Delirium and Long-Term Cognitive Impairment: an Overview

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Introduction to delirium as a neurobehavioral syndrome

Delirium is a common neurobehavioral syndrome that occurs in medical, surgical, critical care, and long-term medical care populations, and is associated with adverse outcome. Unfortunately, there is limited research on long-term cognitive outcomes associated with delirium. This report reviews the current evidence regarding the relationship between delirium and cognitive decline in non-demented hospitalized elderly individuals. It appears that an association exists between delirium and cognitive impairment, although significant questions remain about the nature of this association. Additional research on long-term delirium-related effects on cognitive function delirium is needed.

Prolonged hospital stay may lead to adverse post-discharge outcomes

Delirium is a neurobehavioral syndrome characterized by acute confusion, inattention, disorganized thinking, and a fluctuating course (Meagher, Hanlon, Mahony, Casey, & Trzepacz, 2000; Justic, 2000). As others have observed (Meagher, 2001), it may be the most common psychiatric condition experienced by hospitalized elderly, affecting between 15% to 20% of general hospital patients (Levkoff et al., 1992; Lipowski, 1989), 25% to 65% of surgical patients (Galanakis, Bickel, Gradinger, Von Gumpenberger, & Forstl, 2001; O’Keefe & Chonchubhair, 1994) and as many as 80% of patients in intensive care unit (ICU) settings (Ely, Siegel, & Inouye, 2001; Ely et al., 2001). Once
considered benign (McGuire, Basten, Ryan, & Gallagher, 2000), recent evidence has linked delirium with a wide-range of adverse outcomes, including prolonged hospitalization (Thomas, Cameron, & Fahs, 1988; Inouye, Rushing, Foreman, Palmer, & Pompei, 1998; Elg et al., 2002; Chisholm, Deniston, Igrisan, & Barbus, 1982; Rabins & Folstein, 1982; Dolan et al., 2001; Uldall, Ryan, Berghuis, & Harris, 2000), poor recovery from surgery (Marcantonio, Michaels, Resnick, & Flacker, 2000; Marcantonio et al., 1994; Galanakis et al., 2001), and increased morbidity and mortality (Jitapunkul, Pillay, & Ebrahim, 1992; McCusker, Cole, Abrahamowicz, Primeau, & Belzile, 2002).

To date, very few studies conducted have explored post-discharge cognitive outcome following delirium. The purpose of this article is to review the relationship between delirium and cognitive decline, to offer possible explanations for their relationship, and to provide recommendations for future research and clinical practice.

**Association between delirium and negative cognitive outcomes**

Research on the relationship between delirium and cognitive outcomes is limited to eight studies, although these investigations have consistently demonstrated a link between acute and long-term cognitive impairment (Table 1). Of these, four reported greater declines on cognitive measures at follow-up among patients experiencing delirium during hospitalization relative to matched controls. Dolan et al. (2001) studied geriatric patients with hip fractures (excluding those with a diagnosis of dementia based on chart review) and found that individuals with delirium were almost twice as likely to have cognitive impairment at two-year follow-up. Francis and Kapor (1992) investigated community dwelling elderly who were hospitalized, and found that individuals with an episode of delirium had slightly lower MMSE scores at six-month follow-up (24.7 vs. 26.7) and experienced further cognitive decline over the next 18 months relative to the comparison group which showed no decline. Because the two groups were matched on the highest hospital MMSE score (mean = 27) which indicated relatively good cognitive function and the statistical analysis adjusted for pre-existing cognitive impairment, the small but significant cognitive decline in patients with delirium was not due to pre-existing clinical dementia. McCusker et al. (2001) studied hospitalized geriatric patients following treatment in the emergency department (excluding those with pre-existing dementia based on the IQCODE) and found that the MMSE scores of patients with delirium were nearly five points lower than those of patients without delirium at one-year follow-up. These investigators controlled for potentially confounding variables such as pre-morbid function, co-morbid diseases, and illness severity. Katz et al. (2001) evaluated geriatric nursing home and assisted living residents over a 12-month period using a brief neuropsychological test battery, excluding individuals with severe cognitive impairment as assessed by the BMICT. Those patients who experienced an episode of delirium during hospitalization showed significant cognitive decline on neurocognitive measures including the MMSE. Since baseline (pre-hospitalization) MMSE scores did not predict who would develop delirium, this difference was not likely attributable to pre-existing dementia (Katz et al., 2001).

Three studies found higher incidence rates of dementia at long term follow up among elderly patients with a history of delirium during hospitalization. Rahkonen et al.
(2001) studied a sample of patients 85 years or older, excluding individuals with dementia based on a clinical interview and the use of MMSE and measures of activities of daily living and instrumental activities of daily living. They found that subjects with an episode of delirium during hospitalization were significantly more likely to be diagnosed with dementia at three-year follow-up than the subjects who did not develop delirium. Rockwood et al. (2001) studied geriatric patients from a general medical service (after evaluating for dementia at baseline) over a three-year period. They found that 60% of patients with delirium on admission were diagnosed with dementia compared to only 18.5% of the subjects without delirium. The incidence of dementia was 18.1% per year for individuals with delirium versus 5.6% per year for those without delirium. Koponen et al. (1989) reported 1-year follow-up MMSE scores in 70 patients diagnosed with delirium during psychiatric hospitalization, showing that one third evidenced cognitive deterioration. Interpretation of these results is limited by the absence of a comparison group, the fact that the majority of patients had a diagnosis of Alzheimer’s or vascular dementia, and the lack of assessment of pre-existing cognitive impairment.

One study identified persistent cognitive impairment in nearly one in three patients with delirium at six-month follow-up (Jackson et al., 2003). This study failed to find a relationship between duration of delirium and poor cognitive outcome. Jackson et al. (2003) assessed a cohort of 34 mechanically ventilated ICU survivors six months post-hospital discharge, all of whom experienced at least one episode of delirium. At follow-up, subjects were administered a battery of neuropsychological tests and classified as cognitively impaired or non-impaired. A trend was found for a longer duration of delirium in impaired than non-impaired cohorts, but it did not reach statistical significance in this small sample. Importantly, subjects in this study were not primarily geriatric patients, as their mean age was substantially lower than in the other studies cited here (M=53.2 yr.). Given the acute nature of their illness, even the elderly patients in this study may have had better pre-morbid health than the frail elderly populations in the other studies reviewed. The absence of a robust relationship between duration of delirium and cognitive functioning suggests that the presence of delirium may be more critical than its duration in predicting long-term cognitive outcome.

What do we know theoretically to explain the association?

Various theories have been proposed to explain the relationship between delirium and cognitive decline. These theories include the potentially adverse effects of medical illness on cognition, particularly among frail elderly, (Patrick, Gaskovski, & Rexroth, 2002; Sands et al., 2002), the common pathological processes underlying delirium and dementia (Gibson, Blass, Huang, & Freeman, 1991; Eikelenboom & Hoogendijk, 1999), and the impact of sedatives and analgesics on long-term cognitive function (Moore & O’Keefe, 1999). To date, studies examining the relationship between delirium and cognitive outcomes have not focused on putative mechanisms.

The findings of cognitive decline among hospitalized elderly are consistent with the literature which suggests that medical illnesses in general, and cumulative illnesses, may signal the beginning of the process of cognitive deterioration (Patrick et al., 2002;
Doraiswamy, Leon, Cumings, Marin, & Neumann, 2002). For so-called “frail” elderly (Hammerman, 1999), who are physically and medically vulnerable due to factors such as diminished physical status and compromised nutrition, even minor insults can have a profound impact and lead to cognitive impairment and functional disability (Nourhashemi et al., 2001). Burgeoning evidence points to an association between numerous medical conditions such as Acute Respiratory Distress Syndrome (ARDS) (Rothenhausler, Ehrentraut, Stoll, Schelling, & Kapfhammer, 2001; Hopkins et al., 1999), Hepatitis C (Hilsabeck, Perry, & Hassanein, 2002), and congestive heart failure (CHF) (Almeida & Flicker, 2001) and the development of cognitive impairment. Additionally, the emergence of cognitive impairment following surgery in individuals with normal pre-morbid cognitive function is well documented (Newman et al., 2001). The underlying physiological changes that mediate the effects on cognition are unclear and undoubtedly variable, but the preceding list of medical conditions suggests that hypoxia is a likely contributing factor in some cases.

It remains unclear why cognitive deterioration is accelerated in medically ill subjects with delirium. A contributing factor may be that subjects with delirium tend to be more severely ill than matched controls, and that the delirium may be caused or potentiated by features of their illness. This suggestion is consistent with the fact that in all of the studies reviewed here examining the severity of illness, delirium cohorts were more ill than matched controls. In addition to having a high prevalence of neurological disease, the patients with delirium also tended to suffer from more cardiovascular disease and high systolic blood pressure, conditions which have been implicated in the development of vascular dementia (DeCarli, 2003; Antonelli Incalzi et al., 2003; Lopez et al., 2003). Among patients who are predisposed by their pre-existing illnesses to develop cognitive impairment, it may be that delirium is a harbinger of emerging cognitive abnormalities. Some researchers have speculated that delirium is a marker for early or sub-clinical dementia-causing illness, and that the same pathogenetic mechanisms might underlie both of these syndromes (Eikelenboom et al., 1999), although from a clinical standpoint they share both similarities and differences. For example, inflammatory processes contribute to the development of delirium, but are also present in the brains of individuals with Alzheimer’s disease (McGeer, Schulzer, & McGeer, 1996). Similarly, other studies have suggested that elevated cytokines (interleukin-1) may play a central role in the pathogenesis of delirium (Stefano, Bilfinger, & Fricchione, 1994; Lindesay, MacDonald, & Starke, 1990). More generally, delirium may be a marker of reduced brain reserve capacity even in the absence of a sub-clinical or early dementia causing processes.

Another possible explanation for the association between delirium and cognitive decline relates to the effects of medications, such as sedatives and paralytics, on long-term neuropsychological function. Many medications used for sedation or pain control are widely recognized to cause or worsen delirium, and their use contributes to the high delirium prevalence rates in both surgical and critically ill populations (Winawer, 2001; Dyer, Ashton, & Teasdale, 1995; Somprakit et al., 2002; Granberg, Malmros, Bergbom, & Lundberg, 2002). Although data on the impact of anesthetics and sedatives on long-term cognitive function is conflicting, numerous reports have suggested that
they may have toxic effects on the brain, particularly for high risk groups such as the very old (over 75 years) or those with a recent history of cognitive impairment (Ancelin et al., 2001; Dodds & Allison, 1998).

Although delirium may be a sign of emerging neuropsychological impairment, it is clearly not the case that the cognitive decline experienced by large numbers of patients with delirium is solely or primarily related to pre-existing cognitive impairment or an early dementia causing process. Methods used for pre-existing cognitive impairment screening may have shortcomings. However, many investigations used methods likely to identify even mild dementia (Jackson et al., 2003; Rockwood et al., 2001; McCusker et al., 2001), and found that patients with delirium performed poorly on cognitive measures at follow-up (Table 2).

In one study, Jackson et al. (2003) only included ICU patients experiencing delirium; but based on an assessment, they excluded those with probable early dementia. Exclusion was based on a conservative cut-off score on the MBDRS. Included patients were studied six months afterwards in follow-up, and one third of them demonstrated mild to moderate impairment indicative of dementia. This high number by itself suggests that delirium is not simply a marker of pre-existing sub-clinical or early dementia, but other factors may influence its onset.

Conclusion

The relationship between delirium and long-term cognitive impairment has been ignored or overlooked for many years, due to the common perception that delirium is a benign condition. However, the growing recognition that delirium is associated with a wide variety of adverse outcomes has led to greater concern about this common condition. Although much progress remains to be made, clinicians working with patients at risk for delirium can consider monitoring patients for delirium, while focusing on delirium prevention or on interventions that reduce its' frequency. Clinicians can also be sensitive to the possibility that individuals with delirium may experience adverse cognitive outcomes and should consider referring these individuals to psychologists or neurologists when necessary, especially if symptoms of delirium persist after hospital discharge.

In a similar vein, researchers would be well advised to continue addressing the relationship between delirium and long-term cognitive impairment, with particular attention to a few key issues including the pathogenesis of cognitive decline associated with delirium, the identification of patients at highest risk for cognitive decline following delirium, and the possible causal link between medications (e.g. sedatives) and long-term cognitive impairment in populations of patients with delirium. This is particularly important for ICU populations, who receive large doses of sedatives.

As the result of a thoughtful focus on both clinical interventions and the development of innovative and rigorous research, it may be possible to address the problem of delirium with increasing effectiveness and reduce its frequency among high-risk patients. Such a goal is critically important, as delirium appears to be
significantly implicated in the development of cognitive impairment in large numbers of ICU survivors, as well as other medical patients.

References


<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Study Design</th>
<th>Follow-Up Period</th>
<th>Delirium Measure</th>
<th>Cognitive Outcome Measure</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koponen and Riekkinen (1989)</td>
<td>70</td>
<td>Geriatric psychiatric hospitalized patients</td>
<td>Prospective</td>
<td>1 year</td>
<td>Clinical Rating</td>
<td>D-Test⁸</td>
<td>Cognitive deterioration associated with delirium observed in 36% of patients at 1-year follow-up</td>
</tr>
<tr>
<td>Francis et al (1992)</td>
<td>22</td>
<td>General hospitalized medical patients</td>
<td>Prospective</td>
<td>2 years</td>
<td>Chart review, clinical interview, MMSE</td>
<td>Modified Telephone MMSE</td>
<td>Decline in MMSE scores in patients with delirium compared to controls</td>
</tr>
<tr>
<td>Rockwood (1999)</td>
<td>20</td>
<td>General hospitalized medical patients</td>
<td>Prospective</td>
<td>3 years</td>
<td>DRS³, MMSE⁶, Clinical Judgment, CIRS⁵</td>
<td>MMSE, Blessed Dementia Rating Scale, Geropsychiatr. interview</td>
<td>Delirium was associated with increased dementia at follow-up</td>
</tr>
<tr>
<td>Dolan et al (2000)</td>
<td>68</td>
<td>Hip replacement surgery</td>
<td>Prospective</td>
<td>2 years</td>
<td>Chart review, proxy interviews using a modified CAM version</td>
<td>MMSE</td>
<td>Subjects with delirium were more likely to have cognitive impairments at 2-year follow-up</td>
</tr>
<tr>
<td>McCusker et al (2001)</td>
<td>31</td>
<td>Medical patients</td>
<td>Prospective</td>
<td>1 year</td>
<td>CAM²</td>
<td>MMSE</td>
<td>Patients with delirium had lower MMSE scores at 1-year follow-up compared to controls</td>
</tr>
<tr>
<td>Katz et al (2001)</td>
<td>10</td>
<td>Residential care patients</td>
<td>Prospective</td>
<td>1 year</td>
<td>Clinical evaluations</td>
<td>MMSE, Buschke Selective Reminding Tests, Stroop Test, Verbal Vigilance</td>
<td>Subjects who develop delirium within the context of a medical illness demonstrated greater cognitive decline</td>
</tr>
<tr>
<td>Rahkonen et al (2001)</td>
<td>19</td>
<td>Community-dwelling patients</td>
<td>Prospective</td>
<td>3 years</td>
<td>Surrogate interviews, clinical interviews, chart review</td>
<td>MMSE, ADL⁶, IADL², Chart Review</td>
<td>Increased risk for new diagnosis of dementia among “oldest old”</td>
</tr>
<tr>
<td>Jackson et al (2003)</td>
<td>34</td>
<td>Medical ICU patients</td>
<td>Prospective</td>
<td>6 mths</td>
<td>CAM-ICU¹</td>
<td>Comprehensive neuropsychological battery</td>
<td>No significant association between delirium duration and cognitive outcomes</td>
</tr>
</tbody>
</table>

¹CAM-ICU=Confusion Assessment for the Intensive Care Unit; ²CAM=Confusion Assessment Method; ³DRS=Delirium Rating Scale; ⁴Mini-Mental State Exam; ⁵Cumulative Illness Rating Scale; ⁶ADL=Activities of Daily Living; ⁷IADL=Instrumental Activities of Daily Living; ⁸D-Test= No explanation was available in the text or elsewhere.
Table 2. A selective list of delirium screening tools

<table>
<thead>
<tr>
<th>Test</th>
<th>Author (year)</th>
<th>Duration of admin. (minutes)</th>
<th>Test description</th>
<th>Cut-off score</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Hart et al, (1996)</td>
<td>10-15 mins</td>
<td>A scale that assesses five areas of functioning (orientation, attention, visual memory, and conceptual reasoning)</td>
<td>Total Score equal or less than 19 (out of a possible 30) indicates delirium</td>
<td>Correlates with the MMSE in delirious patients</td>
</tr>
<tr>
<td>CAM&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Inouye et al, (1990)</td>
<td>Less than 5 mins</td>
<td>A 9-item test assessing onset/fluctuating course, inattention, disorganized thinking, and altered level of consciousness</td>
<td>Delirium is diagnosed when both Features 1 and 2 are positive, along with Feature 3 or Feature 4</td>
<td>Consists of nine operationalized criteria from the DSM-IV</td>
</tr>
<tr>
<td>CAM-ICU&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Ely et al, (2001)</td>
<td>1 min</td>
<td>A highly abbreviated version of the CAM, which was designed for the rapid assessment of non-verbal patients</td>
<td>Delirium is diagnosed when both Features 1 and 2 are positive, along with Feature 3 or Feature 4</td>
<td>The only tool validated for use in ICU populations</td>
</tr>
<tr>
<td>DRS-R-98&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Trepacz et al, (1988)</td>
<td>15-30 mins</td>
<td>A 16-item clinician rating scale that assesses a wide variety of symptoms associated with delirium</td>
<td>Total Score equal or over 15.25 (out of a possible 39) indicates delirium</td>
<td>Designed to measure delirium severity</td>
</tr>
<tr>
<td>MDAS&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Breitbart et al, (1997)</td>
<td>10 mins</td>
<td>A 10-item instrument that assesses delirium severity and is designed for repeat administration during the same day</td>
<td>Total score equal or over 13 indicates delirium</td>
<td>Integrates behavioral items with cognitive testing</td>
</tr>
<tr>
<td>NEECHAM Confusion Scale</td>
<td>Neelon et al, (1996)</td>
<td>10 mins</td>
<td>A bedside assessment tool that assesses processing (attention, commands, orientation) and behavior (appearance, motor, verbal)</td>
<td>Total Score less than 25 (out of a possible 30) indicates delirium</td>
<td>Detects early manifestations of acute confusion</td>
</tr>
</tbody>
</table>

<sup>1</sup>CDT= Cognitive Test for Delirium,  <sup>2</sup>CAM= Confusion Assessment Scale,  <sup>3</sup>CAM-ICU= Confusion Assessment Method-Intensive Care Unit, <sup>4</sup>DRS-R-98= Delirium Rating Scale Revised 98, <sup>5</sup>MDAS= Memorial Delirium Assessment Scale

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