Delirium in the elderly: biomarkers and outcomes

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Chapter 1

General introduction
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Preface

Delirium is the most common neuropsychiatric syndrome among persons who are 65 years and older and who are admitted to the hospital. Delirium is characterized by disturbances of consciousness and attention and a global loss of cognitive faculties. Usually delirium is described as a transient, reversible syndrome that is acute and fluctuating in nature and heralds the presence of a medical condition. However, despite its alleged temporary nature clinical experience and research suggest that delirium may be associated with permanent functional and cognitive losses, especially in the elderly. In addition, delirium can be a frightening and extremely stressful experience for patients and caregivers, and has been associated with high morbidity and mortality, longer hospital stays, higher rates of institutionalization and increased health care costs. Despite its importance, delirium is often unrecognized – and as a result not adequately managed - by physicians and nurses. Although interest in delirium has increased during the last decade, before that time this highly prevalent neuropsychiatric syndrome with its severe impact has been largely ignored by the biomedical scientific community.

The cardinal features of delirium are fluctuating awareness and impairment of attention. Additional symptoms include, among others, impairment of memory, orientation and language, and the presence of delusions, hallucinations, disorganized thinking and sleep-wake cycle disturbances. Delirium is a bedside, syndromal diagnosis, Therefore there are no ancillary diagnostic tests to document its presence. The diagnosis of delirium is based on clinical history, behavioural observations, and bedside assessment of attention and cognitive function. Conditions that may mimic delirium, such as dementia, psychotic disorders, non-convulsive epileptic seizures and depression should be excluded.

Delirium is rarely caused by a single factor; rather the etiology of delirium is multifactorial. Current ideas concerning the development of delirium are based on the interrelationship between precipitating and predisposing factors. Severe illness of any kind, infections, ranging from sepsis to uncomplicated cystitis, and noxious insults, such as hip fracture or surgical procedures, are all important precipitating factors. Depending on the vulnerability of the patient these precipitating factors elicit the behavioural and cognitive features that characterize delirium. A multitude of factors have been identified that increase the susceptibility for delirium. Besides aging, cognitive impairment is considered to be the most important predisposing factor, with two thirds of delirium cases occurring in elderly individuals with cognitive deficits or dementia. The vulnerability for delirium of elderly individuals with cognitive impairment underlines the strong interrelationship between delirium and dementia and shared pathogenetic mechanisms have been proposed. Yet, the
extent to which the neuropathological processes that are associated with aging and dementia predispose individuals to delirium remains unknown. Identifying accurate biomarkers for delirium may shed light into the pathophysiology of delirium and the interrelationship between delirium and dementia. A better understanding of the pathologic mechanisms underlying delirium is also critical for developing more effective preventive and treatment strategies and for informing patients and caregivers. Although prevention is the best way to minimize the occurrence of delirium no more than an estimated 30-40% of delirium cases can be averted with the best preventive strategies available today. The understanding that prevention of delirium is not effective, and most probably will remain so in a significant number of cases is beginning to transform current ideas concerning the counselling of patients with present or previous delirium. Besides ‘the primary prevention’ of delirium itself (e.g. Kalisvaart et al.), resources are beginning to be directed at preventing the poor long-term outcomes of elderly patients who have had delirium. Yet, several issues concerning these long-term poor outcomes need further clarification in order to correctly inform patients and design effective treatment strategies aimed at averting the negative consequences that are associated with delirium. Whether delirium independently contributes to poor clinical outcome or merely represents a marker of an individual’s vulnerability is especially relevant and given the close interrelationship between delirium and dementia one particular intriguing question is whether delirium contributes to dementia or not.

**Aims and structure of the thesis**

The general aims of this thesis were to study biomarkers and outcomes of delirium. To delineate the aims of this thesis more specifically it has been divided in two major parts. The research questions for each part are described below. The first part of this thesis consists of a series of prospective cohort studies in elderly hip fracture patients aimed at elucidating biomarkers for delirium. According to Marcantonio et al. biomarkers may serve as risk markers for delirium, that is, they are present before delirium onset and help to identify vulnerable individuals. Given the susceptibility for delirium of elderly individuals with cognitive impairment and the increased risk of dementia following delirium we examined whether preoperatively measured levels of CSF β-amyloid, tau, and hyperphosphorylated tau, as correlates of neuropathological processes that underlie cognitive impairment, are risk markers for the development of postoperative delirium (Chapter 2). This way we hoped to disentangle a part of the intricate relationship between neurodegenerative processes and delirium.
In Chapter 3 we investigated the association between preoperative CSF levels of pro- and anti-inflammatory cytokines and the occurrence of postoperative delirium. Cytokines act as messengers between (immune) cells to regulate and coordinate the immune response to injury and disease. Cytokines are also known to affect neuronal functioning. Ageing and neurodegenerative disease are both associated with increased activity of the CNS innate immune system which can result in an exaggerated CNS cytokine response after peripheral immune stimulation.10-13 Given this exaggerated CNS immune response it was hypothesized that altered CNS cytokine profiles before the operation, that is, stimulated by the fracture, can be considered risk markers for development of delirium after the operation.

In Chapter 4 a related hypothesis was tested. In elderly and cognitively impaired individuals feedback regulation of cortisol is often impaired which leads to higher levels of cortisol, particularly under stressed conditions, and a slower return to baseline cortisol levels following acute stress.5,14-16 As sustained high levels of cortisol can have harmful effects on the brain causing inattention and other cognitive deficits we investigated whether hip fracture patients who developed delirium after the operation already had higher preoperative CSF cortisol levels before the operation, that is, stimulated by the fracture.

The second part of this thesis concerns the long-term outcomes following delirium. Because delirium results from the interaction of multiple precipitating and predisposing factors - that all may markedly contribute to poor outcome themselves - it is difficult to disentangle the direct effects of delirium from the effects of specific characteristics of the study population. Chapter 5 describes a comprehensive meta-analysis that examines the association between delirium and mortality, institutionalization and dementia. The main objective of this meta-analysis was to investigate whether delirium predicts poor outcome independently from important confounders that may themselves be associated with a poor prognosis. In Chapter 6 we describe a 3 month follow-up study of a cohort of elderly patients who were initially hospitalized for surgical repair of hip fracture. We used a comprehensive neuropsychological approach, focusing on multiple cognitive domains, to examine whether the observed association between delirium and long-term cognitive impairment indicates the presence of dementia or whether alternative explanations have to be considered, such as the persistence of symptoms of delirium or an aggravation of depression after hospital discharge.

Chapter 7 provides a brief summary of the main findings of this thesis together with a discussion of the implications. Finally, Chapter 8 contains a summary of the thesis in Dutch.
REFERENCES