Improving outcomes of patients with Alzheimer's disease

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Chapter 1
General Introduction, aims and outline of this thesis
Alzheimer’s disease
It is estimated that by 2030 about 65 million people will be affected by dementia worldwide. Dementia has been declared as a public health priority by the World Health Organization as it is a costly condition in its social, economic, and health dimensions. Alzheimer’s Disease (AD) is the most frequent cause of dementia and characterized by cognitive impairment, functional decline and neuropsychiatric symptoms. As a consequence, AD has substantial effects on the quality of life of patients and their caregivers.

The cause of AD is to a large extent unknown; it is thought that AD develops as a result of multiple factors rather than a single cause. Several risk factors are linked to AD such as age, family history, apolipoprotein (Apo) E4 status and head injury. In addition, it is believed that the clinical features of AD are associated with brain pathology, including amyloid plaques and neurofibrillary tangles. Plaques are deposits of amyloid, a small protein with a beta-sheet structure. Tangles consist of accumulation of tau, a microtubule-associated protein. These microscopic abnormalities may lead to macroscopic brain atrophy, which can been seen on structural brain imaging such as Magnetic Resonance Imaging (MRI) of the brain.

Diagnosing Alzheimer’s disease
In the Netherlands, memory clinics have been established for the diagnosis and treatment of dementia. A memory clinic is an ambulatory facility with multidisciplinary teams that focus on diagnosis, treatment and counselling of patients with cognitive impairment, especially dementia. The role of research within a memory clinic is very important because memory clinics provide an appropriate setting for standardized inclusion of patients. In addition, memory clinics are important settings for the implementation of new interventions and evaluation of the effect of these new interventions.

The Dutch memory clinics provide care according to the Dutch dementia guideline. According to this guideline, patients are evaluated by a physician and a specialized geriatric nurse. Anamnesis, heteroanamnesis, physical-, neurological-, and cognitive assessment are performed, including cognitive screening tests such as the Mini Mental State Examination (MMSE) and the clock-drawing test. When a diagnosis can not be established, additional tests are ordered such as extensive neuropsychological testing and brain imaging. When the diagnosis probable or possible AD, according to the criteria of the National Institute of Neurological and Communicative Diseases-Alzheimer’s Disease and Related Disorder Association (NINCDS-ADRDA) is established, patients are offered pharmacological and non-pharmacological interventions and outpatient visits are scheduled to evaluate the effect of these interventions.

Pharmacological and non-pharmacological interventions for Alzheimer’s disease
Unfortunately, there is currently no curative treatment for AD. Since the 1990s, two types of symptomatic pharmacologic treatments are available: the N-Methyl-D-aspartate glutamaterceptor...
Antagonist memantine and the cholinesterase inhibitors (ChEIs) rivastigmine, galantamine and donepezil\(^20\). ChEIs are recommended for the management of mild to moderate AD\(^15,16,21\), memantine for moderate to severe AD\(^15,16,21\). ChEIs and memantine influence neurotransmitter systems associated with the underlying degenerative processes. ChEIs increase the amount of acetylcholine at the synaptic cleft by preventing its breakdown by the enzyme acetylcholinesterase\(^20\). Memantine is believed to act by reducing glutamate mediated toxicity\(^20\).

Randomised controlled trials (RCTs) have shown beneficial effects of ChEIs on cognition, global clinical state, activities of daily living and behaviour\(^22,23\). However, it is difficult to draw firm conclusions about their long-term effectiveness as most trials lasted on average six months\(^20,22,23\). In addition, RCTs are performed in selected groups of patients with strict inclusion and exclusion criteria. Consequently, AD patients enrolled in RCTs may not be representative of AD patients treated in a ‘real-life’ setting, limiting the external validity of the results\(^24,25\). Moreover, in the past years, it is not just the pharmacological treatment that has changed the management of AD. Drugs are given in addition to multiple non-pharmacological interventions such as dementia case management, respite care and occupational therapy\(^15,16\). Knowledge of the long-term course of AD in light of current pharmacological and non-pharmacological interventions provided in a ‘real-life’ setting, i.e. outside of clinical trials, is scarce. This knowledge is of great importance as it gives the possibility to assess the long-term effect of these interventions and to plan future care.

In addition, it is important to know what clinicians should do in case of absence of an initial response to ChEI treatment. Some guidelines on the management of AD propose to evaluate the effect of ChEI treatment three or six months after the ChEI is started\(^15,26,27\). In case of deterioration of global, cognitive, functional or behavioral function during the first months of treatment, the patient is considered to be a non-responder and discontinuation of treatment is recommended\(^15,26,28\). However, the evidence demonstrating that it is appropriate to stop treatment in non-responders is limited\(^27\). In contrast, it has been shown that the beneficial effects of ChEIs disappear within six weeks after discontinuation\(^29\). Understanding the relation between the initial response to ChEI treatment and the subsequent course of AD is relevant given the potential negative consequences of stopping treatment\(^29\). Hence, it may help clinicians, patients and their caregivers to make an informed decision.

Alzheimer’s disease and nutritional status

Since there is no curative treatment for AD, it is of crucial importance to seize every opportunity to improve the outcomes for AD patients. In 1907, Alois Alzheimer described weight loss in his first patient\(^30\) and weight loss is currently recognized as a clinical feature of AD\(^39\). Weight loss, a characteristic of undernutrition\(^31\), has been described in approximately 20% to 45% of community-dwelling AD patients\(^32-37\) and is associated with an accelerated progression of cognitive decline\(^32,34,38,39\), increased dependency\(^34,38,39\), a higher incidence of behavioural problems\(^38\), increased morbidity\(^32\), decrease in quality of life of the patient and his caregiver\(^37\), a higher rate of institutionalization\(^40\) and
increased mortality\textsuperscript{41-43}.

Although weight loss is frequently described in AD patients and its association with the mentioned adverse outcomes, little is known about the prevalence of undernutrition in community-dwelling AD patients, especially in newly diagnosed AD patients. Early detection of poor nutritional status, and its causes, is crucial for adequate interventions to prevent or diminish the adverse outcomes. Nevertheless, in the current guidelines on diagnosis and treatment of AD\textsuperscript{15,16,26,44,45}, no attention is given to what clinicians should do in case of poor nutritional status in community-dwelling AD patients. In general, there are various interventions to increase nutritional intake in individuals who are undernourished or at risk of undernutrition, such as dietary fortification and oral nutritional supplements (ONS)\textsuperscript{46}. Before implementation of such interventions in AD guidelines, fundamental questions about their effectiveness in community-dwelling AD patients need to be addressed systematically. There are several guidelines and studies on the treatment of weight loss and undernutrition in older people without AD\textsuperscript{47,48}. However, these results cannot be extrapolated to AD patients because the mechanisms and causes of weight loss in AD patients are probably not the same as in individuals without AD.

The various hypotheses regarding the causes and mechanisms for weight loss in AD patients are summarized in figure 1\textsuperscript{30,32,49-52}. The factors that may contribute to weight loss in AD patients can be divided in primary and secondary factors\textsuperscript{51,52}. Primary or disease-related factors are related to AD, such as cognitive disturbances, behavioural problems and an altered taste and smell function (figure 1)\textsuperscript{51,52}. Secondary factors are general factors that may contribute to weight loss, such as adverse effects of medication and comorbidity (figure 1)\textsuperscript{51,52}. These primary and secondary factors may lead to loss of appetite, inability to shop and prepare meals, refusal to eat, finally resulting in an imbalance between energy intake on the one hand, and energy expenditure on the other hand, and hence in weight loss (figure 1)\textsuperscript{30,32,49-52}.

\textbf{Figure 1:} Hypotheses regarding the causes and mechanisms for weight loss in patients with Alzheimer’s disease\textsuperscript{1}  
\textit{Figure 1 is based on the following studies:} \textsuperscript{30,32,49-52}  
1 Biological disturbances: hormonal changes, inflammatory abnormalities, endocrine and metabolic changes; 2 Cognitive disturbances: restricted time, cognitive problems; 3 Behavioural disturbances: restlessness, pacing, repetitive tasks; 4 Biological Disturbances: medial temporal lobe atrophy; 5 Motor disturbances: loss of muscle mass; 6 Taste and smell dysfunction; 7 Side effects of medication; 8 Refusal to eat; 9 Increased energy expenditure; 10 Forgetting to eat; 11 Loss of appetite for example preparing meals; 12 Imbalance between energy intake and energy expenditure; 13 Loss of muscle mass; 14 Increasing age; 15 Comorbidity; 16 Social factors: increasing age, no social support, loneliness, poverty.
None of the proposed mechanisms or causes of weight loss in AD has been proven. A better understanding of the causes and mechanisms of weight loss in AD patients is relevant given its adverse outcomes. As shown in figure 1, some authors hypothesized that AD patients lose weight as a result of atrophy of the medial temporal lobe\textsuperscript{30,32,49,53,54}. The medial temporal lobe is a brain area which is involved in the regulation of food intake\textsuperscript{53-55} and a site where AD pathology is typically present\textsuperscript{12}. In addition, it is supposed that ChEIs may contribute to weight loss due to gastrointestinal side effects such as nausea, vomiting and diarrhea\textsuperscript{49}, which may be caused by the cholinergic action of ChEIs on stomach and intestine\textsuperscript{56}. Given the increasing number of patients treated with a ChEI\textsuperscript{57,58}, it is important to establish the role of ChEIs as a potentially contributing factor to weight loss.

**Aims of this thesis**

Since Alzheimer’s disease is one of the most disabling and burdensome health conditions worldwide\textsuperscript{3}, it is of crucial importance to improve the outcomes for AD patients. In order to improve the outcomes for AD patients, this thesis will focus on the long-term course of AD in patients treated in a ‘real-life’ setting and their nutritional status. We used data from the Frisian Alzheimer’s Disease Cohort Study, a ‘real-life’ study of the long-term course of AD in patients treated with pharmacological (i.e. ChEIs) and non-pharmacological (i.e. case management, respite care) interventions provided according to the Dutch Dementia guideline at the memory clinic of the Medical Center Leeuwarden. In addition, for one study we used data of AD patients seen at the memory clinic of the Slingeland Hospital in Doetinchem. These patients were also treated according the Dutch Dementia guideline.

The research aims of this thesis are:

1. Providing insight in the long-term course of AD in patients treated with pharmacological and non-pharmacological interventions in a ‘real-life’ setting.
2. Investigate the relation between the initial response to treatment with ChEIs and the subsequent long-term course of AD.
3. Determine the prevalence of undernutrition and the relation of various factors to nutritional status in newly diagnosed AD patients.
4. Elucidate the possible role of the medial temporal lobe and ChEIs as mechanisms of weight loss in AD patients.
5. Assess the current evidence regarding the effect of nutritional interventions in community-dwelling AD patients with a poor nutritional status.

**Outline of this thesis**

The first research aim is addressed in chapter 2.1 of this thesis. We investigated the disease course of 576 patients from the Frisian Alzheimer’s Disease Cohort Study. Disease course was described by changes in cognition and number of types of professional care during 3.5 years. In addition, behaviour and psychological symptoms, proportion of nursing home admission and deaths were...
investigated.

The relation between the initial response to ChEi treatment and the subsequent long-term course of AD is explored in chapter 2.2 by comparing the long-term course of cognition between initial non-responders and responders.

In chapter 3.1, we determined the prevalence of undernutrition and its relation to various factors in 312 community-dwelling elderly with newly diagnosed AD seen at the memory clinic of the Slingeland Hospital in Doetinchem. To determine the prevalence of undernutrition, we used the Mini Nutritional Assessment (MNA), which is specifically developed and validated to identify undernutrition in older people59-62.

In chapter 3.2 and 3.3, we focus on causes and mechanisms of weight loss in AD patients of the Frisian Alzheimer’s Disease Cohort. In chapter 3.2, we explored the role of atrophy of the medial temporal lobe in weight loss in AD patients. The role of ChEIs as a potentially contributing factor in weight loss is examined in chapter 3.3.

Chapter 3.4 describes the current (lack of) evidence regarding the effect of nutritional interventions in community-dwelling AD patients with a poor nutritional status.

Chapter 4 summarizes our main findings and discusses the clinical and scientific implications of the results.
REFERENCES


25. Rothwell PM. (2005) External validity of randomised controlled trials: ‘to whom do the results of this trial apply?’ Lancet 365:82-93


17

General introduction, aims and outline of this thesis


