The wave called delirium, from onset to consequences
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Chapter 10

Summary
A major part of delirium research in elderly patients has been in heterogeneous populations. Patients develop delirium in the presence of an underlying medical condition which is the reason for hospital admission, which hinders baseline assessment of predisposing factors. In contrast, the research in this thesis was done in a homogeneous group with baseline data available, as well as longitudinal and follow-up data on several factors.

The general aim of this thesis was threefold. We wanted to increase our knowledge on several aspects of delirium: predisposing and precipitating factors, phenomenology and symptoms throughout the delirium episode, and conclude with the (long-term) outcomes of delirium.

PART 1: ANESTHESIA AND INFLAMMATORY MARKERS FOR DELIRIUM
Delirium is most often considered a multifactorial syndrome, an interrelationship between predisposing and precipitating factors.\(^1\) Cognitive impairment and advanced age are well known predisposing risk factors for delirium.\(^2\) Presence of precipitating factors, such as (bladder) infections, severe illness or surgery, increase the risk of development of delirium. Anesthetic technique has been suggested as precipitating factor because the physiologic effects on cerebral blood flow, metabolism and oxygen delivery might between regional and general anesthesia, with the latter having more chance on development of postoperative delirium. It has also been suggested that merely the surgical procedure itself, such as hip surgery, is a precipitating factor of delirium. A surgical procedure elicits an inflammatory response, which can induce delirium, especially in susceptible patients.\(^3,4\)

In Chapter 2 we examined the effects of general anesthesia on the risk of incident postoperative delirium. Patients were 70 years or older and admitted for hip surgery. Predefined risk factors for delirium were assessed prior to surgery. A total of 60/526 patients (11.4%) had incident postoperative delirium, 337/526 (64.1%) received general anesthesia and 189/526 (35.9%) regional anesthesia. 18/189 (9.5%) general anesthesia patients developed postoperative delirium, vs. 42/337 (12.5%) regional anesthesia patients. General anesthesia had no distinct effect on incident postoperative delirium in geriatric hip-surgery patients compared to regional anesthesia. We controlled for baseline cognitive impairment, age, acute admission, gender, visual impairment, physical status and dehydration. Delirium was not independently associated with specific drugs nor the medication classes opioids, benzodiazepines and anticholinergics. Chapter 3 examined the time course of CRP levels over multiple days (baseline, postoperative day 1 through 5) and the association between postoperative delirium and CRP. Also, the association between CRP levels and delirium severity, cognitive impairment, illness severity and delirium duration were investigated. Longitudinal analysis showed that postoperative delirium was associated with a higher CRP level. Analyzing separate days showed that CRP levels were increased after surgery and that they were higher from postoperative day 2 and onwards in patients with delirium compared to patients who did not develop
postoperative delirium. Delirium severity was associated with CRP levels. No significant differences in CRP levels were found between the short and more prolonged delirium group, nor between the highest CRP level and pre-fracture cognitive decline or illness severity.

**PART 2: CLINICAL SYMPTOMATOLOGY**

The second part of the thesis concerned the clinical symptomatology of delirium and delirium duration. Special emphasis was on the relation between symptomatology of delirium and delirium duration and predisposing factors. Severity and symptom profile at the onset of delirium might be predictive of the duration of delirium. Delirium duration is suggested to be associated with mortality risk and long-term cognitive impairment. Delirium has different phenotypes and diagnosis of delirium is based on the key features of delirium and exclusion of conditions that have great resemblance with delirium. Delirium is often accompanied by changes in motor activity, but the longitudinal expression of these features and etiological and prognostic significance of clinical subtypes defined by motor activity is unclear.

The **fourth chapter** focused on features that may allow early identification of patients at risk of prolonged delirium, and therefore of poorer outcomes. We determined if pre-operative delirium risk factors and delirium symptoms (at onset and clinical symptomatology during the course of delirium) were associated with delirium duration.

In a case control study patients having short delirium (1 or 2 days) were compared with patients who had more prolonged delirium (≥3 days) on DRS-R-98 (Delirium Rating Scale Revised-98) symptoms on the first delirious day. Delirium symptom profile was evaluated daily during the delirium course. Only pre-existent cognitive decline, not severity of individual delirium symptoms at onset, was associated with prolonged delirium.

Chapter 5 compared baseline characteristics and outcomes according to longitudinal pattern of motor subtype expression (predominantly hyperactive, predominantly hypoactive, predominantly mixed, no motor subtype and variable). Motor subtype categorization was performed with the DRS-R98. We also investigated the longitudinal stability of motor subtypes across the delirium episode. The full course of the delirium episode could be defined for 42/62 (67.7%) patients who experienced in-hospital delirium postoperatively. Of the patients with multiple days of delirium only 4/30 (13.3%) patients had a consistent motor subtype profile throughout the delirium episode, while 26/30 (86.7%) patients had a variable course. Of the patients with multiple days of delirium, 5/30 (16.7%) were predominantly hypoactive in profile, 7/30 (23.3%) predominantly hyperactive, 6/30 (20%) predominantly mixed, 1/30 (3.3%) had no motor subtype and 11/30 (36.7%) had a variable profile. The subtype categorization according to dominant
motor subtype across the delirium episode identified groups with similar characteristics and outcomes.

In **Chapter 6** we investigated the reliability and validity of the Delirium Motor Subtype Scale (DMSS) that was translated to Dutch. The DMSS was developed to capture all the previous different approaches to subtyping into one new instrument and emphasize disturbances of motor activity rather than associated psychomotor symptoms. Elderly patients who had undergone hip fracture surgery received the Dutch version of the DMSS and the Delirium Rating Scale revised 98. A diagnosis of delirium was defined according to the Confusion Assessment Method. The internal consistency of the DMSS was acceptable (Cronbach’s alpha=0.72). If an item was removed at random the internal consistency of the scale remained the same. Similarly the concurrent validity of DMSS was good (Cohen’s kappa=0.73) while for each motor subtype the Cohen’s kappa ranged from 0.58 to 0.85. The sensitivity and specificity of DMSS to detect each subtype ranged from 0.56 to 1 and from 0.88 to 0.98 respectively. These results suggests that the Dutch version of the Delirium Motor Subtype Scale is a reliable and valid instrument, that could allow for greater precision in further research on motor subtypes.

**PART 3: THE CONSEQUENCES OF POSTOPERATIVE DELIRIUM: COGNITIVE AND AFFECTIVE FUNCTIONING**

The last section of this thesis focused on the consequences of delirium. Until recently it was assumed that when the underlying causal factor was eliminated and delirium resolved a successful recovery would follow. Although it is well documented that delirium is associated with negative long-term consequences such as impaired cognition and a high rate of institutionalization, less is known about the impact on specific domains of cognitive and affective functioning. It is suggested that delirium can contribute to poor cognitive and affective functioning, although not all research is consistent with this. Differences in results might be because of different patient populations, type of surgery or methodology.

In **Chapter 7** we investigated the long-term neuropsychological sequelae of delirium. Delirium is a risk factor for long-term cognitive impairment and dementia. Yet, the nature of these cognitive deficits is unknown as is the extent to which the persistence of delirium symptoms and presence of depression at follow-up may account for the association between delirium and long-term cognitive impairment. Before surgery baseline characteristics, depressive symptomatology, and global cognitive performance were documented. Presence of delirium was assessed daily during hospital admission and 3 months after hospital discharge when patients underwent neuropsychological assessment. Elderly hip fracture patients with in-hospital delirium suffer from impairments in global cognition and episodic memory three months after hospital discharge, even after adjustment for age, gender, and baseline cognitive impairment. In contrast, no
differences were found on tests of attention. Our results suggest that inattention, as a cardinal sign of persistent delirium or depressive symptomatology at follow-up cannot fully account for the poor cognitive outcome associated with delirium.

Chapter 8 investigated whether in-hospital delirium is associated with increased anxiety and depressive levels, and posttraumatic stress disorder symptoms three months after discharge. Patients who had experienced in-hospital delirium showed more depressive symptoms at follow-up after three months compared to the 30 patients without in-hospital delirium. This association persisted in a multivariate model controlling for age, baseline cognition, baseline depressive symptoms and living situation. The symptoms of depression in patients with previous in-hospital delirium could also not be fully explained by persistent (sub)syndromal delirium. The level of anxiety and symptoms of post-traumatic stress disorder (PTSD) at follow-up did not differ between both groups.
REFERENCES


