NEUROCRITICAL CARE

# Critical illness, delirium and cognitive impairment

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**Survivors of critical illness can experience substantial morbidity long after the event. Recent findings provide further support that long-term cognitive impairment is frequent in these patients, and that in many cases, delirium due to encephalopathy has a causal role in its development.**

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Owing to expanding utilization of intensive care units (ICUs), and improved odds of survival of patients admitted to the ICU, the number of survivors of critical illness is growing. Unfortunately, misery does not end with cure of critical illness. Individuals who have survived can experience substantial long-term morbidity, including post-traumatic stress disorder, depression, cognitive impairment, and ICU-acquired weakness. These conditions have considerable impact, not only for the patients because of reduced quality of life, but also for society as a whole due to increased direct and indirect costs, such as limited ability to return to work. However, data on long-term outcomes after critical illness are scarce.[1] The recently published BRAIN-ICU (Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors) study has illuminated the issue of long-term cognitive impairment after critical illness.[2]

In this study, 821 ICU patients were evaluated during hospital admission, for delirium, which occurred in 74% of cases.[2] 3 months and 12 months after hospital discharge, survivors were tested for global cognition and executive function by means of the Repeatable Battery for the Assessment of Neuropsychological Status and the Trail Making Test. At 3 months, 40% of the patients had global cognition scores that were 1.5 SDs below the population means, which is similar to scores for patients with moderate traumatic brain injury. In addition, 26% of the patients had scores 2.0 SDs below the population means, which is comparable to scores from patients with mild Alzheimer disease. These deficits persisted at 12 months' follow-up, with 34% and 24% of all patients scoring 1.5 SDs and 2.0 SDs, respectively, below the population means. A longer duration of delirium during hospitalization was independently associated with worse global cognition and executive function scores at 3 months and 12 months.[2]

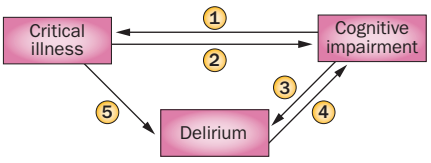


**Figure 1** | The complex relationship between critical illness, delirium and cognitive impairment. Patients with cognitive impairment are at increased risk of critical illness (1).[7] In turn, critical illness increases the risk of long-term cognitive dysfunction (2).[2] Cognitive impairment is a risk factor for delirium (3),[6] and delirium increases the risk of cognitive impairment (4).[2,6] Critical illness increases the risk of delirium (5).[4]

The authors are to be congratulated, as this type of research is difficult to perform. Intensivists do usually not follow up their patients after ICU discharge. As a consequence, the number of studies on long-term outcomes after critical illness is limited.[1] BRAIN-ICU was a large, prospective, multicentre study, and follow-up cognitive testing could be performed in 79% of survivors after 3 months, and in 75% of survivors after 12 months. Patients were evaluated daily for delirium by trained research personnel.[2] The latter aspect is important, as delirium screening as part of routine daily practice can lack sensitivity.[3]

In the BRAIN-ICU study, the duration of delirium during ICU admission was found to increase the risk of long-term cognitive impairment.[2] Delirium is a serious neuropsychiatric syndrome characterized by an acute change in mental status. Patients with delirium show disturbed attention and other cognitive deficits, altered alertness, and, usually, a disturbed sleep pattern. The aetiology of delirium is heterogeneous and complex, as it is usually impossible to attribute delirium to one single cause. Common predisposing factors for delirium include pre-existing cognitive impairment and frailty. Infectious diseases, trauma and surgery are common triggering factors. Delirium can be disturbing for affected patients, and is associated with extended durations of hospital admission, as well as increased mortality and costs.[4]

There is some debate over whether the relationship between delirium and long-term cognitive impairment is truly causal (Figure 1, association 4). In the BRAIN-ICU study, adjustments were made for several indicators of comorbidity and disease severity, which, in contrast to previous studies, included estimates of disease severity during ICU admission.[2] However, contrary to usual practice in critical care research, no additional adjustments were made for the Acute Physiology and Chronic Health Evaluation IV score. Assuming that there is no residual confounding, causality can be evaluated according to the criteria outlined by Hill in a landmark paper in 1965.[5] However, the validity of several of these criteria (for example, specificity and analogy) is questionable.

> "Delirium ... is severely understudied in relation to its status as a major public health problem"

Important criteria for causality are strength and consistency. The findings of the BRAIN-ICU study are relatively robust and in line with previous investigations showing that delirium is a risk factor for incident dementia and for acceleration of existing dementia.[6] Temporality—that is, the exposure precedes the outcome—might also indicate causality, but this is difficult to judge, as pre-existing cognitive impairment is a risk factor for delirium (Figure 1, association 3).[6] Furthermore, critical illness is not a randomly occurring event, and people with cognitive impairment seem to be at increased risk (Figure 1, association 1).[7] These factors can hamper conclusions that long-term cognitive dysfunction is attributable to critical illness *per se*.

The optimal approach to investigate the causal link between critical illness and cognitive impairment would be a population-based study with repeated assessments to test cognitive function before ICU admission.[7,8] In the BRAIN-ICU study, an alternative strategy was used, which seems to be reasonably valid. Relatives were interviewed

at baseline, and patients who were suspected to have pre-existing cognitive impairment were excluded.[2]

A third criterion for causality is a biological gradient, or a dose–response relationship. In the BRAIN-ICU study, longer durations of delirium were independently associated with worse global cognition scores at 12 months.[2] In addition, the findings should be biologically plausible, coherent, and supported by experimental evidence. A possible source of confusion in this regard is that delirium is a behavioural syndrome, and behaviour in itself is unlikely to impair outcome. However, delirium is always a manifestation of an underlying encephalopathy. Important risk factors for delirium in critically ill patients, such as infection and trauma, are associated with increased systemic inflammation. Experimental and autopsy studies show that peripherally produced pro-inflammatory cytokines enter the brain and activate microglia, in synergy with central cholinergic dysfunction.[9,10] As demonstrated in rodents, this neuroinflammatory response can persist for months after a single challenge.[9,10] In some situations, such as pre-existing cognitive impairment, microglia are already primed, which may lead to overactivation in response to new stimuli, resulting in neuronal apoptosis and brain atrophy.[9,10] However, delirium is not always associated with increased systemic inflammation, and it is unclear whether long-term cognitive dysfunction is truly caused by delirium in the absence of such an association.

In conclusion, delirium is likely to have a causal role in the development of long-term cognitive impairment after critical illness in many cases. Delirium is one of the most common complications among hospitalized elderly individuals, and is severely understudied in relation to its status as a major public health problem—a deficiency that studies such as BRAIN-ICU are attempting to address.

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**Competing interests**
The author declares no competing interests.

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