Delirium in older adults: a chronic cognitive disorder?

Delirium is defined as a neurocognitive disorder characterized by sudden onset, fluctuating course, and disturbances in level of consciousness, attention, orientation, memory, thought, perception, and behavior (American Psychiatric Association, 2013). It occurs in hyperactive, hypoactive, or mixed forms in up to 50% of older hospital patients (Inouye *et al.*, 2014) and 70% of older long-term care residents (McCusker *et al.*, 2011), many with pre-existing dementia (Fick *et al.*, 2002).

The course of delirium is thought to be transient. Recovery is expected to be complete in the majority of affected individuals if the underlying putative cause (e.g. physical illness, drug toxicity) is promptly corrected or self-limited. The outcomes are presumed to be good (American Psychiatric Association, 2013). Among older adults, however, many well-conducted studies report that the outcomes of delirium are poor: delirium is associated with significant increases in cognitive impairment and functional disability, length of hospital stay, rates of institutionalization, and rates of death, independent of many socio-demographic and clinical variables (Witlox *et al.*, 2010).

How to explain the poor outcomes? Increasing evidence suggests that delirium in a substantial proportion of older adults may be a chronic cognitive disorder and the persistence of delirium and symptoms of delirium may account for the poor outcomes.

Persistent delirium

Recovery from delirium refers to the sustained return to the pre-delirium level of mental function. Levkoff (Levkoff *et al.*, 1992) and Rockwood (Rockwood, 1993) were among the first investigators to assess recovery systematically and reported that many older adults with delirium recovered in hospital but many others had not recovered by the time of discharge. More recently, a systematic review of 18 cohort studies reported that many older patients recovered from delirium but the combined proportions with persistent delirium at discharge from hospital and at 1, 3, and 6 months were 44.7%, 32.8%, 25.6%, and 21%, respectively (Cole *et al.*, 2009). If the definition of persistent delirium includes patients with partial recovery, the frequencies of persistence may be even higher. In one study, the combined proportions with partial and no recovery from delirium at 1 and 3 months among patients with and without dementia were 85.9% and 72.7%, and 67.9% and 51.9%, respectively; predicted probabilities of partial and no recovery at 6 months were 62% and 37%, respectively (Cole *et al.*, 2015). Given the apparent asymptotic decrease in the frequencies of persistent delirium over time, it appears that a substantial proportion of older adults with delirium may never recover fully. The longer term outcomes (cognition, function, nursing home placement, mortality) of adults who recover appear to be good (Cole *et al.*, 2008b) but the outcomes of adults who do not recover appear to be consistently worse than the outcomes of those who recover (Marcantonio *et al.*, 2000; McCusker *et al.*, 2003; McAvay *et al.*, 2006).

Persistent symptoms of delirium

The emerging literatures on partial recovery from delirium, subsyndromal delirium (SSD) and persistent symptoms of delirium probably describe different facets of the same broad phenomenon: presence of symptoms of delirium (not meeting criteria for delirium), occurring either before or after episodes of delirium or independently of episodes of delirium. As for partial recovery, rates of partial recovery ranged from 20% to 42% at hospital discharge (Levkoff *et al.*, 1992; O'Keeffe and Lavan, 1997; McAvay *et al.*, 2006); rates of partial recovery at 12 and 24 weeks were 15% and 18%, respectively (Cole *et al.*, 2015). To date, there have been no studies of longer term outcomes but given the poor outcomes associated with persistent delirium, partial recovery is probably associated with poorer outcomes than full recovery.

As for SSD, estimates of prevalence in older adults range widely (5%–61%), perhaps related to differences in diagnostic criteria or patient populations (Cole *et al.*, 2013a; Zuliani *et al.*, 2013; Meagher *et al.*, 2014). In a systematic review, the combined estimate of prevalence was 23%; the combined estimate of incidence was 13% (Cole *et al.*, 2013a). SSD persisted at 12 weeks in 29% of older hospital inpatients (Cole *et al.*, 2016) and at 24 weeks in 22%–25% of older long-term

care residents (Cole *et al.*, 2013b). Over time, many symptoms of SSD appear to become more frequent and persistent (Meagher *et al.*, 2012; von Gunten *et al.*, 2013). The longer term outcomes (cognition, function, length of hospital stay, rates of institutionalization, and death) of patients with SSD are poor and intermediate between the outcomes of patients with delirium versus no delirium (Cole *et al.*, 2013a). Notably, the 6-month outcomes of patients who had not recovered from SSD at 8 weeks were worse than the outcomes of patients who had recovered (Cole *et al.*, 2008a).

As to persistent symptoms, some symptoms of delirium persist after episodes of delirium in up to 65% of patients for at least 12 months, irrespective of the presence of dementia (Levkoff *et al.*, 1992; Rockwood, 1993; McCusker *et al.*, 2003; Cole *et al.*, 2012a; Witlox *et al.*, 2013). Moreover, symptoms often occur for long periods before episodes of delirium. One or more symptoms preceded 92.7 % of incident episodes; the estimated median duration of symptoms before episodes was 27 weeks; the types of symptoms present were most often inattention or disorganized thinking (Cole *et al.*, 2012b). The mean number of symptoms present appears to increase over time (Ciampi *et al.*, 2011); the mean number of symptoms increases before episodes of delirium and is greater after episodes than before (Cole *et al.*, 2012b). Persistent symptoms may occur independently of an identified episode of delirium: one or more symptoms were present in up to 67% of older adults without delirium and with or without dementia (Cole *et al.*, 2002; Leonard *et al.*, 2009; Meagher *et al.*, 2014). Of note, the presence of one or more symptoms appears to be risk factor for incident delirium weeks or months later; the more symptoms present, the greater is the risk (Cole *et al.*, 2013c). In the shorter term, persistent symptoms are associated with cognitive and functional impairment and mood and behavior problems, similar to full delirium or intermediate between full delirium and no symptoms (Cole *et al.*, 2014). To date, there are no studies of the longer term outcomes but given the prognostic significance of even one symptom of delirium in the SSD literature, patients with persistent symptoms probably have poorer outcomes than patients with no symptoms.

Partial recovery, SSD, and persistent symptoms appear to have similar frequencies, courses, and outcomes in older adults. Often, the symptoms occur after episodes of delirium. If the symptoms persist for a long period of time, the temporal relationship between the symptoms and an episode of delirium may be lost; then, such symptoms may be seen as SSD, persistent symptoms, or symptoms that precede the next episode of delirium. Sometimes, the symptoms may occur independently of an episode of delirium, perhaps markers for underlying medical conditions (e.g. infection) not severe enough to cause full delirium; again, such symptoms may be seen as SSD or persistent symptoms. Over time, the symptoms appear to become more frequent and persistent. The presence of symptoms, whatever the label, appears to be associated with poorer outcomes.

Proposed hypothesis

Advances in knowledge depend on creative tension between observations and ideas (hypotheses). Observations cry out for explanation; a hypothesis is proposed; the hypothesis is tested by making more observations . . . and so on (Bernard, 1957). During the past 25 years, research on delirium in older adults has generated a mountain of observations. We propose that delirium in a substantial proportion (perhaps 20%–40%) of many older adult populations with or without dementia is a chronic cognitive disorder characterized by a chronic fluctuating course, periods of acute exacerbation that are labeled episodes of delirium, increasing symptom frequency and persistence over time and poor outcomes. Figure 1 illustrates the course of this hypothesized condition. Some symptoms of delirium are present continuously, though fluctuating in number. At times, the number of symptoms present may cross the threshold for a diagnosis of delirium. Over time, the symptoms become more frequent and persistent.

Persistent symptoms of delirium may be markers for underlying medical conditions (e.g. hypoxia, drug toxicity) that may eventually become severe enough to cause full delirium. Alternatively, persistent symptoms may reflect abnormalities in neuroanatomical structures (Mesulam, 1985; MacLullich *et al.*, 2008; Field *et al.*, 2012) or neurotransmitter systems (Gaudreau and Gagnon, 2005; van Gool *et al.*, 2010), or aberrant stress responses (i.e. exaggerated brain inflammatory responses, LPHA axis dysfunction, MacLullich *et al.*, 2008) that may interact with putative precipitating conditions (e.g. urinary tract infection) to induce delirium. Aberrant stress responses are potentially neurotoxic (Barrientos *et al.*, 2006; MacLullich *et al.*, 2008). Persistent delirium, partial recovery, SSD, and persistent symptoms may reflect the persistence of neurotoxicity. Persistence of neurotoxicity may lead to brain atrophy and white matter disruption (Morandi *et al.*, 2012) and poorer outcomes.

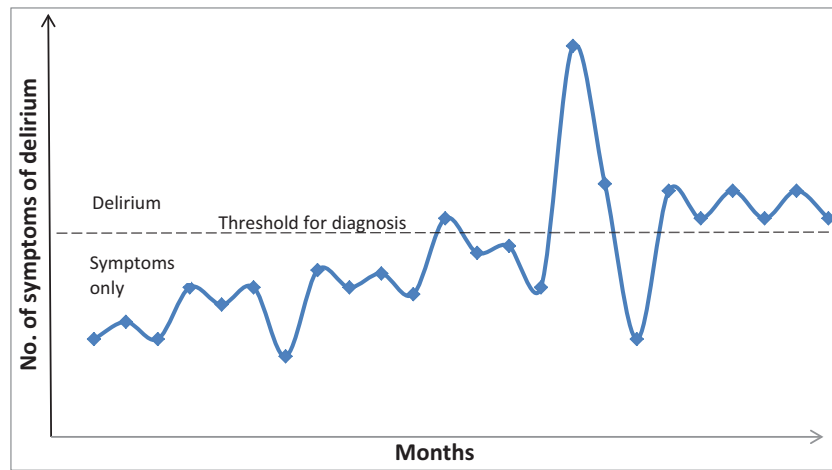The putative precipitating conditions above may be classified into two categories (MacLullich *et al.*,

Figure 1. (Colour online) Hypothetical course of persistent symptoms of delirium in one older adult.

2008): direct neuronal insults (e.g. hypoxia, trauma, drug toxicity) that induce delirium directly and systemic illnesses (e.g. infection, organ failure) that induce delirium by interacting with abnormalities in neuroanatomical structures, neurotransmitter systems, or stress responses. Delirium induced by direct neuronal insults may be more likely to recover fully if the putative cause is promptly treated or self-limited whereas delirium induced by systemic illnesses may be more persistent. A recent study attempted to explore the relationship between putative causes of delirium and recovery but small sample size prevented definitive conclusions; indeed, the only putative cause significantly associated with partial or no recovery in one model was fluid/electrolyte abnormality, a finding seemingly inconsistent with the above proposal (Cole *et al.*, 2015).

Interestingly, the proposed hypothesis may be analogous to current understanding of the pathogenesis and course of chronic obstructive pulmonary disease (COPD). COPD is characterized by a chronic fluctuating course with periods of acute exacerbation. Exacerbations result from exposure to noxious agents (e.g. bacteria, air pollution), increases in inflammatory mediators, airway wall infiltration, and decreased airflow. Repeated exacerbations may accelerate decline in lung function (Papi *et al.*, 2006).

Clinical implications

The proposed hypothesis has implications for clinical practice. First, it suggests that current approaches to prevention and treatment of delirium in a large proportion of older adults may address only factors leading to exacerbation of symptoms beyond the threshold for diagnosis. Second, it is possible that persistent symptoms and the associated cognitive and functional impairment may interfere with patient self-management of chronic medical conditions (e.g. poor compliance with diet or medication) which may, in turn, contribute to poor outcomes. Third, it may be useful to explore the application of elements of the chronic disease management model to the care of older patients who have persistent symptoms of delirium such as new clinical information systems to monitor delirium symptoms, decision support algorithms for patients who continue to have symptoms, and delivery system redesign to support interventions (Bodenheimer *et al.*, 2002). On this point, a small quasi-experimental trial provides preliminary evidence of the potential benefit of continuing care of older adults who have had an episode of delirium in terms of delayed institutionalization (Rahkonen *et al.*, 2001). Finally, patients at risk of persistent delirium and delirium symptoms may become the focus of preventive interventions modeled on interventions to prevent delirium (Inouye *et al.*, 1999).

Research implications

The proposed hypothesis has implications for research. First, delirium may not be a unitary condition: persistent symptoms may identify a delirium sub-type with an unique etiology and pathogenesis, and poor prognosis; controvertibly, persistent symptoms may be a marker for an underlying brain vulnerability such as dementia. Second, it may be important to monitor the longer term course (e.g. 24–36 months) of delirium symptoms to document any increases in frequency

and persistence; however, better methods (e.g. type and frequency of follow-up assessments) and measures (e.g. a delirium instrument designed to measure symptom persistence) will be required to study the presence and course of persistent symptoms. Third, it is not clear whether the persistence of symptoms is related to chronic medical conditions (e.g. infection, drug toxicity) or abnormalities in neuroanatomical structures, neurotransmitter systems, or stress responses. It may be useful to explore whether interventions to manage chronic medical conditions or moderate the predisposing abnormalities can increase rates of full recovery and improve longer term outcomes. Fourth, there may be a dose-response relationship between the severity and duration of symptoms, recovery status, and longer term outcomes. Greater severity of symptoms has been associated with partial and no recovery (Cole *et al.*, 2015); greater severity and duration of symptoms has been associated with poorer long-term outcomes (McCusker *et al.*, 2003; Morandi *et al.*, 2012); SSD, a clinical state characterized by the presence of symptoms not meeting criteria for delirium, has outcomes intermediate between full delirium and no symptoms (Cole *et al.*, 2013a). Thus, development of pharmacologic and non-pharmacologic strategies to decrease the severity and duration of symptoms of delirium may lead to better longer term outcomes (Friedman *et al.*, 2014).

Conclusion

Is delirium a chronic cognitive disorder? Current evidence suggests that many older adults with delirium may recover fully and have good outcomes but in a substantial proportion of older adults delirium may be a chronic cognitive disorder characterized by a chronic fluctuating course, periods of acute exacerbation, increasing symptom frequency, and persistence over time and poor outcomes.

Conflict of interest

None.

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