Cholinergic deficiency and inflammation in cognitive dysfunction
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Chapter 1

Introduction
Dementia is a non-specific term encompassing a spectrum of clinical syndromes of cognitive decline and behavioral disturbances caused by a variety of disease processes. Alzheimer’s disease (AD) is the most common pathologic entity causing dementia, followed by vascular dementia, Dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). Parkinson’s disease dementia (PD) and Creutzfeldt-Jakob disease (CJD) represent other examples of diseases that are accompanied by dementia. At the moment the number of patients with dementia in the Netherlands is approximately 200,000. With the rising life expectancy the prevalence of dementia in the Netherlands is estimated to reach 400,000 in 2050\(^1\). Although dementia is in the top 10 of diseases leading to death in the Western world and subject of intense research activities throughout the world, many questions are still unanswered. Among these questions are: ‘which processes contribute to the symptoms that ruin the lives of patients suffering from these diseases’ and ‘how can we optimally manage these symptoms’. This thesis aims to contribute to answering some aspects concerning these questions.

**Cholinergic deficiency**

The renaissance of the interest in AD in the 1970’s led to intensified investigations into the etiology of this disease\(^2\). Although nowadays much more is understood of the molecular and genetic basis of the different disease mechanisms causing dementia, the therapies that are currently available are founded on the research of decades ago. An important line of research in the 1970-1980’s was focused on the relationship between neurotransmitters and cognitive (dys)function. Fuelled by the success of the discovery of the involvement of the dopaminergic system in PD and the subsequent relieve of symptoms by substitution of dopamine, different neurotransmitter systems were investigated for their role in cognitive deficits. One of the findings that attracted intense scrutiny was the loss of cholinergic neurons in the basal forebrain in postmortem examination of brains of patients with AD\(^3\). Drachmann and Leavitt were among the first to describe the relationship between the central cholinergic system and cognitive functions by studying the effects of cholinergic and anti-cholinergic agents in human subjects\(^4\). Administration of the anticholinergic agent scopolamine revealed a sequence of symptoms resembling that seen in patients with dementia. The cholinergic hypothesis became a widespread trigger for research in the AD-field and culminated -5 to 10 years later- in the demonstration that cholinesterase inhibitors could indeed lead to some improvement of symptoms in patients with AD\(^5\). Numerous clinical trials followed in want of proving that finally a rational treatment was available for this devastating disease. But after years of
extensive clinical research one has to conclude that the effect of cholinesterase inhibitors in AD is truly limited. If strict responder criteria are used, and putative placebo effects are accounted for, CEI therapy is successful in only 5 to 15% of AD patients, whereas patients who are treated with CEIs frequently encounter serious side-effects (Cochrane reviews).\(^6\) With the advancing scientific insights in disease mechanisms it is now known that AD is a highly heterogeneous entity. Currently, beta-amyloid and presenilins are considered by many to be the most important factors in the process that leads to widespread degeneration of cortical networks underlying dementia in AD.\(^9\) It is widely acknowledged that loss of cholinergic transmission alone cannot account for the whole clinicopathological picture of AD. Notwithstanding these new insights in the pathogenesis, CEIs are the only available drugs that are licensed. Across numerous clinical trials there is a consistent effect of CEIs, not only in patients with AD but also with other forms of dementia such as DLB and Parkinson’s disease dementia (PDD).

Factors that might a priori predict a response to cholinesterase inhibitors have not yet been identified.\(^10\) In the first part of this thesis we discuss the issue of cholinergic deficiency and response to CEI therapy in different ways. In Chapter 2 it is hypothesized that a cholinergic deficiency syndrome can be delineated that may occur in various forms of dementia and that can serve as indication for therapy with CEIs. Based on literature this syndrome is suggested to resemble the symptoms seen in delirium. In Chapter 3 a prospective study is described that investigates in detail the clinical characteristics of responders to therapy with the CEI rivastigmine. These features are thought to constitute the hallmarks of the cholinergic deficiency syndrome. Chapter 4 describes the role of electroencephalography in identifying responders to CEI-therapy in addition to clinical measures. A putative clinical correlate of the cholinergic deficiency syndrome is discussed in Chapter 5 where neuroleptic sensitivity as a manifestation of cholinergic deficiency leads to a false diagnosis of Creutzfeldt-Jakob disease. Rational and cost-effective use of CEIs has also been the subject of the guidance of the United Kingdom’s National Institute of Clinical Excellence and health (NICE). This guideline caused a major uproar in societal and political sense in the UK in 2007. Chapter 6 is a reaction to these events. This paper advocates the concept of the cholinergic deficiency syndrome as indication for therapy with CEIs and urges pharmaceutical companies to release trial data in order to gain more insight into the clinical characteristics of responders to CEI-treatment.
Inflammation

Not long after the intense interest in the role of specific neurotransmitter systems subsided, a new area which focused the attention in the field of dementia research developed. Availability of specific antibodies in the 1980’s stimulated increasing insight in the immune system and inflammatory processes. It became clear that inflammatory processes in the brain affect cognitive functioning. This was based on the discovery of three disease mechanisms. First, neurodegenerative diseases are accompanied by an inflammatory response. Pathological studies showed that microglia, the macrophages of the brain, become activated and release cytokines. Whether these inflammatory mediators have a primarily causative, a facilitating or counter-regulatory function remains controversial. It is remarkable in this context that the pathological hallmarks of neurodegenerative disease such as amyloid-beta plaques in AD, tau in FTD or alpha-synucleine-pathology in DLB, do not completely explain the clinical symptoms. Second, it became widely acknowledged that aging itself is accompanied by a low-grade inflammatory state expressed by alterations in concentrations of circulating pro- and anti-inflammatory cytokines in serum. This is associated with age-related diseases such as atherosclerosis, diabetes mellitus and AD. In the brain similar immunological changes occur as a result of aging as expressed by the presence of activated microglia. This could be elicited by other pathological changes in the brain as mentioned before. Alternatively it has been proposed that microglia activation in elderly is a result of aging of the microglia themselves. It is proposed that inflammation in combination with neuro-endocrinological changes and sarcopenia, conceptualized as frailty, put an older person at risk for adverse outcomes. This concept, however, is still in need of support by robust evidence from observational or experimental studies.

Important to the understanding of the role of inflammatory markers and cognitive function was the elaborate research on infectious processes. Inflammation in peripheral tissue is accompanied by a systemic reaction of release of cytokines in the blood. As a result of the infection the body creates a new homeostasis accompanied by fever, reduced appetite, and neurobehavioral changes, collectively known as sickness behavior. It is now well established that raised levels of circulating cytokines induce these behavioral changes through interaction with the brain, especially via interleukin-1. Several pathways have been proposed that may play a role in this cross-talk between the peripheral immune system and the brain, but the activation of microglia in the brain parenchyma seems to be pivotal.
The current knowledge leaves several issues to be elucidated. In what way does systemic inflammation influence the brain? Are immunological changes in the brain responsible for cognitive impairments and what is the mechanism? In the second part of this thesis we address some of these problems.

In Chapter 7 the hypothesis is tested that raised inflammatory markers in elderly subjects mediate vulnerability as based on the frailty concept. It is investigated whether these markers are an independent risk factor for the development of delirium. In Chapter 8 microglia activation in postmortem brains of patients who died with sepsis are compared with controls. This could be the first step in identifying the mechanism(s) in humans of the interplay between systemic inflammatory changes and the brain, since animal experiments have suggested that activation of microglia occurs in sepsis. In the discussion section the results of the various studies described in part I and II are put in perspective and suggestions for future research are made. A possible link between inflammation, cholinergic deficiency and cognitive dysfunction is hypothesized.

References
1. NationaalKompasVolksgezondheid.
   http://www.rivm.nl/vtv/object_document/o1470n17535.html