Protocol version 1

Neurological manifestations of SARS-CoV-2 infection

INDEX

NEUROSCIENCE SUB-STUDY RESEARCH GROUP (alphabetical)

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1. Introduction and background

In late December 2019, a novel coronavirus was identified in Wuhan, China[1]. The rise in daily confirmed cases lead the World Health Organization (WHO) to declare severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection a global pandemic[2–7]. The typical initial manifestations of COVID-19 combines fever (98%), cough (76%), lymphopenia (63%), leukopenia (25%), myalgia and asthenia (18%). Upper airway involvement is rare[8]. Hospitalization is frequently required in those patients who are infected and present severe respiratory distress (67%)[9]. Intensive care unit (ICU) admission is reserved for the most severe patients (from 5% in China to 7-12% in Italy and Spain)[10][11]. Recent findings suggested that COVID-19 patients may also develop a disproportionate rate of neurological manifestations, including central nervous system disorders, peripheral nervous system disorders and skeletal muscle symptoms) compared to general ARDS patients[12]. For example, retrospective data from Wuhan indicating a 5% incidence of stroke amongst hospitalized patients with SARS-CoV-2[12]. Interestingly, stroke was also reported at an increased incidence associated with SARS-CoV-1 in 2004[13].

The underlying pathogenesis remains unclear, with the systemic inflammatory process, the hypercoagulability state, and the possible viral neurotropism associated with the primary insult (SARS-CoV-2 infection) all postulated mechanisms. The development of secondary brain damage may also influence neurological outcome. Most commonly, COVID-19 patients are admitted to ICU with hypoxia, hypotension, and microvascular abnormalities which can promote neuroinflammation and excitotoxicity with increased permeability of the blood brain barrier[14]. The aim of this observational multicentric international study is to define the prevalence of neurological complications in critically ill confirmed COVID-19 patients and, in doing so, assess the associated

risk factors, predictors, and outcomes.

2. Study Objectives

2.1 Aim

To report and characterize the incidence, risk factor, predictors, and outcome of neurological complications in patients with COVID-19 who require admission to the intensive care unit, mechanical ventilation and/or ECMO.

3. Study design

This is a sub-study of the observational international multicenter COVID-19 Critical Care Consortium (CCCC) observational study. As such, it will both prospectively and retrospectively recruit patients with COVD-19 requiring ICU admission at participating sites.

4. Methods

4.1 Number of subjects

We will include all patients with COVID-19 who meet the inclusion (and with no exclusion) criteria at participating sites. Participating sites will be sourced from those within the CCCC who volunteer to also participate in this sub-study.

4.2 Primary and secondary outcomes

Primary Outcomes:

To identify the type and incidence of neurological complications (**Appendix 1**) of COVID-19 patients admitted to ICU.

Secondary outcomes

1. Mortality or case fatality due to neurological complication and Modified Rankin Scale (mRS) at ICU discharge or 28 days (**Appendix 2**)

    a. Not due to withdrawal of life support therapy (WLST)

    b. Deaths due to withdrawal of life support therapy

        Causes of WLST

            1. Neurologic

            2. Cardiac

            3. Respiratory

            4. Multi-organ

            5. Futility/Resource allocation

2. Hypoxic ischemic brain injury (**Appendix 2**)

3. Duration of ICU and hospital stay with neurological complication

4. Delirium and Cognition

5. Pre and intra-hospital factors related to Neurological complications

6. Neurological injury due to the antiviral therapy (pre-hospital and intra-hospital)

7. Neurological complications during extra corporeal membrane support oxygenation (ECMO) support.

    a. Bival vs heparin in ECMO patients

8. Magnetic resonance images (MRI) or computed tomography (CT) evidence of microhemorrhage, cSS, (including number, volume and area of brain infarction)

9. Neuromonitoring and diagnostics in COVID-19

a. Blood flow/perfusion: Cerebral near infrared spectroscopy (NIRS), Transcranial doppler (TCD) blood flow and emboli, single-photon emission computed tomography (SPECT), CT perfusion

b. Electrical activity: Electroencephalogram (EEG), Bispectral index (BIS)/Entropy

c. Non-invasive intracranial pressure: Optic nerve sheath diameter (ONSD), TCD, pupillometer

d. Motor and sensory pathways: Somatosensory evoked potential (SSEP), Motor evoked potential (MEP), Electromyography (EMG), electroneurography (ENG)

2. Serum biomarker

a. Neuronal injury marker (S100B, NSE) if available

b. Endothelial dysfunction marker if available

c. Inflammatory markers if available

3. Cerebral spinal fluid (CSF) study

4. Brain Autopsy

5. Recruitment

Potential patients will be identified and recruited in participating ICUs by the local investigators.

5.1 Eligibility

Inclusion Criteria

1. Laboratory-confirmed COVID-19 infection by real-time PCR and/or next-generation sequencing

2. Admission to an intensive care unit

Exclusion Criteria

1. Patients treated with mechanical ventilation for other concomitant causes

2. Patients treated with ECMO for other concomitant causes

6. Methodology

Study population

All confirmed COVID-19 patients (≥18 y/o) admitted to ICU for receiving critical care.

Clinical and laboratory assessments

Data collection: Data collection method will follow the parent ECMOCARD study (**Appendix 4**).

7. Statistical Methods

Continuous variables will be presented as median (interquartile range [IQR]), while categorical variables as number (percentage). The primary study analysis will be the calculation of the incidence rate of neurological complications in COVID-19 patients. To this aim, incidence rate will be calculated as the number of events per ICU days. Actual confidence intervals of the incidence rate estimate will be calculated by means of the exact mid-p test for the secondary study analysis (assessment of predictors of 28-day case fatality), predefined, potential demographic and clinical predictors will be first tested for their association with the outcome in univariable logistic regression models. Then, factors potentially associated with 28-day case-fatality in univariable analysis ($p <$ 0.10) will be included in an initial multivariable logistic regression model, and further selected for the final model by means of a stepwise backward selection procedure. Additional analyses (e.g., addition of a propensity score term to logistic regression models, use of penalized logistic regression techniques, or comparison of survival in subgroups through Kaplan-Meier curves) will be considered according to results of standard models, if deemed pertinent. The use of generalized linear mixed models based on logistic regression will also be considered for evaluating the impact on the outcome of center as a random effect. Covariates and outcome will be presented as nonlinear associations. For

statistical significance a *P* value <0.05 will be considered. Analyses will be performed using SPSS statistical software (Version 23).

8. Administrative Aspects

Confidentiality. Study protocol, data collected, and other information will be strictly confidential. All data collected in eCRF will be anonymized (each center and each patient will receive an identification number).

Ethical consideration. The study will be conducted in compliance with the current version of the protocol. Protocol version and subsequent modifications will be approved by the local Ethic committees in compliance to national standards.

Financial disclosure and conflict of interests. All researchers are obliged to declare all their financial interests and conflict of interests.

9. Publications policy

Upon study completion, data will be published in peer-reviewed journals.

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APPENDIX

Appendix 1. Neurological complications

Central nervous system (CNS) complications:

- Ischemic stroke (Definition: neurological deficit due to an acute focal injury in the CNS caused by vascular involvement such as occlusion and cerebral infarction)[15]

- Intracranial hemorrhage (Definition: bleeding that occurs inside the skull)

o Hemorrhagic stroke (Definition: neurological deficit due to an acute focal injury in the CNS caused by vascular involvement with intracerebral or subarachnoid hemorrhage)[15]

o Subdural hematoma (Definition: collection of blood under the dura mater)[16]

- Encephalitis/meningitis (Definition: severe inflammatory disorder of the brain or meninges) [17]

- Transverse myelitis and other spinal cord pathology (Definition: inflammatory disorder with acute or subacute motor-sensory and autonomic spinal cord dysfunction)[18]

- Seizures (Definition: disease of the brain defined by any of this: at least two unprovoked seizures in >24 hours; one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two episodes of seizures within the next 10 years; clear diagnosis of epilepsy syndrome)[19] and non-convulsive epileptic status (NCES) (Definition: defined as changing in behaviour and/or mental processes associated with continuous epileptiform discharges in the electroencephalogram)[20].

- Delirium (Definition: acute change in consciousness and attention caused by an organic condition)[21]

Peripheral nervous system (PNS) complications:

- Guillain-Barré Syndrome (GBS) or GBS variants (Definition: inflammatory immune-mediated polyradiculoneuropathy with acute onset that manifests with tingling, progressive weakness, autonomic disfunction and pain)[18]

- Critical illness myopathy/neuropathy (Definition: neuromuscular weakness in the intensive care setting)[22]

- Hypogeusia/hyposmia (Definition: quantitative disorders characterized by reduction of taste or smell)[22]

- Others neuropathy or myopathy

Appendix 2. Modified Rankin Scale (mRS)

0	No symptoms
1	No significant disability. Some symptoms but able to carry out all usual activities
2	Slight disability. Able to perform daily activity without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, unable to walk alone without assistance.
4	Moderately severe disability. Needs for assistance for own bodily needs, unable to walk alone without assistance.
5	Severe disability. Unable to attend own body needs without constant assistance, nursing care and attention. Incontinent.
6	Dead.

Appendix 3. Hypoxic ischemic brain injury

Definition: reduction in blood supply, oxygen supply or utilization that determines a decreased oxygen delivery to the brain)[23] and post cardiac arrest hypoxic ischemic brain injury (Definition: reduction in blood supply, oxygen supply or utilization that determines a decreased oxygen delivery to the brain due to cardiac arrest [24].

Appendix 4. Addendum to ECMOCARD CRF for the Neuroscience sub-study