The wave called delirium, from onset to consequences
Slor, C.J.

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Chapter 1

General Introduction
PREFACE
Delirium is a common and serious postoperative complication in hospitalized elderly patients. The characterizing features of delirium are the acute onset of disturbances in consciousness and the fluctuating of symptoms within 24 hours. Patients suffer from disturbances in consciousness and attention. This neuropsychiatric syndrome is usually considered a brief transient state, compared to dementia, which is usually considered a chronic state. However, delirium can persist and/or have long-term negative outcomes like cognitive deterioration and institutionalization.1-3 Although delirium as a clinical disorder is well known since ancient times, it was a neglected topic in the medical research till 20 years ago. Since then research on delirium has expanded, focusing on risk factors, assessment, prevention and underlying pathologic mechanisms among others. Although our knowledge on several aspects of delirium has increased, there are still many gaps in our understanding of its pathogenesis, recognition and treatment. The focus of this thesis has been threefold. First, we wanted to increase knowledge on risk factors of delirium, secondly we aimed to study phenomenology and the trajectory of delirium symptoms, and finally we sought to characterise the (long-term) outcomes after delirium has resolved.

In elderly patients it is usually not possible to link delirium to only one causal factor. It is the understanding that delirium is most often a multifactorial syndrome, an interrelationship between predisposing and precipitating factors.4 The prevalence of delirium depends on the study population, and is especially high in acute medical and surgery settings. The incidence of in-hospital delirium ranges from 6% to 56%, and postoperative delirium occurs in 15% to 62% of elderly patients.5,6 Cognitive impairment and advanced age are well known predisposing risk factors for delirium.7 Presence of precipitating factors, such as (bladder) infections, severe illness or surgery, increase the risk of development of delirium. Anesthesia is considered as a possible precipitating factor for postoperative delirium, assuming that the physiologic effects on cerebral blood flow, metabolism and oxygen delivery would differ between regional and general anesthesia, with the latter having more chance on development of postoperative delirium.

However, next to anesthesia also the surgical procedure itself can be a precipitating factor in postoperative delirium. Recent research indicates that surgical procedures lead to increased levels of proinflammatory cytokines, which can induce delirium in susceptible patients.8,9 Both aging and neurodegenerative disease are accompanied by impaired immune function resulting in a heightened inflammatory state under normal conditions and an exaggerated inflammatory response in reaction to inflammatory stimulation.10,11 This pro-inflammatory state may explain why older and cognitively impaired individuals are more susceptible to delirium in the presence of precipitating factors that may elicit an inflammatory response, such as surgical procedures.
In addition to predisposing and precipitating factors for the risk of development of delirium, it is also interesting to know whether these factors are associated with duration of the episode with delirium. Severity and symptom profile at the onset of delirium might be predictive of the course of delirium. The clinical diagnosis of delirium is based on the key features of delirium and exclusion of conditions that mimick delirium. The diagnosis is further complicated by the fact that delirium itself has different phenotypes. For example, delirium is often accompanied by changes in motor activity and has been classified into two motor subtypes, i.e. hyperactive and hypoactive. Later on, the mixed category was added to recognise cases when elements of both subtypes occur within a short time frame. Studies suggest that these subtypes may have important differences in pathophysiology, treatment needs and prognosis. The hypoactive, quiet, delirium subtype is most likely to be missed or misdiagnosed. However, much remains unknown about the different subtypes and their stability across the delirium episode or their outcomes. Study results on differences in risk factors and prognosis between motor subtypes are inconsistent. This might be related to differences in clinical populations studied, or also by the use of different methods for defining clinical subtypes.

Until recently it was assumed that elimination of the underlying causal factor would lead to successful recovery. However, recent research suggests that delirium contributes to poor outcomes, such as poor cognitive or affective functioning and, in elderly patients, to increased cognitive deterioration. Although it is well accepted that delirium is associated with negative long-term consequences such as impaired cognition in global terms, less is known about the long-term impact on specific domains of cognitive and affective functioning. If long-term disturbances in cognitive and affective functioning are associated with delirium this my be a rationale for adequate treatment and follow-up assessment of patients who had delirium, in order to diminish the possible interference with recovery or rehabilitation.

AIMS AND OUTLINE OF THE THESIS
A major part of the delirium research in elderly patients has been in heterogeneous populations. Patients develop delirium in the presence of an underlying medical condition which was the reason for hospital admission, which hinders baseline assessment of predisposing factors. 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: (1) predisposing and precipitating factors, (2) phenomenology and symptoms throughout the delirium episode, and (3) conclude with the (long-term) outcomes of delirium.
The first part of this thesis focuses on precipitating factors of delirium. It remains unclear if anaesthesia technique or the surgical procedure itself is a precipitating factor of delirium. Chapter 2 of the thesis is concerned with the effect of general anaesthesia on postoperative delirium in a large homogenous patient group. We compared patients having general anaesthesia with patients undergoing regional anaesthesia, while also considering predisposing factors of delirium. Also, effects of classes of medications on postoperative delirium were explored. In Chapter 3 we examined CRP levels, from before the start of full syndromal delirium and across days after surgery. Several studies have examined the association between levels of CRP and delirium, although not all studies found differences. We did a time-course study, and examined the level of CRP at baseline, before surgery, and several consecutive days after surgery.

The aim of Chapter 4 was to identify patient characteristics that are associated with prolonged delirium. Because delirium duration has been associated with an 11% increased risk of death for every 48 hours that delirium lasts, we wanted to gain more insight into the determinants of delirium duration beyond the first two days. Since we had daily delirium assessments available, we also explored if different lengths of delirium episodes have different characteristics throughout the episode. Thereafter, this thesis is directed at the presentation of delirium. We investigated motor subtypes of delirium, their risk factors and outcomes, and most importantly their stability across the delirious episode (Chapter 5). Hypoactive delirium has been associated with worse outcomes, but this association is not consistently found throughout different studies. Few studies examined motor subtypes of delirium in hip surgery patients. Moreover, the available longitudinal data on delirium motor subtypes comes mostly from studies in palliative care patients. Different methods have been used to identify motor subtypes of delirium, which may differ in pathophysiology, treatment needs and prognosis. The Delirium Motor Subtype Scale (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. We translated this scale developed to identify different delirium motor subtypes and investigated the psychometric properties of this translation in a Dutch elderly hip fracture population (Chapter 6).

The third part addresses the long-term outcomes of delirium and consists of two studies. Chapter 7 describes a 3-month follow-up study of elderly hip fracture patients. Patients were presented a comprehensive neuropsychological test battery in order to evaluate cognitive functioning at follow-up, and consider different cognitive domains. In this study we examined the role of inattention, as an important sign of persistent delirium and depression, as important features of the neuropsychological profile of patients who have had delirium three months earlier during their hospital admission. Chapter 8 is concerned with the association between affective functioning and delirium.
We simultaneously investigated anxiety and depression levels, and post-traumatic stress disorder symptoms three months after hospital discharge, and their association with delirium. In an attempt to clarify why previous studies have found contradicting results, this study used a variety of measurements for each symptom domain, including screening questionnaires and structured diagnostic interviews.

A general discussion and summary of the main findings of this thesis is provided in Chapter 9 and 10. A summary of the thesis in Dutch in Chapter 11 concludes this thesis.
REFERENCES

General introduction


