Cognitive dysfunction in intensive care survivors

Cognitive dysfunction is increasingly recognized as a common, often prolonged and potentially disabling complication of critical illness. While demonstrable in patients who have survived a variety of both medical and surgical conditions, its causes remain unclear. Screening of patients in intensive care units and at follow up may help identify those who could benefit from cognitive rehabilitation.

As a relatively young branch of medicine, critical care has evolved rapidly over the past few decades. This has been reflected in the improved survival rates for patients admitted to intensive care units (ICU), including those with such serious diagnoses as severe sepsis and acute respiratory distress syndrome (ARDS). Follow up of these survivors has shown that they suffer frequently from both physical and neuropsychological sequelae after ICU admission, which can be long lasting and prevent a return to their pre-morbid quality of life.

Cognitive dysfunction is one of the neurological complications seen in a proportion of ICU survivors (Hopkins and Brett, 2005). Simply defined, cognition is 'the mental process of knowing'. Within a neuropsychological framework it is further categorized as the brain functions involved with memory, attention/concentration, speed of mental processing, visuo-spatial abilities, general intellect and executive function. This latter term encompasses the assimilation and interpretation of information, decision making based upon this and the ability to follow rules. Cognitive dysfunction is the clinically significant abnormality of one or more of these brain functions. Neuropsychological testing allows the recognition of impairments of cognitive abilities, which can be quantified with reference to normative data. The effects of such dysfunction depend on both the absolute magnitude of the abnormality, and the change in relation to the patient's pre-morbid condition. For example, a previously highly-functioning individual may suffer a level of cognitive impairment classified as mild, which ought not to prevent 'normal' levels of thought and performance. For the individual, however, it may be a significant disruption to what they experienced as normal beforehand.

Impact of cognitive dysfunction

The impact of cognitive dysfunction can be broad. The ability to perform simple tasks associated with daily living and more complex procedures such as driving may be impaired. There may be increased reliance on others to look after affairs such as finances. Returning to work may not be possible. Moreover, the financial burden upon the individuals who cannot regain employment will be great, and will also be borne by their families and society as a whole as their need for support increases.

Studies looking at the relationship between cognitive dysfunction and quality of life have yielded mixed results. Sukantarat et al (2005) followed up 51 patients who had been admitted to a general ICU. They showed an impairment of cognitive function and a reduction in health-related quality of life at both 3 months and 9 months following ICU discharge, but there was no relationship between them. A similar result was shown by Hopkins et al (2004), who studied 66 survivors of ARDS. The small sample size in each study may have prevented an association being shown. Other studies of ARDS survivors have shown worse health-related quality of life scores in those with cognitive impairment (Rothenhausler et al, 2001; Christie et al, 2004), and this has also been demonstrated in patients following other serious illnesses (Hopkins and Brett, 2005). Overall life satisfaction can certainly be reduced. Tellingly, one study found that nine of ten seriously ill patients would rather die than survive with severe neurocognitive disability (Baumgartner et al, 1999).

Prevalence of cognitive dysfunction

There have been relatively few studies looking at the prevalence of cognitive dysfunction in ICU survivors. Hopkins et al (1999) reported on 55 ARDS survivors. All demonstrated neurocognitive impairment at hospital discharge, and 78% showed dysfunction in at least one modality (memory, attention, mental processing speed) at 1 year. A 2-year follow up of an expanded cohort showed cognitive dysfunction in 73% at hospital discharge, 46% at 1 year and 47% at 2 years (Hopkins et al, 2004) – performing at below the sixth percentile for the normal distribution of cognitive function. Rothenhausler et al (2001) retrospectively studied 46 ARDS survivors a median of 6 years after ICU treatment and found that 25% had neurocognitive impairment. All of these studies showed a reduced quality of life in the cohorts reported, but given other confounding variables, an independent

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direct relationship between cognitive impairment and health-related quality of life is very hard to demonstrate.

Studies have looked at a more general ICU population. Jackson et al (2003) examined neuropsychological function 6 months after discharge in 41 patients who had been mechanically ventilated. Seven were excluded because of apparent pre-existing cognitive dysfunction. Of the remaining 34, 32% demonstrated impaired cognition, primarily speed of processing, memory, verbal fluency and visuo-construction. The impairment shown was comparable to clinical dementia of at least mild severity, a level known to disrupt social and occupational functioning.

Sukantarat et al (2005) examined their patients for both general cognitive dysfunction and, more particularly, impairment of executive function. Three psychometric tests were used. An abnormal result was defined as one below the fifth percentile of an age-matched normal population. At 3 months after hospital discharge 55% of patients had an abnormal result in one, and 35% an abnormal result in two or more tests. At 9 months the figures were 27% and 4%.

Comparison of all published data is difficult as there are inconsistencies in patient populations, study design, diagnostic methods, definitions of impairment and time of follow up. However, the evidence suggests that cognitive dysfunction affects 25–78% of ICU survivors and that although there is demonstrable improvement over the first months of recovery the residual impairment may persist for years (Hopkins and Brett, 2005).

Diagnosis of cognitive dysfunction

Diagnosis of cognitive dysfunction requires the use of neuropsychological tests (Jackson et al, 2004). Many exist, although fewer are used in clinical practice, and they are objective, sensitive and validated to assess the domains of cognition. The tests involve a battery of questions and tasks. These differ according to the modality being assessed and correlate with differing brain areas. For example, tests of visual and verbal memory evaluate hippocampal function, whereas tests of executive function (planning, initiation, organization and response suppression) are associated with frontal lobe function.

Most tests rely on a large bank of normative data from population samples, which standardizes the results and allows quantification of the magnitude of impairment. For an individual this relies on knowledge of a baseline level of function. This is not generally available for ICU patients, so either comparison has to be made to matched population data or an estimation made of pre-morbid functional level. The former relies on normative data being derived from a population which is representative of the subjects being studied, but there is likely to be a bias towards those with the time and inclination to undergo investigation as part of test development. Similarly, estimation of pre-morbid function may be affected by the confounding factor of anxiety and depression, present in 24–47% of ICU survivors.

Several other factors may affect the determination of the true incidence of post-ICU cognitive impairment. First, most studies to date have only included a small sample (10–15%) of possible subjects. The level of cognitive impairment in those not studied may have prevented their attendance because it was severe, but equally if it was mild or absent and they were thus otherwise occupied. Second, many studies have reported significant anxiety and depressive symptoms in this group of patients (e.g. Sukantarat et al, 2007), and significant affective disorder may reduce motivation and performance on taxing psychological tests. Finally, it is well recognized that cognitive dysfunction can follow anaesthesia and surgery. Postoperative cognitive dysfunction (POCD) has been seen 3 months after surgery in 6% of middle-aged (Johnson et al, 2002) and 10% of elderly patients (Moller et al, 1998). In the elderly impairment persists for at least 1–2 years (Abildstrom et al, 2000). As many critically ill patients undergo surgery, POCD will likely contribute to any observed cognitive impairment. However, it is thought to be the process of hospitalization and surgery that leads to POCD rather than simply the operation performed or anaesthetic technique, and many elements of this will be common to critical care as well as surgery. Furthermore, much of the impact of POCD seems to have gone after a year, but that of critical illness appears longer lasting.

All neuropsychological tests are time consuming which, along with other factors such as mechanical ventilation, sedation, coma and disease severity, makes them impractical in the ICU setting. The difficulty with diagnosing cognitive dysfunction in the ICU means that other methods need to be used to identify susceptible patients who might benefit from more formal assessment. These methods are the recognition of patients particularly at risk, and the use of simpler screening tests both in hospital and at early follow up. These latter tests include the mini mental state examination (MMSE), which has 17 items (maximum 30 points) and can identify moderate to severe cognitive impairment. Other screening tests take even less time, and there is also benefit from subjective observation and the views of family members, particularly with regards to personality changes, memory loss or problems with functional tasks such as following instructions.

Risk factors for cognitive dysfunction

Identification of those ICU patients at risk of cognitive dysfunction is difficult as the cause is elusive and likely to be multi-modal, although predisposing factors include advanced age, pre-existing cognitive defects, impaired vision or hearing, and abuse of drugs or alcohol. Several associations have been demonstrated, which offer insight into the mechanisms involved and possible therapeutic interventions (Milbrandt and Angus, 2006). Neurotransmitter abnormalities, particularly a reduction in cholinergic activity with resultant dopamine excess, have been linked to cognitive performance. Many drugs used in the ICU have central anticholinergic properties,

including opiates, benzodiazepines and propofol. Endogenous production of anticholinergic substances may also occur with severe illness. Serum anticholinergic activity is raised in surgical ICU patients with delirium.

Critical illness is characterized by multi-organ injury caused by hypoxia, hypoperfusion, inflammation and microvascular thrombosis, and the persistence of cognitive changes suggests a structural brain injury has occurred. Hopkins et al (1999) demonstrated a correlation between periods of hypoxia and hypotension and subsequent cognitive impairment in ARDS patients. Hopkins et al (2006) showed computed tomography evidence of brain atrophy in some patients with ARDS. However, the degree of atrophy did not correlate with disease severity or the level of cognitive defect. More sophisticated imaging, such as high-resolution three-dimensional magnetic resonance imaging, may be able to demonstrate more subtle changes in tissue structure. Brain injury may also be shown by the measurement of serum markers such as S-100B, neuron-specific enolase and myelin basic protein, which have been shown to have been raised following head injury. Hyperglycaemia is also known to worsen the effects of hypoxic-ischaemic brain injury.

Delirium is an acute form of cognitive dysfunction which is common in ICU patients and is an independent risk factor for increased length of hospital stay, persistent cognitive impairment and increased 6-month mortality (Ely et al, 2004). Assessment in the ICU is possible with the confusion assessment method for the ICU (CAM-ICU), which is validated for use in this setting (Ely et al, 2001) and can be particularly useful for diagnosing the less obvious hypoactive delirium. Training and resources for the use of CAM-ICU is available via www.icudelirium.org, under 'delirium assessment'.

Prevention

Prevention of post-ICU cognitive dysfunction should focus on attending to the above risk factors. This would include minimizing use of anticholinergic medications (e.g. by the use of daily sedation interruption), avoiding hypoxia and hypotension and strict control of blood glucose. There is an argument for screening for delirium on the ICU with treatment when it occurs (e.g. with haloperidol). Furthermore, screening at discharge and at early follow up might be used to identify those at risk of cognitive dysfunction, who can then be more formally tested and, if appropriate, referred for cognitive rehabilitation.

Conclusions

Cognitive impairment in survivors of intensive care is common. It can be severe enough to have a markedly detrimental effect on an individual's ability to return to their normal way of life. The exact causes of this impairment remain unclear, but risk can be minimized. Its presence should be suspected and screened for in ICU survivors. **BJHM**

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KEY POINTS

- Cognitive dysfunction is increasingly recognized as a complication of critical illness.
- It affects 25–78% of intensive care unit survivors, and can be demonstrated years after discharge.
- The level of dysfunction can be equivalent to mild/moderate dementia, and markedly affect the ability to lead a normal life.
- The mechanisms involved remain unclear, but candidates include neurotransmitter imbalances and brain injury following hypoxia or hypotension.
- Neuropsychological testing is difficult on the intensive care unit, so an assessment of neurocognitive function should be part of the follow up of critical care patients.
- Screening for delirium on the intensive care unit may help identify patients at risk of prolonged cognitive dysfunction.
- Sophisticated imaging techniques and measurement of specific markers of brain injury may in future help to predict post-intensive care unit cognitive dysfunction.