Pathophysiologic studies in delirium: a focus on genetics
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Chapter 1

Delirium
Delirium is an important neuropsychiatric syndrome with frequencies in the elderly population of up to 56% during hospital admission. The prevalence is approximately 0.4% in the total population and 1.1% in persons above 54 years. It is defined by a fluctuating consciousness and an acute change in cognition or a perceptual derangement. Three clinical subtypes of delirium (hyperactive, hypoactive, and mixed subtype) are distinguished based on the symptoms present. Delirium can be precipitated by any somatic factor, which includes a variety of different illnesses, surgery, or substance (medication) intoxication or withdrawal. Predisposing factors are higher age and cognitive and functional impairment, among others. Though patients usually recover after treatment of the precipitating factor, delirium is independently associated with an increase in mortality, impaired physical and cognitive recovery, and increased hospital costs, estimated at $2,500 per patient. Since the number of elderly people with greater risk for delirium continues to grow, the absolute number of patients with delirium and associated problems can be expected to rise as well.

Delirium recognition rates are low (12–43%), and its management remains consequently inadequate in up to 80% of the patients. This is the main reason the Dutch Health Inspection has decided in 2006 to make the proper management of delirium one of the indicators for the quality of care in Dutch hospitals. The diagnosis of delirium has to be made by an experienced clinician with use of a classification scale like the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases. Missing the diagnosis is often related to the manifestation of the syndrome. First, symptoms develop acutely, and the duration of delirium is limited to a few days if the precipitating factor is adequately treated. Therefore, the time frame for making an adequate diagnosis is short. Second, symptoms of delirium fluctuate over time; because symptoms are mostly present during the night, the patient has to be closely observed for 24 hours. Finally, the hypoactive subtype, with its absence of overt distress or disturbance, is especially likely to be overlooked. Apart from failure to recognize the symptoms, misdiagnosis is a considerable problem since depression and dementia are important differential diagnoses for hypoactive delirium. Hyperactive and mixed subtype of delirium may falsely be diagnosed as functional psychosis, dementia, (hypo)mania, anxiety disorders, or akathisia.

The pathophysiology of delirium
Despite growing interest in delirium in elderly patients, relatively little studies have attempted to elucidate the pathophysiology of delirium. This may be partly attributable to specific methodological issues related to these types of studies. However, pathophysiological studies are urgently required to make any further progress in finding markers for early recognition and to improve treatment.

A number of hypotheses have been put forward in an attempt to explain the pathophysiological processes leading to the development of delirium. Several
theories describe involvement of different systems in the brain, such as the (1) ‘neurotransmitter’, (2) ‘inflammatory’, (3) ‘physiological stress’, (4) ‘cellular-signaling’, (5) ‘oxygen supply’, or (6) ‘sleep-wake cycle’ system. The burden of proof for the diverse hypotheses varies from almost hypothetical (the role of melatonin) till fairly proven (dysbalance between dopamine and acetylcholine activity in the brain).

1) The most widely propagated theory centers on the neurotransmitter system. This theory states that relative acetylcholine deficiency and dopamine excess could mediate the characteristic symptoms of delirium\(^{186}\). This is supported on the one hand by that fact that delirium can be evoked by dopamine agonists and anticholinergic medication and on the other hand because delirium can be successfully treated with dopamine receptor antagonists and probably also by cholinesterase inhibitors\(^5\).

2) Proinflammatory cytokines are known to contribute to the development of sickness behavior. This syndrome is characterized by symptoms overlapping with delirium and can be induced by a wide variety of clinical conditions just like delirium\(^{152}\).

3) There is some evidence that dysregulation of the limbic–hypothalamic–pituitary–adrenal axis, with pathologically sustained high levels of cortisol occurring with acute stress, can precipitate and/or sustain delirium\(^{118}\).

4) The “cellular-signaling hypothesis” suggests that more fundamental processes like intraneuronal signal transduction may be disturbed, thereby affecting neurotransmitter synthesis and release\(^{119}\).

5) The “oxygen deprivation hypothesis” proposes that decreased oxidative metabolism in the brain causes cerebral dysfunction because of abnormalities in various neurotransmitter systems\(^{119}\).

6) Disruption of the sleep–wake cycle is an important characteristic of delirium. Melatonin, a hormone involved in the circadian rhythm, could be responsible for the disturbance in this system\(^{110}\). Several case studies have shown a difference in melatonin secretion in patients with delirium compared to patients without delirium\(^{110,176}\).

Since many of the above systems interact, these theories are probably not mutually exclusive. On the contrary, since the syndrome of delirium is the result of a wide variety of combinations of predisposing and precipitating factors, the concept of a final common pathway seems to be the most plausible\(^{186}\). The candidate system for this final common pathway, most widely supported by the existing evidence, is the neurotransmitter system. The suggested pathophysiological mechanisms may differ within the diverse subtypes of delirium.
Chapter 1

Genetics in delirium
Genetics, the science of heredity and variation, is a promising field of research for delirium. Genetic research offers new possibilities in unraveling the pathophysiological mechanisms lacking in conventional research methods. Genetic markers can be easily determined in DNA obtained from somatic cells, e.g. white blood cells. The second opportunity of genetic research is to identify patients potentially at high risk for delirium. The identification of genetic risk factors for delirium would permit individual patients prone to develop delirium to be identified in advance. Preventive geriatric interventions could then be undertaken. Additionally, delirium would be missed less frequently and patients could be treated at an early stage. Moreover, the possible identification of genetic variations also provides an approach for adjusting pharmacotherapy at the individual level.

Candidate gene association studies are best equipped to study genetics in delirium. This type of studies can test the effect of genetic variants of a potential contributing gene (the candidate gene) in unrelated cases and controls. Most genes contain many known DNA sequence variations called single nucleotides polymorphisms (SNPs). The most interesting variations for association studies are functional SNPs, which can influence the trait of interest by producing proteins with an altered structure, function, or concentration.

Aim
Studies on genetics in delirium in elderly patients have been scarce until now and first results were just published in 2007, while the field of genetics had already acquired a prominent place at that time in pathophysiological research in other psychiatric disorders like dementia, schizophrenia, and depression. Using new high-throughput technology, genetic research has identified several common variations in the human genome as being associated with these psychiatric disorders.212 The aim of the research in this thesis was to explore several pathophysiological factors of delirium in elderly patients and especially the role of genetic factors.

Study cohort
In 2002 the geriatric team in the Academic Medical Center in Amsterdam was founded. The most important focus of the team was recognizing the frail elderly patients at risk for complications out of all patients aged 65 years and older to provide extra geriatric care to these patients. Since delirium is often a sign of frailty, the geriatric consultation team decided to start with the early recognition of delirium in a cohort study at the medical departments and combining care for these patients with collection of data for research. From all patients aged 65 years and older, demographical, medical and biochemical data were collected during admission as well as information about their physical and cognitive functionality at 3 and 12 months after hospital admission. In 2004 the cohort study was extended to patients with a hip fracture, acutely admitted to the department of traumatology or orthopedics of the Academic Medical Center. In 2003 in the medical patients and in 2005 in the hip fracture patients, DNA collection of patients was started to
perform genetic research. Moreover, in hip fracture patients repeated blood samples were drawn for proteomics research and several pathophysiological parameters. Data from both study cohorts provide the basis for the majority of the studies in this thesis.

Outline
The thesis consists of two types of research in delirium, Chapters 2 to 5 focuses on pathophysiological markers in blood and Chapters 6 to 9 focuses on genetic markers.

In Chapter 2, a proteomics study is described that explored the entire human proteome in plasma and serum of patients with and without delirium to identify proteins that are differentially expressed in patients with delirium. Proteomics research provides the unique opportunity to generate new hypotheses about the pathophysiological mechanisms and to discover new biomarkers for identification of delirium.

In the next chapters we report about the association of two markers of cerebral damage, S100B (Chapter 3 and Chapter 4) and neuron specific Enolase (Chapter 3) with delirium. Possibly, the high frequency of dementia after delirium reflects irreversible brain damage caused by the detrimental effects of the pathophysiological mechanisms of delirium on the brain. One of the mechanisms leading to possible cerebral damage may be the inflammatory process, described in Chapter 5. We study the time-course of cytokines before, during and after delirium and compare levels of cytokines between the different subtypes of delirium.

We started our genetic research, with a systematic review of candidate genes that were already known to be associated with delirium. Because no studies in this subject in the elderly were performed, Chapter 6 is a review about all genetic polymorphisms related to alcohol withdrawal delirium. Despite the fact that the symptoms of alcohol withdrawal delirium are similar, it is unknown if the pathophysiological mechanisms are the same as in delirium in the elderly. On the basis of this review and the treatment of delirium with a dopamine receptor 2 antagonist, three genes involved in dopamine metabolism were chosen as candidate genes for the study described in Chapter 7.

The apolipoprotein E (APOE) ε4-allele is strongly associated with Alzheimer’s dementia, which is a major risk factor for delirium. In Chapter 8, the association between delirium and the APOE ε4-allele in medical patients is described in the first hundreds included patients. In 2007 more small studies about this subject were published. In the mean time our study group had included a larger sample, so we repeated the analysis in this larger population. Chapter 9 describes these new results and a meta-analysis of the association between delirium and the APOE ε4-allele.

The general discussion in Chapter 10 elaborates on the observed results and discusses a number of methodological issues. In addition we offer directions for future research.