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Neurology for COVID-19 patients in ICU and beyond

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1.0 Neurological disease in ICU patients with COVID-19

There is an increasing recognition that COVID-19 may result in neurological presentations, complications and sequelae, through a variety of mechanisms[1] including the following: direct viral infection; a variable (but occasionally substantial) burden of hypoxia and hypotension; hypercoagulability, resulting in large vessel occlusion and stroke, or microvascular obstruction and ischaemia; the consequences of a hyperinflammatory syndrome; autoimmune processes triggered by the infection; and the psychological stresses associated with the illness. All of these may cause neurological, psychiatric, and psychological health issues.[2]

Despite multiple case series, rigorous data on the scale, severity and spectrum of COVID-related neurological and psychiatric problems in patients and the general population are lacking. An initial case series[3] reported "neurological findings" in over 35% of a cohort of 214 patients but included softer clinical features such as dizziness and headache under this rubric. Several subsequent smaller case reports or series focused on individual presentations such as stroke and autoimmune neurological disease (see Refs 1, 2 and 6 for review of this literature).

Characterizing the relationship between COVID-19 and neurological disease is not straightforward. Given high rates of COVID-19 infection in the general population, coincidental occurrence of neurological diseases is likely, and we must be cautious about inferring causal linkages. However, we must also recognize that in a pandemic, neurological manifestations of COVID-19 may be overlooked. This dilemma predicates a low threshold for imaging and CSF analysis in COVID-19 patients displaying unexpected neurological symptoms. While this may not make a difference to rehabilitation needs for individual patients, we also need to recognise that many of the purported "COVID-19 related" neurological complications now being published, reflect similar sequelae in survivors of critical care illness in general. For example, the reported increased risk of cerebrovascular disease is similar to that reported in critical illness more broadly,[4] and persistent (and sometimes progressive) cognitive deficits have been reported in 30-80% of survivors of critical illness.[5]

Within the UK, we similarly have no robust description of the incidence of these complications. However, a descriptive analysis of the range and type of neurological and psychiatric problems after COVID-19 are summarised in a recent publication from the CoroNerve Consortium (http://coronerve.com/).[6] This recent preprint described a cohort of the first ~153 COVID-19 UK patients with acute neurological and psychiatric complications (reported to a multidisciplinary registry over the first three weeks of the initiative) along with an up-to-date review of the literature.[5] The collected cases were geographically and temporally representative of overall COVID-19 in UK Public Health reports, with a median (range) age of 71 (23- 94) years. Of these 153, 77 (62%) had a cerebrovascular event (of which 57 were ischemic strokes, nine intracerebral haemorrhages, and one CNS vasculitis). The second most common group were 39 (31%) patients with altered mental status, including 16 with encephalopathy (7 of whom had encephalitis). The remaining 23 (15%) had a psychiatric diagnosis of whom 21 were new diagnoses; including ten with psychosis, six with a

neurocognitive (dementia-like) syndrome, and four with an affective disorder. Cerebrovascular events predominated in older patients. Conversely, altered mental status, whilst present in all ages, had disproportionate representation in the young. This first report of UK patients replicates reports from other countries and national and international efforts aimed at accumulating data on neuropsychiatric complications in COVID-19.[7]

In addition, the recently published FICM Document on Life After Critical Illness (LACI)[8] highlights the following potential neurological problems in a critical care context:

- Heightened risk of ICU acquired weakness (deep sedation, NM blockade, prolonged recumbency
- Neuropraxias, neuropathies, paraesthesia due to prolonged recumbency
- Anosmia/ageusia
- Extreme fatigue
- Memory/concentration/attention/executive function
- Brain fog
- Sleep dysfunction
- Heightened risk of delirium due to
    - exceptional environmental factors (overcrowding/PPE/large numbers of staff/noise) and
    - pharmacological factors (prolonged sedation possibly with longer acting agents, used due to unavailability of usual drugs)
- Stroke/ICH/SAH risk (profound hypoxaemia/ECMO)
- Slowed speed of information processing
- Exacerbation of existing psychiatric illness or new major depression or psychosis

2.0 Existing guidance

Current NICE Guidelines (CG 83) and quality standards for rehabilitation of patients after critical illness recognise the presence of neurological and psychological/psychiatric sequelae after critical illness. However, details for assessment of neurological sequelae are limited, and though mental health outcomes and assessments are discussed in some detail, the instruments suggested are not typically the ones that are in common use in UK ICUs, or those suggested by international consensus publications.[8] Perhaps most importantly, most of these guidelines and publications (very reasonably) focus on general rehabilitation of pervasive and important neuromuscular sequelae of critical illness, rather than focusing more directly on assessments that need to trigger neurological referral and investigation, which is the focus of the current discussion.[9]

3.0 Recommendations for practice

3.1 General functional recovery (overall assessment)

All assessments of need for specialist neurological referral have their foundations in measures of overall recovery. The **PICUPS** tool provides good screening, and careful evaluation for neurology referral is warranted for scores ≤ 3 on any of the Physical/Movement, Mental Health, or Communication/Cognition items, or if there are unexplained problems with bladder and bowel control or airway reflexes. Other tools used in this context include CPAx, Barthel Index (BI), or modified Rankin Score 9Q (mRS-9Q), or Northwick Park Dependency and care needs assessment.

3.2 Screening for neurological symptoms

These screening questions should direct more detailed examination/referral. Except for B.1, the level at which new referral is triggered depends symptom severity, premorbidity and comorbidity, trajectory of recovery, and whether there already is ongoing management by a neurology team. *

1. New seizures or episodes of alterations in consciousness*
2. Specifically ask for symptoms affecting
    a. speech, reading or writing
    b. physical movement/strength
        I. localised (consider neuropraxia/stroke/myelopathy)
        II. generalised (probably critical illness neuromyopathy, but may be autoimmune)
    c. sensation
    d. balance
    e. vision and hearing
    f. taste and smell
    g. swallowing
    h. incontinence
    a. "Is there anything that you can no longer do that you used to do before the illness?"
3. Problems with pain
4. Problems with sleep (falling asleep, frequent awakening, abnormal movements, snoring, stopping breathing, waking up choking). If significant problems consider referral to a sleep disorders service for investigation. *
5. Cognitive problems: memory, concentration, judgement, planning, trouble with everyday tasks/tools (TV remote, smartphone), subjective mental/physical slowing ("Brain Fog"). Objective assessment of cognition requires a screening tool (but this may be normal in some patients with subjective symptoms). *

3.3 Formal assessments

Not all of these assessments will be possible or indicated in all patients. The level at which referral is triggered will depend on severity of symptoms, patient context, and by trajectory of recovery. *

1. Level of consciousness (GCS or CRS-R) and presence of delirium (CAM-ICU)
2. Cognitive screening– many centres use MOCA (cut off for MCI 26/30, reasonable for referral*)
3. MRC Score (MRC Sum score if no focal weakness)
4. Grip strength (dynamometer)
5. Assessment of balance during 6 m walk, or Timed Get Up and Go
6. Especially if sensory symptoms present, assess large fibre function (vibration using 128 Hz tuning fork or joint position) and small fibre neuropathy (loss of pin prick)
7. If neuropathic symptoms (hyperaesthesia, allodynia, burning, pins & needles, electric shock like pain) consider referral to a pain service or using a neuropathic pain questionnaire (e.g. Leeds Assessment of Neuropathic Symptoms & Signs; LANSS) for more detailed evaluation*

4.0 Involvement in a registry

Neurological complications or sequelae of COVID-19 should be registered on the multidisciplinary CoroNerve Registry.

5.0 What should trigger neurological referral before or immediately following transition to ward care?

Access to specialist neurology input may be variable across units, but the expectation is that investigation (see Box 1) and therapy will be most often planned after discussion with or review by a neurologist. Triggers and actions are best considered in three settings:

5.1 Acutely, during ICU course

This is not dealt with in detail here as it is not the focus of this document. However, a neurology opinion should be sought for unexplained (usually = not drug related or known metabolic) alterations in level of consciousness, seizures, new focal deficits (ensure assessment includes cranial nerves, which are less affected by sedation),[10] suspected CNS infection, or evaluation of possible hypoxic brain injury.

5.2 At the point of transition to ward care

Consider referral to a general neurology service if any of the following features. The "softer" symptoms/signs in *italics* below can be present to some degree in many post ICU patients, and clinical judgment will be required to decide whether a neurology opinion is required at this stage – with the decision depending on premorbid state, symptom severity, and trajectory of progress

a. Seizures or unexplained LOC at any stage
b. Persistent delirium
c. MOCA <26/30
d. Inability to regain pre-existing level of speech and language
e. Inability to regain pre-existing level of mobility
f. Inability to regain pre-existing level of manual dexterity
g. Inability to regain pre-existing level of bowel and bladder control
h. Unexplained difficulties with ventilatory weaning (is this a brain stem issue?)
i. Unexplained (e.g. not opioid related) problems with respiratory control (apnoeic episodes)

5.3 As an action to be flagged at the time of discharge home or at the ICU follow up clinic

Flag need for outpatient referral to a neurologist at ~1-3 months by the primary care team or GP if:

a. A neurological complication was diagnosed during the illness (usually arranged by neurologists)
b. Any of the "softer" features above persists, does not improve, or worsens
c. Concerns about sleep disorders (possible central or obstructive sleep apnoea; restless legs).
d. Patients with complex needs for on-going rehabilitation should have a Rehabilitation Prescription[12]

5.4 Deficits more appropriately addressed by another team (i.e. not neurology)

These are important to recognise as they may present with cognitive problems but require referral to a psychologist or psychiatrist; or simply indicate the need for rehabilitation:

1. ICU acquired weakness that is not disabling and is recovering (rehabilitation team)
2. Psychological health (probably an issue for the follow up clinic, rather than ward transition:
    a. Depression (PHQ-9; PHQ-2 for quick screen);
    b. Anxiety (GAD-7; GAD-2 for quick screen);
    c. PTSD (PCL-5; TSQ)
    d. Alcohol abuse (AUDIT questionnaire) or drug abuse/dependence (DAST questionnaire)

Box 1. Investigations that may be indicated at presentation, during ICU course, or at ward transition:

These will often (though not always) be undertaken in discussion with the neurology team

a. CT or MRI may be indicated for
    i. Diagnosis of focal neurological deficit
    ii. Assessment of unexplained (e.g. not drug related) altered level of consciousness
    iii. Exclusion of focal pathology in patients with new seizures
b. Lumbar puncture may be indicated (after brain imaging if appropriate) to:
    i. Exclude or confirm suspected meningitis (special precautions for SARS-CoV-2 PCR)[1]
    ii. Investigation of autoimmune CNS disease (CSF autoantibody levels)
    iii. Investigation of suspected autoimmune polyradiculitis (Guillian Barre Syndrome)
c. EEG may be indicated for:
    i. Seizures – particularly to differentiate from non-seizure disorders (e.g. myoclonus)
    ii. Unexplained low level of consciousness (nonconvulsive epilepsy, hypoxic injury?)
    iii. To monitor/titrate sedation – particularly deeper levels and for seizures
d. Nerve conduction studies and/or EMG may be indicated for:
    i. Investigation of significant ICU-acquired weakness
    ii. Investigation of suspected Guillian Barre syndrome
    iii. Investigation of a suspected pressure/traction related nerve injury
e. Additional blood investigations may be indicated. Examples include:
    i. For CNS autoantibody measurement

[1] The presence of direct CNS infection by SARS-CoV-2 is a subject of considerable research interest, but convincing reports of virus in CSF are very rare. It is **not** common clinical practice to send CSF for detection of the virus. If CSF **is** sent for PCR for SARS-CoV-2, it is important to recognise that the technique is exquisitely sensitive and take steps to minimise the possibility of false positive results because of contamination from other sources of viral RNA, such as respiratory secretions. Consequently, it may be advisable to:

a. Not undertake a lumbar puncture within 1 hour of an aerosol generating procedure
b. Double glove and remove outer gloves after cleaning and before handling equipment (needles, manometer) or sample bottles, or performing the lumbar puncture

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