

Short- and Long-Term Cognitive Consequences of Acute Non-Neurological Hospitalization

Most neurologists are not surprised to hear that a patient has cognitively or physically deteriorated after hospitalization, but what is the evidence and mechanism for this?

BY RONALD DEVERE, MD

Part I

Clinical neurologists are often challenged with elderly patients (>65yrs.) who develop cognitive decline following an acute hospitalization of varied severity. This includes patients who were cognitively normal or who were known to have cognitive impairment at various levels including dementia, prior to hospitalization.

Most neurologists are not surprised to hear that a patient has cognitively or physically deteriorated after hospitalization, but what is the evidence and mechanism for this? Do the cognitive and activities of daily living (ADLs) improve, stabilize or progress over time? This is a very important clinical question because we have to know whether the patient's worsening needs further neurological workup at the time of the visit, and help decide the cause of the cognitive decline. For example, does a patient with amnesic multiple domain mild cognitive impairment prior to hospitalization—and progresses to dementia after the acute hospitalization—have Alzheimer's disease or a temporary worsening that will remain stable? Does a patient with normal cognitive function who develops non-amnesic MCI after acute hospitalization have the same risk of progression as the non-hospitalization group?

These cognitive changes after hospitalization can also impair activities of daily living, behavior and increase caregiver stress that may not have been there prior to hos-

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pitalization. Can we do something to minimize these outcomes? Can we help play an active role, if consulted in the hospital, or help educate our medicine and surgical colleagues about this problem and what can be done to minimize its development? The articles discussed in this paper are the main ones that have studied a very large series of patients and more importantly have pre-hospitalization cognitive scores and longer follow up, making the data and outcomes more clinically meaningful.

This review will not discuss the post-operative effects on cognitive function associated with anesthesia and surgery. This will be covered in part II.

CLINICAL COMMENTS

As our population continues to age, acute illnesses such as sepsis, pneumonia, urinary tract infections and the need for mechanical ventilation are increasing in incidence, occurring much higher in adults 65 years and older, with increasing number of survivors.^{1,2}

This topic was recently addressed by Ehlenbach, et al. 2010 in *JAMA*.³ They studied a very large population of elderly to determine whether decline in cognition was greater in those individuals who experienced acute hospitalization (critical or non critical causes), compared to a group not requiring hospitalization. What was unique about this study compared to others was that objective measures of cognitive function were included prior to and following acute hospitalization, and follow up data were present for a number of years. A total of 2,929 patients were studied over a mean follow up of six years. Sixteen-hundred (55 percent) had no hospitalization, 1,287 (42 percent) were hospitalized for non-critical illness, and 43 (two percent) had critical illness hospitalization. All patients were under study for a median of four years before any hospitalization. The initial follow up visit after hospitalization discharge varied from a median of 307 days for the non-critical illness patients to 365 days for the critical illness group. The study used a Cognitive Ability Screening Instrument (CASI) which measured attention, orientation, concentration, immediate and long term memory, language, fluency, visual perception, judgment and abstract reasoning. The scoring ranged from zero to 100. A score of 86 equaled a Mini Mental State Exam score of 25-26 (normal).

Adjusting for age, sex, baseline cognitive score, years of education, time since baseline visit including comorbidities, the cognitive score for the non-critical illness hospitalization patients was a mean of one point lower than the non-hospitalized group. The critical illness group scored a mean of 2.14 points lower than the non-hospitalized group, all felt to be statistically significant. What was most important was that the slow rate of cognitive decline in some patients prior to hospitalization did not change post hospitalization. Dementia occurred post acute hospitalization in both critical and non-critical illness. In 263 cases of dementia in the study, 99 were present in the non-hospitalized group, 161 in the non-critical hospitalized group and three in the critical illness group. What was very interesting about the cases that developed dementia after hospitalization versus non-hospitalization was the difference in case mix. In the non-hospitalization group Alzheimer's disease developed in 76 percent, vascular dementia in seven percent and other dementias in 17 percent due to medical diseases and other non-degenerative etiologies (not specified). The non-critical hospitalized

group developed Alzheimer's in 60 percent, vascular dementia in 11 percent, and other dementias in 28 percent. The patients who were hospitalized for critical illness were made up of only five cases that were not enough to give any statistical meaning of dementia causes. A further very important clinical observation was that there was no evidence that the rate of cognitive decline changed after either non-critical or critical hospitalization. This strongly suggested that an acute or critical illness may cause an abrupt loss of cognitive decline rather than steepening the slope of decline or simply being a marker of cognitive impairment. This important information suggests that non-degenerative causes of dementia have to be more aggressively searched for and recognized in post hospitalization patients and not rush to a diagnosis of degenerative disorders like Alzheimer's disease.

Iwashyna, et al. in 2010 discussed long-term cognitive and functional impairment among survivors of severe sepsis.⁴ They defined severe sepsis as requiring an infection and new onset of organ dysfunction during the hospitalization. They studied 9,222 patients and identified 1,194 patients with 1,520 episodes of severe sepsis. Many of these patients died. The surviving group studied included 516 patients who had at least one follow up survey. These cases had also been followed for four surveys (eight years) prior to sepsis and four surveys (eight years) after sepsis. A mean of 6.1 percent of survivors had moderate to severe cognitive impairment before sepsis, which increased to 17 percent at the first survey after sepsis. An equal number of previously normal patients developed MCI after sepsis as patients with MCI pre-sepsis developed moderate to severe cognitive impairment post sepsis. Functional limitations (ADLs) were also evaluated and found to be more impaired in those patients with better baseline physical function and was not concentrated in any particular category of walking, dressing, bathing, grocery shopping, preparing a hot meal, making phone calls, taking meds, and managing money. Overall, in those patients who developed severe sepsis, 60 percent were associated with worse cognitive or physical function or both, among survivors at the first post sepsis survey. These impairments tended to stabilize and gradually improve as early as four months to three years after hospitalization.

On the chance that some other medical or neurological condition could have interfered with the pre- and post- sepsis cognitive and functional outcomes, the authors studied a smaller group of 205 patients with no limitations at baseline, no hospitalization between baseline, and sepsis admission. The outcome of cognitive impairment and functional disability was identical as in the larger group of post sepsis patients.

This study showed that the odds are triple of developing mild to moderate cognitive impairment after sepsis.

The study also independently showed that 1.5 new functional limitations occur post sepsis in patients with none, mild, or moderate preexisting functional limitations and results, as in the previous study, in increasing caregiver burden.

Phelan, et al. just recently published a paper regarding the risk and causes of acute hospitalization in dementia patients, their outcome, and the possibility of prevented hospitalization.⁵ The study enrolled 494 dementia patients (58 percent with Alzheimer's, 16 percent with stroke, and 15 percent with multiple etiologies), who were part of 3,638 individuals who were initially cognitively normal and cognitively followed closely over 14 years or until death. Hospitalization information was obtained retrospectively on the dementia and dementia-free individuals during the study. Of the 494 dementia cases, 290 died with dementia before the end of the study, 170 were followed to the end of the study, and 34 left the study early. In the follow-up period, 86 percent of the dementia group was hospitalized, compared to 59 percent of the dementia-free group. The common potentially preventable disorders causing hospitalization were looked at in earnest (angina, asthma, bacterial pneumonia, cellulitis, congestive heart failure, chronic obstructive pulmonary disease, dehydration, diabetes, duodenal ulcer, ear infections, high blood pressure, hypoglycemia, flu, seizures and malnutrition). Forty percent of the dementia group had admissions for these medical disorders compared to 17 percent of the dementia free group. Looking specifically at five categories of illness leading to admission rates (circulatory, genitourinary, infections, respiratory and neurological) were found to be significantly higher in dementia versus the dementia free cases. This study did not specifically address cognitive decline like the other two studies^{3,4} but gave us more information about the reasons for hospitalization.

Why are dementia patients getting admitted acutely to the hospital in common preventable medical conditions? We already know from the previous two studies that acute hospitalization can itself lead to cognitive decline. The authors discussed the highly probable reasons for dementia causing increased hospitalization:

- Swallowing difficulty occurs in many dementias, such as Lewy Body, Parkinson's and multiple stroke dementia and later stages of AD. This can lead to increased aspiration and development of pneumonia.
- Dementia impairs the person's ability to self-manage chronic medical conditions and pinpoint and alert others to their presence.
- Changes in living conditions of a demented patient can lead to temporary or permanent absence of a caregiver who is familiar with the patient's behavior, usual habits and general medical care.

- Any acute illness in a dementia patient can lead to worsening of brain function through metabolic and other unclear factors, which is more likely to lead to delirium and functional impairment. Pneumonia, congestive heart failure, and urinary tract infections accounted for two-thirds of all preventable admissions among the dementia group.

PATHOGENESIS

The exact cause(s) of cognitive and functional impairments after acute hospitalization are not totally clear. Most authors agree that it is likely due to multiple causes and can include: hypotension and hypoperfusion;⁶ hypoxemia;^{7,8} systemic inflammation;⁹ sedative and analgesic medication;^{10,11} glucose dysregulation;¹² and delirium.^{13,14} In addition, hospitalization may actually be a marker for cognitive decline or dementia that had previously gone undiagnosed. More specific studies are needed to understand these mechanisms, and the role each plays in contributing morbidity in these cases.

These studies have some important limitations. The time frame for the first follow up visit in the first paper was a median of 300-plus days while the second paper did not say specifically when follow up times were related to the sepsis. It is possible that the cognitive function level at the time of the first survey and future surveys of the first study may not have been all related to the acute hospitalization. Unlike the first article, the second article did not describe the causes of dementia that occurred post sepsis, so it is not clear how many were degenerative or related to the medical illness. There is also no real standard definition of critical illness; there is risk of misclassification of some patients.

Another limitation of these important papers is that the term "delirium" was never mentioned to have occurred or looked for in the studies. Delirium however, was used to describe one of the pathogenic mechanisms of cognitive and functional impairment in the acute hospitalized patient. There are many published papers that consider delirium by itself a cause of cognitive and functional decline with variable prognosis. Because of the importance of delirium in acute hospitalization and cognitive outcome, and numerous papers published on this subject, it is necessary to review pertinent information related to this topic.

DELIRIUM

Based on the DSM-IV diagnostic criteria, delirium is defined as: disturbance of consciousness (ie.; reduced clarity of awareness of the environment usually with lethargy, with reduced ability to focus, sustain or shift attention, impaired cognitive function (with or without delusions)), not accounted for by

preexisting dementia. It is usually acute in onset (hours to days), fluctuates, and is often caused by the direct physiologic consequences of a medical disorder. The agitated hyperactive form of delirium is easy to recognize compared to the lethargic form which is more common. The agitated form has a poorer prognosis.^{13,15} Both forms of delirium can be present in the same individual.

Delirium complicates hospital stays in more than 2.5 million older persons yearly and results in increasing need for caregiver, nursing home, and home health services resulting in increased health costs. The prevalence of delirium at the time of hospitalization and that develops during non-surgical hospitalization varies from 14-24 percent in the former and six to 50 percent in the latter.^{13,15,16} It is well recognized that the cognitively impaired or ill elder patient is more likely to develop delirium regardless of the cause. Predisposing risks to development of delirium include preexisting cognitive impairment or dementia, advanced age, dehydration, vision and hearing impairment, chronic renal and liver impairment, and use of multiple medications, to name a few. Precipitating factors for delirium are innumerable and include everything from new medications (especially sedative-hypnotics, narcotics and those that have anti-cholinergic effects), indwelling bladder catheters, dehydration, liver or kidney failure, drug or alcohol withdrawal, infections and electrolyte imbalance to immobilization and physical restraints.¹³

One of the most thorough review studies on the subject of delirium and cognitive decline was published by Jackson, et al. in 2004.¹⁷ They reviewed the entire literature on the subject up to that time. They stated that 15-20 percent of general hospital patients develop delirium and can rise to 80 percent of cases who are in intensive care units. The major limitations of most studies were the lack of uniformity of evaluating cognitive function (clinical interviews, medical chart reviews, various cognitive function scales etc.), assessing delirium (chart review, various delirium scales, MMSE etc.) and assessing cognitive function after delirium (MMSE, telephone interviews, ADL assessments, incomplete neuropsychological testing). Alasdair, et al.¹⁸ reviewed the same topic in papers published from 2004 to 2009. They came to similar conclusion about methodological issues, small sample sizes and inadequate controls. Bearing in mind the limitations in many of these studies, both review studies concluded the following:

- Patients with delirium were overall more ill than non-delirium patients.
- Acute hospitalization with delirium in cognitively normal elderly individuals (>65yrs) often leads to cognitive decline from six months to one year in 25-70 percent of survivors (equivalent to at least a 5 point drop on MMSE). Deficits usually improve in the first year, but can range from six

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months to six years. The length of the delirium period may not be as important as the development of delirium. (Delirium can last as short as a few days to two or more months where the distinction from dementia can be blurred). Precipitants of delirium in acute hospitalization such as hypoxia, and hypotension can lead to permanent brain injury and limit any recovery.

- The greater the pre-hospitalization cognitive impairment, the greater the cognitive decline after delirium (MCI can become dementia, mild dementia can become severe dementia, etc.).
- Some studies concluded that the incidence of dementia following an episode of delirium in a normal cognitive elderly population is more common than those without delirium and recognized shortly after the delirium and two to three years later.^{19,20} (The conclusions in these studies were obtained by chart review only and by lack of a comparison group).
- It is clearly not the case that cognitive decline experienced by a large number of patients with delirium is primarily or solely related to a preexisting cognitive impairment or an early dementia disorder.^{16,21}

The definitive information on cognitive decline and delirium is incomplete and the jury is still out. More studies are needed and should include:

- Unified definition of delirium to include hyperactive, hypoactive, severity and duration, etc.
- Investigators should utilize validated, quantitative instruments to diagnose delirium.
- Using standard agreed upon cognitive testing instruments to measure baseline and post delirium cognitive function.
- More defined mechanisms of the relationship between delirium and cognitive decline.

This will help to further focus on early intervention and prevention of delirium and hopefully eliminate or reduce the poorer long term cognitive outcomes.

ALZHEIMER'S DISEASE AND DELIRIUM

Previous studies have shown that well known factors can influence cognitive decline in Alzheimer's disease that cannot be modified. These include older age, male gender, rapid onset of disease and higher dementia severity.

Delirium, which occurs in 70-80 percent of Alzheimer disease hospitalizations, is preventable.¹³ Fong, et al. in 2009 did a detailed study of delirium and hospitalization in Alzheimer's disease patients at Massachusetts General Hospital.¹⁴ Of 990 Alzheimer patients, 195 were hospitalized and underwent three independent chart reviews. A total of 112 patients developed delirium. Three hundred and thirty six Alzheimer patients were in the non-delirium group and the difference between both groups was controlled for. The study used a cognitive assessment called "Information, Memory and Concentration Test" prior to delirium. For the delirium group, the baseline test score declined by 2.5 points per year. After delirium the decline was 4.9 points per year. For the non-delirium group, the baseline scores of decline remained the same (1.8-2.2 points/yr.). This study confirmed that incident delirium accelerates the trajectory of cognitive decline in hospitalized patients with Alzheimer's disease by 53 percent or an equivalent of an 18-month decline versus a 12-month decline without delirium. Other studies have shown that patients with dementia who develop delirium have increased rates of hospitalization, institutionalization, and mortality. Delirium used to be viewed as a transient cognitive disorder, but this and other studies have shown that it is not always temporary and can lead to persistent functional and cognitive losses.¹⁶

SOME SUGGESTED GUIDELINES FOR CLINICAL NEUROLOGISTS BASED ON THIS CLINICAL REVIEW

- It is very clear that patients who have acute hospitalization for primary non-neurologic causes can often develop cognitive and functional decline after discharge, usually worse if the hospitalization was for a critical illness such as sepsis or requiring mechanical ventilation.
- It is very important in these patients that the neurologist obtains a very detailed cognitive history prior to hospitalization, which may require information from family members and/or friends who do not accompany the patient. Giving out activity of daily living (ADL) assessment sheets to caregiver(s) is usually much more thorough and sensitive than just asking the caregiver a limited number of questions. This detail cognitive and functional pre-hospitalization information can help to determine the extent of decline after hospitalization. For example, if a normal patient develops MCI after hospitalization versus a patient who had MCI before hospitalization and doesn't change or develops dementia post hospitalization helps to determine the extent of cognitive impairment after the acute illness.
- The extent and chronology of impairment is very impor-

tant, since many of these patients improve with time and stabilize. This suggests that degenerative disorders like Alzheimer's are less likely and that further extensive neurological testing may not be necessary. Usually, patients with cognitive impairment in acute hospitalizations, including delirium, often have neurological testing such as CAT or MRI scans, EEG or lumbar puncture to eliminate structural brain lesions, seizures or CNS infection.

- If cognitive decline progresses following acute hospitalization and especially continues to decline after six months, this may not be the norm, regardless of severity of impairment. Degenerative disorders like Alzheimer's or possible vascular dementia needs to be considered (provided all basic neurological tests for cognitive decline have previously been done and were normal). If Alzheimer's disease is suspected, but not clear, based on the chronological history of the illness and hospitalizations, it may be diagnostically helpful to do a FDG PET scan and or lumbar puncture to measure AB42/Tau ratio. If the acetylcholinesterase or glutamate inhibitors are being considered for treatment, than a more definitive diagnosis of the cognitive impairment post hospitalization is needed.
- These patients can be complicated in trying to put together pre-existing, post hospitalization and follow up cognitive impairments, and this needs to be discussed in detail with the caregiver(s).
- If the patient meets clinical criteria for "delirium," it should be documented in the patients' chart. Expect cognitive decline post-delirium to be more severe and take longer to stabilize (six months to one year or more). If the patient is known to have dementia such as Alzheimer's disease prior to his or her hospitalization, expect that the patient will have a significant cognitive decline post delirium, and will have increased rate of decline when the delirium clears.

PREVENTION OF COGNITIVE DECLINE AND FUNCTIONAL IMPAIRMENT IN HOSPITALIZED PATIENTS

Ideally, it would be very worthwhile if acute hospitalization could be prevented because of its detrimental cognitive and functional effects compared to no hospitalization.

This is predominantly in the hands of hospitalists, emergency physicians, internists, general physicians and now neurointensivists. An aggressive education campaign should educate hospitalists, emergency room and general medical specialists on the morbidity of acute non-neurological hospitalizations as it relates to cognitive and functional disability and its detrimental effect on caregivers and quality of life of the patient.

This applies especially, to patients who are not "critically ill" with stable vital signs who are able to swallow, take

pills and are often just admitted for observation. They may remain in hospital for two to three days, undergo numerous tests, and remain in bed till discharge.

If these or more severely ill patients are admitted to the hospital, then: A. Obtain a good baseline of cognitive function. B. Physical therapy, ambulation, and cognitive stimulation should be instituted as soon as possible to help reduce any possible cognitive and functional decline.¹² Cognitive stimulation can be done by family members and nursing staff to include current events, word or card games, reminiscence, orientation board, providing the day's schedule, to cognitive consultation with hospital professionals. C. Eye glasses and hearing aids should be worn as much as possible to reduce sensory deficits. D. Mobility, self care, and independence must be encouraged as much as possible. E. Clocks and calendars should be provided, to assist in orientation. F. Noise should be reduced to the minimum. G. Frequent unnecessary night time interruption of sleep should be reduced to the absolute minimum, which requires coordination of nursing and medical procedures such as medications, vital signs, intravenous fluids, and various treatments.¹⁶

Neurologists who are consulted in the hospital should contact the referring physician to explain these issues and recommend or order these preventive measures.

Over-sedation can lead to increased morbidity, and impair patient ability to partake in therapies mentioned in B. Sedation should be only used when absolutely necessary and at the lowest possible doses. If needed medical therapy is prohibited by patients' behavior (delusions, agitation or delirium), then neuroleptics in parenteral form (IM, IV or oral such as Haloperidol, Thioridazine, or Risperidone) at lowest possible doses should be considered.¹⁶

The neurologist can play an important role in reducing the possibility of acute hospitalization of his/her cognitively and/or physically impaired office patients. This can be done by educating and encouraging the caregiver and patient to: exercise and increase ambulation, cognitive stimulation (current events, card and/or board games, puzzles etc.), frequent bladder emptying, and eliminate or reduce unnecessary medication. Emphasizing the risks of acute hospitalization with or without delirium, can help the patient and/or caregiver understand more fully the importance of these preventive measures. Writing prescriptions for some of these outpatient measures (physical and/or cognitive therapy) or consulting a home health agency to provide these services in the home is very helpful.

CONCLUSION

As our society continues to age and our elderly population continues to increase, acute hospitalizations will continue

to grow. With the increasing focus of shorter hospital stays based on medical costs and necessity of more hospital beds, more patients are likely to develop cognitive and functional decline when acute hospitalization occurs. Despite the limits of the current literature, some guidelines have been mentioned about hospital and outpatient evaluation of cognitive and functional impaired patients who experience acute hospitalization with or without delirium. Neurologists can play an important role in reducing these declines when they are consulted in the hospital by educating their physician colleagues and writing hospital orders that focus on reducing the risk of cognitive and functional decline as outlined in this paper. The neurologist can also help to prevent and reduce acute hospitalization of their cognitive and/or physical impaired patients during office visits by educating caregivers and the patient. Suggesting the use of home health consultation to provide assistance in some of these time consuming activities, can be very helpful and also provide education for caregivers. Far more uniform studies are needed to provide further information on the short and long term cognitive and functional complication of acute hospitalization with and without delirium. ■

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