



# A complication of coronavirus disease 2019: delirium

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## Abstract

COVID-19 is predominantly a respiratory disease. However, some cases exhibit other features including Central Nervous System symptoms. In the older adult, COVID-19 may present with atypical symptoms, including delirium and its complications. The objective of this study is to describe the relationship between the new type of coronavirus infection and delirium. Systematic research (Cochrane Library and PubMed) was carried out (only upper time limit: April 2020). Publications found through this indexed search were reviewed and manually screened to identify relevant studies. Search terms used included “COVID-19, Delirium, Dementia, Intensive Care Unit”. We manually added articles identified through other sources (i.e., key journals). Older people are at the greatest risk from COVID-19. If infected, they may present delirium. Moreover, it is not exclusive to older people. Delirium is not inevitable; rather, it is preventable. Delirium prevention programs are even more crucial in the era of COVID-19 and cannot be allowed to wither despite the challenges of integrating delirium prevention with COVID-19 care. An acute change in condition, behaviour, or mental status should prompt a delirium screen. As regards the treatment, it is advisable to use non-pharmacological interventions first where possible. Medication may be needed for patients with agitation where there is intractable distress or high risk to self/others.

**Keywords** COVID-19 · Delirium · Dementia · Intensive-care unit

## Introduction

Coronavirus disease 2019 (COVID-19), first reported in Wuhan, a city in the Hubei Province of China, in late December 2019 [1], is characterized by severe acute respiratory syndrome designated as SARS-CoV-2. It has affected many people, rapidly spreading, and resulting in a pandemic in a short period. The novel coronavirus was identified as a non-segmented, positive-sense RNA virus [2]. In January 2020, ACE2 was identified as the functional receptor for SARS-CoV-2, which is present in multiple human organs, including the nervous system and skeletal muscles [3].

While the primary target of COVID-19 is the lungs, it does not stop there. Other organs such as the heart, liver, kidneys, and brain could also be damaged. Central nervous system symptoms (CNS) were the main form of neurologic injury in patients with COVID-19 [4]. It is not clear whether these neurologic syndromes are a direct cause of the virus entering their CNS, or an indirect response (a systemic inflammatory storm with a massive release of cytokines, chemokines, and other inflammation signals). A significant number of individuals that are infected remain asymptomatic [5]. Patients who required intensive care were more likely to have underlying comorbidities and complications and were significantly older than those who did not (at the median age of 66 versus 51) [6]. There is no specific antiviral treatment recommended for COVID-19. Critically ill show a high percentage of delirium [7]. With this article, we intend to describe the relationship between the new type of coronavirus infection and delirium.

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All co-authors have contributed significantly confirming their agreement to this submission.

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## Methods

Systematic research (Cochrane Library and PubMed) was carried out (only upper time limit: April 2020). Publications found through this indexed search were reviewed and manually screened to identify relevant studies. Search terms used included “COVID-19, Delirium, Dementia, Intensive Care Unit”. We manually added articles identified through other sources (i.e., key journals).

## General concepts

Delirium is a clinical syndrome which is difficult to define. It is known by several terms, some still in use in clinical practice. These terms include ‘acute confusional state’, ‘acute confusion’, ‘acute on chronic confusion’, and ‘acute brain failure’ or “acute encephalopathy” [8]. It is a relatively common acute disorder, especially in older people with physical illness, having high morbidity and mortality, often

under-recognised and undertreated. Even in the absence of drastic environmental modifications resulting from isolation and personal protective equipment (PPE) shortages, up to 50–70% of critically ill patients, and 10–15% of hospitalized general medical patients, develop delirium [9–11]. According to DSM-5 criteria (Table 1), delirium is characterized by fluctuating disturbance of consciousness, inattention, and reduced awareness, occurring in 20% of acute hospital inpatients [12]. Patients may also experience hallucinations or delusions [13]. The International Classification of Diseases, version 10 (ICD-10) describes delirium as an organic brain syndrome with non-specific aetiology, characterized by disturbance of consciousness, attention, perception, thought, memory, psychomotor behaviour, emotions, and sleep–wake cycle (Table 2) [14]. Delirium is sometimes described using hyperactive, hypoactive, or mixed labels depending on the level of arousal [11]. Hyperactive delirium, the most easily recognized type, is marked by agitation and vigilance, while the hypoactive form is denoted by lethargy, with a substantially decreased level of motor activity [15]. In older adults, hypoactive delirium (sleepy, withdrawn, “pleasantly

**Table 1** DSM-5 diagnostic criteria for delirium

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- (A) A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
  - (B) The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
  - (C) An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)
  - (D) The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
  - (E) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies
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**Table 2** ICD-10 criteria for delirium

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- (A) Clouding of consciousness, i.e., reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention
  - (B) Disturbance of cognition, manifest by both:
    - (1) Impairment of immediate recall and recent memory, with relatively intact remote memory;
    - (2) Disorientation in time, place or person
  - (C) At least one of the following psychomotor disturbances:
    - (1) Rapid, unpredictable shifts from hypo-activity to hyper-activity;
    - (2) Increased reaction time;
    - (3) Increased or decreased flow of speech;
    - (4) Enhanced startle reaction
  - (D) Disturbance of sleep or the sleep–wake cycle, manifest by at least one of the following:
    - (1) Insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep–wake cycle;
    - (2) Nocturnal worsening of symptoms;
    - (3) Disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening
  - (E) Rapid onset and fluctuations of the symptoms over the course of the day
  - (F) Objective evidence from history, physical and neurological examination or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A–D
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confused”) is more common than hyperactive delirium (agitation and anxiety). The role for electroencephalography (EEG) in the diagnosis of delirium is to aid in differentiating delirium from nonconvulsive status epilepticus, focal dyscognitive seizures, or psychiatric conditions [16]. Younger patients with delirium are more likely to be diagnosed as well as to recover fully. Duration is variable, but onset is often abrupt, usually over for hours to days, and ranging in severity. In some people, it can last weeks or months [17]. Elderly patients with apathy, lethargy, or low mood should be evaluated for delirium. The acute confusional state contributes to less desirable outcomes including longer hospitalization, higher rates of nursing home placement, and possibly higher mortality. Critically ill patients are subject to numerous risk factors for delirium. They may involve factors of the acute illness; these factors represent areas of risk that are potentially modifiable by preventive or therapeutic intervention [18]. Drugs are an important risk factor and precipitant for delirium in older people: medications may be the sole precipitant for 12–39% of cases of delirium [19].

## COVID-19 and delirium

According to the World Health Organization, “altered consciousness/confusion” may be a presenting symptom of COVID-19, even before fever and cough [20]. However, in older adults, a viral infection like COVID-19, fever, and hypoxemia may trigger delirium. Moreover, the presence of comorbidities found during the viral infection can facilitate the onset of an acute confusional state [21]. Elevated concentrations of serum pro-interleukins and S100B (recognized as an index of blood–brain barrier disruption) have been observed during delirium in elderly patients [22]. In a case study presented by Chinese researchers [23], the prevalence of specific comorbidities was hypertension (16.9%), other cardiovascular diseases (53.7%) cerebrovascular diseases (1.9%), diabetes (8.2%), hepatitis B infections (1.8%), chronic obstructive pulmonary disease (1.5%), chronic kidney diseases (1.3%), malignancy (11.1%), and immunodeficiency (0.2%). Those people who are critically ill, requiring ICU-level care, are most at risk of developing delirium. This is further exacerbated by the frequent need for high doses of sedation to suppress the severe COVID-19 cough [24].

## Prevention and management

Despite first being described over 2500 years ago, delirium remains frequently unrecognized and poorly understood [9]. It is not inevitable; rather, it is preventable in approximately 30–40% of cases [9]. All older adults who present to a hospital or long-term care home should be screened

for delirium. Prevention is the best management: maintaining hydration encouraging the older adult to drink regularly, ensuring effective communication and orientation (for example explaining where the person is, who they are, and what your role is), ensuring adequate lighting, and explaining to those providing care how they can help are important measures for prevention [16]. Other effective interventions are early mobilization to avert immobilization, treating pain, maintaining oxygenation, and prevention of sleep deprivation [9, 25]. Between the precipitating factors in delirium are described physical restraint and bladder catheter use [26]. Isolation environments may worsen symptoms of delirium. In addition to being isolated from visitors, these patients also have minimal contact with staff, including nursing and rehab services, largely to preserve personal protective equipment (PPE) and reduce exposure [24]. Once delirium occurs, the key steps in management are to address all evident causes, provide supportive care, prevent complications, and treat behavioral symptoms [9]. Initial management of the delirious patient should start with the standard assessment of airway, breathing, and circulation. Hyperactive delirium may present particular challenges in the context of the COVID crisis. Sedation should be avoided where possible as it could precipitate worsening of hypoactive delirium. The current evidence does not support the use of antipsychotics for treatment (or prevention) of delirium in hospitalized older adults [16]. The use of neuroleptics should only be considered if the person is suffering from severe distressing hallucinations/delusions, if the patient is very agitated or if he/she is at immediate risk of harm to themselves or others. The National Institute for Health and Care Excellence (Nice) makes the therapeutic proposal [27] indicated in Table 3. In the course of delirium from COVID-19, the Italian Society of Psychiatry suggests the options, as shown in Table 4 [28]. It is, however, necessary to consider that in COVID-19 patients undergoing pharmacological treatment, QTc prolongation is possible both with chloroquine/hydroxychloroquine, both with some antibiotics and antivirals. It is, therefore, preferable to limit or to avoid the use of drugs that cause prolongation of the Q–T interval preferring drugs with a lower risk of QTc prolongation. Current advice is to start with low-dose lorazepam or haloperidol and increase dose and frequency slowly if needed. It is necessary being aware that benzodiazepines may cause respiratory depression. In severe cases, both antipsychotics and lorazepam may be needed [29]. Table 5 shows the “Key Steps in the Supportive Care of Delirious Patients” according to the American College of Physicians [30].

**Table 3** Treatments for managing delirium (according to National Institute for Health and Care Excellence)

## Able to swallow

Haloperidol 0.5–1 mg at night and every 2 h when required. Increase dose in 0.5–1-mg increments as required (maximum 10 mg daily, or 5 mg daily in elderly patients)

The same dose of haloperidol may be administered subcutaneously as required rather than orally, or a subcutaneous infusion of 2.5–10 mg over 24 h

Consider a higher starting dose (1.5–3 mg) if the patient is severely distressed or causing immediate danger to others

Consider adding a benzodiazepine such as lorazepam (0.5–1 mg 4 times a day as required—maximum 4 mg in 24 h-; reduce the dose to 0.25–0.5 mg in elderly or debilitated patients—maximum 2 mg in 24 h-) or midazolam (2.5–5 mg subcutaneously every 2–4 h as required; reduce dose to 5 mg over 24 h if estimated glomerular filtration rate is less than 30 ml per minute) if the patient remains agitated

## Unable to swallow

Levomepromazine 12.5–25 mg subcutaneously as a starting dose and then hourly as required (use 6.25–12.5 mg in the elderly)

Maintain with subcutaneous infusion of 50–200 mg over 24 h, increased according to response (doses greater than 100 mg over 24 h should be given under specialist supervision)

Consider midazolam (2.5–5 mg subcutaneously every 2 to 4 h as required) alone or in combination with levomepromazine if the patient also has anxiety

**Table 4** Delirium in COVID-19 (by the Italian Society of Psychiatry)

Dexametomidin (for ICU patients): alpha 2 agonist, sedative anxiolytic-analgesic that does not cause respiratory depression

Tiapride: useful if the patient is agitated (hyperkinetic delirium) and in therapy with Lopinavir/Ritonavir. The dosage has the range 50–300 mg in 24 h

Promazine via i.m. (if not contraindicated for coagulation problems), with a dosage that can vary from 50 mg to max. 300 mg in 24 h

Aripiprazole: useful for hypokinetic delirium

Haloperidol: low risk of respiratory depression

Avoid benzodiazepines unless delirium tremens is suspected

**Table 5** Key steps in the supportive care of delirious patients (according to the American College of Physicians)

Minimize indwelling catheters and other “tethers,” such as intravenous lines, electrocardiography leads

Eliminate physical restraints and mobilize the patient as soon as possible

Monitor urinary and bowel output; avoid urine retention and fecal impaction, which can contribute to delirium

Address nutritional needs, including assistance with meals and possible hand-feeding—delirious patients may have difficulty attending to food and are at risk for acute malnutrition

Provide adequate sensory input, including use of glasses and hearing aids, provision of clocks, calendars, and adequate lighting

Provide frequent orientation and structured interpersonal contact to facilitate cognitive “reconditioning”

Adopt healthy sleep–wake cycles, encouraging night sleeping by reducing environmental stimuli, including minimizing staff noise, using vibrating (silent) pagers, eliminating waking for vital signs except if essential, reducing hospital ward lighting, and turning off televisions and radios

## Conclusion

COVID-19 is an emerging, rapidly evolving situation. A severe course of COVID-19 illness is expected in particular in elderly patients with multimorbidity. It has been demonstrated that coronaviruses, especially  $\beta$ -coronaviruses to which the SARS-CoV-2 belongs, do not limit their presence to the respiratory tract and frequently invade the CNS and data indicate that severe systemic comorbidities including acute neurologic illness are associated with the novel viral infection and lead to significant outcome differences [31, 32]. Some patients with COVID-19 may show non-specific neurological symptoms, such as delirium, that may precede

symptoms of fever and cough. Older adults experiencing delirium are vulnerable. Compared with non-delirious patients, delirious patients are more likely to consume more hospital staff time and precious life-support resources, stay longer, and develop in-hospital complications. While created to minimize contagion, policies that increase isolation and immobility for hospitalized patients, combined with acute illness, produce a high-risk environment for delirium [24]. COVID-19 precautions can make the management of delirium challenging. Considering advance care planning with older adults during COVID-19 is extremely important for patients, family members, and clinicians.

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### Compliance with ethical standards

**Conflict of interest** The authors declared that they have no conflicts of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** For this type of study formal consent is not required.

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