5): Date of discharge	((MM/DD/YYYY))

NCC Questionnaire Supplementary

NCC additional values
- ○ Yes ○ No
(Optionally you have the possibility to fill out the NCC CRF)

Patient's ethnicity
- ○ Hispanic or Latino
- ○ Not Hispanic or Latino
- ○ Unknown
- ○ Not reported
- ○ Other, specify
(self-reported)

If patient's self-reported ethnicity is other, define
_____

Empiric COVID 19 treatment
- ○ None
- ○ Hydroxychloroquine
- ○ Zithromax
- ○ H+Z combo
- ○ IVIG
- ○ Remdesivir
- ○ lopinavir/ritonavir
- ○ Other, specify
(What empiric COVID 19 treatemt(s) was given)

If empiric COVID 19 treatment is other, which?
_____
(Empiric COVID 19 tx (other))

Pre-Existing Code Status
- ○ Full ○ DNR ○ DNI
- ○ CMO ○ Other
(Pre-existing code status prior to presentation to hospital)

ATII-RA
- ○ Yes ○ No
(Did the patient receive angiotension -II-receptor antagonists within last 30 days before admission)

Corticosteriods
- ○ Yes ○ No
(Did the patient take nonsteriodal or corticosteriods 30 days prior to admission)

Other immunosuppressives
- ○ Yes ○ No
(Did the patient receive other immunosuppresive medications)

Plegia/paralysis
- ○ Yes, specify ○ No
(Did patient develop new plegia/paresis, including single limb plegia/paresis, hemiplegia/paresis, and quadriplegia/paresis)

If plegia/paralysis is yes, please specify
_____
(Describe new plegia or paralysis including limb, location)

Aphasia
- ○ Yes ○ No
(Did patient present with new aphasia or develop aphasia during hospitalization)

Abnormal tone	◯ Yes, specify ◯ No (Did the patient have abnormal tone)
If description of abnormal is other, please specify	_____ (If abnormal tone, describe (other))
Movement disorder	◯ Tremor ◯ Stiffness ◯ Change in facial expression ◯ Disturbances of dexterity ◯ Micrographia ◯ Weakness ◯ Dystonia ◯ Ambulatory/Axial Difficulties-Freezing ◯ Ambulatory/Axial Difficulties-Lack of arm swing ◯ Ambulatory/Axial Difficulties-Leg dragging ◯ Ambulatory/Axial Difficulties-Shuffling of gait ◯ Ambulatory/Axial Difficulties-Postural imbalance ◯ Ambulatory/Axial Difficulties-Falls ◯ Ambulatory/Axial Difficulties-Slowness of gait ◯ Ambulatory/Axial Difficulties-Stooped posture ◯ Ambulatory/Axial Difficulties-Other abnormality of posture or gait ◯ other, specify (Indicate the type of new movement disorder experienced)
If movement disorder is other, please specify	_____
Abnormal brainstem reflexes	◯ abnormal corneal ◯ abnormal pupillary ◯ abnormal cough ◯ abnormal gag ◯ no abnormal reflexes ◯ other, specify (Specify if any of the following brainstem reflexes abnormal)
If abnormal brainstem reflexes is other, specify	_____
Did patient exhibit or report new sensory symptoms	◯ Yes ◯ No (Did patient exhibit or report new sensory symptoms)
Best GCS	_____ (BEST documented Glasgow Coma Score AFTER onset of severe neurological complication. For intubated patients: please use imputed GCS (1 - 15))
Baseline Oxygen Saturation (SPO2)	_____ ((0.000 - 100.000))

Baseline respiratory rate

((0 - 50))

Baseline arterial blood gas Ph
(first available since acute hospital admission)

((6.00 - 8.00))

Baseline arterial blood gas PaO2
(first available since acute hospital admission)

((10.00 - 200.00))

Baseline arterial blood gas PaCO2
(first available since acute hospital admission)

((10.00 - 100.00))

Baseline arterial blood gas HCO3
(first available since acute hospital admission)

((10.00 - 40.00))

Baseline arterial blood gas O2 sat

((40 - 100))

Pre-intubation Oxygen Saturation (SPO2)

((0 - 100))

Pre-intubation Respiratory Rate

((0 - 50))

Pre-intubation arterial blood gas Ph

((6.00 - 8.00))

Pre-intubation arterial blood gas PaO2

((10.00 - 200.00))

Pre-intubation arterial blood gas PaCO2

((10.00 - 100.00))

Pre-intubation arterial blood gas HCO3

((10.00 - 40.00))

Pre-intubation arterial blood gas O2 sat

((40 - 100))

Days on Mechnical Ventilation

((0 - 60))

WBC on presentation

((0.00 - 50.00) (unit: 10^9/L))

Lymph on presentation

((0.00 - 50.00) (unit: 10^9/L))

Neuroimaging type

☐ CT scan head
☐ MRI head
☐ MRI spine
☐ none
☐ other, specify
(Describe the type of neuroimaging performed
(Multiselect))

If neuroimaging type is other, please specify

ICU LOS

(Number of days patient received care in the
critical care unit (0 - 100))

Hospital LOS

(Number of days patient received care in the
hospital (0 - 100))

Discharge disposition

○ home
○ nursing home/SNF
○ LTACH
○ hospice
○ acute rehab
○ subacute rehab
○ other, specify
(State the discharge location)

If dischare disposition type is other, please specify

(Discharge disposition (other))

Finally

Any comment

ANNEX 3

PROFILE OF PARTICIPATING CENTRE

General characteristics of the participants in the ENERGY registry

Investigator name and surname	
Centre name	
Centre's ID	/__/__/__/
University hospital	/__/
General hospital	/__/
Outpatient service	/__/
Other (specify)	/__/__/
Town	/__/__/
Country	/__/__/
Does the institution have a record of all patients assessed for COVID infection?	/Yes//No/
Number of patients assessed in the institution for COVID infection	
Estimated	/__/__/__/
Calculated (absolute numbers)	/__/__/__/
Number of patients with confirmed COVID infection	
Estimated	/__/__/__/
Calculated (absolute numbers)	/__/__/__/
CENTRE profiling	
Data first patient entered	/__/__//__/__//__/__/
Data last patient entered	/__/__//__/__//__/__/
Consecutive patients with neurological problems	/R//P/
Consecutive patients with neurological problems seen by a neurologist	/R//P/
Consecutive patients admitted to the hospital/unit	/R//P/
Non-consecutive patients seen by a neurologist	/R//P/
Non-consecutive patients admitted to the hospital evaluated by a neurologist	/R//P/
Non-consecutive patients admitted to the hospital/unit	/R//P/

P, prospective; R, retrospective.